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PHENOMENON OF DEMIKHOV.
At the Sklifosovsky Institute (1960-1986).
Approaches to solving the problem of organ and tissue transplantation in the USSR and abroad (1967)

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Abstract

Analysis of the materials of the 2nd All-Union conference on the problem of tissue incompatibility, conservation and transplantation of tissues and organs (Odessa, 1967) showed that Soviet and foreign scientists had similar approaches to solving the problem of organ and tissue transplantation. Soviet scientists spoke about overcoming tissue incompatibility by hybridization of plants and chimerization of animals, about the effect of drug sleep on transplant immunity, about neurohumoral immunological shifts and the role of the central and peripheral nervous systems in the acceptance of

grafts, about the impact of external factors on immunity. They also discussed the characterization of the antigenic structure of grafts, the role of DNA in immunity, the genetic transformation of homomaterial, the use of pharmacological agents to suppress immunogenesis, the cryopreservation of auto- and homo-organs and tissues with perfusion of their vascular bed, and the study of immunogenesis at the molecular level. A year earlier, the Americans discussed immunological paralysis, the effect of transfused donor blood and its components on the recipient's immunity, as well as biochemical studies of immunity. At the same time, without any ethical doubts, American scientists conducted experiments, including clinical ones, with multiple passages of homologous skin, with exchange transfusion of blood to newborns and subsequent transplantation of donors' homoskin to them, with irradiation of recipients with potent doses of X-rays. It is shown that most of the trends that had been developed by V.P. Demikhov, were approved by the 2nd All-Union Conference. But what he lacked was a close and comprehensive integration with morphologists, physiologists, immunologists, biochemists, pharmacologists and, however sadly, with clinical surgeons. Based on the research conducted, an unambiguous conclusion can be drawn: Soviet scientists should not have criticized V.P. Demikhov for his "misunderstanding" of immunology; they had better help him in every possible way, directing his energy in the right direction.

Keywords: history of medicine, transplantation, homoplastic organ and tissue transplants, approaches, similarities and differences, V.P. Demikhov, 1967

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Introduction

In our previously published paper, we briefly described the path taken by South African surgeon C. Barnard from his first being acquainted with V.P. Demikhov's experiments on heart and head transplantation in spring of 1959 to his first human-to-human heart transplant operation in the world at the end of 1967 and we also discussed his approaches to organ transplantation [1]. In the previous article aimed at reviewing the Preface to the Spanish translation of V.P. Demikhov's book "Experimental Transplantation of Vital Organs" (Madrid, 1967), we showed how V.P. Demikhov's approaches to homotransplantation differed from those that C. Barnard followed [2]. It seemed that the differences were cardinal, on the basis of which we can make a hasty conclusion that V.P. Demikhov lagged behind his foreign colleagues.

However, the question arises: to what extent did V.P. Demikhov's opinion about the paramount importance of asepsis and the technique of joining vessels, as well as the biological methods he developed to overcome tissue incompatibility, coincide with the position of Soviet scientists: morphologists, physiologists, immunologists, surgeons of that time? As in the background of C. Barnard's triumph, the problems of biological incompatibility of organs and tissues during homotransplantation were solved in the USSR? In other words, did V.P. Demikhov's colleagues in the

"transplant shopfloor" have the right to criticize and reject his position? Was their criticism justified? Finally, to what extent and in what ways did the positions of Soviet scientists differ from those of their Western colleagues or coincide with them?

To answer this question, we analyzed the materials of the 2nd All-Union Conference on the Issues of Tissue Incompatibility, Preservation, and Transplantation of Tissues and Organs, which was held in Odessa in 1967.

The 2nd All-Union Conference on Tissue Incompatibility, Preservation and Transplantation of Tissues and Organs (Odessa, 1967)

The Conference was held in Odessa on the base of V.P. Filatov Research Institute of Eye Diseases and Tissue Therapy (Fig. 1). The venue was not a random choice. Academician V.P. Filatov (1875-1956) (Fig. 2), an ophthalmologist by profession, became famous for the development and implementation of two plastic surgery techniques in practice: a) the cadaveric corneal transplantation technique (keratoplasty) and b) the technique of a tissue defect replacement with a full-thickness skin-fat flap based on the "suitcase handle" or "walking stem" principle. Over time, this method, named after the author ("Filatov stem"), gained many supporters in reconstructive plastic surgery, and V.P. Filatov became a recognized specialist in the field of homo-(cornea) and auto- (stem) transplantation.

Fig. 1. Institute of Eye Diseases and Tissue Therapy n.a. V.P. Filatov National Academy of Medical Sciences of Ukraine [Available at: https://ru.wikipedia.org/wiki/Институт_глазных_болезней_и_тканевой_терапии_имени_В._П._Филатова_НАМН_Украины]

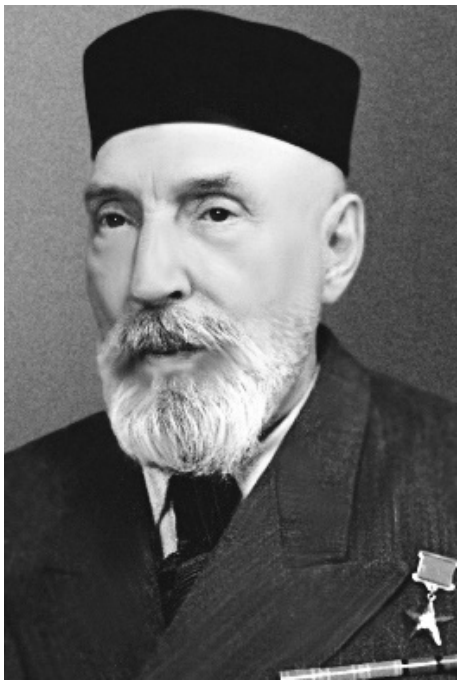

Fig. 2. Academician V.P. Filatov (1875-1956) [Museum of A.N. Bakoulev National Medical Research Center for Cardiovascular Surgery]

It is obvious that the Conference reflected the opinion of the leading specialists of the USSR in the field of transplantology, and the Editorial Board of *the Book of Conference Proceedings* included the most prominent of them. The Responsible Editor was Professor N.V. Puchkovskaya, the Director of V.P. Filatov Research Institute of Eye Diseases and Tissue Therapy in Odessa, Hero of Socialist Labor (1960), Corresponding Member of the USSR Academy of Medical Sciences (1908-2001), who worked in keratoplasty. The Deputy Editor-in-Chief was Professor I.N. Maisky, the Director of the Experimental Biology Institute of the USSR Academy of Medical Sciences, an immunologist and a longtime opponent of V.P. Demikhov. The Editorial Board Executive Secretaries were Professor V.V. Voino-Yasenetsky[1] from V.P. Filatov Research Institute of Eye Diseases and Tissue Therapy, Odessa, and Associate Professor P.M. Chepov from the Institute of Experimental Biology of the USSR Academy of Medical Sciences.

