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PHENOMENON OF DEMIKHOV

At N.V. Sklifosovsky Institute (1960-1986).

Paradigm shift in homologous[1] organ transplantation: from overcoming biological incompatibility to artificial immunological tolerance (1960-1970)

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Abstract

The analysis of literature on experimental and clinical transplantation for the period of the 1968-1969 demonstrated that in the period from 1960 to 1970 the world transplantation saw a paradigm change in the field of homoorgan transplant: instead of overcoming the incompatibility between the donor organ and the recipient's body by using biological and physiological methods to influence the organ, which V.P. Demikhov had been dealing with for many years; surgeons and scientists, first abroad, and then

[1] The article uses the terms "homo logical", "homoplasty", "homoorgan", etc. applied in the 1960s–1970s. Today, instead of them, the terms "allogeneic", "alloplasty", etc. are used.

in the USSR started developing and applying the creation of artificial immunological tolerance by using various physical, chemical and biological methods to impact recipient's body. The change of paradigms significantly influenced the implementation of organ transplantation techniques in clinic, including those of vital organs, and the further development of clinical transplantology. The data on the first heart transplants in 1968 and lung transplants in 1963-1970 have been presented.

Keywords: history of transplantation, homoplastic organ transplants, biological incompatibility, immunological tolerance

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CPB (pump), cardio-pulmonary bypass pump (heart-lung machine)

HBO, hyperbaric oxygenation

VAD, ventricular assist device

Introduction

After receiving the Nobel Prize in Physiology or Medicine "for the discovery of artificial immunological tolerance" in 1960 by P.B. Medawar and F.M. Burnet For, the view of the homoplasty problem began gradually changing, shifting from the graft antigenic properties to recipient's immune

system.

The first kidney transplants from unrelated donors in the United States (by J. Murray, 1961; et al.), in Europe (R. Nagel, W. Brosig, 1963) [1], and in Russia (B.V. Petrovsky, 1965; et al.) [2], as well as lung transplants (Hardy, 1963; G. Magovern, 1963; et al.) [3], liver and spleen transplants (T. Starzl, 1963) [4], heart transplants (C. Barnard, 1967, 1968; A. Kantrowitz, 1967, 1968; N. Shumway, 1968; and others.) [5, 6], and cardio-pulmonary complex transplants (D. Cooley, 1968; C.W. Lillehei, 1969) [3] were performed under conditions of pharmacological immunosuppression and other methods of influencing the recipient immune system (including ionizing radiation or x-ray), and became the "starting point" (according to I. Lakatos) [7], which opened up a new era of homoplastic organ transplantation. Its paradigm[2] was the impact on the recipient's body by using non-specific and specific methods in order to form its immunological tolerance to the transplanted organ.

However, in the USSR, most research in the field of homoplasty was still conducted within the framework of the old paradigm formulated by A. Carrel at the beginning of the twentieth century. So, the analysis of the Proceedings of the 2nd All-Union Conference on the homoplastic problem (Odessa, 1967) [9], showed that in the mid-1960s, the approaches of the majority of Soviet scientists and immunologists to the problem of organ and tissue homotransplantations were aimed at *overcoming the tissue incompatibility* (convergence/leveling of immune differences between donor's and recipient's bodies) by applying biological and physiological methods: hybridization, chimerization, the impact on the central nervous

[2] "Paradigm" is a term introduced into the scientific circulation by T. Kuhn (1962). Paradigm was defined by T. Kuhn as universally recognized scientific achievements which for a certain time were the model of setting-up the problems and searching their solution by the scientific community [8].

system (drug-induced sleep, neurolepsy), the impact of external physical factors (cryopreservation) on the graft, and others. It was also spoken on the necessity to study the antigenic structure of homografts and even the genetic transformation of the homomaterial. And only a few reports were devoted to the transformation of the recipient's immune system by pharmacological means.

But didn't Soviet scientists, who steadily adhered to the traditional views of Michurin's biology and Pavlov's physiology (for example, overcoming the tissue incompatibility by cryotherapy of the graft or by introducing the recipient into the drug-induced sleep), know what was being done in this direction abroad? That's just it, they knew. But this knowledge reached them with a delay.

On the state of research in the field of transplant immunity in the United States and Europe in the first half and mid-1960s

In spring of 1968 (that is, after the 2nd All-Union Conference on Homoplasty), a remarkable book was published, which is little cited in the literature on transplantology and is now a bibliographic rarity (Fig. 1) [4].

Fig. 1. Cover of the monograph by I.D. Kirpatovsky "Foreign experience in organ transplantation." Moscow: Medicine Publ., 1968. [Museum of A.N. Bakoulev National Medical Research Center for Cardiovascular Surgery]

It turns out that in September 1963, in order to get acquainted with the research and clinical centers of the United States, France, Norway, Belgium, and Sweden working in the field of organ transplantation, a group of Soviet specialists was sent to these countries for several months. The scientists returned to the country in spring of 1964, but the manuscript of the book about the results of their trip was submitted for publication only on April 10, 1967, and signed for publication on January 30, 1968 (that is, a month after the 2nd heart transplant surgery performed by C. Barnard). We don't yet know why such a much-needed book for Soviet transplantologists came out in press so late. This section of our article is devoted to the book analysis.

In the monograph Preface written by V.V. Kovanov, he said that in recent years (i.e., in the first half of the 1960s), the attempts were made in clinics in different countries to transplant liver, intestine, spleen, lung, and heart to a human, but the most significant success was achieved in kidney transplantation. According to V.V. Kovanov, clinics in Denver (Colorado

State University), Boston (Harvard University), and Richmond (University of Virginia) had the greatest experience in this area. That is why Soviet scientists spent most of their business trips in the United States, obviously, in order to get the necessary information in this particular area of transplantology.

