

# Cardiopulmonary and heart transplantation: 100 years of history and 40 years of existence

*Transplante cardíaco e cardiopulmonar: 100 anos de história e 40 de existência*

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In June 2007, we celebrate the 40<sup>th</sup> anniversary of the first homologous human orthotopic heart transplant operation successfully performed on December 3 1967 at Groote Schuur Hospital, Cape Town, South Africa by the cardiovascular surgeon, Dr. Christiaan Neethling Barnard. A little more than a 100 years ago (1905), the first experimental surgical studies on tissue and organ transplantation, such as the heart, were performed by a surgeon born in Lyon, France, Dr. Aléxis Carrel, who later on moved to the United States of America, start practicing at the Rockefeller Institute and the John's Hopkins, where he performed most of his experimental studies.

Dr. Aléxis Carrel was awarded the 1912 Nobel Prize in Physiology and Medicine for these efforts. It was the first Nobel Prize awarded to a scientist from an Experimental Laboratory.

Orthotopic heart transplant operation was preceded and succeeded by a number of other studies in "anima nobile".

This transplantation, when it was performed, gave an extraordinary impulse to the study of tissue rejection reactions, to its diagnosis, and to medical and preventive treatment.

Techno-surgical advances concerning the so-called heterotopic heart transplant operation (particularly heart in parallel) were also numberless, as well as the simultaneous transplantation of one heart and two lungs.

This is undoubtedly an exciting scientific history.

We are going to try to describe it as most objectively as possible.

## BACKGROUND

In 1905, the first circulatory vessel system transplantation and, subsequently, of several organs was performed by Carrel and Guthrie [1]. Their studies about experimental surgical research were developing rapidly and,

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in 1907, Aléxis Carrel presented techniques for heart transplantation [2]. His description about a greater survival of the autotransplant (autograft) concerning to the homograft (allograft) was the main reason to be awarded the Nobel Prize in 1912. It was the first Nobel Prize awarded to a medical research study carried out in the United States of America.

In 1933, Mann et al. [3] working at the Mayo Clinic and the Georgetown University with heterotopic heart transplant in canine neck, demonstrated that the problem of the execution was not of the techno-surgical nature. They were the first to observe a graft rejection phenomenon. What histologically attracted considerable attention was that the heart transplanted to the neck demonstrated an infiltration by lymphocytes and polimorphonuclear leukocytes in its walls.

Between 1918 and 1920, Dederrer [4,5] proved in cases of kidney transplantation that there was no rejection problem, when transplantation was performed between identical twins.

In 1948, Sinitsyn [6] was the first to describe a model of functioning heterotopic heart transplantation.

Back in the mid-1940s, Vladimir Demikhov of the Soviet Union successfully implanted the first heterotopic heart allografts in dogs, followed by orthotopic heart-lung and heart transplantation. He used a very simple technique before the advent of cardiopulmonary bypass (CPB) and the hypothermia techniques. The simplicity of this technique was critical for the success in his experiments. The transplanted heart managed to beat 32 days after the implant without any problem, according to the author. Unfortunately, Demikhov believed that the transplantations failures were due to technical reasons, not implying any graft immunological reaction. On his 15<sup>th</sup> experiment of lungs and heart transplantation, the animal (a dog) was removed alive from the operating table. The animal resumed breathing with a respiratore rate of seven deep movements per minute (long inspiratory time). The respiratory pattern was kept by the abdominal muscle and regions of neck movements, keepinh the animal with the mouth open. These changes of the respiratory pattern were identified as a “state of total cardiopulmonary denervation of the dogs”. His experiments, however, demonstrated that from the technical standpoint these heart or heart-lung transplant operations were feasible. The greatest survival of heart-lung transplant operations was six days in a dog named and worldwide known as “Dog Damka”. The Demikhov’s studies only came under the Western medicine notice in 1962 [7].

In 1951, Marcus et al. [8] of the Chicago Medical School started focusing on techniques to preserve the organ to be transplanted.

With the advent of CPB, everything was set to start the orthotopic heart transplant operation research.

In 1958, Golberg et al. [9] tried a surgical technique for orthotopic heart transplant operation, in which a left atrium “cuff” (a crescent of the posterior wall) was preserved, eliminating the need of individual anastomosis in the pulmonary veins.

