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PHENOMENON OF DEMIKHOV.

At the Sklifosovsky Institute (1960-1986).

Demijov V.P. Transplante experimental de órganos vitales.

Madrid: Editorial Atlante, 1967[1]

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Abstract

For the first time, the article introduces into scientific circulation and analyzes the Preface by V.P. Demikhov to his book "Transplantation of vital organs in experiment", published in 1967 in Spanish under the title "Transplante experimental de órganos vitales". Judging by the facts mentioned in the text, V.P. Demikhov wrote it in 1966, reflecting his views

on the current state and prospects of homoplastic tissue and organ transplantation. As in previous publications, in particular, in the Preface to the German edition of the book published in Berlin in 1963, V.P. Demikhov substantiated the concept that the main condition for a successful transplantation of homoplastic organs was to restore the blood circulation in them. In his opinion, the success of engraftment depends, first of all, on the ideally performed vascular suture and the immediate inclusion of the transplanted donor organ into the blood circulation of the host body, as well as on the sterility of the undertaken intervention. Having discussed the use of pharmacological immunosuppression as a method of overcoming the biological incompatibility of homologous organs during their transplantation, V.P. Demikhov pointed out the toxicity of the drugs used for this purpose he tested experimentally, as well as his experiments, indicating the possibility of overcoming incompatibility by means of other methods (the selection of the donor and recipient with regard to the blood group, mixing the blood of the donor and recipient by parabiosis, etc.). In this text V.P. Demikhov again mentioned the scheme he had developed for two-stage transplantation of an additional heart as a reserve organ to maintain the function of the patient's decompensated heart and named the main stages of the operation: implantation on the femoral vessels (stage 1) and transplantation into the chest (stage 2). As in the Preface to the German edition of the book, V.P. Demikhov spoke in detail about the model of a "living physiological system" he had developed in 1963 aimed at creating a bank of reanimated organs that would retain their viability until transplanted into another body. Projects for growing the organs in anencephalic newborns for the rejuvenation of the elderly were also outlined.

Keywords: history of medicine, transplantation, V.P. Demikhov, V.P. Demijov, Transplante experimental de órganos vitales, 1967

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Introduction

After V.P. Demikhov's book "Experimental Transplantation of Vital Organs" had been published in Russian in Moscow [1], in 1962 it was translated into English and published in New York [2]; and in 1963, it was published in German in Berlin [3]. In October 1967, the book started being published in Spanish under the title "Transplante experimental de órganos vitales" in Madrid (Fig. 1, 2) [4,~~5~~].

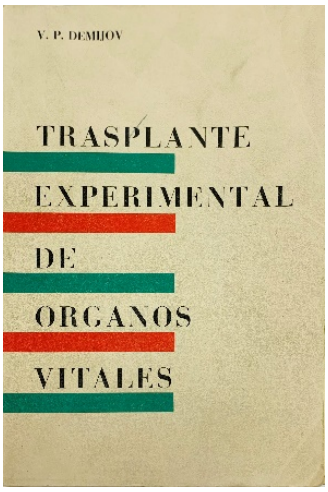

Fig. 1. The cover of the book by V.P. Demikhov "Transplante experimental de órganos vitales" (Madrid, 1967) [Museum of A.N. Bakulev National Medical Research Center of Cardiovascular Surgery]


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Fig. 2. Fragment of the ABC daily newspaper of October 19, 1967. (Madrid, Thursday, morning edition) [copy from A. Werner's archives]

In this regard, we would like to emphasize three facts:

1) Since that time, the book by V.P. Demikhov became the only surgical monograph known to us published in four leading European languages: Russian, English, German and Spanish;

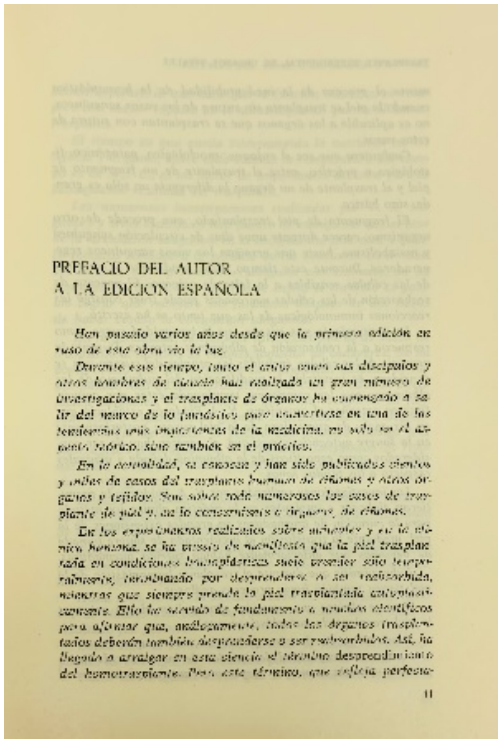
2) Currently, Spanish ranks second among the languages in the world by the number of native speaker (it is spoken by 460 million people); English is the third most widely spoken language in the world (379 million people), but the first among the UNO official languages (followed by French, Russian, Chinese, Arabic, and Spanish); Russian ranks 8th in the world by the number of native speakers (154 million), German ranks 17th [5];

3) Nevertheless, English prevails in modern scientific literature: 64% of publications are issued in English, which in a sense becomes a barrier to the dissemination of scientific knowledge, especially among the Hispanic community [6].

The latter fact is proved by bibliometric studies: despite the presence of publications which authors cited V.P.Demikhov's book in

Spanish, their cited references, as a rule, included the title of the book and the transcription of the author's surname in English and, thus, they fell into the English-speaking rather than Spanish-speaking citation statistics. Therefore, it was not possible for us to draw a conclusion about the citation of the Spanish-language translation of the book [7].

Let's note one more detail: the translation of V.P. Demikhov's book *into Spanish* was made from its *English edition*. Dr. Fernando Cardenal became the translator of the English text. Recall, however, that the English version of the book published two years after the Russian original did not have a Preface by the author. The book was preceded only by a short text "From the Publishers'". The first author's Preface, written by V.P. Demikhov, was published in 1963 in the German translation of the book; we discussed it earlier [8]. The translation of the author's Preface from Russian into Spanish was made by A. Fierro, the famous translator of Soviet scientific and journalistic literature. Unfortunately, we do not have its Russian original. Y.G. Shatunova translated from Spanish into Russian. The paragraph indentations in the text (paragraphs) are based on the Spanish original, which, as in the book, is given in italics (Fig. 3). We only added short headings to structure of the text and the necessary comments.



PREFACIO DEL AUTOR
A LA EDICION ESPAÑOLA

Han pasado varios años desde que la primera edición en ruso de esta obra vio la luz.

Durante este tiempo, tanto el autor como sus discípulos y otros hombres de ciencia han realizado un gran número de investigaciones y el trasplante de órganos ha comenzado a salir del marco de lo fantástico para incorporarse en una de las tendencias más importantes de la medicina, no sólo en el aspecto teórico, sino también en el práctico.

En la actualidad, se conocen y han sido publicados cientos y miles de casos del trasplante humano de riñones y otros órganos y tejidos. Son sobre todo numerosos los casos de trasplante de piel y, en lo concerniente a órganos, de riñones.

En los experimentos realizados sobre animales y en la clínica humana, se ha visto de manifiesto que la piel trasplantada en condiciones inmunológicas suele tender sólo temporalmente, terminando por desprenderse o ser reabsorbida, mientras que siempre prende la piel trasplantada autógenamente. Ello ha servido de fundamento a muchos científicos para afirmar que, análogamente, todos los órganos trasplantados deberán también desprenderse o ser reabsorbidos. Así, ha llegado a arraigar en esta ciencia el término desprendimiento del homotrasplante. Pero este término, que refleja perfecta-

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Fig. 3. The first page of the Preface to the book by V.P. Demikhov "Transplante experimental de órganos vitales" (Madrid, 1967) [Museum of A.N. Bakulev National Medical Research Center of Cardiovascular Surgery]

Four years had passed then from the moment of the book's publication in Germany (Preface to the German Edition) to its translation into Spanish, so we considered it important to introduce the reader to the concepts and contemplations of V. P. Demikhov, which he had developed by 1966, when, in our opinion, he wrote the Preface to the Spanish-language Edition of his book (Fig. 4).

