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PHENOMENON OF DEMIKHOV.
In the Sklifosovsky Institute (1960-1986).
Scientific Revolution in Transplantation (1960–1964)
Achievements of the USA and the USSR in the field of transplantation and transplant immunity (1962)

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The article presents the evidence of a scientific revolution in transplantology that occurred in the world in 1960-1964 with the shift of the paradigm from the impossibility of homoplastic organ transplants to the hope on their feasibility. It began in 1960 with awarding the Nobel Prize to P.Medawar and F. Burnet for the discovery of artificial immunological tolerance, it had its continuation in 1961–1962 with the advances in experimental transplantation of vital organs undertaken in conditions of mechanical circulation (R. Lower, N. Shumway) and immunosuppression (K.

Reemstma), and completed with human transplantations of lung in 1963 and of heart in 1964 (J. Hardy). In those years, the concept of mechanical support for an ill heart by using an implanted mechanical assist device was developed and introduced (1963). But even against that background, V.P. Demikhov's achievements in homologous organ transplantation and the development of biological techniques to overcome tissue incompatibility looked impressive. His highest achievement was the transplantation of a supplemental heart to the dog Grishka in June 1962, and the dog survived with it for 141 days. However, after the discoveries in the field of transplantation immunity, the train of experimental transplantation where V.P.Demikhov was riding, began picking up speed very quickly, and the Soviet surgeons were to jump on its footboard.

Keywords: V.P. Demikhov, N.V. Sklifosovsky Institute for Emergency Medicine, scientific revolution in transplantology, 1960–1964

Scientific revolution in transplantology

Facts indicate that in 1960-1964 a *scientific revolution* took place in biology, medicine and surgery, and more specifically, in the field of *transplantation*: the paradigm of the impossibility of homoplastic organ transplantations was replaced by the hope of their feasibility.

Its precursor was the kidney graft rejection reaction first described by a group of French surgeons led by J. Hamburger in 1959 [1].

The revolution was strated with the Nobel Prize awarded in 1960 to P.Medawar and F.Burnet for the discovery of artificial immunological tolerance (Fig. 1, 2). It is clear that those scientists made their discovery much earlier, but its “Nobelization” made the issue generally recognized and brought it to the rank of a biological law.

Fig. 1. Peter B. Medawar (1915–1987).

[https://commons.wikimedia.org/wiki/File:Peter_Medawar.jpg]

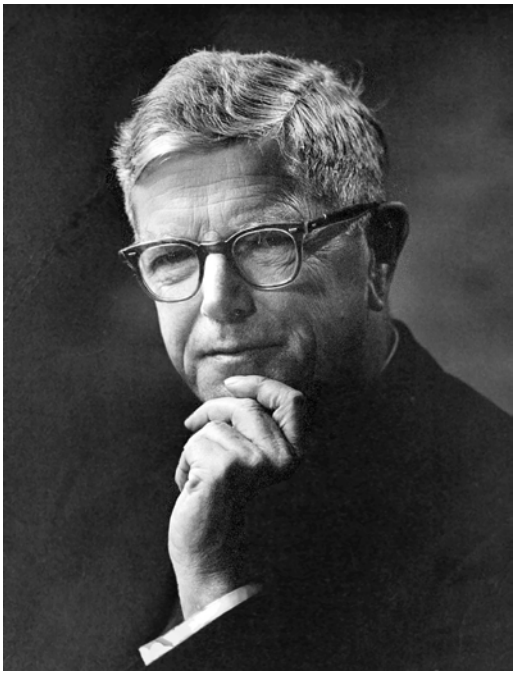

Fig. 2. Frank M. Burnet (1899-1985).

[https://en.wikipedia.org/wiki/Frank_Macfarlane_Burnet]

In the USSR, that event coincided with the publication of V.P. Demikhov's monograph *Experimental Transplantation of Vital Organs* where the author developed the basics of experimental transplantology [2]. It is no coincidence that the book was translated into English in 1962, and into German in 1963 and was carefully read in English-speaking countries [3]. Although the opinion has rooted in the literature that the book is devoted to the technical aspect of homotransplantations rather than to immunological ones [4, 5], we believe that the main idea originally developed by the author in his fundamental research covered the biological ways to overcome the homologic organ incompatibility, which were known only to the outstanding experimental surgeon, in particular, the idea of crossed-circulation. By the way, the concept of acquired biological tolerance fits perfectly into the paradigm that existed in the biology of that time, at least in the USSR, that a change in the graft metabolism inevitably entails a change in its genetic nature [6]. But let's go further.

In 1960, in London Guy's Hospital, R. Brock, one of the pioneers of British heart surgery conducted a series of experiments on heart transplants, stitching the great vessels of the donor and recipient hearts, and implanting vena cava and pulmonary arteries on the sites prepared of atrium walls. R.Brock did not know that much earlier, a similar method of transplanting a beating heart was developed and applied by V.P. Demikhov in 1951 to transplant an isolated heart in dogs [2, p. 112]. But the Englishman went further than his Soviet colleague and compared the survival rates between animals after heart auto- and homotransplantation. It is clear that the result was not in favor of homo-transplans [5]. We should mention, as we have repeatedly stressed that V.P. Demikhov was never doing heart autotransplantatons. Apparently, the result of such a procedure was obvious

for him. Convinced that the future was for homotransplantations, he sought for engrafting *working homoorgans* using *biological methods*; and by 1960 he had almost come close to solving that problem, having achieved long periods of animal survival, and proceeded to the preparation of organ transplantation in clinic. For this purpose in September, 1960, he officially came to work in the Sklifosovsky Institute of Emergency Medicine.

But the history of transplantation had already turned in the direction of operations made in conditions of artificial blood circulation and drug immunosuppression.

Starting from December 1959, during the spring and summer of 1960, R. Lower and N. Shumway (Fig. 3, 4) from Stanford University (California, USA) developed and performed a series of orthotopic transplantations of a pre-cooled heart[1] in conditions of artificial blood circulation by forming three anastomoses: biatrial, aortic, and pulmonary ones to join it to the recipient's heart. Five of 8 dogs survived for 6 to 21 days. In the same time period, the surgeons performed several transplants of the cardiopulmonary complex. Six dogs recovered their breathing, and 2 of them survived for 5 days. We should note that the authors themselves called their operations “surgical tricks”, understanding that they had to overcome the immunological barrier. Soon, the same surgeons performed several heart autotransplantations. The experiment was aimed at observing the function of denervated autologous heart. The result was impressive: the dogs lived for over 2 years. After following 2 years, the heart innervation in surviving animals recovered, and their activity was normalized [5, 7, 8].