The preservation of the biatrial (right and left) “cuff” was developed posteriorly between 1959/1960 by Lower and Shumway [10] and used later on by Barnard, in 1967.

It is worth mentioning that the first case published regarding a (unsuccessful) human heart transplant operation was performed by Hardy et al. [11] in 1964, when they transplanted a chimpanzee heart to a human patient. The chimpanzee heart beat, but due to the smaller size of the primate heart. The primate died of heart failure.

It is interesting to report that in 1966, a surgery designated “mirror-image” surgery performed by Hardy was carried out at the Medical College of Virginia by Lower, a true unusual surgery. A heart from a human cadaver was removed, reanimated and successfully implanted in a baboon, a well-known smaller size primate from Africa. The donor’s greater heart size prevented the baboon chest to be closed. However, the circulatory support was kept for several hours until the experiment was electively suspended. Medical literature has never reported such an event, however, it confirms that the human heart can be successfully stopped, resuscitated, and transplanted in other mammalian species.

In 1959, Cass and Brock [12], working at the Guy’s Hospital, London, presented experimentally in dogs six cases of autograft to test the denervated heart reactions; immunological reaction was not observed. In case number 6, they performed an orthotopic heart transplant operation using both right and left atrial cuffs to perform an orthotopic anastomosis to the heart. This occurred in the same very year and almost simultaneously with the beginning of Lower and Shumway experiments abovementioned.

In 1959, Guertzenstein E and Rodrigues da Silva P, in the discipline, Experimental Surgical and Operation Technique, a discipline taught by Professor Dr. Sá Fortes Pinheiro, at the University of Rio de Janeiro School of Medicine and Surgery, Uni-Rio, Rio de Janeiro, RJ, performed an experimental study of heart transplant operation in dogs with intrathoracic orthotopic and heterotopic grafts into the region of neck. This study is the pioneer study in Brazil, entitled “Transplante cardíaco homólogo em cão” (Homologous Heart Graft in dogs). Those who in 1958 and 1959 followed the research and experimental studies regarding orthotopic cardiac transplantation know that there has already been questionings between the advantages of the transplant with sutures at left atrium level over the suture of the pulmonary vessels alone. Similarly, the same is true regarding the right atrium, with no need of using sutures of the vena cavae alone. There was no doubt that the

anastomoses at atrial level were technically easier and, thus, they would reduce the overall execution time of orthotopic grafts. The abovementioned surgeons performed 11 experiments with dogs. Concerning orthotopic graft, the same authors recommended back then in 1959, the bicaval anastomosis for several long-term functional reasons based on theoretical reasoning at the occasion when the anastomosis of the right portion of the heart was performed, as is the technique of choice currently. The technical times, both neck grafts and orthotopic grafts with bicaval anastomosis, all are presented in the previously mentioned study.

As it is known, current surgeons recommend annular plication for tricuspid valve repair, when they are going to perform the biatrial anastomosis technique in order to avoid or minimize tricuspid insufficiency with regurgitation through this valve and increase of right atrium auricle as happens in prolonged heart postoperative transplanted patients.

The study by Guertzenstein and Rodrigues da Silva was presented by both cardiovascular surgeons in November 23 1959 at the Brazilian College of Surgeons (BCS), Rio de Janeiro, being edited by BCS in its journal "Revista Brasileira de Cirurgia" as "Original Article", volume 39, no. 1. January 1960 [13].

In 1960, Lower and Shumaway published an impressive experimental study, which has already been previously cited [10] concerning orthotopic cardiac transplant operation. These authors, pioneers in several experimental heart transplant studies, published their technique of orthotopic cardiac transplant operation by using bicaval anastomosis in eight dogs. Of the eight dogs, five transplant recipients survived for six to twenty-one days eating and exercising on a normally basis postoperatively. This was the first description in the world of a routinely successful technique for orthotopic cardiac transplant operation in mammals, in which the recipient resumed its normal activities. The circulatory support was completely maintained by a transplanted heart. Interesting is that no immunosuppressant medication was given to these animals and death was due to a myocardial failure picture that has rapidly developed. This clinical picture was associated to massive infiltration of rounded cells (histologically) associated to interstitial hemorrhage.