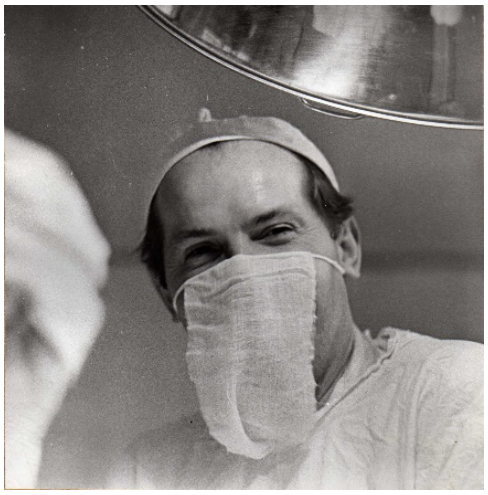

Fig. 4. V. P. Demikhov. 1960s. [Museum of A.N. Bakulev National Medical Research Center of Cardiovascular Surgery]

Over the years, there were developments in the field of transplantation that had changed the views of surgeons and immunologists on the problem of homologous organ transplantation and the ability to control organ adherence. In particular, the role of blood lymphocytes in the process of alien tissue rejection by the body was studied. It was shown that the nucleated cells of homologous organs contain proteins that play the role of antigens binding to the recipient's blood lymphocytes. These cells infiltrate the tissues at the junction of the homoorgan and the recipient's body, resulting in the graft rejection. In addition, the importance of early contact of animal and human embryos with protein antigens for their recognition on the principle of "native – alien" was proved. It was for these studies that in 1960 P. B. Medawar (1915-1987), the Englishman from London, and F. M. Burnet (1899-1985), the Australian from Melbourne, were awarded the Nobel Prize [9]. After the discovery of the immunological tolerance phenomenon, a new theory of transplantation immunity appeared, according to which the ability to recognize one's native and other people's proteins is not inherited by the body, but develops

during the fetus intrauterine life.

Thanks to the new paradigm, pharmacological drugs (hormones, 6-mercaptopurine, anti-lymphocytic serum, etc.) that block the immune response were used in organ transplants, which result was a significant progress achieved, in particular, in the field of transplanting the kidneys explanted not only from related donors, but also from cadavers. In 1965, the first successful related kidney transplantation in the USSR was performed by B. V. Petrovsky.

The analysis of the translated text showed that V. P. Demikhov was familiar with all these achievements, but agreed only with some. First, because the new theory of immunity had not yet become generally accepted by 1966, at least in the USSR [10], and second, the results of his own observations did not fit into its framework.

Demijov V.P.
Transplante experimental de órganos vitales.
Madrid: Editorial Atlante, 1967

AUTHOR'S PREFACE TO THE SPANISH EDITION

"Several years have passed since the publication of the first edition of this work in Russian (1960 – *Author*'s note).

During this time, the author, his students and other scientists have made a lot of research, and organ transplantation began to go beyond fiction to become one of the most important areas in medicine, not only in the theoretical aspect, but also in the practical one.

Currently, hundreds and thousands of cases of kidney and other organs and tissues transplanted to humans are known and published. There are especially many cases of skin transplants, and as in relation to organs, of kidneys."

On skin transplantation

*"In experiments conducted on animals and humans, it has been shown that the skin transplanted under homoplastic conditions tends to take root temporarily, eventually getting detached or reabsorbing, while the autoplastically transplanted skin always takes root. This has allowed many scientists to argue that homoplastically transplanted organs should also get detached (*when referring to "detachment" of organs hereinafter in the text, we will use the term "rejection" – *Author*'s *note*) *or be reabsorbed. Thus, the term "homotransplant detachment"* (Spanish: desprendimiento del homotransplante. – *Author's note*) *appeared in transplantation. But this term, which reflects [4, p.11]*[2] *the process of homoplastic detachment of the skin transplanted without connecting the blood vessels, is not applicable to organs transplanted on vascular anastomoses.*

Regardless of the approach: morphological, pathological, physiological or clinical, the difference between the skin fragment transplantation and organ transplantation is not only great, but also fundamental.

The transplanted skin fragment, which has been taken from another body, has no blood circulation, so there is no metabolism in it for several days until the blood vessels regenerate. During this time there occurs necrosis of the oxygen-sensitive cells. The process of their reabsorption entails immunological reactions, which have much been written about.

Immunology teaches us that immunity occurs as a response to the reabsorption of alien albumins. In necrotic cells transplanted from another body, there is a change in the chemical composition of albumin, which they consist of and which will inevitably become aliens to the host. N.A. Fedorov[3] *found that in skin burns, it is possible to detect the autoantibodies*

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2 The first figure in square brackets means the ordinal number of the source, the second one stands for the page in it.

3 Fedorov N.A. (1904-1983), a Soviet pathophysiologist, Full Member of the USSR Academy of Medical Sciences (1963), Academician-Secretary of the OMBN of the USSR Academy of Medical Sciences; he worked as an Editor-in-Chief of the Journal "Pathological Physiology and Experimental Therapy".

in the blood of the victim, which are specific for albumin of the damaged skin and neutral with respect to healthy tissues.

The studies conducted by N. A. Fedorov allowed him to develop and implement into clinical practice a method for treating burned people with extensive burns by transfusing blood taken from people who had previously suffered burns.

It is generally accepted that similar processes occur in homoplastic skin grafting.

But the question arises, why then autoplastically transplanted skin adapts and takes root."

On the importance of restoring blood circulation in transplanted tissues (skin, blood) and organs (kidneys)

"From a physiological point of view, it can be assumed that the response of burn wound tissues during autotransplantation is less prominent compared to that in homotransplantation [4, p.12], which leads to a faster restoration of blood circulation in the transplanted skin during its autotransplantation than during homotransplantation.

The time during which the blood supply to tissues and organs is interrupted, especially at a body temperature of +37.5°C, is a crucial factor for the subsequent viability of the graft.

Numerous studies by V.A. Negovsky[4] *and other scientists have shown that halting blood circulation in the brain for 10-15 minutes leads to loss of its function. On the other hand, in experiments conducted on animals, it was shown that if the brain was pre-cooled, it could be forced to restore its functions even two hours after the blood circulation had stopped.*

Currently, there are several hundreds known cases of kidney transplantation to a sick person, the kidney being taken from corpses. It has been shown that if the kidneys are transplanted after more than 2 hours

4 Negovsky V.A. (1909-2003), a Soviet pathophysiologist; twice laureate of the USSR State Prize, full member of the USSR Academy of Medical Sciences (1975); the founder of Reanimatology (Critical Care Medicine) as a medical specialty and scientific discipline, created and headed the world's first Institute of General Reanimatology (now the V.A. Negovsky Research Institute of General Reanimatology of the Federal Research Center of Reanimatology and Rehabilitation).

from the moment of halting blood circulation in them, they either do not restore their function or undergo degenerative changes. To reduce the risk of these changes, after explantation the kidneys are cooled by immersion in cooling solutions.

Evaluation of the time factor seems to have played an important role in the success achieved in cadaveric kidney transplantation.

A statistical digest published in the New York Journal of Transplantation in 1965 provides some very interesting data.

Until 1963, 45 human kidney transplants were performed from cadavers, and only in one case the result was positive.