[1] After having been trained in Minneapolis (Mississippi, USA) at Dr. F.J. Lewis's, the pioneer of heart surgery under hypothermia, N. Shumway knew well the general hypothermia principles and developed his own method of cooling an isolated heart with ice prepared of saline [7].

Fig. 3. Richard Lower (1929–2008). [Shumacker H. The evolution of cardiac surgery. Indianapolis: Indiana Univ. Press, 1992]

Fig. 4. Norman Shumway (1923–2006). [https://www.flickr.com/photos/40390680@N08/5124585378]

Interestingly, the Experimental Laboratory of the Department of Surgery at Stanford Lane Medical School in Palo Alto was located in "*relict*" premises, as his contemporaries wrote, where "*on rainy days the silence of dark and gloomy interiors was interrupted by the sound of rainwater falling from the ceiling into the exposed buckets*", but was pretty well equipped: in addition to modern operating tables, operating lamps, anesthesia equipment and electrocardiographs, it was equipped with a "heart-lung machine" with the Key Cross disk oxygenator, the most advanced one for that time [7]. Despite the fact that Stanford was a private University, a scientific grant was issued by the *State* National Institute of Health in Bethesda [8].

In February 1962, K. Reemtsma (Fig. 5) from the University of Tulan in New Orleans (Louisiana, USA), having previously studied the metabolic changes in the blood of experimental animals with non-contractile homologic hearts attached to cervical vessels in conditions of immunosuppression by metatrexate, reported a 26-day graft survival, while hearts without immunotherapy rejected after 6–10 days [9]. At the end of 1962, a New York group of surgeons headed by D.Blumenstock conducted similar experiments. Half of the animals died within 24 hours, but four dogs survived for 17-42 (!) days [5].

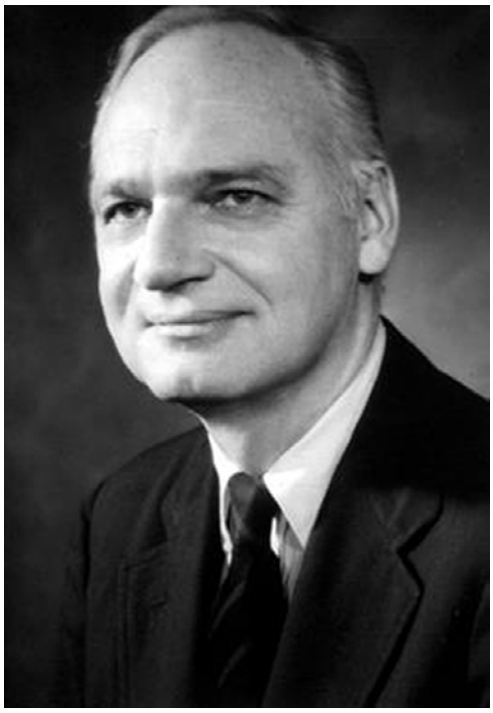

Fig. 5. Keith Reemtsma (1925–2000). [https://en.wikipedia.org/wiki/Keith_Reemtsma]

Further events unfolded rapidly. On June 11, 1963, J.D. Hardy (Fig. 6) from the University of Mississippi in Minneapolis (Mississippi, USA) performed the world's first lung transplantation to a 58-year-old patient. Despite immunosuppression with azathioprine, prednisolone, and irradiation exposure, the patient lived for 18 days and died of concomitant renal failure having an underlying cancer disease. We should note that the University Surgical Clinic where J.D. Hardy worked had no intensive care units; there was a relatively weak anesthetic service, limited funds for nursing staff to care for severe patients, and there was no artificial kidney machine there [10]. All this suggests that the operation was essentially a clinical experiment. However, the seriously ill person was a criminal serving his sentence for a murder, which partly served as an excuse for the doctors who made the decision to undertake that experiment.

Fig. 6. James D. Hardy (1918–2003). [Shumacker H. The evolution of cardiac surgery. Indianapolis: Indiana Univ. Press, 1992]

Later on, in the period from November 5, 1963, to February 10, 1964, K. Reemtsma undertook a series of chimpanzee kidney transplantations onto the femoral vessels of several patients who were dying of renal failure. Immunosuppression included actinomycin C, corticosteroids, and irradiation exposure. Patients survived from a week to 2 months and died of xenogaft rejections or associated infection [5].

J.D. Hardy visited K. Reemtsma Laboratory at the end of 1963 and was impressed with his results. On January 24, 1964, he conducted the first ever human heart transplant from chimpanzee using the R. Lower-N. Shumway biatrial technique. And although J.D. Hardy had gained an experience of about 200 heart transplants to animals by that time, that surgery was an operation of despair, since the 68-year-old patient was dying of severe heart failure that was refractory to any treatments, including defibrillation. Interestingly, there was a suitable brain dead donor after

trauma in the clinic, but his heart was beating, and it was forbidden to harvest a beating heart in such a situation in the USA at that time. Therefore, a monkey's heart of suitable dimensions was taken, having been chosen from the hearts of four animals. The transplanted organ worked for 1 hour only, but J.D. Hardy suggested that in order to prolong the life of an isolated heart before a transplant, it must be subjected to deep cooling under conditions of the coronary bed perfusion [10].

Almost contemporaneously with the above experiments, the idea of supporting a diseased heart with an implanted mechanical device arose that precursed the future concept of a “bridge to transplantation”. In 1961, M. DeBakey (Texas, USA), the Head of the Surgery Department of the Baylor Medical College in Houston, learned that Dr. D.S. Liotta working at the Cleveland Cardiac Surgery Clinic designed and applied several models of an implantable "total artificial heart" in dogs and invited him to Baylor to work in that field together. At that time, patients often died of cardiogenic shock after cardiotomy; and M. DeBakey's technique of bypassing the left ventricle from the left atrium to the femoral artery using a roller pump was ineffective.