This experiment allowed, at the occasion, a suggestion that if the host immunological mechanism was controlled with medication, so there were no deterioration of the transplanted hearts, all the animals would live with adequate cardiocirculatory function during their normal lifespan.

It is beyond doubt that the study by Lower et al. [14] was yet very significant. It was published in 1956 describing the use of surface electrocardiogram (ECG) as an indicator of the rejection phenomenon. During the period of rejection,

the ECG demonstrated a definite voltage decrease. The administration of azathioprine and methylprednisolone restored the ECG pattern to normal. With this technique, they managed to prolong the survival of adult dogs with heart transplant for 250 days.

In 1964, Shumway and Lower [15] stated based on their huge experimental study: "Technically, much has already been achieved and that truthfully only the immunological barrier stood as an obstacle to enter a new radical era of the treatment of severe heart diseases".

In December 3 1967, the cardiovascular surgeon, Dr. Christiaan Neethling Barnard, tutored in General surgery by Owen H. Wangsteen, at the University of Minnesota, and in Cardiothoracic Surgery by C. Walton Lillehei, successfully performed at the Groote Schuur Hospital, Cape Town, South Africa, the first homologous orthotopic heart transplant in the world, in a patient with left ventricular failure [16].

Dr. Barnard implanted in his patient, Mr. Washansky, the heart of a decerebrated young boy. The transplanted patient left the operating theatre alive with atrioventricular block controlled by a pacemaker. The transplanted heart had a 14-minute ischemia during the procedure and the patient remained in extracorporeal perfusion for 117 minutes. The first transplanted patient has succumbed 17 days after cardiac transplantation due to pneumonia secondary to pseudomonas.

In the postoperative period and taking into consideration what existed at that occasion, the patient received immunosuppressants, such as azathioprine associated with steroid injections and some radiation sessions of the transplanted heart at each electrocardiographic alteration compatible with transplant rejection.

Despite the resistance offered by some authors and surgeons – particularly the North Americans' – because the pioneer Normann Shumaway was not the author of the first homologous human heart transplantation, Dr. Christiaan Neethling Barnard gave yet many other scientific contributions in this field, as we will see next.

In his second heart transplant operation, performed in 1968, Dr. Christiaan Barnard, as we refer to him, did a small and definite modification in the way of incising the posterior right atrial wall of the heart to be transplanted, which is currently used up to the present day, thus avoiding definitively the atrioventricular block appearance, as occurred in his first case.

Instead of using this incision from the inferior vena cava cephalad towards the superior vena cava (as he did in his first case), he begun to drive this incision of inferior vena cava towards the oblique base of right auricle and, thus, avoiding any chance of postoperative atrioventricular block.

Three days after the successfully transplant operation performed by Dr. Barnard, Kantrowitz et al. [17], in

Brooklyn, New York, transplanted the heart of an anencephalic newborn to another newborn patient, born with the Ebstein disease, using deep hypothermia. The idea was to take advantage of the fact that a newborn infant does not have an immunologic system developed enough, and as it was, there would have been fewer chances of the patient to have rejection to the transplanted organ. For reasons considered at the time as being of metabolic origin, the transplanted heart only beat suitably for six and half hours.

In March 26 1968, Professor E. J. Zerbini, in a pioneered way in both Brazil and South America, performed the first successfully human orthotopic heart transplant operation. Delmont Bittencourt was the surgeon who harvested the donor's heart. Also, the following Brazilian cardiac surgeons, such as Geraldo Verginelli, Miguel Barbero Marcial, Sérgio Almeida Oliveira e Euclides Marques, took part of this outstanding Brazilian surgery [18].

It is important to stress that Professor E. J. Zerbini was the first to perform an attempt to transplant a heart in patients with Chagasic cardiomyopathy.