The Editorial Board also included: Professor N.N. Zhukov-Verezhnikov (1908-1981) dealing with the immunology of microorganisms, full member of the USSR Academy of Medical Sciences from the Experimental Biology Institute of the USSR Academy of Medical Sciences, and Professor V.V. Kovanov (1909-1994), full member of the USSR Academy of Medical Sciences, from the 1st MOLMI named after I.M. Sechenov, where the Organ and Tissue Transplantation Laboratory of the USSR AMS was established at the Department of Operative Surgery and Topographic Anatomy. The next

1 V.V. Voino-Yasenetsky (1913–1992) Doctor of Medical Sciences, Professor, the youngest son of V.F. Voino-Yasenetsky (St. Luke); Head of the Pathomorphology Laboratory of Odessa Research Institute of Eye Diseases and Tissue Therapy named after V.P. Filatov.

was Professor B.V. Petrovsky (1908-2004), a Corresponding Member of the USSR Academy of Medical Sciences, who performed the first clinical kidney transplantation in the USSR in 1965, and became the Minister of Health of the USSR in the same year.

Let's mention some of the Editorial Board members: Professor A.N. Studitsky (1908-1991), a pathologist from the Biology-and-Soil Faculty of M.V. Lomonosov Moscow State University; Professor P.I. Androsov (1906-1969), the specialist in plastic surgery of the esophagus; Professor T.E. Gnilorybova (1901-1970) from Minsk who worked in transplantation of endocrine organs on a vascular pedicle; Professor P.P. Kovalenko (1919-2008) from Rostov-on-Don, the specialist in the field of bone and joint homoplasty; Professor G.I. Kositsky (1920-1988), Head of the Normal Physiology Department of the 2nd Moscow State Medical Training Institute named after N.I. Pirogov, who was elected a Corresponding Member of the USSR Academy of Medical Sciences in 1980; Mikhail Tarasov (1904-1973) Director of N.V. Sklifosovsky Institute for Emergency Medicine; Professor V.F. Tsel (1898-1974), a plastic surgeon from Arkhangelsk; M.M. Kapichnikov, Candidate of Sciences (Biology), Head of Laboratory at the Experimental Biology Institute of the USSR Academy of Medical Sciences, A.G. Lapchinsky, Candidate of Science (Biology), an employee of the Research Institute of Experimental Surgical Equipment and Instruments (NIIEKhAiI) who was dealing with the problems of cryopreservation, and a number of other scientists.

Today they are little known. And in 1967, these scientists were the country's leading specialists in various issues of organ and tissue transplantation. However, most of them were working in tissue transplants and were only indirectly related to organ transplantations. It was only V.P.

Demikhov who was dealing with the issue of heart transplantation in the country, though who, for some reason, was called as a candidate of medical sciences rather than as a doctor of biological sciences. We should also note that the vast majority of presentations were devoted to experimental work and only a few to clinical transplantations.

We will make a content analysis of some works.

On the state of modern immunology and the problem of tissue incompatibility (N.N. Zhukov-Verezhnikov et al.)

This presentation opened the Conference first meeting devoted to general issues of transplantation. A group of authors headed by N.N. Zhukov-Verezhnikov [3] from the Experimental Biology Institute of the USSR Academy of Medical Sciences (Fig. 3) presented data on the state of modern immunology and on tissue incompatibility issues, postulating that "the immunological nature of tissue incompatibility had definitively been proven" and that the group, typical, and individual antigens were responsible for these reactions. In authors' opinion, their detection was an important task of modern immunology. On the other hand, in practice, a number of those antigens could be ignored by resorting to: 1) influencing the recipient in order to a) achieve tolerance, or b) suppress its immunological resistance; and 2) influencing the graft in order to a) destroy or b) neutralize antigens that impede compatibility.

Fig. 3. Full Member of the USSR Academy of Medical Sciences Professor N.N. Zhukov-Verezhnikov (1908-1981) [Available at: http://saratovregion.ucoz.ru/people/science/zhukov-v.htm]

The authors referred the experiments of M. Hašek (Czechoslovak Republic) and P. Medavar (Great Britain) to the immunological tolerance studies (1a) not applicable in humans. The suppression of resistance (1b) was achieved by X-ray irradiation (including in combination with glucocorticosteroids), as well as by prescribing pharmaceutical agents, for example "serum against gamma globulins", that affect immunological cytogenesis.

«However, the main findings probably lie on the way of the development of the greatest biological problems. So, for example, over the recent decades, many works have appeared on the study of the so-called chimerization, or rather, the hybridization of tissues in plants. < ... > Of course, the mechanism of this phenomenon differs from similar processes in animals. Recently, however, attempts have been made to produce

mosaics from heterogeneous cells of animal tissues. Anyway, the mechanism of chimerization... should attract the most serious attention of all those who are interested in the problem of biological incompatibility" [3].

Speaking about the ways to impact on the graft, N.N. Zhukov-Verezhnikov gave a hypothesis about the possibility of antigenic transformation of the graft by means of exogenous DNA (2a). Recognizing this method difficult to implement, the speaker focused on the experiments on the preservation of the graft, treating it with enzymes and antibodies (2b). However, he referred all these prospects mainly to tissue transplants. In the author's opinion, "intra-family transplants" (from related donors) and the ways of weakening the recipient's body reactivity are still promising for organ transplants (1b).

In conclusion, N.N. Zhukov-Verezhnikov urged scientists of the country "together with scientists of the fraternal countries to overcome the barrier of biological tissue incompatibility" standing on the way of contemporary surgery development by putting this "medical problem important for the people" in one row with "the studies of cancer enigma, using the energy of nuclear fusion, or space flights to other planets" [3].

We shall comment this material. In two areas of transplantation development: (1) the effect on the recipient's body and (2) the effect on the homograft, the Soviet scientists moved on a level with their foreign colleagues, mostly replicating their achievements. Perhaps, the most advanced results at that time were the research by A.G. Lapchinsky on cryopreservation and, paradoxically, V.P. Demikhov's research on the creation of parabiont chimeras from a donor and a recipient. Indeed, talking about the effect of pharmaceutical drugs on the recipient's body aiming at

suppression of its immunological resistance, through which C.N. Barnard achieved his success, N.N. Zhukov-Verezhnikov immediately spoke about the prospects of studying "hybridization" and "chimerization" that V.P. Demikhov had been doing for many years. The fantastic idea of changing heredity by using external factors, which was being developed at the Experimental Biology Institute of the USSR Academy of Medical Sciences seemed to be inspired by T.D. Lysenko's ideas of the 1940s; and putting this issue on a par with the problems of atomic energy and space flights was more the desired idea rather than the reality. In fact, there were three actual trends: suppressing the recipient's body immune response to the graft, reducing the graft immune properties by various methods, and "intra-family transplants".