I must say that V.P. Demikhov was not among them. On the one hand, since 1959 (after two trips to Germany), he was "banned from traveling", and on the other hand, at that time, he was preparing for a Meeting of the USSR Health Ministry Council for Coordinating Research and Implementing Scientific Achievements in Practice, the Meeting which in October 1963 considered the issue "On the state and development of scientific research on organ transplantation" [10, 11]. We should note that Professor I.D. Kirpatovsky[3], the author of the book, was a member of the Committee that inspected the V.P. Demikhov's Laboratory work and was well aware of this Laboratory activities and the achievements of its Head. But since he was on a business trip, he didn't attend the Council Meeting.

I.D. Kirpatovsky's book "represents the first publication in our country generalization that summarized the foreign experience in this new and important branch of theoretical and practical medicine" [4; p. 3] and is essentially a brief guide to the theory and practice of transplantology. In the

[3] Igor D. Kirpatovsky (1927–2014), a Soviet and Russian transplant surgeon, Honored Scientist of Russia, a Member-Correspondent of the Russian Academy of Medical Sciences. After graduating from the 1st MMI named after I.M. Sechenov (1951), his postgraduate course (1953), and having defended his thesis on the topic "Foot fascia and cellular tissue plane" (1954), he worked as an Assistant at the Department of Operative Surgery and Topographic Anatomy of the 1st MMI, where he defended his doctoral thesis on the topic "Theoretical foundations of the intestinal suture" in 1961. He was the follower of V.V. Kovanov. From 1963 to 1997 he headed the Department of Operative Surgery and Topographic Anatomy at the P. Lumumba Peoples' Friendship University; from 1997 he was the Professor of this Department. From 2001 to 2014 he headed the Department of Andrology of this University and at the same time (since 1976) he headed the Clinical Center for Andrology and Endocrine Organ Transplantation. He made a great contribution to operative surgery and topographic anatomy, experimental and clinical neuroendocrine transplantology, surgical treatment of male infertility and endocrine forms of impotence.

Preface, the author gave three features that, in his opinion, characterized organ homotransplantation to humans: (1) the "two-pronged" nature of the operation performed by two groups of surgeons, and consisting of explanting the organ and simultaneous transplantation; (2) ethical and deontological problems associated with the organ removal either from a living donor or from a corpse that used to be a living organism some time ago; (3) perfect surgical technique combined with suppressing the recipient's immune response to the graft.

In section 1, devoted *to the study of transplant immunity and methods for overcoming* it, the author showed that in the early 1960s, research on transplant immunity was particularly intensive in the United States, where subtle biochemical methods were used to study both the transplant antigens, and tissue and humoral antibodies formed during their administration. Most of these studies were conducted at Harvard University (by W.J. Wilson, H. Katz et al.[4]) and at the University of New York. The model for the study was mice that were transplanted with skin homologous flaps. Several experiments were conducted in humans. Stereomicroscopy and histochemistry were used to detect signs of rejection at the preclinical level.

Previously, we showed that V.P. Demikhov (Fig. 2), for whom the methods of detecting the tissue antibodies were unavailable, used the hemagglutination method and, not finding humoral antibodies in the blood of recipients, complained about the "roughness" of methods he had to use. The humoral response to homoplasty with using a highly sensitive cytotoxic lymphocyte test was studied by scientists from the University of California (P. Terasaki et al.). It turned out that lymphocytes were more specific for

[4] Here and below only some of the names of foreign scientists given in the book of I.D. Kirpatovsky are mentioned. And the initials are marked by us, as they are absent from the original text.

studying the immune response than red blood cells.

Fig. 2. V.P. Demikhov in his working office. Late 1960s

Scientists from the University of Colorado (D.W. Talmage et al.), studying the synthesis of specific antibody proteins by lymphoid cells, confirmed the leading role of cell factor in transplantation immunity. Note that working closely with surgeons (T. Starzl et al.), the immunologists from Denver had the opportunity to study the transplantation immunity in clinic in the patients with transplanted kidneys and liver; so they were among the most competent experts in the United States. Recall that it was to Denver where C. Barnard departed to work with T. Starzl in 1966 before bringing his transplantation program to life, first transplanting a kidney and then a heart [12].

Studies by the Denver group showed how important was the selection of a donor for a successful homoplasty. It was found that a considerable role in this is played by the relations between the donor and the recipient, the compatibility of their blood factors, both relating to red blood cells (which was proved in kidney transplants from unrelated donors) and to white blood cells (about 10 antigenic systems were found in leukocytes). Also, for the

purpose of selection, a method of co-culturing blood lymphocytes from unrelated individuals was proposed.

In February 1964, the United States hosted the 6th International Conference on Transplantation, which was attended by I.D. Kirpatovsky and the Soviet scientists sent on that trip with him. The donor selection methods, including those based on leukocyte systems, was discussed, as well as the possibility of detecting leukoagglutinins in the recipient after homotransplantation. It was found that in addition to red blood cells and white blood cells, platelets can be the carriers of antigens (note that neither leukocytic nor platelet factors were discussed in Odessa in 1967).

I.D. Kirpatovsky divided the methods of influencing the recipient's body to increase the graft life expectancy into two groups: 1) non-specific and 2) specific.

I.D. Kirpatovsky referred the use of "immunodepressive" drugs, as well as thymectomy, splenectomy, ionizing radiation, etc. to the group of *non-specific methods*. These methods disrupted the lymphoid tissue development and the production of immunocompetent cells. According to the literature and the experience of American scientists, the following immunosuppressive drugs were recognized as the most promising (for the mid-1960s): antimetabolites (6-mercaptopurine, 6-methylmercaptopurine, imuran first used in kidney transplantation[5] by Murray, methotrexate, cyclophosphamide, etc.), corticosteroid hormones (cortisone, prednisolone[6]), and antibiotics

[5] Before the first kidney transplants in clinic, this group from Peter Bent Brigham Hospital in Boston (R.Y Calne, J.E. Murray, G.P. Alexandre et al) performed over 1000 (!) transplantations of homologous kidneys in dogs, in which 24 (!) schemes for overcoming the transplantation immunity with medications were studied. The use of imuran and azaserin made it possible to increase the survival time of transplanted organs to 50 days in 90% of animals, and to over 100 days in 50%. The minimum organ survival period was 32 days, the maximum organ survival period was 304 days.