By the end of 1962, a group of doctors and engineers headed by D.S. Liotta and led by M. DeBakey (Fig. 7, 8) constructed a pneumatic device in the form of a tube made of polyurethane, lined with a silicone membrane reinforced by a Dacron, which divided the cavity of the device into an air and blood chamber with ball valves at the inlet and outlet of the latter. In May 1962, the experimentally tested device was presented at the contest of young researchers in Denver [11]. On July 19, 1963, S.Crawford (Fig. 9) and D.S. Liotta implanted the device for the first time in history to a sick man with a severe heart failure at the Methodist Hospital of Houston (Fig. 10).

Again, we should recall that V.P. Demikhov constructed the implanted two-ventricular electromechanical heart supporting the life of the whole animal as early as in 1937, and substantiated a similar concept of an assisted circulatory support in the 1940s in his series of experiments with a second, additional heart transplanted into the chest, which pumped blood from the left atrium to aorta (Fig. 11).

Fig. 7. Domingo S. Liotta (born in 1924). [Shumacker H. The evolution of cardiac surgery. Indianapolis: Indiana Univ. Press, 1992]

Fig. 8. Michael E. DeBakey (1908–2008). [Shumacker H. The evolution of cardiac surgery. Indianapolis: Indiana Univ. Press, 1992]

Fig. 9. E. Stanley Crawford (1922–1992). [https://www.jvascsurg.org/article/0741-5214(93)90165-I/pdf]

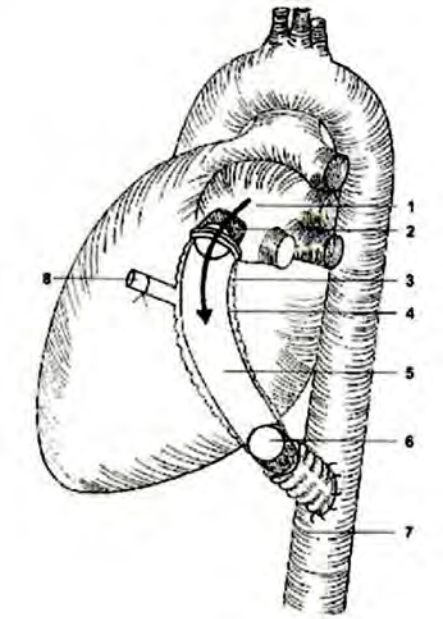

Fig. 10. The scheme of implanting pneumatic-driven pump that partly bypassed the left ventricle according to D.S. Liotta. Houston, Methodist Hospital, July 19, 1963. Legends: 1 − left atrium; 2 − inlet valve; 3 − housing of Silastic, reinforced with Dacron fabric; 4 − air chamber; 5 − blood chamber; 6 − outlet valve; 7 − descending aorta; 8 − plastic tube (internal dimension, 4 mm) for air supply. [From: Liotta D. Early clinical application of assisted circulation. *Texas Heart Institute Journal*. 2002;29(3):229–230. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC124772/]

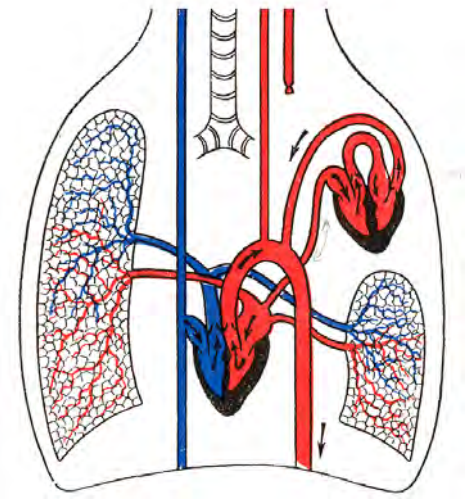

Fig.11. The scheme of supplemental heart transplantation into the chest of a dog to bypass the left ventricle according to V.P. Demikhov. Moscow, A.V. Vishnevsky Institute of Surgery, the USSR Academy of Medical Sciences, 1948. [From: Demikhov V.P. *Experimental transplantation of vital organs*. Moscow: Medgiz Publ., 1960]

On the one hand, these numerous allusions to the achievements of the Soviet scientist, which ran ahead of many developments described above, prove that, in the early 1960s, V.P. Demikhov really worked at the front edge of world transplantation. But on the other hand, the rapid development of events, which we called the *scientific revolution in transplantation,* convinces us once more about how different the approaches to the problem were in the USSR and in Western countries. Judge for yourself.

In 1946, V.P. Demikhov began his experiments at the Fur Institute; in 1947 he moved to work in A.V. Vishnevsky Institute of Surgery, in 1955 he started working in the 1st MOLMI named after I.M. Sechenov, in 1960 he came to work in the Sklifosovsky Institute for Emergency Medicine. But V.P. Demikhov's ideas did not raise a keen interest in Russian scientific circles at that time.

And here is what was happening outside our country in the meantime.

In 1943, the transplantation immunity research began in London, culminating in 1960 with the Nobel Prize. In 1950, the first orthotopic heart transplantations were performed in Philadelphia, and the first orthotopic kidney transplantation to a human was performed in Chicago. In 1954, the first kidny autotransplantation was performed Boston. In 1960, an animal heart was transplanted using artificial blood circulation in California; in 1961–1962, the experiments with immunosuppression were made in Louisiana. In 1963, a lung was first transplanted to a human (under immunosuppression); and in 1964, such heart transplantation was performed, however, from a monkey. But if there had been no ban on the removal of organs from a brain-death human in the USA at that time, the human heart would have been transplanted as early as in January 1964!

Just imagine how wide the geography of research was and how large number of scientists and teams were involved. And although Western laboratories were sometimes located in premises no better than those in which V.P.Demikhov worked, they faced no lack of equipment, medicines, or funding, including that invested from national public sources.

It was all somewhat different in the USSR. But first things first.

In the Sklifosovsky Institute for Emergency Medicine (February – April 1962)

On January 2, 1962, the USSR Healthcare Minister issued Order No. 2 *On the organization of the departments for preparing cadaveric blood and tissues*. Without considering the issues of cadaveric hemotransfusion, let's see if there was anything in that regulatory document that would have permitted to procure not only the cadaveric tissues, but also the organs.

It turned out that there was. Here we present the corresponding abstracts from it.