About plastic surgery and organ and tissue transplantation (V.V. Kovanov and I.D. Kirpatovsky)

What did Professor V.V. Kovanov, Full Member of the USSR Academy of Medical Sciences, and I.D. Kirpatovsky, Head of the Laboratory for Organ and Tissue Transplantation of the USSR Academy of Medical Sciences, future Corresponding Member of the Russian Academy of Medical Sciences, think about the prospects for organ and tissue transplantation [4]?

Fig. 4. Full Member of the USSR Academy of Medical Sciences Professor V.V. Kovanov (1909-1994) [Museum of A.N. Bakoulev National Medical Research Center for Cardiovascular Surgery]

The presentation was mainly devoted to esophagus prosthetics with synthetic materials, the nylon mesh being recognized as the best one, as well as vascular grafting with both synthetic and biological prostheses, including the use of a mechanical suture. Freezing and lyophilization were used to suppress the immune response to a homovessel. We quote their conclusions:

"The problem of organ and tissue transplantation undoubtedly requires joint efforts of doctors and biologists in various fields, surgeons, immunologists, pathophysiologists, biochemists, biophysicists, microbiologists, bacteriologists, etc.

The primary task of surgeons should be to develop the most technically and physiologically advanced models of surgery for transplanting vital organs and tissues.

Taking into account the undoubted optimal physiology of organ transplantation on the arterial and venous vascular pedicels, the issues of vascular suture and vascular transplantation are of great importance in this problem.

The use of synthetic materials to replace a number of organs and tissues also deserves attention and in-depth study.

By jointing the efforts of scientists from different fields and with their close contact, we can hope for a more successful solution of the problems we are facing in the field of organ and tissue transplantation" [4].

The conclusions, in our opinion, are absolutely correct. The first and the last ones are targeted to research complexity, the 2nd and 3rd follow directly from V.P. Demikhov's research and seem to be written by him, with the exception of the phrase about "vital tissues"; and the 4th can be extended to the artificial heart, which was also pioneered by V.P. Demikhov. Thus, the report of V.V. Kovanov and I.D. Kirpatovsky did not say anything in contrast to what their recent employee said and wrote about.

On the biological incompatibility of tissues in homotransplantation and modern concepts of protein metabolism (G.I. Kositsky)

The author of this report, a well-known Soviet physiologist, questioned the hypothesis of immunological incompatibility, which was contradicted by some facts, in particular, "experiments on the fusion of organisms (parabiosis)", in which parabionts lived for up to a year, as well as the results of experiments by V.P. Demikhov, in which transplanted organs and body parts functioned for a month. Obviously, the author concluded, there were some other mechanisms that affected the death of homografts, for example, "the inadequacy of the recipient's internal environment to the graft tissues" or "genetic differences between different organisms of the same species".

G.I. Kositsky proposed his theory of the biological incompatibility mechanism on the basis of "contemporary ideas about the processes of protein metabolism in the body", the proteins being "built not only from a

mixture of amino acids circulating in the blood, but from larger "blocks" – from the blood plasma albumins synthesized by the liver." According to a number of authors whose works G.I. Kositsky referred to, "there is a kind of dynamic equilibrium between blood plasma proteins and proteins of some organs when the blood plasma proteins can pass into tissue proteins... without their preliminary decomposition to amino acids." Based on this, G.I. Kositsky suggested that the homograft "dies not only as a result of an immunological reaction, but also as a result of an impaired protein synthesis in it", losing, when extracted from the donor's body, "individually specific proteins (blocks) necessary for building their structures". And the immunological reactions, which undoubtedly existed, in the author's opinion, only accelerated this process [5]. Comment is superfluous, as they say. The material confirms that in 1967 there were both the views to support V.P. Demikhov and the attempts to explain his success by other, non-immunological laws.

Thus, we have presented three views: the authors of the first one (N.N. Zhukov-Verezhnikov and I.N. Maisky) did not contradict V.P. Demikhov; the authors of the second and the third ones were either indirectly (V.V. Kovanov and I.D. Kirpatovsky), or explicitly (G.I. Kositsky) on his side. And these views were expressed from the platform of the authoritative All-Union Conference.

On the causes of death of organ and tissue homografts (V.P. Demikhov)

V.P. Demikhov (Fig. 5) reported "On the causes of death of organ and tissue homografts". Discussing this phenomenon (we should pay attention to an important detail: the author was not talking about a rejection, but about

the graft death), he stressed that one of the things that makes it difficult to find the causes of such death was the inability to accurately determine the time of its occurrence:

"Many immunologists claim that the death of the homografted skin occurs on the 7th day after surgery, and they consider this day to be critical. Many surgeons observe the death of the grafted skin at later time - from several weeks to several months <...> After the complete resorption of the graft, it is impossible to determine the cause of its death. The cause of homograft death is considered to be antibodies, but many researchers have not been able to detect them yet. If some immunologists had found antibodies, none of them proved whether these antibodies were the cause of the graft death or, conversely, arose as a result of its resorption." [6].

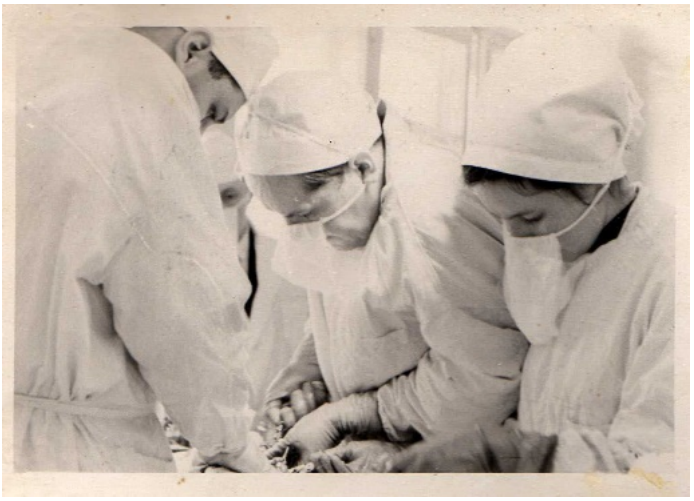

Fig. 5. V.P. Demikhov (center) is operating.