[6] The use of prednisolone allowed achieving the homologous kidney survival in a dog up to 649 days (Ch. Zukoski et al, Los Angeles, California, USA).

having a bacterio-(cyto-)static effect (in particular, actinomycin C and D).

A group of scientists from Boston (J. Murray et al.) obtained important data indicating that a long-term use of immunosuppressive drugs does not completely suppress the immunological reactivity of recipients, that such animals can live in an open enclosure and be free from infectious processes, and that they can develop antigenic adaptation to the graft due to the immune system "paralysis" under antigenic overload. To elucidate the mechanism of this phenomenon, an interesting experiment was made: two renal homografts were extracted after 296 and 544 days of their life in recipient dogs and transplanted to the donors. Both kidneys took root and continued to function normally, which proved that there occurred no *genetic changes* in them. We should note that this fact completely refuted the theory of vegetative hybridization put forward by Soviet geneticists in relation to metabolism changes in the grafted stems (transplanted organs) and, as a result, their hereditary characteristics.

Another important fact was also established: the recipient became tolerant to a long-term functioning organ (for example, kidney), while remaining sensitized to other tissues of the same donor (for example, skin). All this confirmed the possibility to discontinue (in some cases) administering the immunosuppressive drugs without disrupting the tolerance obtained as a result of their use (J. Pierce, R. Varco, University of Minnesota).

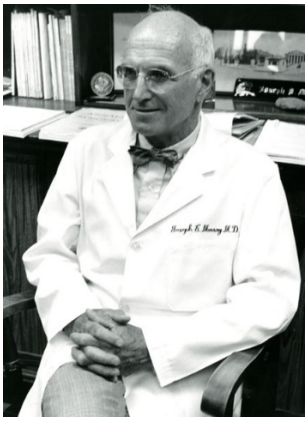

Fig. 3. Joseph Murray (1919–2012), Professor at Harvard University, Nobel Laureate (1990), pioneer of clinical transplantation [Available at: https://cms.www.countway.harvard.edu/wp/?p=7029]

The use of sublethal total-body irradiation of the recipient helped J. Murray (Fig. 3) in 1959 to perform a successful orthotopic kidney transplantation from one twin to another after removing the recipient's native kidneys. The rejection, which began 6 months later, was stopped by repeated irradiation and prednisolone. Subsequently, this patient lived for several years, during which the transplanted homologous kidney functioned normally. However, the use of total-body irradiation both in the United States and in Europe was soon discontinued. Experimental and clinical observations have shown that exposure of the recipient to large doses of gamma rays, besides having a pronounced immunosuppressive effect, caused the destruction of blood cells and bone marrow aplasia, which led to the death of patients from radiation sickness or infectious complications. Local irradiation of the graft, regional lymph nodes, or thymus gland proved to be more effective; but in 1964, this method had not yet gone beyond the limits of a clinical experiment (D.M. Hume et al., Richmond). In a footnote to its description, I.D. Kirpatovsky noted that "in the USSR, the

development of a local X-ray irradiation technique is carried out by our team (Department of Operative Surgery and Topographic Anatomy of the Peoples' Friendship University named after P. Lumumba. - *Author*) together with the Laboratory of Organ Transplantation of the USSR Academy of Medical Sciences" [4; p. 69].

To the *specific methods* of influencing the recipient in order to create immunological tolerance, the author referred the methods based on the phenomenon of "immunological paralysis". So, R. Schwartz and W. Dameshek from Tufts University in Boston showed that a prolonged contact of the body with a large amount of homologous antigen (or a large mass of transplanted tissue) caused an impaired, reduced and even ceased antibody production.

As for V.P. Demikhov, the phenomenon of immunological paralysis was the basis of his methods of transplanting a complex of organs and torso halves. Another modification widely used by V.P. Demikhov was the method of parabiosis, namely the creation of a single circulatory system in the donor and recipient before homotransplantation. But though no one transplanted the torso halves abroad, the parabiosis method was welcome.

Similar research conducted at the University of Minnesota (C. Martinez, R.A. Good, H. Hilgard, et al.), showed that in order to induce tolerance in slight antigenic differences between adult partners, it is enough to connect their circulatory systems for 7 days. However, parabiosis was required for a month or more to produce a similar effect in pair with moderate histocompatibility. With a strong immune barrier, parabiosis did not lead to tolerance at all. The same result was obtained when trying to create tolerance by injecting antigen (extracts of donor lymphoid cells, gamma globulin, etc.). The effect was observed in cases of weak antigenic

differences, with medium and strong ones, it was not possible to achieve it. Unfortunately, V.P. Demikhov did not know about such subtleties of the method.

In general, the opinion of the majority of foreign immunologists in the first half of the 1960s was expressed by P. Medawar in his speech at the Los Angeles Symposium in 1964. He claimed that the solution to the problem of artificial tolerance in adults should be sought, on the one hand, in the further study of the immunological paralysis phenomenon by means of antigenic loading, on the other hand, in the combined use of immunosuppressants with other, including specific, means of influencing the recipient. In particular, P. Medawar mentioned the method being developed by his group aimed at creating tolerance by injecting adult mice-recipients with the extracts of donor lymphoid cells in a non-sensitizing form. In addition, in his opinion, the problems of physiology, operational equipment, and the tasks of the clinic play an important role [4].