From 1963 to March 15, 1965, 82 transplants of this type were performed, and in 43 cases a positive result was achieved.

All surgeons know that if a tourniquet is applied to a damaged limb for more than two hours [4, p. 13], then such a limb usually has to be amputated.

On the other hand, an autoplastically transplanted skin fragment will remain without blood supply until new vessels are formed, and this period lasts for more than 2 hours, but 30-40 times longer. This period seems to be even longer when we are dealing with skin homografting.

From a physiological point of view, this difference can be explained by the following reasons:

1. Different tissues and organs (brain, liver, muscles, blood, skin, cartilage, cornea, etc.) show different sensitivity to temporary circulatory arrest;

2. The upper layer of the skin is less sensitive to the cessation of blood circulation and retains its vital function for a long period of time due to the diffusion of intercellular fluid. On the other hand, the cartilage and cornea do not need blood circulation, since their vital function is ensured by lymph.

3. The transplantation technique used is of great importance. It has long been known that when transplanting organs and large fragments of tissue, their assimilation or adaptation does not occur even in case of autotransplantation. As early as in the XIX century, a Russian oncologist

Novinsky[5] *could check, and in our century, his disciples confirmed that if the tumor divided into relatively large fragments is transplanted, it will not take root, but if it is divided into small particles that can pass through the injection needle, the transplanted cells will maintain their vitality and develop in the host body. Tiny pieces of autoplastic muscle don't take root either. However, if this fragment is disintegrated further, the growth of muscle cells and regeneration of muscle tissue becomes possible even with homotransplantation (experiments by A. N. Studitsky and his students) [4, p. 14].*

When trying to transplant a full-thickness skin fragment to a human, concerns arise even when using autografting. Therefore, only a thin surface layer of the epidermis (split skin flap – *Author's note*) *is used for transplantation, as it is less sensitive to impaired blood circulation, and in which the surrounding interstitial fluid can penetrate through the lymphatic circulation.*

Histological studies have shown that in homoplastic skin grafting, often not the entire graft is peeled off, but only the outer part of it, while the inner part retains its elements.

4. In humans and various animals, the physiological and anatomical features are not identical. In small animals (mice, rats), the skin thickness is small compared to human skin, so the conditions of diffuse nutrition of the graft can be the same as for the thin upper layer of the human skin graft.

From a biological point of view, the difference between various animal types and humans is very large.

Different animals and humans react differently to blood transfusions, skin grafting, kidney transplants, etc.

In dogs, blood transfusion can be performed regardless of blood group match and without negative consequences. We transfused 500.0 milliliters of human blood to the dog. After 30 minutes, hematuria began

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5 Novinsky M.A. (1841–1914), a veterinarian, the founder of Russian experimental oncology; he was the first in the world to perform the transplantation of malignant neoplasms in an experiment on animals; in his Thesis on the topic "On the question of engrafting the malignant neoplasms" (1877), he gave an overview of attempts at tumor transplantation, described the methodology of his own experiments, their results and cited the data of histological studies of transplanted and engrafted tumors.

accompanied by frequent urination, but the dog survived, and by the second day it had completely recovered.

On the other hand, the transfusion of human blood from one individual to another without matching the blood group can lead to a fatal outcome. And vice versa: if blood is transfused taking into account the compatible blood groups [4, p. 15], then the new blood performs the same functions as the native blood.

In rats, homoplastically transplanted skin takes root much better than in rabbits.

In these cases (according to many authors), the homoplastically transplanted skin is rejected on the 7th, 14th, and 21st days, that is, on the days that characterize the immune crisis.

In humans, the homoplastic skin taking root sometimes lasts for several months.

Kidneys that are homoplastically transplanted to dogs perform their functions within two to three weeks and rarely up to 2 months. With the same graft type in humans, the kidneys continue performing their vital functions for many years.

All this tells us that the compatibility problems in tissues and organs when transplanting them to humans should be studied in humans. If blood transfusions had only been studied in animals, we would have never known how to use blood transfusions to save people.

The absence of danger in human tissue and organ transplantation, when all necessary precautions are taken and all technical and postoperative capabilities are available, has been demonstrated by hundreds and thousands of successful operations that have been performed with subsequent monitoring of positive results over many years."

Obviously, he was talking about "hundreds and thousands of successful operations" of autologous skin transplantation and blood transfusion, because by the time V.P. Demikhov wrote this text, apart from several dozens of kidney transplants (1933) and several attempts to transplant the lungs, liver and pancreas (1963-1966), no other organs had

been transplanted to a human. Interesting is V.P. Demikhov's remark about the immune response to necrotic skin proteins (the formation of burn antibodies). Such studies were conducted, in particular, in the Burn Unit of A.V. Vishnevsky Institute of Surgery, AMN of the USSR, which was opened in 1960 and received the status of the All-Union Burn Center in 1967.

On cornea and cartilage transplantation

"Transplantation of the cornea taken from a corpse according to the method developed by V.P. Filatov has restored vision to thousands of people. The cadaveric cornea does not detach or dissolve, unlike homoplastically transplanted skin, although in some cases it loses its transparency. Recently, this is usually considered as a consequence of the added infection during surgery and does not apply to immune reactions. It is also known that the cornea can lose its transparency [4, p.16] even in the absence of trauma or graft infection.

Also, the cartilage transplanted from a corpse to a living creature is taken root very well. The number of operations of this type has been counted in thousands.

Specialists in immunology explain this phenomenon by the complete absence of antigens or their small amounts present in the cornea, cartilage, and other easily adaptable tissues.

From a physiological point of view, homoplastic engraftment of the cornea and cartilage is explained by the fact that these tissues are ideally adapted to exist with a reduced metabolism due to lymphatic circulation, while blood circulation is not beneficial to them, but rather counterproductive, since it can lead to a loss of corneal transparency. That is why these tissues can be stored for a long time after they have been removed from the corpse before being placed in the recipient's body. Once in it, the lymphatic circulation of these grafts is restored many times faster than the blood circulation in the skin fragment."

On bone and joint transplantation

"The transplant of the bones and joints taken from a corpse to a human is successful. In the Soviet Union, several thousands of such operations were performed over the course of several years with controlled positive results.

In 1913, the world-famous German surgeon Lexer unsuccessfully tried to transplant a joint to a person. Failure was explained by tissue incompatibility. Other surgeons agreed with this explanation, which resulted in no bone and joint transplants performed during the last two world wars.

It is now known that for the successful transplantation of bones and joints taken from cadavers, the preservation procedures and the techniques to be used in the operation must be more advanced.

From a physiological point of view, the successful engraftment of such a voluminous organ [4, p. 17] as the knee joint and the hip semi-joint can be explained by the fact that bones and joints are not sensitive to circulation impairments and are able to maintain vital function due to lymph circulation."

Once again about the importance of blood circulation in organ transplantation

"When blood circulation is restored through anastomosed vessels during organ transplantation, there is no long break in the tissue metabolism, the tissues retain their viability, their autolysis does not occur and, as a result, they do not create conditions for the emergence of immune reactions with the aim of rejection.

Numerous experiments in organ transplantation, which we conducted for many years, have shown that the vital function of organs in the new body is preserved as long as the blood circulation goes on. As soon as it is interrupted, necrosis develops, followed by the detachment or resorption of the skin, or by usual degenerative pathological processes in other organs.

It is very difficult to determine both the time during which blood circulation remains interrupted, and the moment when it is restored, when the skin fragment has been transplanted using the usual method.