[Museum of A.N. Bakoulev National Medical Research Center for Cardiovascular Surgery]

It was obviously difficult to object to such arguments. Moreover, the speaker referred to the opinion of V.D. Timakov and L.A. Zilber, Full Members of the USSR Academy of Medical Sciences, who claimed that "immunity to tumor cells arises as a result of their resorption." It was a

logical conclusion:

"Until recently, the prevailing view in science was that all homoplastically transplanted tissues and organs are doomed to die due to biological incompatibility. It was also stated that there were no reliable cases of successful homograft acceptance. However, the facts from experimental and clinical practice do not agree with this statement. Hundreds of thousands of successful blood transfusion cases are generally known (provided that the group and other factors were compatible). It was also found that the transfused blood cells remain viable in the new body for the same time as the native ones. <...> In the clinic of Professor P. I. Androsov, about 100 liters of blood were transfused to one chronic patient, and no pathological reactions were observed. Thousands of cases of successful engraftment of cornea, cartilage, bones, blood vessels, etc. from corpses are known" [6].

And it was difficult to object to this statement, since V.P. Demikhov was convinced: if homoblood cells "remain viable in the new body for the same time as the native ones", then why can't myocardiocytes of the transplanted heart remain alive? Meantime, the key words in the above quote were: "provided that the group and other factors were compatible." Time showed that they were correct: when scientists learned how to select donors, taking into account "the compatibility of the group and other factors", everything fell into place. Homotransplantations became routine.

But then, in 1967, V.P. Demikhov, with his usual tenacity, argued that the main cause of graft death was an impaired blood circulation in it and an infection that joined. After analyzing the thanatogenesis of 250 dogs after an additional heart transplant, he identified the following causes of their death (Table 1).

Table 1. Causes of fatal outcomes of surgery for transplanting an additional heart in the experiment (Demikhov V.P., 1967)

Causes of animal deaths	Number of animals
Death at surgery while developing the technique in first experiments	43
Acute postoperative complications on day 1 (shock, thrombosis, blood loss, etc.)	71
Thrombosis at the sites of vascular sutures with the circulation impairment	32
Secondary bleeding	27
Transplanted heart pleuritis and pericarditis	24
Transplanted heart infarction	18
Bilateral pyopneumothorax	16
The transplanted heart tamponade by inflammatory exudate	4
Pneumonia, bilateral	4
Pneumonia of the lung transplanted together with the heart	3
Killed for demonstration	2
The causes are not clear	2
Aspiration of vomit. Asphyxia	1
Extensive renal infarction. Uremia	1
Peritonitis due to mesenteric thrombosis and bowel necrosis	1
Paralysis of the transplanted heart due to the size mismatch between donor and recipient	1
Total	250

"Therefore," concluded V.P. Demikhov, "the graft death occurred from 16 causes, rather than from one, as it seems to immunologists. In more than 30 dogs that lived with the transplanted heart for 9 to 32 days, good graft acceptance by surrounding tissues was noted, and there was no rejection in any of the cases. During the Conference (obviously, the 1st All-Union Conference in 1957 - *Auth.*), we demonstrated 3 macropreparations of the chest of dogs with two hearts. In all three cases, it was possible to make sure that the transplanted heart was well accepted. The dogs died from various causes: the 1st one that lived for 12 days died from pleurisy; the 2nd dog that lived for 19 days died from

mesenteric artery thrombosis; and the 3rd one that lived for 30 days died from secondary bleeding resulted from necrosis of the recipient's aortic stump under the ligature.

Of the 20 operated dogs that received the 2nd head transplantation, the transplanted head died within 1 to 7 days in 19 cases. The cause was ... thrombosis of vascular anastomosis, wound infection, vein compression, blood congestion, and graft edema. In one case, the transplanted head lived for 29 days. <...> In the postoperative period, there was a very good intergrowth (with primary intension) of the graft skin with the recipient's skin, and the suture suppurated only for 5-6 cm. This site has become a source of infection. From here, on 26-27 day after the operation, hypodermic edema began to spread, which spread to the entire transplanted head... [On day 29] the transplanted head was removed; the recipient dog remained quite viable.

Histological examination of the transplanted head tissues, except for hypodermic edema, did not reveal any pathological alterations" [6].

He obtained similar results when transplanting kidneys, sternum with skin, and skin flaps on vascular pedicels. All these organs and tissues after their removal were studied by morphologists from the 2nd Pirogov Moscow State Medical University, but besides edema caused by compression of the veins by scars, "no signs of rejection were seen" in any of the cases, according to V.P. Demikhov."

We shall quote the end of his presentation, which indicates the state-scale approach of the speaker to solving the problem of organ transplantation:

I.V. Davydovsky at the 1st All-Union Conference on Tissue Incompatibility, Preservation and Transplantation of Organs and Tissues (Moscow, 1957 – *Auth.*) said that the problem of organ and tissue transplantation was a problem of national significance. However, to this day, this problem has not been treated as a state-important one. Many researchers develop the problem disparately, without being provided with staff, necessary means and facilities, equipment, and proper care for experimental animals. If attention is

paid to the development of this problem, then in the coming years we can expect not only many tissues to be transplanted to a human, but also entire organs" [6].

V.P. Demikhov's preparation for clinical heart transplantation started in the early 1960s was evidenced by the presentation made by his assistant V.M. Goryainov who spoke on the ECG study of the transplanted and revived heart [7].

"We conducted electrocardiographic monitoring during the attempts to revive the heart in the corpses of suddenly deceased people in the first 1-2 hours after death. <...> At death from cardiovascular diseases (for example, an 84-year-old man who died from a left ventricular infarction - *Auth.*) the revival, as a rule, was partial. Only atria or atria with one of the ventricles began contracting. The most complete recovery of cardiac activity was observed in the corpse of a 46-year-old woman who died from a skull injury. <...> Less complete, it was with the body of a girl who died from trauma" [7].

Yu.M. Zaretskaya, who worked with V.P. Demikhov, shared her experience of experimental homoplastic sternum transplantation on vascular pedicles. After transplantation onto the neck vessel, the graft remained viable for up to 18 days. Hematopoiesis was observed at puncture on the 5^{th}-7^{th} day after the operation. Jointly with Dr M.M. Tarasov, the Director of the Sklifosovsky Research Institute for Emergency Medicine, an option of sternum transplantation with the surrounding tissues and skin was developed. But the method was not implemented in clinic.

V.P. Demikhov planned to transplant the human sternum in two stages: first, the graft placed in a plastic case was to be connected to the vessels of the arm or thigh, and then, depending on the organ function and the patient's condition, it was removed or moved to an orthotopic position [8]. It should

be noted that this pioneering report was not supported by the Conference participants, although the topic of bone marrow transplants was discussed.

Some ways to overcome the recipient immunity to a homograft (M.I. Efimov)

The second session of the Conference entitled "Methods for overcoming tissue incompatibility" was opened by M.I. Efimov from Frunze [9]. The message reflected the experimental experience and views of the author and his Department.