Other contributions from Brazilian cardiac surgeons were also important:

- Ivo Nesralla – Performed the first nation-wide transplant in the era of cyclosporine followed by the cardiac transplantations of this new phase consecutively performed by the Adib D. Jatene e Danton Rocha Loures' surgical teams;
- Carlos Figueroa – Performed the first cardiac transplantation in a female patient in Brazil;
- Bayard Gontijo F<sup>o</sup> e Mário O. Vandrecic – Gave a significant contribution to the improvement of cardiac transplantations, especially regarding the support related to tissue typing and histocompatibility;
- José Teles de Mendonça – From the North/Northeast group, with a new donor/recipient approach. This original project started in March 1986, in Aracajú, SE, with José Wanderley Neto, Marcos Ramos e Ricardo de Carvalho Lima;
- Noedir Stolf – Besides important contributions to cardiac and lung transplants in Brazil (since his experimental studies with Euclides Marques) has had relevant participation in the development of noninvasive protocols for early diagnosis of cardiac rejection;
- Noedir Stolf – Performing heterotopic transplantations;
- José Pedro da Silva – Brazilian successfully cardiopulmonary (en block) and heart-lung transplantation pioneer;
- José Pedro da Silva – Successful heart in-parallel thorax implantation;
- Luiz Carlos Bento de Souza – Expressive contribution to nation-wide development of en block cardiopulmonary transplantation;

- Miguel Barbero Marcial – Cardiac transplantation in newborn infant with complex congenital heart disease (infant with 20 days of life);
- Adib D. Jatene e Luiz Felipe Moreira – They have distinguished themselves with the application of the cardiomyoplasty technique (Carpentier's). They contributed to the nonfunctioning muscle flap laboratory noninvasive diagnosis after the performance of a cardiomyoplasty with the latissimus dorsi muscle;
- Domingo M. Braile – Use of cardiomyoplasty technique in a Chagasic patient, concluding that the cardiomyoplasty in Chagasic patients renders a better outcome than heart transplantation;
- Randas Batista – “Autograft” for giant atrium and atrial fibrillation treatment;
- In terms of mechanical heart and mechanical assisted circulation, we should pin point the experimental studies by Adib Jatene back in 1970s; Kenji Nakiri at the InCor; and Domingo M. Braile in São José do Rio Preto, being this performed with bovine pericardium mechanical “ventricle” [18];
- Rendas Batista, with his worldwide pioneer contribution and visionary view in terms of technical future, performed and published the partial resection of failing left ventricle regarding left ventricular failure with cavity dilation. Thus, besides controlling left ventricle insufficiency, it reduces the number of patients with severe heart diseases requiring cardiac transplantation [19].

In 1974, Christian Barnard and Losman (the latter one born in Holland, i.e., from the same Barnard's grandparents country) presented and performed for the first time in the world, a thoracic homologous heterotopic heart transplantation in parallel to the patient failing heart. The heart was kept in situs while still at the Groote Schuur Hospital, Cape Town, South Africa [20].

This worldwide pioneer surgery was performed in the sense of providing assistance to the patient's left ventricle. Initially, they operated on two patients using this technique; one of them survived for four months, dying of pulmonary embolism. Another patient operated on with this same technique, using two thoracic hearts, one in parallel, survived well for 8 years. However, in 1974, Barnard started in humans the biventricular assistance technique with the heart implanted in a parallel fashion. He proved that this was the ideal technique for patients with left ventricular failure associated to pulmonary arteriolar hyperresistance (more than 6 Woods units), when the simple orthotopic transplantation is contraindicated, at first.

From this date on, this turned to be the only cardiac transplantation method in Dr. Barnard's Service [21].

The greatest series of cardiac transplantation in a parallel

fashion outside of Cape Town took place at the Harefield Hospital, UK. It was performed by Yacoub et al. [22].

Yacoub et al. [22] reported better outcomes with transplantations in a parallel fashion than that achieved with the classic orthotopic transplantation. This surgery is a more technically complicated surgery and its good outcome is directly related with the quality of the surgical technique used.

Barnard proves that using heterotopic heart transplantation in a parallel fashion, when a rejection immunological reactions occurs, the heart can reasonably support the patient's circulatory requirements, thus providing time and conditions for a drug action of the rejection reversion episode.

In 1979, Barnard et al; [23] proved the advantages of performing the transplantation in a parallel fashion in relation to the orthotopic transplantation to handle the crises of acute rejection in transplanted patients.

We would like to relation that when visiting Dr. Barnard's service in South Africa and later on when escorting him in his daily visit to his postoperative transplanted patients, one patient with a transplanted heart in a parallel fashion complained about feeling a little dizzy. It was evidenced by the patient's ECG scan that one of the hearts (the transplanted one) was fibrillating. The patient kept a lower blood pressure but physiologically adequate. Without rushing around, the patient was fibrillated, and he returned to normal immediately. This event came to prove and to confirm to me, more than ever, that with this technique only one of the hearts functioning can keep the patient alive.