Through a thin layer of transplanted skin, the blood vessels of the recipient's open wound release heat to the surrounding area, as a result of which the transplanted skin is easily heated. Therefore, this criterion that can help to determine the vital function of a skin graft (the transplanted skin flap temperature measured by contact or at a distance. – *Author's note) cannot be used.*

There is no final criterion – histological analysis of the graft, as it either peels off in the form of a dry crust or in an amorphous state, or dissolves completely without a trace, leaving nothing for histological examination. Meanwhile, the processes of detachment and dissolution are detected by an observer only when several days have passed since the moment of circulatory arrest in the graft [4, p. 18]. Thus, on these days, the dead graft remains at its body temperature (from +37°C to +38°C) and in contact with the surrounding microbial flora.

Under these conditions, two to three days after death, the human corpse begins decaying, and even the skin that has not been transplanted is macerated; that is, it changes on its own, without the participation of humoral or agglutinogenic antibodies.

Under normal conditions, it is difficult to observe maceration or detachment of the upper layer of the corpse skin, since either relatives bury the corpse, or if the corpse is in the morgue, it is stored in a cold room.

During the war, on hot summer days, being as a military pathologist (in 1941-1945, V.P. Demikhov served in the army pathoanatomical laboratory. – *Author's note*), *I could observe these phenomena, unfortunately, quite often. In dead animals, maceration of the upper layer (with the exception of the mammary gland area in females) practically does not occur because of the hair covering the skin.*

Detachment of the upper layer of the skin is also often observed in living people, especially in open areas, due to prolonged exposure to sunlight. If this exposure is quick, then a sunburn occurs, which leads to

hyperemia of the skin and, after three to four days, to its exfoliation, that is, to the detachment of the upper layer without the participation of bacterial flora.

Skin detachment due to these three different phenomena (detachment of a free transplanted skin flap, detachment of macerated skin in a cadaver, and skin detachment after sunburn – *Author's note*) *is induced by the same cause: tissue necrosis due to the cessation of blood circulation.*

The graft detachment, maceration, or exfoliation occur only if the surface layers of the skin have been transplanted or the skin mid-layer captured. But when transplanting visceral organs, their detachment does not occur, although this term [4, p.19] is purely mechanically referred to, for example, the limbs during their homologous transplantation (wet or dry gangrene). The mechanical (non-functional) use of this term is explained by the fact that most specialists in the field of immunology often encounter cases of skin detachment during skin grafting, but they do not know what happens to visceral organs during their transplantation. They also do not have the opportunity to observe the histological structure of the skin homograft, as it either peels off, dissolves, or dries out.

In a monograph on skin transplantation published in 1966, S.S. Khundadze[6] *described the results of the histological examination of skin grafts that was performed using biopsy.*

The author concluded that "during the first 48 hours after homotransplantation, pyknosis is observed in the nuclei of the homograft epidermal cells and the depolymerization of the cytoplasmic nuclei of nucleoproteins is seen. Graft necrosis terminates five days after surgery; and after 15 or 20 days, the skin fragment completely detaches from the recipient's body tissues."

Thus, the detachment of homoplastically transplanted skin occurs many days and weeks after it death due to the lack of revascularization.

On the other hand, when skin and even limb transplantations are performed in small animals, such as rats, using temporary parabiosis

6 Khundadze S.Sh. On the issue of free skin grafting. - Tbilisi: Sabchota Sakartvelo, 1966.

(experiments by Justin Schvind[7], A. G. Lapchinsky[8], etc.), after 9 days the homograft adapts to new living conditions, and the adaptation remains until the animal's natural death. Under conditions of parabiosis, a good fusion of the skin of two animals is achieved. This circumstance was first noticed by the famous German surgeon Sauerbruch[9]. This was subsequently confirmed by many researchers. The author of these lines also achieved perfect skin fusion of two rats in parabiosis, without resorting to any specific therapy [4, p. 20].

Specialists in immunology are of the opinion that skin fusion in two organisms under conditions of parabiosis occurs as a result of adaptation of one organism to another as a result of the immunological paralysis phenomenon. From a physiological point of view, this can most likely be explained by the optimal conditions of blood circulation between the tissues joined together.

The author managed (in the experiment. – *Author's note*) *to develop a procedure for transplantation of the sternum and the skin covering it with almost instantaneous restoration of blood circulation by stitching the vessels feeding the transplanted fragment. In all cases where infection and/or thrombosis did not occur, the fusion of the homoplastically transplanted skin by primary intention was observed. When blood circulation was maintained in the graft, it did not detach or dissolve.*

The transplanted skin of the head or one of the limbs also perfectly took root by primary intention, if blood circulation in the transplanted fragment was restored immediately. In these cases, the death of the graft without detachment or resorption was caused by the blood circulation cessation."

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7 The correct spelling is Schwind, "American Demikhov"; from 1936 he studied the problem of homoplastic organ transplantation; in 1962 he published an article on homoplasty of the extremities under parabiosis [11].

8 Lapchinsky A.G. (1908-1982), a Soviet transplant surgeon; from 1960, he headed the Organ Transplant Laboratory at the Central Institute of Traumatology and Orthopedics named after N.N. Priorov; in 1970 he defended his Doctoral Thesis on the topic "Experimental limb autotransplantation and homotransplantation."

9 Perhaps V.P. Demikhov meant: Sauerbruch R, Heyde M. Ueber Parabiose kunstlich vereinigter Warmbliiter. *Munch Med Wochenschr.* 1908;55:153-156.

On the impact of circulatory disorders in a transplanted organ

"In skin or limb transplantation, the processes that follow the cessation of blood circulation are of the gangrene type, whereas in visceral organ transplantation, they occur by the type of degenerative changes that are observed in the general human pathology (necrobiosis).

Around the organ that begins to die, a local inflammatory reaction occurs in the form of edema and cell infiltration, followed by the formation of a fibrous capsule.

Blood circulation is usually interrupted as a result of thrombosis at the site of one of the arterial vascular sutures or the formation of dense fibrous cords [4, p.21], squeezing the veins through which blood returns from the graft.

Thrombosis in the area of vascular sutures occurs only in those areas where the intima is damaged, or it extends beyond the outer layer of blood vessels.

When the vascular suture is applied perfectly, and the damaged intima does not extend beyond the artery wall, its thrombosis does not occur.

It is known that an infected wound is granulating for a long time, with the formation of connective tissue.

Similar tissue also forms around the large blood vessels supplying blood to the graft. Blood pressure in the artery is usually high, so the amount of blood flowing to the graft is actually unchanged. But the blood pressure in the vein is low, so the blood outflow from the graft due to slow compression of the vein begins gradually decreasing. This leads to venous congestion, edema, and subsequent death of the transplanted organ.

Surgical removal of adhesions around a compressed graft vein leads to a rapid (within one to two hours) resolution of edema and restoration of vital function. This clearly demonstrates the fact that edema, which is often observed during auto- and homotransplantation of limbs, is of physiological, and not immunobiological origin."

And again, for the umpteenth time, V.P. Demikhov postulates two main (in his opinion) causes of transplantation failure: thrombosis of the

artery blood-supplying the graft and the compression of the vein by scars, disturbing the blood outflow from the graft. As for the immunological causes, in which, however, V.P. Demikhov did not believe, he would say below.

On antibodies in organ transplantation

"Often, in immunological studies, antibodies are not detected, or, if they exist, their titer is very small. In the remaining cases, the increase in antibody titer and the skin graft detachment do not coincide in time.

So far, despite the fact that many scientists from many countries have been conducting immunological studies related to skin transplantation for almost 50 years, an important issue has not been solved: whether the antibodies appearing in the blood are the cause of graft death or the consequence of its death [4, p. 22]. It is also unknown whether these antibodies affect the graft vital function."