"USSR HEALTHCARE MINISTRY

ORDER No. 2

On the organization of the departments for preparing cadaveric blood and tissues

Moscow, January 2, 1962

In order to expand the preparation of the cadaveric ***organs*** (hereinafter highlighted by us - SG) and tissues (bones, blood vessels, skin, bone marrow, etc.)...

I ORDER:

I. To the Healthcare Ministers: of RSFSR (Comrade Vinogradov N.A.) ...:

1) ... to organize ... in institutions ... during 1962-1963 the departments for preparing cadaveric tissues and blood, according to Appendix No. 1.

To develop the work of the departments harvesting cadaveric ***organs***, tissues, and blood on the base of the morgue of one of the large hospitals in the respective cities, in which concentrate making the forensic and pathologic autopsy of the corpses of all the suddenly died.

<...>

3) Oblige the Forensic Bureau ... to ensure a timely examination of the corpses of persons who died suddenly (no later than within the first 4 hours after death) in order to decide on the possibility of removing ***organs*** and tissues ... for medical use.

<...>

III. The Central Institute of Hematology and Blood Transfusion together with the ***Moscow City Scientific Research Institute for Emergency Medicine named after N.V. Sklifosovsky*** (Director c. Tarasov M.M.):

1) Develop within two months and submit for approval a provision on the procedure for removing ***organs*** and tissues (including blood) from the corpses of people who have suddenly died at home, in institutions and enterprises, as well as in medical institutions.

<...>

USSR Healthcare Minister

S.KURASHOV"[12].

We deliberately omitted the issues of premises allocation, staffing, funding, and other organizational issues because we want to emphasize the main thing, i.e. that Order allowed the removal of donor organs, and that the N.V. Sklifosovsky Institute was authorized to develop and submit for approval the "Regulation on the removal of organs and tissues" from suddenly deceased people. Otherwise, the official permission for the *removal of cadaveric organs* was obtained. But they still needed a permission to transplant them.

This may explain the fact that at the beginning of February 1962, V.P. Demikhov addressed the Presidium of the USSR Academy of Medical Sciences with his request to consider the state of organ transplantation issue in the USSR in order to proceed to clinical organ transplantation. He believed that if the Presidium had addressed the USSR Ministry of Public Health with the appropriate petition, and the consent would have been given, then no one and nothing would prevent the problem from being solved. On February 14, 1962, a Meeting of the Presidium of the USSR Academy of Medical Sciences took place, where the 4th point of the agenda was devoted to considering the issue "On V.P. Demikhov's letter" [13]. The presentation

was made by N.N. Blokhin, the President of the USSR Academy of Medical Sciences; V.P. Demikhov had not been invited to the Meeting. The letter of reply was prepared by F.V. Kerbik, a Member of the Presidium of the USSR Academy of Medical Sciences. The answer was positively negative, like: "Yes, such a problem exists, and it must be solved. But not now."

In other words, the Presidium of the USSR Academy of Medical Sciences designated to reveal everything the newest in medicine, to study it and put into practice, considered the problem of organ transplantation untimely and irrelevant. But without a "command from the top", nobody was going to solve this problem in the Sklifosovsky Institute, at least in 1962. This can be evidenced by the following facts.

On April 4, the Institute Scientific Council considered at its Meeting the issue "On changing the Institute structure in connection with the USSR Council of Ministers Resolution No. 987 of November 5, 1961, "On improving the urgent and emergency medical care service for the population". In particular, it was proposed:

> "... on the 1st floor of the Institute's surgical building, to locate an Anti-shock Unit, Laboratory and Operating Room for emergency patients, rooms for tracheostomy and open-chest (cardiac) massage <...> to give the right to the ambulance teams to deliver all patients and casualties requiring emergency care to the Surgical building, bypassing the Emergency Department, and there the staff [of the Anti-Shock Unit] shall immediately enter into the struggle for the life of a patient or an injured and continue this struggle until they are removed from a severe condition ... "[14, p. 79].

All this is wonderful! But the authors of the proposal did not take into account the opposite side of their innovations. But what if a patient or injuried with a trauma could not have been brought out of a serious, for

example, comatose condition by means of mechanical ventilation and direct cardiac massage; their brain would have died and their heart suddenly would have worked? What then? What to do with such "revived bodies"? Where to put them?

V.P. Demikhov thought over that question much more comprehensively. He proposed to use those "bodies" either for the removal of working organs for the purpose of their transplantation, or for prolonging the vital activity of isolated organs before their transplantation; in other words, to create a kind of a "bank of organs" where isolated organs and organ complexes would have been connected to a body with a beating heart.

But, the initiators of establishing a new Department, namely I.M. Grigorovsky, the Head of the Methodologic-organizational Department, and A.F. Shvedov, the Head of the Ambulance Station did not even remember about that idea! Fairly saying, the proposal never was implemented in practice in 1962. No Anti-shock Unit was established in Sklifosovsky Institute. But the complete disregard of the idea of a possible organ harvesting in conditions of such a Unit speaks volumes. However, V.P. Demikhov was not going to give up.

"Bomb" under the transplantation immunity (June 1962)

June 20, 1962, was a routine operative day in V.P. Demikhov's Laboratory. An Eastern European Shepherd Dog named Grishka who was destined to enter history as an animal that placed an atomic bomb under the transplantation immunity, was laid on an operation table for transplantation of an extra heart. In any case, that was exactly what the reporters wrote about the event. After all, without any effect posed on the immunity from outside, Grishka lived with an extra heart and a lung lobe for over 4 months!

Still, that was an extraordinary surgery. First, for that time V.P. Demikhov decided to try out the new scheme, which was similar to scheme No. 18 (Fig. 12), but the bronchus of the transplanted lung was connected to the bronchus of the two upper removed lobes of Grishka's left lung (Fig. 13). And second, according to our data, an American anesthetist from Columbia University Jane Henley took part in that surgery[2]. Dog Grishka survived, and lived as long as for 141 days (Fig. 14).