As mentioned before, Demikhov, in 1948, has already demonstrated experimentally the technical feasibility of the intrathoracic transplantation of the heart, see the case of "Dog Damka" that has survived for six days with this operation.

Some facts and experimental contributions should also be mentioned regarding heart-lungs transplantation intrathoracically.

In 1953, Neptune et al. [24] of the Hahnemann Medical College of Philadelphia performed this technique in dogs, using hypothermia e circulatory arrest.

In addition, in 1953, Marcus et al. [25] using dogs implanted a heart and lungs connected to the abdominal aorta with the trachea being ventilated externally, which has worked for 75 minutes.

In 1957, Webb and Howard [26] performed four experiments in dogs, transplanting heart and lungs orthotopically. They identified that heart function was adequate; however, the animals could not breathe spontaneously. It was clear then that cardiopulmonary denervation was not well tolerated by the dogs. The same authors suggested a heart-lung (only one lung) transplantation, thus respiratory paralysis would be compensated by the other lung kept non denervated.

In 1961, Lower et al. [27] based on heart-lungs transplantation in six dogs emphasized that in performing the surgery one must maintain the vagus and phrenic nerves undamaged. Two of the dogs survived for four days breathing.

In 1967, Nakae et al. [28] performed cardiopulmonary transplantations in different species of animals. When they used primates despite the mediastinal denervation, there has been a postoperative recovery in the relatively normal respiratory pattern. This study came to confirm the one presented in 1963 by Haglin et al. [29] which stated that the denervation of both lungs would not avoid the return of the adequate breathing postoperatively in primates, oppositely to what happened with the dogs.

In 1972, Castañeda in two published studies proved that the fact above mentioned was true, once he had performed transplantations (to avoid the rejection phenomenon) in baboons using total respiratory denervation and the baboons survived well in a cardiorespiratory fashion for several years. Based of these experiments, Castañeda et al. [30,31] preconized that heart-lungs transplantation would be successful in human patients.

In 1981, Reitz et al. [32] at the Stanford University, Palo Alto, California, simplified the surgical technique and achieved a greater postoperative survival in primates.

In 1981, Reitz et al. [33] based on the aforementioned experiment performed the first orthotopic human heart-lungs transplantation at Stanford University with a 5-year survival. It was the first time a bicaval anastomosis was used in humans.

It was also defined at the Stanford University that the phenomena of pulmonary rejection occur regardless of those of cardiac rejection.

Much attention has been attracted since the first cardiac transplantation to the fast identification and expected, if any, of the cardiac rejection crisis.

In 1970, Barnard [34] stated that despite all the diagnostic means used, there has not been a single parameter to allow an unmistakable rejection diagnosis.

In 1944, Medawar [35] revolutionized the idea regarding the phenomena occurred during transplant operations. He verified the effects of a rabbit skin transplantation to another one and observed that the reactions were different when a rabbit skin transplantation to another one was performed comparatively to the rejection reactions when these rabbits were identical twins.

Medawar was the one who demonstrated the lymphocyte tissue infiltration that occurs in the transplanted skin when it is performed between non-twins, which leads to graft destruction between seven to ten days.

In addition, Medawar gave the term "rejection process" to this phenomenon. Phenomena that we analogously know occur in cardiac transplantations to date.

Likewise, Medawar demonstrated that a second skin transplant operation in the same recipient from the same donor leads to a faster destruction of the implanted skin (between five to 10 days postoperatively) than that occurs in the first transplant operation. This is due to the action of the antibodies (lymphocytes) preformed in the first transplant operation. To this, we call "hyperacute reaction"; fortunately, this event happens increasingly less after cardiac transplantation. Medawar also showed that rejection phenomena were due to a number of genetic diversity between individuals (inclusive in those of the same species).

Medawar initiated the studies to develop substances capable of controlling the rejection.

In 1950, Madawar suggested that drugs such as corticoids (shortly after discovered in 1955) could help preventing rejection.

The concept of Medawar regarding acquired immunological tolerance awarded him the 1961 Nobel Prize [36]. Only in 1960, Merrill et al [37] reported a successful transplant operation using moderate immunosuppressant therapeutic.