On the role of lymphocytes in organ rejection

«P. Medawar, a Nobel Prize winner for his work on skin transplantation, wrote in the Discovery Journal (No. 3, 1965, London) that he, like many others, had the opinion that there were no antibodies circulating in the blood during transplantation; but this has not been confirmed (this V.P. Demikhov's phrase is not entirely clear: not confirmed by whom and when? – *Author's note*). *Currently, it is assumed that the lymphocyte-associated antibodies rather than free antibodies must have induced the graft destruction. "The lymphocytes excited by their contact with alien cells enter the lymphatic vessels and accumulate in the zonal nodes, where they divide, and then their progeny circulates around the body and destroys the graft.* Some of the recent experiments conducted by Govans seem to support this explanation, although, in fact, all this is nothing more than fiction" (P. Medawar. – Italics canceled by V.P. Demikhov).

This hypothesis might be true in the processes that occur during skin transplantation, but it is not confirmed in experiments on transplantation

of organs such as limbs, head, heart, etc. If lymphocytes had destroyed a homoplastically transplanted organ, they would have penetrated in its vessels and tissues, but in practice this was not observed."

In this passage, it is easy to understand V.P. Demikhov's principle of proof; he was used to trusting his eyes and relying on his own experience: if that was not in his experiments, then it could not be. But hence it is also clear that V.P. Demikhov was familiar with all the novelties of the world press devoted to organ transplantation and the study of immunity. And he was very critical towards these publications.

On transplanting the head of a donor dog to the blood vessels of a recipient dog

"It is easy to check if the blood circulation in the transplanted head is disturbed.

As thrombosis increases in the area of the artery suture, anemia of the sclera and tongue mucosa appears, and conditional and unconditional reflexes begin to fade.

With thrombosis in the area of the vein suture, and even more often with compression of the vena cava, cyanosis of the sclera and tongue appears, followed by edema, exophthalmos and disappearance of reflexes. But even if the reflexes are extinguished, and the venous edema from external compression of the veins is resolved, then cyanosis of the sclera and tongue [4, p. 23], as well as all reactions, are completely restored. Without any external stimuli (Fig. 5).

Fig. 5. Feeding the puppy's head transplanted onto the vessels of the neck of an adult dog [Bild der Wissenschaft. Januar, 1966. P. 31; from A.Werner's archives]

The author of these lines could not observe the rejection of the transplanted head, because when it dies, it is removed without waiting for the corpse to decay, and the dog that acts as the recipient is saved for another experiment. One of these large dogs, after it had recovered from the previous experiment, had three heads being transplanted one by one (on the vessels of the neck, liver and iliac vessels). In head transplantation, the most vulnerable area is the venous blood flow, but its characteristics differ from those which occur in the extremities. When head transplantation is performed onto the vessels of the neck, the jugular vein, through which the venous outflow passes, is easily squeezed at turning the neck. When the head is transplanted onto the blood vessels of the thorax, pleural complications (pleural effusion, pneumothorax) occur. If kidney vessels are used for head transplantation, the veins are compressed by the abdominal organs and postoperative adhesions, which are extremely compact in this cavity.

In the case of a dog with two heads named Pirate that lived for 29 days, the skin took root by primary intention, but the fibrin deposition (due to inflammation. – *Author's note.*) *transformed into fibrous tissue that disrupted the venous blood outflow from the head, which was manifested by progressive edema. The author tried to relieve the vein from adhesions,*

but they were so dense that the vessel mobilization was impossible. I had to remove the transplanted head, which retained conditioned reflexes during the surgery. The dog-recipient still remained alive.

Histological examination of the surgical skin suture area revealed healing by the primary intention type. The remaining tissues, with the exception of the edematous subcutaneous layer, retained their normal structure. ***No lymphocytic infiltration was detected*** (in bold by us. – *Author's note*). *The wall [4, p. 24] of the graft vena cava attached to the right jugular vein of the recipient dog was 4-5 times thicker due to fibrous deposits."*

On histological studies of the transplanted heart

"Histologists T. A. Grigorieva, I. A. Chervova[10] *and M. F. Vuistrova analyzed more than 20 transplanted hearts that functioned for 5 to 141 days. In all cases, the muscular structure of the heart was well preserved, and there was no endothelial and endocardial infiltration with blood cells.*

The nerve ganglia had the same appearance as in the experiments on modeling a heart failure without its (heart) transplantation, which were conducted by T. A. Grigorieva.

If lymphocyte-associated antibodies affect the graft, then the endocardium of the transplanted heart and the endothelium of coronary vessels shall be infiltrated with lymphocytes. But in practice, this is not observed (in bold by us. – *Author's note).*

Rejection of transplanted visceral organs, as described in the literature, has not been recorded in any of our numerous experiments (in bold by us. – *Author's note*). *The changes were similar to those in circulatory disorders of a particular organ as described in the human general pathology."*

The fact that by 1966 V.P. Demikhov knew about the role of blood lymphocytes in the rejection reaction is beyond doubt. But the whole

10 Chervova I.A. (1924–2016), a Soviet morphologist, Professor; in 1963-1990 she was the Head of the Histology Department at the 2nd Moscow State Medical University named after N.I. Pirogov (now the Morphology Department of the Russian State Medical University named after N.I. Pirogov).

point is that no lymphocytic infiltration in the transplanted organ was found by his co–developers, highly qualified histologists. And here we draw an important conclusion: it is absolutely unjust to accuse V. P. Demikhov of not knowing or not trusting immunology. Immunological reactions were not seen (or were not known as what they meant) not only by him (macroscopically), but also by his co-authors (microscopically).

On the pathoanatomical changes of the transplanted organ

"In some cases, impaired functions of the kidneys, lungs and the second heart connected in parallel were recorded. In several cases, the transplanted extra heart and kidney were not removed immediately after they ceased working, but allowed the recipient dog to live for one to two months. During the pathoanatomical examination, a very dense fibrous fusion of the transplanted kidney, pleura, and pericardium with the surrounding tissues of the host dog was found. It was not the rejection of a kidney or a second heart that was observed, but dense scars in which they were soldered and from which it was quite difficult to mobilize these organs.

After dissecting the scars, the author found necrobiotic degenerated organs of a dense consistency of yellowish-gray color, which, according to A.I. Abrikosov[11], were subjected to coagulation necrosis [2, p. 25].

This type of necrosis is characteristic of the general pathology of a human with heart attacks.

The retained vital function of membranes (renal capsule, pleura, and pericardium) can be explained by the fact that their metabolism was ensured owing to the surrounding lymph and vessels of the scars, which were not very sensitive to circulatory disorders.

11 Abrikosov A.I. (1875-1955), a Russian and Soviet pathologist; Hero of Socialist Labor (1945), Stalin Prize Laureate (1942), Honored Scientist (1929), Academician of the USSR Academy of Sciences (1939) and USSR Academy of Medical Sciences (1944), Vice President of the USSR Academy of Medical Sciences (1944-1948); in the 1920s-1940s he was one of the leaders of Russian pathological anatomy, headed the Institute of Normal and Pathological Morphology of the USSR Academy of Medical Sciences (1944-1955); supervised the autopsy of V.I. Lenin (1924), M.V. Frunze (1925), B.M. Bekhterev (1927), V.P. Nogin (1924), V.V. Kuibyshev (1935) and others.

In two cases of heart transplantation and three cases of lung lobe transplantation, when pleural cavities were infected and antibiotics were not administered, disintegration of the grafts due to their decay was recorded a few days after thrombosis of the main vessels at their suture sites.

In one case, the homograft of an abdominal aortic fragment retained its original appearance 13 years after surgery."

In this text, V.P. Demikhov cites the opinion of the outstanding Soviet pathologist, vice-president of the USSR Academy of Medical Sciences, Academician A.I. Abrikosov about the nature of changes in transplanted organs during their prolonged stay in a non-functioning form in the host body: according to A. I. Abrikosov, they were subjected to coagulation necrosis rather than to rejection. In this case, most likely, A.I. Abrikosov did not know the pathological anatomy of the organ rejection reaction, but for V.P. Demikhov, his opinion was very important. It confirmed V.P. Demikhov's own opinion that the changes in the graft did not go beyond the general pathological changes.