Two years later, speaking on September 21, 1966, in Moscow at the Transplantation Branch of Moscow and the Moscow Region Surgical Society, P. Medawar reported that it had already developed a method for suppressing the rejection reaction of the skin homografts in mice by using a specific anti-leukocyte serum obtained by immunizing rabbits with mouse lymphoid cells. The effect of prolonging the life of the skin flaps depended on the dose of the administered serum, the starting time of its administration (when administered before transplantation, the effect was significantly greater than when administered after transplantation), and the intervals between injections. In a number of cases, the skin flap remained viable for 200 days. The combined use of serum with local X-ray irradiation or corticosteroids increased the efficacy of the exposure [4].

Analyzed results of the studies conducted by various groups of scientists showed that the greatest effect in organ transplantation was achieved by the combined use of several methods of influencing the recipient's body. For example, in animal and human kidney homotransplantations, the longest graft survival was achieved with a combination of antimetabolites (imuran), corticosteroids (prednisolone), and antibiotics (actinomycin C).

Thus, by the mid-1960s, it became clear that the basis of the immunological tolerance phenomenon is the weakening or inhibition of the immunological reactivity of the recipient's body rather than the leveling of the graft immune properties. Explaining its mechanism, immunologists came to the conclusion: when the ratio of the homologous antigen amount to the number of immunologically active recipient cells is small, the response to administering the antigen will be the production of antibodies (immunization); when this ratio increases, the tolerance occurs (G. Mathe et al.; University of Paris, Center for Immunogenetics and Cancer).

This justified the use of both non-specific and specific drugs, as well as their combinations that reduce the number of immunocompetent cells in the recipient. So, in kidney transplantation in Denver, a combination of immunosuppressive drugs with thymectomy or splenectomy was used, and in Richmond, chemotherapy and local ionizing radiation were used. Another important area was the development of methods for detecting "strong" transplant antigens and selecting "donor-recipient" pairs based on them.

Section 2 of the book is devoted to the issue *of organ transplantation in experiments and in clinic*. It presents and discusses the results of the first kidney, liver transplants, and limb replantation. Experiments with transplants of the small intestine, stomach, endocrine organs, and spleen have been

mentioned. But we were primarily interested in the results of transplanting vital organs: the heart, lungs, and cardiopulmonary complex.

In September 1965, an International Symposium on Organ Transplantation was held in Paris; most of its presentations were devoted to lung transplants in the experiment and in clinic, and heart transplants in the experiment[7].

The symposium showed that the model of autologous and homologous lung transplantation has been developed in many countries (USA, France, Germany, Great Britain, etc.). The main aspects of improving this model concerned studying the function of the transplanted lung, the timing of its ischemia, the possibility of preservation and creating tolerance to the graft. It was stated that from 1961 to 1965, more than 600 experimental lung homotransplantations were performed worldwide (D.A. Blumenstock, E.S. Büchlerl, J.D. Hardy, K. Reemstma, A.T. Parsa, A. De Bono, M.S. McPhee, O.B. Gago, H. Nettelblad, J. Atuthe); meanwhile, the surviving 140 animals lived from 1 to 13 days (without treatment) and from 15 days to 4 years (under conditions of immunosuppression with imuran, methotrexate, cyclophosphamide, actinomycin C, trenimon, irradiation and exchange blood transfusion in various combinations). After the preservation of isolated homologous lung at a temperature of $+4^{o}C$ under conditions of hyperbaric oxygenation, D.A. Blumenstock successfully transplanted homologous lung to several animals, three of which lived with it for more than 6 months. M.S. McPhee used the technique of organ perfusion with oxygenated blood.

R. Deterling from Boston (the same one who, in 1960, together with a group of delegates to the All-Union Congress of Surgeons, visited the

[7] I.D. Kirpatovsky who was not engaged in the heart and lung transplants attended the Symposium, but V.P. Demikhov did not.

N.V. Sklifosovsky Institute) was engaged in homotransplantation of lung lobes. Using this model, H. Nettelblad studied the possibility of prolonging homograft function by prescribing immunosuppressive drugs. When imuran was used, the dogs lived for 31 days, while the animals in the control group lived for 5 days. The maximum organ survival period was 317 days. In 1965, M.S. Slim studied lung function after replantation and proved the possibility of survival of animals with totally denervated lungs[8]. The function of reimplanted autolung and transplanted homolung was also studied in the United States by J. Hardy (University of Mississippi), G. Magovern (University of Pittsburgh), N. Shumway (Stanford, Palo Alto, California), K. Reemtsma (Tulane University, New Orleans, Louisiana), and others.

In the reports on heart transplantation, the issues of developing experimental models, studying the function of the transplanted heart and the possibility of preserving its vital activity before surgery (preservation) were considered. What success did foreign surgeons achieve? J.-P. Cachera (University of Paris, France) re-implanted autologous hearts in dogs under conditions of cardiopulmonary bypass and/or hypothermia, but the operated animals lived only from 2 to 6 days after recovery of cardiac activity. J. Barrie (Grenoble, France) was engaged in heterotopic additional heart transplants, and A. De Bono (London, UK) was doing cardiopulmonary complex transplants. For the heart preservation, V. Mirkovitch (Lausanne, Switzerland)) used hyperbaric oxygenation (HBO) in combination with hypothermia for 3 days, after which restored the heart vital functions. To prolong myocardial anoxia before transplantation, N. Shumway (Stanford, USA) preserved the heart with cold, and C.W. Lillehei (New York

[8] In the USSR, such operations were performed by E.N. Meshalkin aimed at developing the method for treating patients with bronchial asthma.

University, USA) used a combination of cold and HBO. In this regard, we recall that V.P. Demikhov performed a heart transplant during normothermia without stopping the heartbeat and without its preservation, by using a cardiopulmonary preparation that he had developed to ensure the vital activity of the organ. Such studies were not conducted abroad in those years.