Considering the problem of homograft acceptance, the author pointed out that a true acceptance occurs when, due to weak antigenic properties, the graft does not have a strong effect on the recipient's immunogenesis (in particular, in "intra-family transplants"). In other cases, the graft acceptance is influenced by the age of the recipient (the younger the rat is, the more likely the homo-skin will take root), the nervous system condition (engraftment was more successful in rats in a state of drug-induced sleep), the organ type (ovaries take root better than the skin), etc.

Explaining the best engraftment under sleep conditions, M.I. Efimov hypothesized that sleep temporarily reduced or even suppressed immunogenesis, while homograft proteins developed "tolerance to the transplanted graft". As a result, two areas of research were proposed: (1) deeper suppression of the immunogenesis system before and after homografting; (2) a stronger effect of donor tissues on the recipient's immunogenesis when the recipient is in an inactive state (i.e. during sleep).

Neuroleptics (medinal, aminazine) and hypothermia were suggested to deepen sleep, and the graft effect was suggested to be enhanced by the administration of donor tissue homogenizate. Experiments were made in 72

rats. The best result (engraftment in 7 of 10 animals) was obtained by "suppressing" the immunogenesis system with medinal, aminazine, and with hypothermia, while simultaneously affecting this system with the transplanted tissue (skin, nerve) homogenizate.

"We, of course, are far from thinking that the methods we use to influence the immunogenesis system are the top of perfection. Here, of course, even more in-depth experimental work should be performed," the author wrote. "As for the trends in the struggle for a true acceptance of the homograft, based on the above facts and considerations, we can assume that they are correct and promising" [9].

This report gives off the all-powerful and all-pervading "Pavlovian nervism" of the 1950s, when medical sleep and novocaine blockades were used to treat diseases of various origins – from stomach ulcers to trophic ulcers on the extremities. However, if we compare the views of M.I. Efimov with those of V. P. Demikhov, we can see that the latter's position was more theoretically justified and practically confirmed.

On transplanting skin, kidneys, and lungs preserved by freezing (A.G. Lapchinsky et al.)

The third session of the Conference was opened with the presentation on cold preservation of tissues and organs [10] made by A.G. Lapchinsky, a pioneer in this field from NIIEHAiI [10]. The purpose of the presentation was to report the study on the viability of auto- and homo-skin flaps after freezing them in liquid nitrogen at a temperature of -196°C and storage like that for 1 h to 7 months.

The best results were obtained after preservation of skin autografts for

up to 1 month. Such grafts took root with retaining all the properties of normal skin. Preserved homografts rejected or resorbed. However, their life spans were longer than when transplanting fresh flaps (up to 65 days instead of 2-3 weeks). Rapid freezing of the kidneys led to ruptures of their parenchyma. Gradual freezing, although not manifested by macroscopic changes, did not lead to the acceptance of warmed auto- and homokidneys. Attempts to use glycerin or petroleum jelly as a protective medium were unsuccessful either [11].

About experimental transplantation of preserved lungs

(S.I. Yutanov)

Against the background of the two previous presentations, the report of Dr S.I. Yutanov from Gorky on experimental lung transplantation looked impressive [12]. Mentioning V.P. Demikhov's experiments of 1947 on lung transplantation as pioneering, the author described the experimental research on lung lobe and lung transplantation from American scientists, and reported on the graft survival prolongation to 42 days under the effect of adrenocorticotropic hormone.

S.I. Yutanov himself presented data of 50 lung transplants in 48 dogs. Of these, 37 dogs underwent lung replantation and 11 underwent lung homotransplantation. The pulmonary artery was anastomozed with a mechanical suture, and the pulmonary veins were implanted with a manual atraumatic suture. Antibiotics were infused into the pleural cavity. The chest wall was sealed.

The animals lived up to 8 months after autotransplantation, and up to 12 days after homotransplantation. Homolungs had been preserved by freezing to -70° C with subsequent storage at a temperature of -14°C and

-30°C. It was found that storage at a temperature of -30°C was preferable. However, after homotransplantation, all the animals died. Histological examination of the transplanted lungs revealed destructive changes with edema of the lung tissue, its infiltration and necrotic foci. In animals that were transplanted with a homolung stored at a temperature of -14°C, the autopsy showed a pronounced edema of the lung tissue "with the necrosis phenomena" [12]. Animals died also from a bronchial anastomosis insufficiency, bleeding, and pleurisy.

Today, it is clear that the authors observed a rejection reaction of varying severity in homotransplants, but, like V.P. Demikhov, they believed that the causes of the failures were purely technical. In addition, despite a large sample size animal study and the comparison between auto- and homotransplants, which revealed a clear advantage of the former, the author did not provide any data on any other method to influence the immune system, except cold that turned out low-effective.

After analyzing the most interesting presentations, we give here the abstracts from M.M. Tarasov's report on the state of the homotransplantation problem in other countries of the world.

On the state of the homotransplantation problem abroad (M.M. Tarasov)

M.M. Tarasov spoke about the 4th Conference on Organ and Tissue Homotransplantation held in New York (USA) in 1966 that was organized by one of the Institutes of the National Medical Center in Bethesda (Washington). Why did M.M. Tarasov attend the Conference (Fig. 6)? The fact was that (in his words), "it was the responsibility of this Institute (meaning the Institute in Bethesda. – *Auth.*) to provide surgical clinics in the

United States with various types of human tissue that could be used in surgery to transplant and replace destroyed tissues of a human body." Thus, this American Institute was essentially the "organ and tissue bank" of the United States and was dealing with investigating all transplantation issues: procurement, preservation, storage, and clinical use of homografts.

Fig. 6. A.G. Lapchinsky (left) and M.M. Tarasov (2nd from the left) in the USA. New York, 1966 [Divilkovsky S.I. Warrior and ambulance worker for people. To the 100th anniversary of M.M. Tarasov's birth. Available at: https://www.divilkovskiy.com/tarasov]

In terms of the number of presentations (more than 30), this Conference was far behind the 2nd All-Union Conference (200 presentations). M.M. Tarasov allocated all the presentations into 5 groups.

The first group included the following presentations: on the effect of genetic differences between the donor and recipient on the nature of tissue incompatibility in fish; on the effect of gender differences between the donor and recipient on the skin homograft acceptance in newts (in some cases,

"immunological paralysis" was mentioned); on a better homograft survival in "related donor transplantations" in mice; on the anemia mechanism in animal parabiosis; on the specificities of skin homografting in Syrian hamsters, when the graft rejection being caused by incompatibility reaction.

The second group included experiments on extending the homograft survival by blood transfusion from the donor to the recipient; on suppressing the response to transplanted lymphatic tissue by injecting donor leukocytes to the recipient; and on extending the skin homograft survival in humans by shortening the time between repeated transplants.