Interesting was his observation about a 13-year survival of an abdominal aortic homograft that could hardly have been subjected to pre-conditioning.

On the role of infection for the survival of transplanted organs

"Some experts in the field of immunology establish an equality sign between the reactions that occur during transplantation of tissues and organs within the species, and the reactions caused by the vital activity of bacteria in the human body. From a biological point of view, such identification should logically lead to the conclusion that it makes little difference to the human body whether they mix their own blood with the blood of another human or provide him with an extract of pathogenic bacteria.

The albumin of bacteria, intermediate organisms between plants and lower animals, differs from the albumin of higher animals. And the more alien is the albumin of pathogenic bacteria compared to the albumin of a compatible blood group and, consequently, of tissues.

It is also known that there is a big difference between bacteria in their effects on a human body. Some bacteria (such as plague, etc.) cause deadly diseases. Others (for example, those that cause acid fermentation of milk, etc.) contribute to the creation of nutrient products that people use" [4, p. 26].

Here V.P. Demikhov formulates the idea that the antibodies observed during organ transplantation can appear in response to the penetration of bacterial protein into the blood of the recipient's body when a tissue infection occurs in the transplant area. Thus, the third cause of the transplantation failure is the addition of infection, which entails not only the formation of scars, but also the appearance of antibodies against bacterial proteins.

On the importance of donor and recipient blood groups in organ transplants

"According to immunological hypotheses, the death of transplanted tissues and organs should occur no later than at 7, 14 and 21 days after transplantation.

But the truth (sic! – *Author's note.*) *is that in most experiments, these timeframes do not coincide in any way.*

The most numerous are millions of lucky cases of homoplastic transplantation (transfusion) of liquid tissues (blood), taking into account the group factor. There was a time when blood cells transfused into a new organism were believed to have to die quickly due to incompatibility. But studies with labeled atoms have shown that red blood cells introduced into a new organism live for more than 100 days, that is, the same period as the recipient's red blood cells. Repeated blood transfusions from the same donor also do not cause negative reactions.

Blood is the most versatile tissue in the entire body. Together with the cellular components, it contains all the soluble constituent elements of all body tissues, including those that can be antigens. The tissue groups must match the blood groups, since the factors determining them are dissolved in the blood. Therefore, a priori it can be assumed that organ transplantation in humans, considering the compatibility of blood groups and additional factors taken into account during transfusion, should not cause incompatibility reactions.

In addition to the main groups, many hundreds and thousands of additional factors have been found in the blood, but they are not of practical significance for blood transfusions and, therefore, should not be relevant for organ transplantation."

The idea of the need to match the donor and recipient blood groups, which V.P. Demikhov came to empirically, turned out to be very fruitful: transplantology still adheres to it.

About the dog Grishka and its extra heart that worked for 141 days[12]

"In 1962, our team improved the procedure for heart-lung complex transplantation in experiments on dogs. This made it possible to extend the life of transplanted organs [4, p. 27].

According to the new method of operation, the longest survival (141 days) was observed in the dog Grishka that had a second, additional heart transplanted and the part of the left lung replaced.

The recipient dog was an Eastern European shepherd dog, the donor was an adult, small-sized mongrel. Despite belonging to different breeds, the recipient dog did not show any incompatibility reaction in relation to the graft.

Until the last day, the transplanted heart was functioning normally, the rhythm was regular. In response to physical exertion (running), the transplanted heart, like the native one increased its rhythm. At 10 minutes

12 This section of the Preface generally repeats the similar section of the Preface to the German edition of the book (1963), but is put in different words.

after the end of running, the transplanted heart returned to its previous rhythm, and it did this much earlier than the recipient's heart.

On the 141st day after surgery, the transplanted heart sounds were no longer heard at auscultation. An electrocardiogram taken at this time showed broad peaks with low potential. After intravenous administration of heparin, the heartbeat of the transplanted heart was again auscultatable. On the electrocardiogram taken By V.M. Goryainov, the peaks corresponding to the studied heart returned to their normal appearance.

However, the next day, the transplanted heart completely stopped beating. The dog had to be put down. An autopsy revealed a large blood clot in the right atrial auricle, blocking blood flow to the graft. The cause of this blood clot could be: circulatory disorders due to excessive physical effort (running) or as a result of an external injury, since the auricle of the atrium was very close to the external wall of the dog's chest[13].

At macroscopic examination, the myocardium of the donor heart did not differ in any way [4, p. 28] from the myocardium of the biological heart of the recipient. Fibrotic junctions with surrounding recipient tissues were found at the junctions with the donor heart. In other sites, the graft's pleura and pericardium showed no adhesions or visible changes. To make histological studies, I. A. Chervova, Professor of the Histology Department of the 2nd Moscow Medical Institute, and N.K. Permyakov, the Head of the Pathological Anatomy Department of N.V. Sklifosovsky Institute took the graft fragments and sent them to Boston (USA) in response to a request from Dr. Matlof (from the Clinic of Professor R. Deterling)[14]*, who received news about the experiment from some American colleagues who had seen that the dog Grishka was still alive.*

The dissected pericardium and pleura healed by primary intention, histological studies conducted by I. A. Chervova showed the preserved

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13 The death of the dog, which occurred on the night of November 7 to 8, 1962, led to various speculations about its causes, up to hit by a car resulted from an undue care for the animal during public holidays.

14 We have no data on the results of these studies. Perhaps V.P. Demikhov did not have them either; otherwise he would have reported them.

graft muscle fibers, and if some of the nerve cells died, the rest were completely preserved.

Residual phenomena were observed in the epicardium after its inflammation. No changes were recorded in the endocardium. The qualitative process that occurred in the transplanted organ was similar to that in hearts with reduced contractility, which histological studies were performed by the aforementioned Department.

The inflammatory response observed in the epicardium can be explained by a reaction to trauma during surgery and postoperative inflammation of infectious or aseptic nature.

There were also differences seen in the functions of different transplanted organs. So, in our experiments, the kidneys that were homoplastically transplanted to dogs usually stopped functioning between the 2nd and 3rd weeks; by this time, their tissues were significantly changed. On the contrary, the transplanted heart and part of the lung [4, p. 29] changed little even after a few months (141 days).

This can be explained by the fact that the kidneys, as a filter of the body, are more sensitive to changes in its internal environment, as well as to injuries, exhaustion, and infection."

About making ligatures at suturing

In the course of a large number of experiments, we came to the conclusion that success in applying vascular sutures is largely due to the correct ligature. When the sutures are tightened loosely, the knots slip or untie, leading to bleeding. Conversely, if the ligatures are tightened excessively, the intima is damaged, resulting in a blood clot that can disrupt blood circulation in the transplanted organ.

Prophylactic use of heparin and fibrinolysin for a month after surgery, if properly controlled, can prevent the formation of blood clots in the areas of vascular sutures and stumps of ligated arteries. In dogs, this is difficult to achieve from a technical point of view."