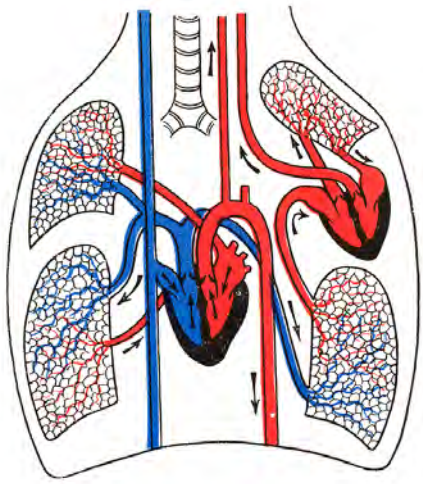

Fig. 12. Scheme No. 18: the transplantation of a supplemental heart with a lung lobe into the dog's chest according to V.P. Demikhov. Moscow, 1950s [From: Demikhov V.P. *Experimental transplantation of vital organs*. Moscow: Medgiz Publ., 1960]

[2] In 1962, besides J. Henley (USA), the laboratory was visited by Dr. Kessel and E. Shirokov (USA) and Dr. P. Sen (India) who participated in surgical experiments on dogs. However, our request to the Archives of the Federal Security Service of the Russian Federation was answered that there was no information about any contacts of V.P. Demikhov with foreign experts.

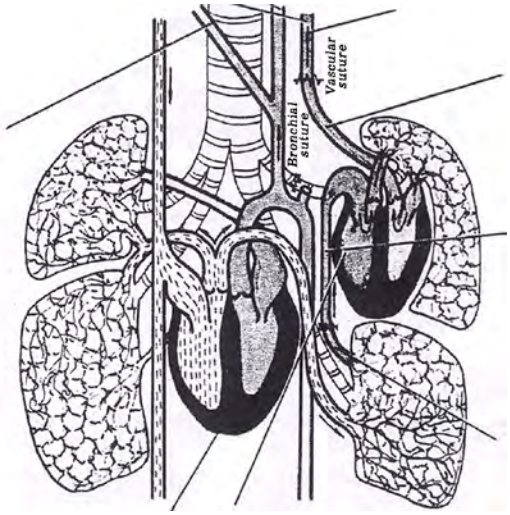

Fig. 13. The scheme of the transplantation of a supplemental heart with a lung lobe into the dog's chest according to V.P. Demikhov. Moscow, N.V. Sklifosovsky Institute for Emergency Medicine, June 20, 1962. [Scientific archives of A.N. Bakulev National Medical Research Center of Cardiovascular Surgery]

Fig. 14. V.P. Demikhov and dog Grishka after surgery. Photo E. Tikhonov. Summer, 1962.

Here, as the Soviet press wrote about it:

"It was a sensation. <...> When the stream of journalists subsided, and newspapers everywhere spread the news of the "two-heart" Grishka dog, the

Organ and Tissue Transplantation Laboratory of the Moscow Sklifosovsky Research Institute for Emergency Medicine was visited by the director of another institute. He spent a long time examining Grishka, silently listened to the explanations of Demikhov, the Head of the Laboratory, and then quietly asked:

- Do you understand what you have done?

Demikhov was taken aback.

- It's an atomic bomb under immunology!

Demikhov only shrugged his shoulders: "So, what can I do?" Of course, immunologists should study how the body protects itself against the invasion of alien tissue. But what if Grishka's body does not want to defend itself from another's heart?

When, at a lecture in the Polytechnic Museum, a stethoscope was brought to the left side of the dog's chest, the clear beats of heart were heard from the loudspeaker connected to an amplifier.

“Knock-knock, knock-knock ...”, Grishka's own heart was beating, fast and not very regular.

“Knock, knock, knock ...”, the second heart measured out clear beats. They were confident, full of spring. Silence was bursted out with applause.

And at that moment, quite different sounds occurred to my mind. Those very ones that five years ago had shaken the whole world: “Beep-beep ... Beep-beep ... Beep-beep ...”

I listened to the heartbeats, and the signals of the first Soviet satellite were ringing in my ears. The coincidence was too astounding! After all, the second heart is also a satellite. And if in 1957 the first satellite opened a new era, the era of space flight, then why Dr. V.P. Demikhov's experiment on the successful engraftment of another's heart could not have been the beginning of a new era in biology and surgery". [15, p. 32–34].

The director of which institute came to V.P. Demikhov? Who was he? What a real thing did he do to solve the problem of organ transplantation,

apart from comparing Grishka with the atomic bomb? While, unfortunately, we do not know[3]. But it seemed to us that it was deeply symbolic that both Soviet inventions in cardiovascular surgery, the Gudov's vessel-suturing circular apparatus" (VCA), and V.P. Demikhov's technique of extra heart transplantation, were compared with the flight of the first Soviet satellites into space at that time. So, it turns out, that besides modern poets and writers of the sixties, the Polytechnic Museum was also a forum for masters of a scalpel who made their presentations there in 1960s and broke no less applause than masters of a word!

What were the cause of such long Grishka' survival and of his sudden death? Here, (from V.P. Demikhov's words) how a reporter wrote about that:

> "It is still early to draw final conclusions. The success in the experiment with Grishka who survived for 141 days, of course, was contributed to by the improved scheme of the operation, excellently refined surgical techniques and the principle: as little "massacre" and injury, as possible. And, of course, reliable sterility, antibiotics, and good care after surgery. Vessels should not be crushed or twisted, says the surgeon. Blood to Grishka's heart ran through both lungs (the donor's and recipient's ones - SG). They produced heparin, which impeded coagulation. That is why the risk of insidious blood clots was reduced. But Grishka still died of a blood clot. It originated in the right atrium of the transplanted heart. But was the incompatibility the fault? After all, a similar thrombus could have happen from various causes...
>
> Perhaps crossed circulation is a prerequisite for any organ or tissue transplantation? " [9, p. 32].

[3] This could be either S.A. Kolesnikov, or the Director of A.V. Vishnevsky Institute of Surgery of the USSR Academy of Medical Sciences. But, most likely, it is a legend.

Comparing the achievements in the field of transplantation and transplant immunity between the USA and the USSR (1962)

Here the reader has the right to be indignant: how, it was the end of 1962, the Americans were already using immunosuppressants with might and main, and the correspondent still repeating after V.P. Demikhov his "tale" about crossed circulation? But let's not rush to conclusions. In Vol. 99 of the "Annals of the New York Academy of Sciences" *for 1962,* an article by J.V. Schwind entitled "Homotransplantation of extremities by parabiosis" was published [16]. In that, the author, one of the organ homotransplantation pioneers[4], having referred to, among others, *V.P. Demikhov's research* on the use of parabiosis in homotransplantation, presented the results of homoplastic limb transplants in rats onto their backs after preliminary having joined the donor and recipient torsos and the creation of a single ("crossed") blood circulation in two bodies.