According to N. Shumway, the surgical and physiological issues of heart transplantation had mostly been resolved by the mid-1960s. Between yesterday and tomorrow of a new era in the treatment of heart diseases by means of its transplantation, only an immunological barrier remained[9]. In those years, N. Shumway himself was engaged in heart autotransplantation under conditions of cardiopulmonary bypass and hypothermia, working out the technique of organ removal and biatrial implantation he developed together with R. Lower (Fig. 5). Dogs that survived after such interventions lived for several years and even gave birth. After heart homotransplantation, the untreated animals lived from 7 to 21 days. Administration of imuran or 6-mercaptopurine extended lifespan of animals with homotransplants to 5 weeks, and up to 1 year in some cases. K. Reemtsma (Tulane University, USA), when transplanting homologous hearts into the chest, achieved experimental animals survival in conditions of immunosuppression for 32 days, while untreated animals died mean after 10 days.

[9] Note that the Americans didn't even remember about the moral and ethical problems of heart transplantation that restrained the enthusiasm of Soviet scientists.

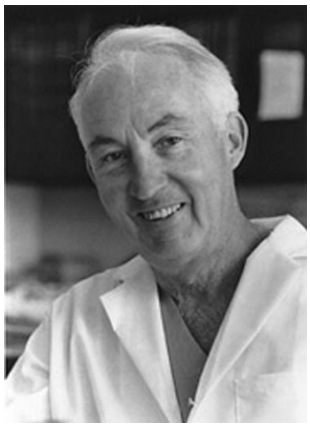

Fig. 4. Norman Shumway (1923-2006), Stanford University. Performed the 2nd heart transplantation in the USA in clinic [Available at: https://www.jtcvs.org/article/S0022-5223(11)00973-1/fulltext]

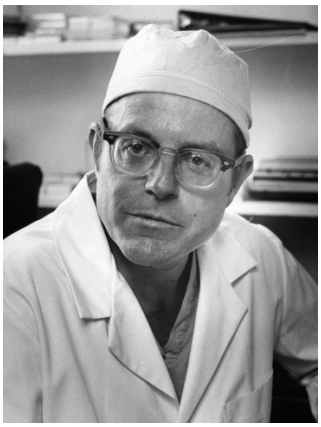

Fig. 5. Richard Lower (1929–2008), Stanford and Virginia Universities. One of the developers of the biatrial heart transplant technique [Available at: https://www.mcvfoundation.org/news/stories/MCVHeart-History]

Commenting on the above mentioned, we emphasize that N. Shumway's words were very important for understanding what V.P. Demikhov had done and achieved so far. Continuing to improve his technique, in the mid-1960s the Soviet scientist increasingly paid attention to

immunological research and the methods for overcoming immunological incompatibility, in particular, the parabiosis method he developed. Let's recall, however, his dog Grishka who lived 141 days without any immunosuppression, and compare these results with the results obtained by K. Reemtsma.

In addition to research in the field of organ auto - and homoplasty in the 1960s, intensive research was conducted in the United States to create a mechanical heart. Among the leaders working in this area were the groups of W. Kolff from the Western Reserve University (Cleveland, Ohio) and M. DeBakey from Baylor College (Houston, Texas). By 1965, W. Kolff group managed to create a pneumatic prosthesis made of silastic plastic, with which calves lived up to 30 hours after orthotopic implantation.

M. DeBakey group worked in several directions. Scientists tried to create a ventricular assist device (VAD), a pneumatic shunt to bypass the left ventricle (in V.P. Demikhov's developments this function was performed by an additional heart) and a balloon placed in the left ventricle cavity and helping to push blood out of it. By 1965, M. DeBakey had performed VAD implantation in several patients suffering from heart failure, but they survived in such conditions for no more than 4 days. Note that initially M. DeBakey's research did not find support among his contemporaries, who bitterly criticized their colleague for experiments on humans and demanded that he be stripped of his license to practice. Only his reputation of already a well-known American surgeon saved him from reprisals.

On January 18, 1964, the pioneer of lung transplantation J. Hardy (Fig. 6) of the University of Mississippi made an attempt to transplant a chimpanzee heart to a human, but due to great technical difficulties, this search operation ended up in the patient's death.

Interestingly, none of the foreign surgeons tried to repeat V.P. Demikhov's experiments with heterotopic transplantation of an additional heart.

Fig. 6. James Hardy (1919–2003), University of Mississippi; a pioneer of isolated lung transplantation (June 11, 1963) and isolated heart transplantation (January 24, 1964) in clinic [Available at: https://www.sutori.com/item/james-hardy-of-the-university-of-mississippi-performed-the-first-human-lung-tran]

As we have said, I.D. Kirpatovsky knew well about what V.P. Demikhov accomplished and achieved, but in the book V.P. Demikhov was mentioned only once in a footnote to the text about experimental heart transplantation: "over many years, this question has been studied by V.P. Demikhov who has developed over 20 different schemes of homologous heart-and-lung graft transplantation in the experiment in dogs" [4; p. 143]. And neither here nor in other places was anything said about his work on donor selection, on parabiosis, on heart-and-lung transplantation, on transplantation of the heart with both lungs, of the isolated heart and the

lungs, kidneys, liver, on preserving the viability of organs before transplantation. A reasonable question arises: why was it necessary to go abroad, if almost everything that I.D. Kirpatovsky and his colleagues saw there in the field of creating models for studying the problem was done in our country? In fact, in 1966 C. Barnard went to the United States to learn about immunosuppression techniques and nothing more. He knew well and mastered everything related to the transplantation techniques in the experiment. But what did not V.P. Demikhov have?