On the prospects of heart transplantation

«***If we look at the future of organ transplantation, particularly the heart, we can conclude that time will come when in preventive purposes a human will be transplanted a second, additional (backup) heart, which would function in parallel with the native one*** (in bold by us; this phrase is rendered on the back cover of the book (Fig. 6). – *Author's note*)

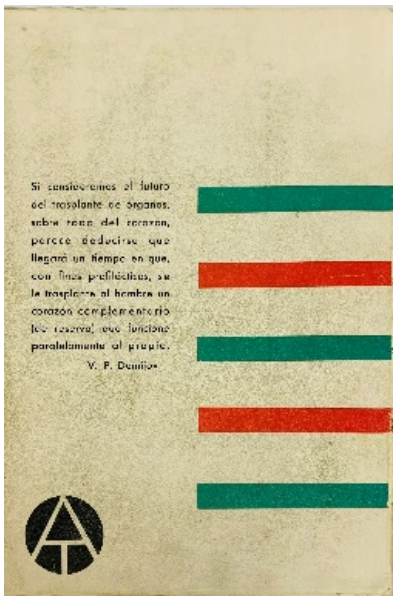

Fig. 6. Back cover of V.P. Demikhov's book "Transplante experimental de órganos vitales" (Madrid, 1967) [Museum of A.N. Bakulev National Medical Research Center of Cardiovascular Surgery]

We will find space for this backup heart in the chest, but not by removing the lobe of the lung, as we have done in many of our previous experiments. To create available space for a second heart without removing the lung lobe, we conducted a series of experiments in which the transplanted heart was enclosed in a transparent plastic case and left outside the body, while its vessels were anastomosed in the chest cavity."

On the impact of obstructive pulmonary diseases on the heart activity

"Observation of the functions performed by the transplanted heart through a transparent plastic case [4, p.30] turned out to be extremely interesting and important.

It is known that after the operation has been completed, the chest cavity is hermetically sealed, and by using a large syringe, excess air is removed from the pleural cavities. A similar air extraction was performed when the transplanted heart was placed in a plastic case. Meanwhile, it was noticed that as a result of the air evacuation and creating a small negative pressure around the heart, it stopped beating. Its right ventricle was seen to be expanding, and its wall could not contract. After the negative pressure around the heart was eliminated by introducing a small amount of air into the plastic case, the cardiac activity was observed to resume.

From a physical point of view, this phenomenon is quite understandable: negative pressure in the pericardial cavity surrounding the heart is an external force that prevents increasing the volume of ventricles and, as a result, their contraction. The wall of the right ventricle is relatively thin, easily stretched, and its resistance is three to four times less than that of the left ventricle wall, which makes it unable to overcome this external force.

The cardiac arrest at creating an external negative pressure clearly demonstrates the fallacy of the centuries-old statement that the suction action of the chest is the main positive force that creates blood flow to the heart (in bold by us. – *Author's note*). *Contrary to this opinion, it seems to us that negative pressure in the chest cavity is the mechanism that causes cardiopulmonary failure in chronic emphysema. It can be assumed that the mechanism of this phenomenon is that in chronic bronchitis, air aspiration is difficult, which leads to negative pressure in the chest cavity. As a result, the right ventricle, overcoming this external pressure, begins to contract intensively [4, p. 31], which eventually leads to hypertrophy of its wall. In cardiopulmonary insufficiency, hypertrophy of the right ventricular wall is a morphological manifestation of excessive negative pressure.*

In the experiments with two hearts (without lungs) conducted earlier, we were often puzzled by the weakened contractility of the transplanted heart after removing air from the pleural cavity. The analysis of the working heart enclosed in a transparent case, helped to find out the cause of this phenomenon."

On a two-staged heart and lung transplantation

"Using a transparent case containing the donor's heart and lungs connected to the recipient's femoral vessels will help make the first stage of heart and lung transplantation virtually safe.

If within one to two months these reanimated organs, placed in a shell and temporarily connected to the recipient's body, do not show a deterioration in their functional activity, then you can perform the second stage of the operation and, only guided by vital signs, transfer them to the chest cavity.

Other visceral organs can be transplanted using the same principle (in two stages)."

On creating a bank of reanimated (live) organs

"As for the preservation of reanimated organs for use as transplants, it is best if they are kept in physiological conditions, that is, at +37.6°C, while providing them with blood circulation with the blood oxygenated by a resuscitated body, to which other visceral organs can be attached ensuring the necessary sterility. Such an organism can be attached to newborns whose brain has died and cannot be resuscitated, and other organs are functioning normally. If in these bodies (with incurable brain injuries) the life of reanimated organs is preserved for a long time [4, p. 32], then it is possible to grow all the tissues and organs necessary for transplantation to patients. Thus, it can be assumed that in the future, organs grown from resuscitated embryos will be transplanted. It is also promising to create a long-term cross-circulation between an elderly body whose aging is planned to slow down, and a young body.

Based on our own extensive experimental data, attempts to resuscitate the heart and lungs of cadavers delivered to emergency

clinics, and on summarizing the research results from other scientists, our team has developed a fundamentally new way to preserve reanimated organs and cultivate them for transplantation (bold is ours. – *Author's note*).

In practice, this can be done as follows: the corpse is delivered to the medical facility within a few minutes after death. As a result of severe trauma, a fatal brain injury is registered, but the remaining organs are found undamaged, and they are resuscitated along with the heart. With the help of mechanical ventilation, maintaining the ambient temperature at +37.5°C, adequate sterility and artificial nutrition, this reanimated body, virtually devoid of a head, can be preserved for a long time.

Organs taken from other corpses and still retaining vital activity can be connected to the femoral vessels of this living body, by enclosing them in special covers to revive them and keep them alive. Such a body can also be connected the corpse of a newborn in which the entire body was reanimated except for the brain. Each connected organ will perform its own functions, helping to maintain the vital functions of other organs. ***Thanks to this "self-assistance" of organs to each other, the number of those that are preserved in a living state can be very large*** (in bold by us. – *Author's note*). *Thus, the reanimated body of a child with a fatal brain injury will continue to grow, and its hormones and metabolism [4, p. 33] will help to rejuvenate the entire internal environment of other organs, which will allow growing young organs for transplantation. From this living physiological organ system, blood vessel prostheses of large size and length (several meters) can be led to adjacent premises (rooms). These vessels can be connected to dying patients' peripheral vessels, through which aerated blood will circulate, enriched with all the necessary hormones and nutrients, with normal pressure, taking into account the blood type compatibility.*

If in the future this method can be improved to such an extent that its use in practice will not be dangerous, the elderly might be connected to this organ system or the system of living bodies for a few weeks to change the metabolism in the aging body by means of the young internal environment, since it is known that while cultivating the isolated tissues

by the method of "tissue cultures" after adding the extracts of embryonic tissues, their rejuvenation is observed (bold type by V.P. Demikhov – *Author's note*).

In principle, this method of rejuvenation can be implemented on an individual level by creating a long-term cross-circulation between an elderly body and a resuscitated young organ system, or by connecting bodies using vascular prostheses that are currently used to connect, for example, an artificial kidney."

For the first time, V.P. Demikhov reported on this method of maintaining the life of isolated organs (and in fact, creating their "bank") through using the "living physiological system of organs" at the Meeting of the USSR Healthcare Ministry Board in 1963. Almost simultaneously, this idea was publicized in the Preface to the German Edition of his book published in the same 1963. The fact that it appeared in the Preface to the Spanish-language Edition published in 1967, suggests that this idea was being developed by V.P. Demikhov for several years. Its result was the article published in the "Experimentalnaya Khirurgia" journal in 1969. It is strange that this idea did not seem impossible to anyone either in 1963 or in 1967. In any case, we are not aware of critical statements about it either in the domestic or foreign press.

On acquired immunological tolerance and successful human kidney transplantations

"As for the cultivation of embryo organs, it can be made in conditions that allow modifying the internal environment of future grafts, taking into account that post-transplant immunization reactions should be avoided.

Medawar and Gashek suggest that a small injection of the future recipient's blood into the donor embryo will create the necessary tolerance and prevent the occurrence of biological incompatibility during

future transplantation. This method is practically applicable in the cultivation of human embryo organs [4, p. 34].