According to the author, one and even two limbs from *different* rats successfully survived, and the five-legged and six-legged rats, like the two-headed dogs of V.P. Demikhov, not only surprised the American inhabitants, but were also demonstrated to delegates of scientific conferences, specifically to the delegates to the 5th Conference on Tissue Homotransplantation held in New York, in February 1962. The Conference materials were published in the 99th volume of the Annals of the New York Academy of Sciences in October 1962, reflecting modern views on the issues of organ and tissue transplantation. Here are the titles of some of them:

[4] For the first time, J.V. Schwind reported on successful homotransplantation in rats in 1936.

- "The role of thymus in transplant immunity",
- "Optical and electron microscopy of immunocompetent cells during the graft versus host reaction",
- "The ability of small bone marrow lymphocytes of irradiated rabbits to produce the immune response",
- "Chemical evaluation of transplantation antigens",
- "Immunological reactions to skin homotransplants in rabbits and rats",
- "Homotransplantation antibodies in lymphoid tissue",
- "The destruction of tolerant skin heterografts by serum antibodies and their role in the rejection reaction",
- "The effect of drug therapy on the survival timing of homoplastic transplanted kidneys in dogs"
- "The effect of 6-mercaptopurin on the immunological reactivity of dogs in kidney homotransplantation",
- "A combination of using drugs and radiation exposure as a way to induce tolerance in kidney homotransplantation",
- "Successful kidney homotransplantation in dogs",
- "Kidney homotransplantation in humans"
- "Functioning lung homografts in dogs", etc. etc.

Unfortunately, only *two presentations* from the USSR were made at the conference. The authors of the first entitled "Experimental transplantation of skin preserved by freezing to -196^{o}C in liquid nitrogen" were A.G. Lapchinsky, N.S. Lebedeva, and A.G.Einhorn, and the author of the other one, entitled "Heart Transplantation", was V.P. Demikhov with the results of his latest experiments and the concept of parabiosis, but using cadaver blood[5]. It is clear why. After all, he worked at the Sklifosovsky Research Institute for Emergency Medicine!

[5] The abstract of V.P. Demikhov's report was published in volume 29 of the Transplantation Bulletin of 1962. Probably, A.G. Lapchinsky attended that Conference because his entire presentation was published in

Therefore, it is not surprising that at such an advanced scientific conference, the reports by J.V. Schwind and V.P. Demikhov were presented. Moreover, there were only few reports on parabiosis[6]. But they, by the way, did not create the climate and, as time showed, had been, unfortunately, already yesterday's afternoon of immunology then.

And here is the result of another, purely superficial analysis of the Conference results: of 53 reports from 152 authors, 38 (72%) were devoted to immunological, and only 15 (28%) to the surgical aspects of organ and tissue transplantation. And meanwhile, 104 people took part in the preparation of the former reports, and 48 did in the latter. The wind of world transplantology already blew with might and main in the direction of a close investigation of transplantation immunity and the implementation of the results into practice. But in the Soviet Union other winds were blowing.

In order to present the achievements of Soviet doctors in that "race of transplantologists", we shall compare the American Conference Program and the "Materials on the study of the transplantation problem", which were issued by the Leading Organ and Tissue Transplantation Laboratory of the USSR Academy of Medical Sciences and the Department of Operative Surgery and Topographic Anatomy of the 1st MOLMI. We should remind that the Laboratory that used to be headed by V.P. Demikhov, and also the Department, were headed by his former Chief, Dr. V.V. Kovanov, a Corresponding Member of the USSR Academy of Medical Sciences. Since those materials were sent to printer's on November 29 and signed for publication on December 4, they apparently were issued at the very end of

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the Conference materials, and V.P. Demikhov was not allowed to go to the United States, and the Conference organizers published only the abstracts of his report.

[6] For example, the reports entitled “White Graft Reaction and Parabiosis” and “Induced Tolerance After Parabiosis”, etc. were presented at the Conference.

1962 and reflected the state of transplantology in the USSR at that time period.

V.V. Kovanov and I.D. Kirpatovsky[7] in the abstract of their report "Surgical aspects of the current state of the organ and tissue transplantation problem" mentioned V.P. Demikhov's research on head and heart transplantation; A.G. Lapchinsky and other authors mentioned in their reports V.P. Demikhov's research on the limb replantation, T.T. Daurova (from A.V. Vishnevsky Institute of Surgery), Ya.P. Kulik (from the Blagoveshchensk Medical Institute) and others referred in their works to V.P. Demikhov's ideas on creating synthetic prosthetic organs[8]. Among the achievements in latest years, there were mentioned nerve prosthetics (B.V. Ognev, V.F. Gudov), organ transplantation on vascular pedicles using native-manufactured vascular stapling devices (V.G. Teryaev[9], V.V. Zemlyannikov), the use of vascular prostheses in transplantation (A.Z. Troshin) and organ cooled preservation with simultaneous perfusion of their vascular bed (A.G. Lapchinsky).

It was specifically stated that the practical solution of the transplantation problem depended not only on the improvement of surgical techniques, but also on the knowledge of the biological mechanisms of the interaction between the graft and the recipient's body; and that the transplanted organ rejection was caused by the recipient immunological

[7] Kirpatovsky I.D. (1927–2014), a Soviet and Russian transplant surgeon, the Corresponding Member of the Russian Academy of Sciences; Head of the Department of Operative Surgery and Topographic Anatomy of RUDN University, contributed to experimental surgery and transplantation of endocrine organs.

[8] Professor T.T. Daurova studied the use of polymers in plastic surgery, in particular, for uterine reconstruction; and Professor Ya.P. Kulik created ventricle assist devices of the heart.