In the third group, M.M. Tarasov included presentations confirming the immunological nature of tissue incompatibility. Clinical facts of the possible passive transfer of transplant immunity after four consecutive skin homografting procedures in the clinic were presented. Experiments on rabbits immunized with homo-skin were of interest. After mixing their white blood cells with the donor's blood, the white blood cells were rapidly destroyed. The authors concluded that antibodies were released from destroyed immune cells. The report from England focused on the ability of guinea pig blood serum to inhibit the effect of immune antibodies on mouse tumor cells. In the presentation of the authors from Belgium, mice and rabbits were immunized with the extracts of epithelial cells, and the effect was manifested itself later in whole tissue transplants.

The presentations of the fourth group concerned immunological tolerance. Canadians reported on immunizing newborn goats with human albumin and on a low hemagglutinin titer when the antigen was readministered several months later. The author from the UK studied the immune suppression by X-ray irradiation of the recipient under the protection of preliminary transplanted bone marrow. We can hardly

recognize as ethically justified the studies of a group of authors from the United States with blood transfusions to newborns with rhesus incompatibility, after which the skin homografting was performed to them from the same donors and the phenomenon of temporary immunological tolerance was observed. Another group of researchers conducted experiments on immunization of newborn rats of one breed with RNA from the organs of rats of another breed, and then observed the phenomenon of immunological tolerance in them.

The presentations of the fifth group covered organ transplants. Some authors performed homoplastic transplantation of the thyroid and parathyroid glands and observed their survival for 3.5-7 years. M.M. Tarasov did not report any anti-immune therapy. Other authors transplanted pieces of endocrine glands covered with microporous membranes to humans, dogs, and rats and obtained "significantly better results than conventional tissue transplantation" [13].

The last report was made by a group of authors led by surgeon J. Murray and therapist J. Merrill from Peter Bent Brigham Hospital. It was these doctors who performed the world's first successful orthotopic kidney transplantation to patient R. Herrick from his twin brother on December 23, 1954 [14]. As a result, R. Herrick lived for 9 years. In 1959, the same doctors first transplanted a cadaveric kidney from an unrelated donor. To suppress the immune system, scientists first used a whole-body X-irradiation of the recipient after a bone marrow transplant in clinic [15]. In 1961, J. Murray performed the first kidney homotransplantation using immunosuppression with azathioprine, but the patient died from drug intoxication. The third transplantation performed in the same year was a success [16].

At the Conference in New York, this team reported on a method they developed for whole-body X-irradiation of a recipient at a dose of 600 roentgen[2] after a bone marrow transplant. The kidney homograft worked for 29 days. In another case, after irradiation of the recipient with the doses of 250 and 200 roentgen, the transplanted kidney homograft functioned for 12 months.

M.M. Tarasov's report gives the impression that the Americans, Canadians, and Europeans in their investigations of transplant immunity in homotransplantation did not go as far from their Soviet colleagues as was usually believed. Just as in the USSR, they studied the effects of immunological paralysis, parabiosis, donor's blood transfusion, etc. on the recipient's immunogenesis. However, there were also major differences. For example, the attention might be attracted by scientifically innovative experiments with anti-lymphocytic sera, experiments with immunization of newborn and mature animals, clinical experiments with irradiation of the recipient under the protection of bone marrow transplantation, and strange, from the ethical point of view, studies with skin homografting in human newborns and adults.

The top of transplantology in the first half of the 1960s (before heart transplantation) should be considered the successful renal homograft transplantation under protection of pharmacological immunosuppression, which was performed by the group of J. Murray and J. Merrill in 1961. We should recall that the world's first kidney homoimplantation on femoral vessels was performed by Yu.Yu. Voronoi in 1933, and the first related donor

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2 100 roentgens = 1 sievert. The maximum permissible dose (MPD) of X-ray radiation per year equaling today 100 millisieverts. The given single dose was 60 times higher than the annual MPD.

orthotopic kidney transplantation in the USSR was performed by B.V. Petrovsky in 1965. However, there was no talk of such operations either in the USSR or in the United States.

At that Conference, the USSR was represented by M.M. Tarasov, who spoke about the history and current state of cadaveric blood transfusion being made by Soviet surgeons, and being an undoubted world priority, and by A.G. Lapchinsky (see Fig. 6), who described the method that he had developed for the preservation of the limbs and kidneys in dogs in conditions of cardio-pulmonary by-pass, using a special NIIEHAiI-designed device, and their subsequent autoplastic replantation (Fig. 7). The function of the limbs was followed-up for up to 6 years, and the function of the single kidney transplanted to the neck was followed-up for 3 years [13]. This achievement can also be referred to the world priorities of Soviet scientists.

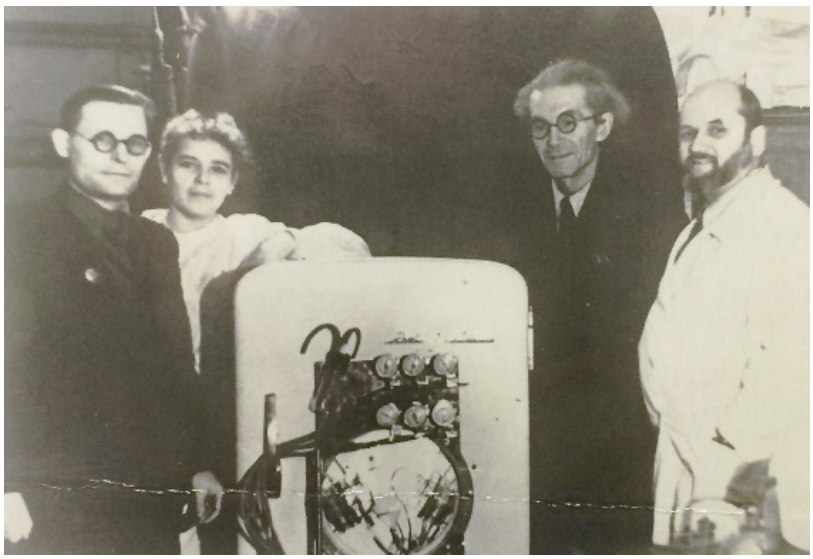

Fig. 7. Apparatus for organ cryopreservation with perfusion of their vascular bed, designed by A.G. Lapchinsky (right). S.S. Bryukhonenko is the 2nd from the right. [Museum of A.N. Bakoulev National Medical Research Center for Cardiovascular Surgery]

What decisions did the 2nd All-Union Conference on Tissue Incompatibility, Preservation, and Transplantation of Tissues and Organs make?