He had 1) neither like-minded people, or a team that would have consisted of cardiologists, neurologists (neurosurgeons), biochemists, immunologists, anesthesiologists, resuscitators, bacteriologists, radiologists, nurses, engineers, etc. whom worked with almost all major surgeons involved in heart transplantation (Fig. 7); it is not without a reason that the main research groups were formed at universities that had specialists in various fields of knowledge; 2) nor equipment or drug support for his technically flawless operations (when Western surgeons could use a heart-lung machine, a HBO chamber, or hypothermia in their experiments, V.P. Demikhov did not have such opportunities; as there was no sufficient amount of drugs for immunosuppression, or for caring for operated dogs, either); 3) nor support from a major scientist at the state level (whom could have become A.A. Vishnevsky in the early 1950s, V.V. Kovanov in the second half of the 1950s, and B.V. Petrovsky in the 1960s who in September 1965 became the Healthcare Minister of the USSR).

Fig. 7. Staff of the Cardiothoracic Surgery Department, Groote Schuur Hospital, University of Cape Town School of Medicine (South Africa). The First Heart Transplant Team. 1968. Professor C.N. Barnard is the 6th from the right, standing [Available at: http://www.cts.uct.ac.za/Historical/Transplant/Team]

But, in our opinion, both the first and second factors largely depended on the third one. The state represented by the Healthcare Ministry of the USSR took a wait-and-see approach to transplantation of vital organs, based on the presumption of the primacy of saving the donor's life over prolonging the recipient's life, which was justified by the Soviet mentality.

"Heart homotransplantation to humans," wrote I.D. Kirpatovsky, expressing this point of view, "is associated both with complex technical, physiological and immunological issues, and also with such a problem as the source of graft collection. In this case, this issue is particularly sensitive: since the vital activity of the heart is a legal and biological criterion for the life and death of the human body, and the strive to get a viable graft can limit the efforts of surgeons during resuscitation" [4; p. 148]

Here is what B.V. Petrovsky said about this at the beginning of 1968:

"As for heart transplantation, it is still an experiment. Without belittling the significance of such an experiment for the future of science, I cannot but note that Soviet doctors have their own point of view about experiments on humans. It is known that Soviet medicine is the most humane. We have no other motivation than to help the patient. Therefore, we must try to save even the most seriously ill patient by all means available to the doctor. There are many methods for resuscitation in the arsenal of the Soviet physician: mechanical circulatory support, mechanical ventilation, hypothermia, < ... > (oxygenation), artificial kidney and many others.

We believe that even if a person has suffered a myocardial infarction or suffers from chronic coronary insufficiency, let him live with his own heart disease keeping a certain regime. <...>

One can only decide on heart transplantation when the heart has stopped, and the patient has died, that is, he is in a state of clinical death, and no resuscitation means can restore the heart function. If a transplanted heart is capable to prolong the life of such a patient – even for a few weeks or months, this will be justified both from a moral and legal point of view."

Choosing a donor is even more difficult. <...> To resolve this issue, the doctor must have a variety of objective information about the state of the internal organs of the deceased person. <...><...>

The problem of organ transplantation is very complex, so we will develop it only in large medical institutions possessing modern equipment" [13].

Let us recall N.M. Amosov who in 1968 was technically ready for heart transplantation, but failed to cross the line between the duty of a doctor to do everything possible to resuscitate a dying patient and the desire to help another dying patient waiting for a donor heart [14].

In the Preface to his book, I.D. Kirpatovsky noted that in the second half of the 1960s, raised the interest in experimental research in the field of organ transplantation and the search for methods to overcome tissue incompatibility increased all over the world. In addition to the United States,

France, and the United Kingdom, this direction began to develop intensively in Belgium, Hungary, the Netherlands, Denmark, Italy, Poland, Romania, Czechoslovakia, Switzerland, and other European countries. In other words, there are practically no countries left in Europe that have not dealt with the problem of organ transplantation.

And what was in the USSR? In the beginning of the monograph, the author listed the research groups that were engaged at that time in studying the problems of immunity and developing methods of influencing it in our country. These were the Institute of Experimental Biology of the USSR Academy of Medical Sciences, whose staff studied the general laws of immunity; the Moscow and Leningrad Institutes of Blood Transfusion, which mainly studied humoral immunity; the Gamalea Institute of Epidemiology and Microbiology, which was dealing with infectious immunity; the Laboratory for Organ and Tissue Transplantation of the USSR Academy of Medical Sciences, as well as groups of scientists led by B.D. Brondz, V.I. Govallo, A.M. Gurvich, M.M. Kapichnikov, R.V. Petrov, G.Ya. Svet-Moldavsky, I.Ya. Uchitel, L.N. Fontalin, A.Ya. Fridenstein, I.L. Chertkov and others. But the fact of the matter is that most of these groups studied rather general issues of immunity, at best, the immune responses to transplanted tissue, than an organ. Because, as we have already said many times, no one except V.P. Demikhov was involved in the problem of organ transplantation in the USSR until the mid-1960s, when B.V. Petrovsky's group transplanted a kidney. This can be seen from the materials of the 2nd All-Union Conference on Homoplasty, held in 1967. And those achievements lagged significantly behind the achievements of our foreign colleagues. Was it possible at that time to take seriously any research on the effect of drug-induced sleep on the homograft acceptance?

But in our country such research took place…

Results of research in the field of transplant immunity in the United States and Europe in the second half of the 1960s

Intensive many-year, multi-vector and multi-center work brought its fruit. By June 1967, there had already been 282 people living in Europe with transplanted homologous kidneys, 168 of whom received a graft from a corpse. Of those, 9 people lived for more than 2 years, and one lived for more than 3 years. As reported by J. Murray to the delegates of the 1st International Congress in Paris (June, 1967), by that time 1,200 kidney transplants had already been performed worldwide. Within a year after the surgery, 75% of transplanted grafts taken from relatives and 65% grafts from unrelated donors functioned. A new direction developed in transplantology by that time was the use of anti-lymphocytic serum for transplanting homo-organs (lung, liver, kidney, intestines). The maximum period of kidney functioning during its use in the experiment was 500 days. T. Starzl (Fig. 8) was the first to use this agent in human kidney homotransplantation, achieving organ survival for 7 months.