[9] In the early 1990s, Professor V.G. Teryaev headed the Sklifosovsky Research Institute for Emergency Medicine, established and worked as the Chief of the Department of Emergency and Urgent Medical Care with the Critical Care Course in Moscow State Doctor's Training Institute of Dentistry named after O.N. Semashko (now A.I. Evdokimov Moscow State University of Medicine and Dentistry); he was one of the founders and organizers of Disaster Medicine specialty and of the relevant service in the USSR and Russia.

response to genetically alien tissue. Worthwhile to note a rather small circle of the Soviet transplantologists who were named in the report and their little-known names (except for V.P. Demikhov, A.G. Lapchinsky and B.V. Ognev) at that time.

As for the ways to solve the problem, they were defined absolutely correctly: 1) the improvement of the surgical technique, and 2) the solution of the biological incompatibility problem. Therefore, the reports were devoted either to purely surgical problems or to immunology issues, the same as in the USA Conference.

The 1st topic was represented with the reports on nerve prosthetics with a metal guide, on the repair of esophageal defects with biological and synthetic materials, the mechanical stapling of vessels in transplantation of limbs, kidneys, and arteries, angioplasty, vascular suture technique, limb replantation, the technique for transplantation of the endocrine gland on a vascular pedicle, as well as physiological methods of assessing the blood flow as an indicator of organ metabolism, improving general hypothermia and perfusion systems, the morphological assessment of esophagoplasty and angioplasy results, biochemical studies of a reperfusion phenomenon.

And the 2nd... This may seem strange, but only 2 of 21 collected materials (10%) were devoted to transplant immunology. They were V.I. Govallo's reports on the methods for detecting serum antibodies and on the state of acquired *humoral immunity* in homoplastic skin grafting and thyroid gland transplantation. And all? And that's it! You must agree, dear reader, that the comparison is clearly not in our favour: there were 53 presentations in the USA and 21 reports in the USSR, 152 transplantologists in the USA

and 20-30 people in the USSR[10], 104 transplant immunologists in the USA and the only one V.I. Govallo with us[11].

For a more visual comparison, let us contrast the headlines of the Conference symposia in the USA and the sections of the "Materials" of the USSR, making the following table:

Table 1. Topics of experimental transplantation research conducted in the USSR and in the USA

Symposia of the V Conference on Tissue Transplantation (New York, February, 1962)	**Sections of "Materials on the study of the transplantation problem" (Moscow, December, 1962)**
1. The role of the lymphoid system in homotransplantation reactions. 2. Isoantigens and isoantibodies in tissue transplant reactions. 3. Cellular and serum antibodies in tissue transplantation. 4. Experimental induction of the rejection reaction in tissue transplantation. 5. Organ transplantation: techniques and experimental approaches.	1. General issues of organ and tissue transplantation. 2. Organ transplantation and vascular suture. 3. Transplantation of the endocrine glands on the arterial venous pedicle. 4. Rationalization and new offers.

We should also pay attention to the fact that when in the USSR they were still studying *humoral immunity* (namely, V.I. Govallo, V.P. Demikhov and others), then in the USA they had already been intensively investigating the *cellular one*. Thus, after having compared the state of American and Soviet transplantation (the trends, and achievements) in 1962, we can draw the following, and unfortunately, unfavorable conclusion. What V.P.

[10] We summed up the number of staff in the Laboratories headed by V.V. Kovanov in the 1st MOLMI, V.P. Demikhov in the Sklifosovsky Research Institute, and A.G. Lapchinsky in the Research Institute of Experimental Surgical Equipment and Instruments.

[11] Of course, much more scientists investigated immunological problems in the USSR at that time, specifically, biologists in the system of both the USSR Academy of Sciences and the USSR Academy of Medical Sciences, but only few ones studied transplant immunity.

Demikhov was doing in the late 1940s and throughout the 1950s was really the most progressive. Very few investigators in the world were studying the organ transplantation issues. But the discovery of acquired immunological tolerance put ahead a fundamental change in transplantation. And the Soviet transplantologists who were working behind the "Iron Curtain" immediately dropped behind. But V.P. Demikhov at least tried to catch up and to get through, if not to surgeons, then to those in power. Soviet surgeons failed to catch the outgoing immunological train that was rapidly gaining speed.

In the Sklifosovsky Institute for Emergency Medicine (1962)

We have already spoken about V.P. Demikhov's enormous plans when presented the Working Plan of his Laboratory for 1961-1962. Here we remind that the Report on his work for 1961 is missing in the Archives. But there is the Report for 1962 [17, p.101-102]. Compare these two documents, considering our comments (*in italics in brackets*). Moreover, the items of the Report almost completely correspond to the items of the Plan:

Table 2. Topics of Organ Transplantation Research Programme planned by V.P. Demikhov for 1961, and the Report on their implementation

Topic title	Scheduled for 1961	Implemented in 1962
1. Experimental heart, lung, and other organ transplantation. Coordinator and Implementator: V.P. Demikhov.	Objective: a) to develop experimentally on dogs and *human corpses* the heart and lung transplantation schemes that could be applicable to humans; b) to improve and develop anew the techniques of connecting blood vessels;	The experiments on heart and lung transplantation are going on. A new scheme has been developed. As a result, the life expectancy of a dog with two hearts and a partially replaced lung increased to 141 days. <...> Animals operated on up to this scheme show a good

	c) by preventing and eliminating complications leading to the death of experimental animals, to achieve their more prolonged survival that could be applicable to humans;	function and the adherence of the transplanted organs to the surrounding tissues, despite the different breeds of donors and recipients. In November 1962, the first experiment on heart and lung transplantation in monkeys was carried out <...> A scheme for transplanting the heart and lungs to humans (temporarily, extracorporeally, safely) has been developed. Experiments on dogs and monkeys will be continued (the *plan was over-fulfilled; the transplanted organ survival period reached 141 days, experiments on monkeys were started - SG*).
2. Immunological reactions in organ transplantation. Coordinator: M.M. Kapichnikov, Implementator: V.P. Demikhov.	Immunological studies shall be made in organ transplantation to search for antibodies in the blood of organ transplant recipients.	Immunological studies are continued in organ transplantation. In most cases, it was not possible to detect the antibodies (the *plan was fulfilled; the humoral immunity was studied - SG*).
3 Morphological studies at different times after organ transplantation. Coordinator: Prof. T.A. Grigorieva, Implementator: V.P. Demikhov.	Purpose: The search for alterations in the transplanted organs at different times after transplantation.	A study of the dog with a transplanted heart and lung, who survived for 141 days, was especially interesting (in scientific terms). In 1963, the morphological studies will be continued (the *plan was fulfilled - SG*).
4. Electrocardiographic investigation of transplanted hearts in the experiment and of revitalized hearts in the clinic. Coordinator:	Objective: to study the electrocardiogram of the transplanted hearts in the experiment and of the revitalized hearts in the clinic.	It has been proved that the transplanted (denervated) heart increases the rhythm with an increase in physical activity, and in a resting state comes to baseline within 10 minutes. This fact refutes the previously established