Main research programs approved by the 2nd All-Union Conference on Tissue Incompatibility, Preservation, and Transplantation of Tissues and Organs

The following areas of comprehensive research involving both theoretical and clinical specialists were identified and approved:

I. ***Study of phenomena and mechanisms of biological incompatibility of organs and tissues.***

I.1. In the field *of clinical research*, it was planned to "further clarify, describe and analyze local and general phenomena accompanying incompatibility in homotransplantations". It was considered necessary to "organize research to identify immunological (neuro-humoral and cellular) changes in the body in the process of homotransplantations". The following provisions, as well as paragraph I.2, fully reflected the views of V.P. Demikhov on homotransplantation of vital organs: "We should arrange a detailed physiological study of the functional activity of transplanted organs and tissues in clinic, and the body as a whole. As experimental data are being accumulated, it is necessary to conduct a clinical trial of the newly recommended methods and means for studying the tissue incompatibility in different tissues." [17].

I.2. In the field *of experimental biological* research, it was recommended to encourage the studies aimed at creating models for studying the transplantation immunity. It was also necessary to develop the study of biological phenomena that were similar in nature to transplant

compatibility and incompatibility (the formation of chimeras, cell mosaics, somatic cell hybrids, etc.). Pavlovian nervism was also mentioned: "It is also advisable to clarify the role of neurogenic factors, the endocrine system, and changes in the reactivity of recipient's body."

I.3. In the field *of immunology*, the Conference participants considered it necessary "to organize studies that would provide a complete characterization of graft antigenic structure, including group, type and individual antigens, regardless of their nature <...> A detailed analysis of the antibody formation and cellular reactions in response to the graft presence should be made, paying special attention to the body's plasmocyte defense system."

I.4. In the field *of morphological and physiological* studies, it was recommended to investigate regenerative processes in surviving and non-surviving grafts. Especially important seemed "the studies related to characterizing the role of the central and peripheral nervous systems in the acceptance and the functional recovery of transplanted organs and tissues." It should be noted that V.P. Demikhov repeatedly put the latter task at the forefront of his experiments with transplanting the head of one animal onto the neck vessels of another one.

I.5. In the field *of physico-chemical and biochemical studies*: "we should study the chemical structure of antigens responsible for incompatibility, as well as the changes in metabolic processes both at the site of transplantation and in the body as a whole. It is important to study the trophism (nutrition) of cells in the graft and in the surrounding tissues. In this regard, the question of artificial nutrition, improving blood supply and oxygen supply to various areas of the graft should be raised." Perhaps, V. P. Demikhov could not study the chemical structure of antigens, but he had

been dealing with the studies of blood supply to the graft for many years. Further tasks in this direction concerned fine biochemical studies (to study the role of DNA in the phenomena of transplantation immunity) or high technologies (to study the effect of ionizing and other types of radiation on graft acceptance).

II. ***Development of methods for overcoming tissue incompatibility.***

II.1. In the field *of clinical* research, it was recommended to "improve the means of graft acceptance basing on the latest achievements in experimental and biological studies, taking into account the tissue nutrition conditions, blood supply, and the possibility of restoring innervation when choosing a transplantation technique. < ... > Of great importance is the development of methods for removing organs and tissues for subsequent transplantations, for which purposes it is necessary to create new equipment and devices" <...> [17].

V.P. Demikhov had successfully developed this area of research for a long time, and his demonstration of V.F. Gudov-designed vascular stapling device for connecting the ends of the transected carotid artery in experiment in Munich in 1959 was highly appreciated by the world surgical community.

II.2. In the field *of experimental biological* research, "it seemed necessary to study the interrelation between the graft and recipient tissues on the basis of studying the phenomena of somatic hybridization and chimerization." Though V.P. Demikhov succeeded in this direction, but the following was beyond his power: "Of particular importance is the development and breeding of pure animal lines necessary for studying the genetics and immunology of incompatibility, as well as the breeding of new animal lines for these purposes"; but the following was well-known: "In experimental animals, it is recommended that we continue to develop the

most cost-effective methods of graft coalescence... with particular attention to the acceptance of entire organs, including the heart, kidneys, limbs, liver, endocrine and other organs." Note that the heart in this list is ahead of the kidneys. After all, by that time the heart transplants had been performed only in experiment, and the kidneys were already transplanted in clinic. We should also note that the list of organs did not include lungs, although they were transplanted by V.P. Demikhov and his colleague S.I. Yutanov from Gorky.

The following recommendation even for today seems fantastic, but it again (as so many times, though partially) fits into the research topics of V.P. Demikhov: "The Conference recommends involving biologists and biochemists in the implementation of artificial transformation of tissues and individual cells of animals and humans (!) in order to immunologically bring donor and recipient tissues closer together. For this purpose, it is necessary to widely develop research on improving the methods of tissue and organ survival outside the body, attempting to create conditions that ensure the reproduction of cells in such organs and tissues. < ... > Methods for growing human fetal organs should be developed to use the latter as grafts and for experiments on transformation. < ... > It is recommended to test three ways to change the specificity of DNA in the grafts by: the induction with protein-based bodies; by chemical effects, and through transformation, that is, the inclusion of donor's DNA in the graft or recipient tissues." If the first part of this passage deals with the creation of a bank of organs and tissues, and also with the cultivation of organs from anencephalic newborns, then the second part deals with the genetic transformation of transplant material, which science may achieve only in the XXI century.

II.3. Recommendations in the field of *immunology* included: "research

aimed at the suppression of body specific reactivity in relation to the graft", including by means of the following methods: "desensitization, neutralization of antibodies, the effect of hypnotics, plasmapheresis, total replacement of blood, X-ray irradiation, cortisone, etc." There was also mentioned the possibility of "using the modern biology achievements in particular the one of parabiosis, in immunological terms".

II.4. In the field *of morphology and physiology* "the development of methods for restoring graft blood perfusion, innervation, and normal metabolism, and also special functions of transplanted organs and tissues (urination, hormone release, etc.) was recognized as "particularly important" [17, p. 579].

II.5. In the field of *physico-chemical and biochemical* research, it was considered necessary to "ensure the issues listed in sub-paragraphs 1, 2, 3, 4 to be investigated at the molecular level".

III. *Studying the methods and conditions for preservation of organs and tissues for transplantation.*

III.1. In the field of *clinical* research, it was recommended to "provide the specific features for the preservation of entire organs (kidneys, limbs, heart, lungs, endocrine organs, etc.)", including "when exposed to low and ultra-low temperatures. <...> It is necessary to continue studying the acceptance of so-called "revitalized" organs preserved with artificial blood supply."

III.2. In the field *of experimental biological* research, it was planned to "improve experimental biological models for standard testing and comparative study of various methods of tissue and entire organ preservation, as well as growing them in artificial conditions." V.P. Demikhov's idea of creating a "living physiological system", which he first

reported to the Board of the USSR Healthcare Ministry in 1963, and then repeated in the Preface to the German (1963) and Spanish (1967) Editions of his book "Experimental Transplantation of Vital Organs", totally fits into this field of research.