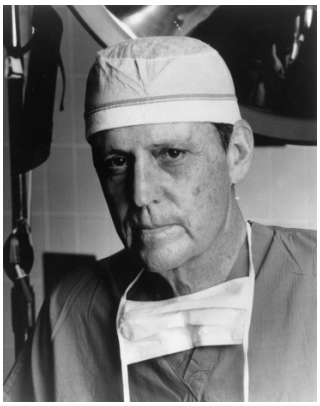

Fig. 8. Thomas Starzl (1926–2017), University of Colorado (1962–1981), University of Pittsburgh (1963) [Available at: https://www.starzl.pitt.edu]

Speaking at that Congress, P. Medawar identified the following approaches to solving the problem of creating artificial tolerance for homotransplantations:

"Exposure to antigen, "enhancement"[10], the use of anti-lymphocytic serum, antimetabolites, steroid drugs, colloidal dyeing, ionizing radiation and a number of other methods. However, immunosuppressive chemotherapy is most widely used, and X-ray irradiation is used when a rejection crisis occurs" [4; p. 168].

Alongside, since all these methods were quite aggressive and could cause side effects, much attention was also paid to the methods of typing the donor and recipient (matching pairs according to leukocyte factors, according to the results of an intradermal leukocyte test, etc.).

Methods of maintaining the viability (preservation) of organs prior to transplantation were considered important. Along with hypothermia, HBO, and their combinations, a method of hypothermic perfusion of grafts (kidney, liver, lung, pancreas, etc.) was developed by using a mechanical micro-circulatory support apparatus (B.D. Humphries, M. DeBakey et al.).

The improvement of the technical skills of surgeons and the success of immunologists, primarily American ones, in the field of creating artificial tolerance led to the fact that on December 3, 1967, C. Barnard transplanted a human heart for the first time in history.

It is known that during 1968 this operation was repeated more than 90 times. The top ten pioneers look like this: C. Barnard (Cape Town, South Africa) 2 operations, A. Kantrowitz (New York, NY, USA) 2 operations, N. Shumway (Palo Alto, California, USA) 2 operations, P. Sen (Bombay, India), C. Cabrol (Paris, France), D. Ross (London, UK) and D. Cooley

[10] Here is obviously "the improvement" of the old methods.

(Houston, Texas, USA) one transplantation each.

Further, during the year, the largest number of heart transplants was performed by D. Cooley (17 operations) (Fig. 9). Ten interventions each were performed by P.R. Grondin (Montreal, Canada) and N. Shumway; 9 operations were performed by M. DeBakey (Houston, Texas, USA).

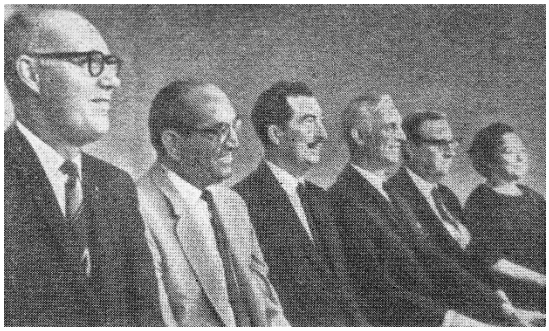

Fig. 9. Patients of D. Cooley after they underwent successful heart transplant operations. 1968 [15; p. 141]

In addition to C. Cabrol, another 6 operations in France were made by C. Dubost 2 and J.-P. Binet (Paris), E. Négre (Montpellier), Michaud (Lyon) and a group of doctors from Marseille. Wilson (Toronto, Canada) and R. Lower (Richmond, USA) performed 4 operations each, Zerbini (Sao Paulo, Brazil) and J.Kaplan (Valparaiso, Chile) performed 3 operations each. Bellizi (Buenos Aires, Argentina), Kemal Beyazit (Ankara) and a group of doctors from Istanbul (both Turkey), 2 groups of doctors in Melbourne and Sydney (Australia) performed 2 operations each. D. Ross (London, UK), J. Bajo (Caracas, Venezuela), P. Sen (Bombay, India), Bordiu (Madrid, Spain), A.A. Vishnevsky (Leningrad, USSR), a group of doctors from Prague (Czechoslovakia), C. Barnard (Cape Town, South Africa) and J. Wada (Sapporo, Japan) made one operation each. Meantime, the operation of A.V. Vishnevsky performed on November 4, 1968, was the 73rd in a row.

In the United States, 1 heart transplant each was also performed in 1968 by H. Bannon (Pittsburgh, PA), T. Starzl (Denver, Colorado), as well as by groups of doctors from Dallas (Texas), Cleveland (Ohio), the Universities of Michigan and Milwaukee [6].

No less impressive were the achievements in lung transplantation in clinic. The top ten operations performed from 1963 to 1968 look like this: J. Hardy (Jackson, Mississippi, USA), G. Magovern (Pittsburgh, Pennsylvania, USA), K. Shinoi (Tokyo, Japan), W.E. Neville (Hines, IL, USA), J.J. White (Montreal, Canada), Y. Tsuji (Nagasaki, Japan), E.S. Bücherl (Berlin, Germany) 2 operations, Y. Nayata (Tokyo, Japan), O.V. Gago (Ann Arbor, Michigan, USA). Further 12 operations were performed from 1968 to 1970, in addition to the 4 performed by A. Logan (Edinburgh, Scotland), D. Ross (London, England), P. Vanderhoeft (Brussels, Belgium) and F. Derom (Ghent, Belgium), all others were held in the USA (Ann Arbor, Minneapolis, New York and Houston). J. Hardy (USA) and E.S. Bücherl (Germany) had the greatest experience (2 operations each). Survival ranged from a few hours to 10 months (F. Derom, Belgium) [3].