Myocardial biopsy has already been preconized and introduced for the first time by Sakakibara e Konno in 1962 in Japan [38].

The first diagnosis advance regarding rejection in transplanted cardiac patients came in 1972 performed by Phillippe Caves who introduced endocardial biopsy to be used for the diagnosis of rejection at the Stanford University [39]. This technique proved to be the most sensitive to the diagnosis of rejection, once it allowed the histological diagnosis four days before the other diagnosis method at the occasion.

Billingham [40], also at Stanford University, in 1981, defined the histological patterns by means of endomyocardial biopsy, proving which phase or stage of rejection was occurring in the transplanted heart. Histologically, Dr. Billingham classified the rejection into the four following phases: light, moderate, severe, and in resolution.

The Stanford University continued helping in the diagnosis and control of the cardiac rejections as follows:

- a) Introducing antithymocitic globulin;
- b) Introducing T cell monitoring technique;
- c) Introducing cyclosporin (Cy) A in the therapeutics of transplanted cardiac patients by Oyer and Shumaway in 1980.

Synthetically and objectively, we can define the chronology of the drugs used to control the rejection crises as follows:

- 1955 – Cortisone and ACTH used in kidney transplantations;
- 1960 – 6-mercaptopurine used in cardiac transplant operations in dogs;

- 1963 – Prednisone and azathioprine (first identified in 1959) helped a lot in the survival and in the outcomes of human kidney transplantations. Along with corticoids, azathioprine was used in the first human orthotopic heart transplant operation performed by Dr. Barnard in 1967;
- 1970 – Antilymphocyte globulin developed at Stanford University is used in cardiac transplant operations in the severe phases of acute rejection;
- 1978 – Cyclosporine A was discovered and initially introduced in kidney transplantations;
- 1981 – Monoclonal antibody was introduced in kidney transplantations;
- 1985 – OKT3 monoclonal antibody that acts against the T cells. At this time, its use was initiated in cardiac transplant operations.

It is important to stress that cyclosporine A helped to give a new drive for the performance of cardiac transplant operations, causing this procedure to be for severe heart disease patients an effective treatment.

Cyclosporin A is a specific drug against T cells, avoiding or inhibiting their production regarding the immunological response. There is no doubt that due to this action cyclosporin A has increased between 75% to 80% the survival of surgical cardiac transplant patients by 75% to 80%.

Monoclonal and polyclonal antilymphocyte antibodies eliminate the harmful effects of T cells binding to them, neutralizing their action.

As it is well known, in cases of acute rejection when OKT3 is administered, one should reduce the other immunosuppressants, such as cyclosporine and azathioprine, trying to minimize the risk of infections. There are new drugs such as the FK506, rapamicine, and other fungus-related drugs.

Generically, there are some problems related to transplanted hearts namely:

- The transplanted heart is denervated; this being said and taking into consideration the high incidence of coronary arteriopathy, the patients do not present the symptoms of cardiac angina pectoris. In these cases, only an endomyocardial biopsy is diagnostic. Injuries are only proximal truncal (as occurs in atherosclerosis in non-transplanted patients) when the disease is in a much more advanced stage;
- The faster coronary disease of the transplanted heart and its development is, the older is the donor's age.
- Antiplatelet medication, diabetes control or cholesterol drug control delay the development of coronary disease of the transplanted heart;
- The only proven resource for the treatment of coronary disease of the transplanted heart is the re-transplant operation. At Stanford University, the 1-year survival in re-transplant was markedly inferior to that of the first transplant, i.e., it was of 55%;

- Due to the use of cyclosporine, the transplanted patients present systemic blood pressure, which regardless what occurs in non-transplanted patients, it does present itself night and day.
- Due to the use of cyclosporine, these patients can present diabetes, osteoporosis, and hypercholesterolemia;
- Apparently, the neoplastic manifestations are more often among the non-transplanted patients.

Much has been succeeded, but there is still much to be done regarding cardiopulmonary and cardiac transplant operations.

Regardless what has been said shortly here to allow a continuation of this exciting scientific history, it will be necessary the efforts of those more experienced, young and ambitious for progress, finally, it will be necessary the effort of us altogether.

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