V.P. Demikhov, Implementator: V.M. Goryainov.		assertions in science that denervated organs cannot adapt to changes in external conditions (the *plan has been fulfilled; the proves have been presented refuting the earlier existing views on the need to germinate nerve endings into a transplanted organ in order to restore its function - SG*).
5. A long-term maintenance of life in a revitalized human body (with irreversible brain abnormalities) Coordinator: V.P. Demikhov, Implementators: V.P. Doroshchuk, V.P. Demikhov, and V.M. Goryainov	The revival of the corpses delivered by ambulances... After confirming the brain revival impossible, the question of organ transplantation from such a body to especially needy patients may be raised The life of the revived body will be maintained in a special unit, with a special round-the-clock care provided by the scientific and practical personnel, following the aseptic technique. These experiments can be started only after the validity issue of using a corpse has been resolved with the forensic authorities.	*Not a single corpse was revived, as no corpses were delivered to the laboratory for this purpose - S.G.* *Not a single question about organ transplantation has been raised - S.G.* *Maintenance of life was not undertaken due to no revived corpses, units, personnel, or care - S.G.* *It is possible that the above-mentioned details of the Plan were not fulfilled due to an unresolved issue with forensic doctors - S.G.*
6 The study of various mechanical ventilation modes in experiments on animals and while maintaining the life of revitalized organs and tissues (except for CNS) in the whole human body. Coordinator: V.P. Demikhov,	Objective: To achieve a long-term maintenance of life in a revitalized heart-beating [human] body without the brain.	35 experiments on dogs were performed; the effect of various mechanical ventilation (MV) modes on the occurrence of atelectases was studied. The effect of various MV modes on the function of the respiratory center in various patients (*this item of the plan was not fulfilled due to the non-*

Implementator: V.P. Doroshchuk.		*fulfillment of item 5 - SG*).
7 Bone marrow (of the sternum) transplantation in the experiment. Coordinator: Prof. A.V. Lebedinsky, Implementators: V.P. Demikhov and Yu.M. Zaretsky. .	Transplantation of the whole bone marrow (of the sternum) on a vascular pedicle in order to 1) ensure a positive effect in blood diseases caused by radioactive irradiation; 2) restructuring of body hematopoiesis.	The work was performed in cooperation with the Biophysics Institute of the USSR Academy of Medical Sciences, but due to the change of he Institute management, the research was temporarily suspended. The results were reported at the 1st All-Union Conference; the research will be continued in 1963 (the *plan was fulfilled - SG*).
8. Limb transplantation in the experiment. Coordinators and Implementators: V.P. Demikhov and P.I. Androsov.	Objective: the justification of making such operations in clinic.	*The data on these operations are unavailable in the report for 1962. The plan was not fulfilled for an unknown reason - S.G.*
9. To study the possibility of applying a coronary mammary anastomosis for the treatment of coronary circulation insufficiency in clinic. Coordinators and Imlementators: V.P. Demikhov and P.I. Androsov.	Objective: to improve the technique in experiments on human corpses, including those with the use of vascular stapling devices.	The authors improved the technique in experiments on corpses (the *plan was fulfilled - SG*).

What do we see? First, for those two years V.P. Demikhov worked very intensively and had implemented all the items of the plan *depended on him* and even overfulfilled some of them, such as, for example, heart transplantation in monkeys, the development of a scheme for temporary heart and lung implantation in a human corpse, as well as an

electrocardiographic study of the transplanted heart function. Moreover, studying that item, he empirically disproved the views he had 10 years ago.

Only those items appeared unfulfilled that were not dependent personally on V.P. Demikhov's efforts. For those two years, not a single corpse was delivered to V.P. Demikhov Laboratory for revival purposes. As a result, not a single “body” was revived, and the question of organ harvesting, not to mention their transplantation, was never raised to the Institute Management, probably because of the failure to agree the issue upon with forensic physicians. But most likely, there were simply no appropriate conditions for fulfilling this item.

Not a single limb was transplanted for 2 years, neither in experiment, nor, especially, in clinic. But in the interview given in October 1959, V.P. Demikhov mentioned its intention to transplant a limb to a limb-amputated woman. The cause why it did not happen remained unclear. And although, in general, a lot had been done in all topics, not a single printed work or report had been done outside the walls of the institute by V.P. Demikhov for 2 years, and not a single manuscript had been submitted for publication. Perhaps, it so happened because he did not move forward towards the clinic in his research.

While reading the reporting sheets of the Organ Transplantation Laboratory, the question of its staff inevitably arose. According to the documents [18, p. 43], the staff included 12 employees. But the names of other employees, except V.P. Demikhov and V.M. Goryainov, were not mentioned in any paragraph of the plan; and V.V. Doroshchuk no longer appeared in the Laboratory’s reporting documents after defending his thesis in the physiology of mechanical ventilation in 1962.

For comparison: in 1961-1962, there were 11 employees working in the Experimental Laboratory of the Sklifosovsky Institute, 14 employees in the Blood Transfusion Laboratory, and 7 employees in the Pathophysiological Laboratory.

Thus, the obstacles on V.P. Demikhov's way to his dream - to perform any organ transplantation in clinic - did not disappear, they were multiplying. Nevertheless, despite the enormous organizational difficulties, he was persistent in his efforts to improve his techniques, step by step developing new ones, moving from experiments on dogs where he reached the top, to the experiments on monkeys and human cadavers.

However, after discoveries in the field of transplant immunity, the train of world experimental transplantation picked up speed very fast. At the beginning of the article we called it the scientific revolution in transplantology. And although V.P. Demikhov had long been driving in one of its carriages, the Soviet surgeons were still to jump on its footboard. What carriage? Time will tell...

(To be continued.)

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