In the late 1960s, 2 transplants of the cardiopulmonary complex were performed. The first operation was performed on September 15, 1968, by D. Cooley (Houston, USA), the second, in 1969, by C.W. Lillehei (New York, USA). The first patient lived for 14 hours; the second lived for 8 days [3].

Conclusion

The analysis of the above material allows us to draw the following conclusions.

First, it is noteworthy that there were numerous groups of surgeons and scientists of other specialties who dealt with organ transplantation problems

in the United States and other countries. In the USSR, as we recall, V.P. Demikhov was the only speaker on this issue at the Meeting of the Council on the Implementation of Research Results in Practice under the USSR Health Ministry. And no matter how much he tried to involve other teams in his research over the years, he did not succeed. Thus, in 1963, while preparing for a speech at the USSR Health Ministry, he listed almost all groups and individual scientists from all over the country with whom he could cooperate in solving immunological issues, but he failed to attract any of them to this cooperation. The Ministry was not puzzled by this question either.

Second, unfortunately, most of the active creative activity of V.P. Demikhov (1946-1966)[11] was dedicated to his efforts to overcome the tissue (organ) incompatibility by biological and physiological methods. However, working for almost 20 years in this paradigm, he intuitively tried to find new ways.

Thus, in the early 1960s, V.P. Demikhov's main research areas were: 1) selection of donors and recipients by blood groups and kinship relationships (as a rule, for a donor he took a puppy from the litter of the recipient-mother); 2) the creation of a single circulatory system for the donor and recipient before transplantation (the parabiosis method, the "immunological paralysis" phenomenon); 3) surgical methods to prolong blood circulation in the graft during transplantation using the most advanced methods of mechanical suture using Gudov's suture device and biological micro-AIC (the invented by him heart-lung machine to ensure a coronary circulation); 4) restoring a long-term organ function after transplantation (cardiac

[11] In 1946, his research in the field of homoorgan transplantations began; and in 1966, he wrote a Preface to the Spanish Edition of his book "Experimental Transplantation of Vital Organs", in which he outlined his vision of the homoplasty problem.

contractility, respiratory function of the lung, excretory function of the kidney); 5) immunological and morphological control of research (was carried out sporadically through personal friendship relations with immunologists and morphologists).

Of great importance were his methods (more than 20 options) of transplanting an additional heart instead of an isolated one. On the one hand (within the framework of the old paradigm), V.P. Demikhov believed that this method was more promising: in case of the second heart rejection, the biological one would remain, that is, the recipient would not suffer, and the rejected graft can be replaced with a new one. On the other hand, this technique, in our opinion, became the prototype of widespread technologies of blood circulation support with the use of mechanical assist devices.

He was well aware of the new trends in immunology. As V.I. Burakovsky said in his report on the work of the Committee for checking the activities of V.P. Demikhov and his Laboratory [11], V.P. Demikhov could not help but recognize the biological incompatibility of homotissues. He only asked to convince him that it exists in practice and for transplanted organs, while his experiments said the opposite. Moreover, the first immunosuppressants turned out to be unsafe: in 1963, V.P. Demikhov, in the presence of an American pharmaceutical company a representative, tested 6-methotrexate obtained from the United States, but after losing several dogs due to its toxicity, he refused the drug, continuing to develop less aggressive physiological methods.

Third, the successful human kidney homotransplantation stimulated the research into creating artificial immunological tolerance, which led to a paradigm shift in organ transplantation. It turned out that suppressing the recipient's immune response is more effective than affecting the graft,

reducing its immune properties or bringing them closer to the properties of the host body (for example, using parabiosis or "immunological paralysis"). It was in patients with transplanted homokidneys that the schemes of using immunosuppressive drugs were developed, and many features of their action mechanism (for example, antigenic adaptation) were studied.

In 1965, homokidneys were transplanted to humans at the Institute of Clinical and Experimental Surgery of the USSR Health Ministry under the leadership of B.V. Petrovsky. By 1967 B.V. Petrovsky, G.M. Solovyov, V.S. Krylov and others had performed more than 20 similar operations. The second clinic where this operation was implemented was the clinic of the Department of Urology of the 2nd Moscow State Medical University named after N.I. Pirogov (N.A. Lopatkin, Yu.M. Lopukhin, Yu.A. Pytel, etc.).

In 1967, it was from kidney homotransplantations, as an already well-known operation by that time that C. Barnard initiated his organ transplantation program. After testing the schemes of the donor and recipient preparation for transplantation and treatment of the recipient after it, he conducted a training session for his team, went to the United States, where he learned how to use immunosuppressive drugs and, after returning home, transplanted a heart. In 1968, this organ was transplanted more than 90 times worldwide. A human lung was first transplanted in 1963, but advances in this area of transplantation were not so significant, which was due to physiological characteristics of the organ.

Thus, in the period from 1960 to 1970, in the world of transplantation, there was a change of paradigm: instead of overcoming incompatibility between the donor organ and the recipient body using biological and physiological methods of influencing the organ, which had been being developed by V.P. Demikhov for over 20 years, surgeons and scientists first

abroad and then in the USSR began to develop and implement the creation of an artificial immune tolerance by influencing the recipient's body with different physical, chemical and biological methods.

It was this paradigm shift with transferring the attention from the donor organ onto the recipient body that significantly influenced both the implementation of organ transplantation methods, including those of vital ones, to the clinic, and the further development of clinical transplantation, as shown by the example of heart transplantation in 1968 and lung transplantation in 1963-1970.

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