III.3. In the field *of immunological* research, it is necessary to "improve methods for studying the antigenic structure of preserved grafts and the recipient responses to them."

III.4. In the field *of morphological and physiological* studies, it was necessary to investigate changes in cell morphology during preservation and subsequent engraftment", as well as the physiology of grafts during their preservation and storage [17, p. 580].

III.5. In the field *of physico-chemical* studies, it was recommended to focus on the dynamics of metabolic processes in the graft during preservation.

IV. *Improvement of surgical methods of homo-, hetero-, auto- and alloplastic transplantations.*

IV.1. In the field *of clinical* research, the task was set to improve the organization of large "banks" of tissues, to develop various types of these banks, as well as "their location in accordance with the location of medical institutions". Most likely, this paragraph was included by M. M. Tarasov based on his trip experience to the United States.

Moreover, "we should continue to work on further improving surgical techniques for performing all types of transplantation." Surgeons were also encouraged to improve methods for transplanting blood vessels, skin, cornea, bone marrow, bone and muscle tissue, nerves, joints, and solid organs. The following was said about them: "Given some progress in the theory of transplantation, it is considered appropriate to get prepared for the

transplantation of entire organs, using all clinical potential for this." The Conference also recommended that "clinical institutions should prepare for more complex forms of transplantation, given that the advances in modern biology, physics, and chemistry in the coming years may make it possible to transplant organs that are currently impossible to be replaced." As if following this recommendation, C. Barnard transplanted a heart human to a human on December 3, 1967.

IV.2. In the field *of experimental biological* research, it was recommended to "expand the development of experimental surgery aimed at helping surgeons to develop plastic surgery techniques, while using the most advanced biological models."

IV.3. In the field *of immunological* research, it was "necessary to provide for clinical studies using immunological methods both in evaluating the transplant material and in characterizing the response to the graft."

IV.4. In the field *of morphological and physiological* studies, "it is necessary to achieve a comprehensive evaluation of the graft viability during transplantation and its impact on the recipient." It was recommended to establish "extensive contacts of transplant clinicians with morphologists and physiologists, immunologists, and biochemists for a comprehensive study of the issue." Again, it was absolutely true. We should note that all these principles were implemented only in 1969 by establishing the Research Institute for Organ and Tissue Transplantation of the USSR Academy of Medical Sciences.

IV.5. In the field *of physical and chemical* studies, attention was paid "to the selection of appropriate plastic materials in order to create the most perfect internal and external prostheses for tissue defects" [17].

With this, the 2nd All-Union Conference concluded its work.

Conclusion

Thus, the analysis of the materials of the 2nd All-Union Conference on Tissue Incompatibility, Preservation and Transplantation of Tissues and Organs (Odessa, 1967) showed that in general, the approaches to solving the problem of organ and tissue transplantation among Soviet and foreign scientists were similar. However, there were differences.

Among the traditional methods, Soviet scientists talked about overcoming tissue incompatibility by means of plant hybridization and animal chimerization, about the effect of drug-induced sleep on transplantation immunity, neuro-humoral immunological shifts and the role of the central and peripheral nervous systems in graft acceptance, and the impact of external factors on immunity. Alongside, they spoke of really up-to-date methods: of the "complete characterization" of the graft antigenic structure, the role of DNA in immunity, the genetic transformation of transplant material, the use of pharmacological agents (in particular, cortisone) to suppress immunogenesis, freezing of limbs for replantation, cryopreservation of isolated organs (kidneys) with perfusion of their vascular bed, and the study of the immunogenesis mechanisms at the molecular level.

Americans discussed I.I. Mechnikov's concept of immunological paralysis, the effect of transfused donor blood and its components on the recipient's immunity, which was in the spirit of plant hybridization according to I.V. Michurin. Even when it came to subtle biochemical studies of immunity, they didn't get very far. Meanwhile, we should note the experiments, including clinical ones, with multiple passages of homoskin, with exchange blood transfusions to newborns with subsequent transplantation of donor skin homografts to them, and recipient irradiation

with high doses of X-rays.

Despite the criticism of V.P. Demikhov's views on transplant immunity, Soviet scientists could offer nothing to help him. No one in the country was eager to study the problem of vital organ transplantation. Worthwhile of attention was the sternum transplantation technique proposed by V.P. Demikhov for bone marrow transplantation, which could have provided hematopoiesis after immunosuppression or irradiation, but it remained unclaimed.

If we list the trends that V.P. Demikhov had developed, it turns out that almost all of them were approved by the 2nd All-Union Conference. These were: creating experimental biological models for studying transplant immunity, studying the functional activity of transplanted organs, studying the effect of parabiosis on immunity, studying the role of the central nervous system in the engraftment of a complex of organs, studying the metabolism in a graft, improving the methods for ensuring adequate blood supply and innervation of transplanted organs, using vascular stapling devices for connecting major vessels, creating a bank of living organs and tissues for transplantation, cultivating organs from embryos, restoring and preserving the viability of grafts in conditions of artificial circulation. And even the recommendation for "clinical institutions to prepare for more complex forms of transplantation" was at least five years late.

But what V.P. Demikhov really lacked was a close and comprehensive integration with morphologists, physiologists, immunologists, biochemists, pharmacologists and, sad as it might be, with clinical surgeons. These shortcomings were overcome by C. Barnard, A. Kantrowitz, D. Cooley, and several dozens of other surgeons from different countries who performed more than 90 clinical heart transplants in 1968.

From the analysis performed, we can draw an unambiguous conclusion: Soviet scientists who declared absolutely correct postulates should not have criticized V.P. Demikhov for his "lack of understanding" of immunology, but should rather have helped him in every possible way, directing his energy in the right direction. As time showed, attempts to catch up with the world's transplantology would shortly be made. In 1968, Professor A.A. Vishnevsky, Full Member of the USSR Academy of Medical Sciences, would perform the country's first clinical heart transplantation at the clinic of the Hospital Surgery Department of the Military Medical Academy named after S.M. Kirov in Leningrad; and in 1969 on the initiative of Academician B.V. Petrovsky, the USSR Healthcare Minister, the Research Institute of Organ and Tissue Transplantation of the USSR Academy of Medical Sciences would be opened and implement in practice an integrated approach to solving the problem of organ and tissue transplantation.

However, V.P. Demikhov no longer participated in those historical events. Right was F. Schiller, who in 1783 said the prophetic phrase: "Der Mohr hat seine Arbeit getan, der Mohr kann gehen" ("The Moor has done its work, the Moor can go").

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