Over the recent 2-3 years, more than 1,000 human kidney transplantations have been performed in different countries. According to world statistics, as of March 15, 1965, 719 kidney transplants were performed, of which 36 were performed between monozygotic twins and 241 were performed with a kidney taken from a cadaver. Initially, it seemed that only a transplant between identical twins could be successful. Currently, the differences in kidney transplantation results between twin donors and donors without consanguinity, as well as of cadaveric kidneys, have been reduced. There are already many people who have been living for several years with kidneys taken from others rather than their twins.

In 1963, of 45 transplanted kidneys taken from corpses, only one switched on (Spanish: prendió). In 1965, 43 of 82 kidneys switched on."

On the unproven immunosuppression effect

"Many cases of kidney transplantation from monkey to human have been described, when the organs of animals functioned for up to 100 days. As is known, immunological reactions develop only during the 1st, 2nd, and 3rd weeks after entering foreign albumin (again the same: the 7th, 14th, and 21st days. – Author's note).

In many cases of human kidney transplantation, immunosuppressive drugs such as 6–mercaptopurine, imuran, etc. are used, thereby trying to explain the success of the transplantation. But numerous animal experiments do not confirm the efficacy of these drugs, although, according to some researchers, the skin and kidney graft survivals in some cases increase by several days.

The author of these lines conducted a large series of experiments on dogs with lung and kidney transplantation and the use of mercaptopurine-6 and became convinced of the toxicity of this drug, doubting its efficacy (in bold by us. – *Author's note*).

If the transplanted kidneys had survived in humans due to the use of immunosuppressive drugs, then one should bear in mind that the use of these same drugs for kidney transplantation in dogs should have also led

to their longer functioning. However, contrary to expectations, this did not occur [4, p. 35]. Maximum duration of renal function in dogs (under conditions of immunosuppression. – *Author's note*) *makes from 2 to 3 weeks and, rarely, from 1 to 2 months, while in humans it is counted in years.*

The use of immunosuppressive drugs requires further studying."

On creating conditions for organ transplantation at the national level

"The treatment and care conditions in the postoperative period contribute to the success of human kidney transplantation.

It is also necessary to ensure constant monitoring of blood clotting, create special conditions for sterility and patient care, and employ highly qualified personnel. Currently, there is no doubt that the best results in clinical kidney transplantation can be achieved when the donor and recipient have been selected based on the compatibility of their blood types (rather than their relationship).

In order to put into practice the positive results achieved in organ transplantation, special conditions should be created at the national level.

The Soviet Government considers this issue to be of great importance. Academician B. V. Petrovsky, a great surgeon and the most prominent in the USSR, who successfully performed a large number of human kidney transplants, was appointed the Healthcare Minister.

V.P. Demikhov" [2, p. 36].

Conclusion

Thus, the analysis of V.P. Demikhov's Preface to his book "Experimental Transplantation of Vital Organs" published in Spanish under the title "Transplante experimental de órganos vitales" in 1967 showed that V.P. Demikhov outlined in it his views on the current state and prospects of homoplastic transplantation of tissues and organs that he had developed by that time. As in previous works, in particular, in his Preface to the German Edition of the book (Berlin, 1963), V.P. Demikhov substantiated the proposition that the main condition for a successful homoplastic organ

transplantation was the restoration of blood circulation in them. In his opinion, the success of the engraftment depends, first of all, on an ideally made vascular suture and the immediate inclusion of the transplanted donor organ into the blood circulation of the host body, as well as on the intervention sterility.

Having discussed the use of pharmacological immunosuppression as a method for overcoming the biological incompatibility of homologous organs during their transplantation, V.P. Demikhov pointed out the toxicity of the drugs used for this purpose that he had tested under experimental conditions, as well as his experiments, indicating the possibility to overcome the incompatibility by using other methods (a donor-recipient selection by the blood group, mixing the blood of a donor and a recipient by means of parabiosis, etc.).

In this work, V.P. Demikhov again described and substantiated the 2-staged scheme he had developed for transplanting an additional heart as a backup to support the function of the weakened biological heart of the patient: stage 1 implied the implantation on the femoral vessels, stage 2 included the transplantation into the chest; but he did not describe the surgical technique of performing stage 2. *"We will find space for this backup heart in the chest,"* he said, *"but not by removing the lobe of the lung, as we have done in many of our previous experiments. To create available space for a second heart without removing the lung lobe, we conducted a series of experiments in which the transplanted heart was enclosed in a transparent plastic case and left outside the body, while its vessels were anastomosed in the chest cavity."* However, it is not clear from this text how V.P. Demikhov was going to "*create available space for the second heart without removing the lobe of the lung*?" We can conclude from his words that he himself did not perform such a two-staged transplantation. In any case, we are not aware of such experiments.

As in the Preface to the German Edition of the book, V.P. Demikhov again outlined the model of a "living physiological system" developed by him in 1963 for creating a bank of reanimated organs in order to maintain their vital function before transplantation, as well as for growing organs in anencephalic newborns and for rejuvenating the elderly.

The peculiarity of this text, which we first introduced into scientific circulation, is as follows. On the one hand, numerous facts indicate that in the first half of the 1960s, V.P. Demikhov carefully followed all literary innovations in the field of transplantology and transplant immunity, including foreign sources published in 1965, and he included the references to them in the text of the Preface he provided for translation into Spanish. On the other hand, if we compare the Prefaces to the Berlin (1963) and Madrid (1967) Editions, we can easily see that there are no fundamental differences between them.

This may indicate that during those years, despite the change in the paradigm in the field of homoorgan transplantation, V.P. Demikhov's views on this problem remained the same and had already become archaic by that time. His fundamental biological and physiological education and many years of personal experience in the development of biological methods for overcoming tissue incompatibility in homoplastic organ transplantation (Fig. 7) firmly tied him hand and foot, not allowing him to step or look ahead.

Fig. 7. V.P. Demikhov (center) in the operating room [Museum of A.N. Bakulev National Medical Research Center of Cardiovascular Surgery]

If we consider this situation from the standpoint of I. Lakatos's (1922-1974) *Methodology of Scientific Research Programs*, then the "hard core" of V. P. Demikhov's long-term research work would be his conviction that the biological incompatibility of tissues and organs could be overcome. In the final length, it turned out that V. P. Demikhov was absolutely right in this.

This is the most important conclusion that enables us to consider the research he was conducting for over 20 years not to be not a dead-end branch of transplantology, but rather one of its initial, largely empirical stages.

In this case, a "protective belt" of V.P. Demikhov's program was his theory about the leading role of restoring the blood circulation and long-term graft function in its engraftment, and his positive heuristic included his experiments that do not fit into the Procrustean bed of contemporary immunological theories, which he easily refuted (for example, the timing of rejection on the 7th, 14th, and 21st day, which were postulated by his contemporaries; or lymphocytic infiltration, which high-level professional morphologists did not find in his experiments, etc.).

At the same time, in our opinion, in the second half of the 1960s, V.P. Demikhov's research program had already passed its progressive stage and gradually began to regress. This is confirmed by the fact that the empirical content of the "protective belt" V.P. Demikhov had built up (for example, the fact of the dog Grishka's second heart survival for 141 days in 1962) could not be considered as a positive heuristic, and, in turn, it was denied by a 593-day survival of Philip Blaiberg, the second heart transplant patient C.Barnard operated in January, 1968.

From this point of view, the "Spanish trace" in V.P. Demikhov's life can be considered one of the elements of the negative heuristic of his program, when the main efforts of the scientist were not directed at the further development of its "hard core" but rather at patching up holes in its "protective belt" by searching for more and more new hypotheses selected by adhoc[15].

Unfortunately, the time was coming when the connection of the "protective belt" with the "hard core" of V.P. Demikhov's research program would weaken so much that he had to admit its failure. I. Lakatos called this moment “the saturation point”, when an alternative program comes to replace the existing one [12].

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[15] Latin expression meaning "specially for this", "on a special occasion." Latin expression meaning "specially for this", "on a special occasion."

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