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PHENOMENON OF DEMIKHOV.
At the Sklifosovsky Institute (1960-1986).
Demichow W. Die experimentelle Transplantation lebenswichtiger Organe. Berlin: VEB Verlag Volk und Gesundheit, 1963

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The article has discussed V.P. Demikhov's views on a homoplastic transplantation of tissues and organs in 1963 and his achievements in experimental transplantation by that time. The authors first translated the monograph Die experimentelle Transplantation lebenswichtiger Organe (1963) from German into Russian and presented V.P. Demikhov's Preface *to it. In this text, having critically analyzed the current provisions in the field of immunobiology, V.P. Demikhov came to the conclusion that a number of his achievements contradicted those provisions and did not fit into the framework of existing immunobiological laws. In 1963, confessing the primacy of function over structure, V.P. Demikhov believed that the restoration of blood circulation in transplanted organs played the main role in their survival, and the subsequent functioning of the transplanted organ for a long time meant its engraftment. In this text V.P. Demikhov for the first time substantiated the model of a "physiological organism" he had invented for reviving a human in a state of agony, for creating a bank of organs, growing it in infants and rejuvenating the elderly.*

Keywords: history of transplantology, V.P. Demikhov, W. Demichow, Die experimentelle Transplantation lebenswichtiger Organe, 1963

VAD, ventricle-assist device

In previous articles [1, 2], we described and analyzed an important event for the history of Soviet Transplantology: in October 1963, the Meeting of the Presidium of the USSR Healthcare Ministry Council for the Coordination of Scientific Research and Implementation of the Scientific Achievements took place in Moscow, where for the first time, the issue on the state and development of scientific research in organ transplantation was discussed. The main speakers were V.P. Demikhov and V.I. Burakovsky. The rest spoke in debate. Opinions were reduced to the fact that V.P. Demikhov's work should be supported, but with pointing out to him the fallacy of judgments about the possibility of overcoming biological incompatibility in homoorgan transplantations using technical methods.

Moreover, from V.P. Demikhov's speech and his answers to the questions asked, it was seen that he began to move away from his views on overcoming incompatibility by modifying the metabolism in a transplanted organ by means of combining its vascular system with the vascular system of the host's body (artificial parabiosis), about which he had spoken and written until 1959 [3]. In 1963, his provisions that the transplanted organ function recovery contributes to its adherence (following the function recovery, the structure is restored) rested on I.P. Pavlov's physiology basis. To prove this position, V.P. Demikhov had a vivid and inexplicable by immunobiology laws of that time example of the dog Grishka, who lived with two hearts (his native heart and the donor's heart) beating in his chest for 141 days.

But until recently, we did not know when V.P. Demikhov had formulated these provisions if, after the publication of his monograph “Experimental Transplantation of Vital Organs” [4] in 1960, and later on, its translation into English, he published no other studies on the topic of overcoming biological incompatibility. Note that the English edition of the book published in 1962 in New York in the author’s revision under the title “Experimental Transplantation of Vital Organs” [5], contained an authentic translation of the Preface to the Russian edition stating that the Medgiz Publisher does not share the author’s opinion about his postulated methods of overcoming biological incompatibility. The Russian and English editions had no author's Prefaces.

And only after we asked our friend and co-author A. Werner from Düsseldorf (Germany) to translate into Russian the author's Preface to V.P. Demikhov's monograph “Die experimentelle Transplantation lebenswichtiger Organe” [6] (Fig. 1) published by VEB Verlag Volk und Gesundheit Publisher in Berlin in 1963 (translator Dr. Klaus Fichtel), everything fell into place.

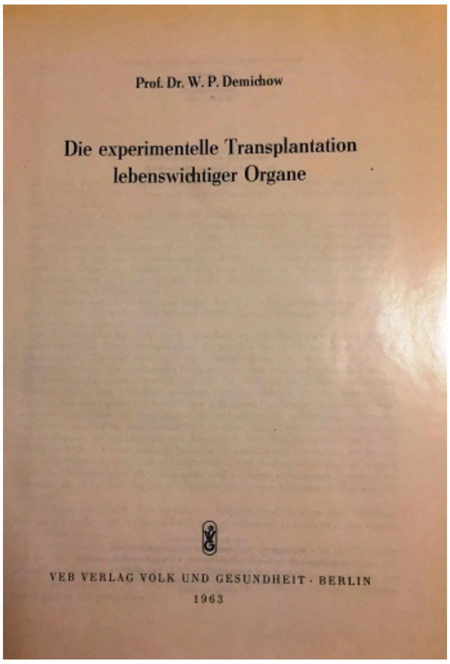

Fig. 1. The cover of the book: Demichow W. Die experimentelle Transplantation lebenswichtiger Organe. Berlin: VEB Verlag Volk und Gesundheit, 1963. (From A. Werner's Library)

It is in that text, which had not previously been translated into Russian and therefore until now remained unknown to Russian-speaking readers (Fig. 2), V.P. Demikhov critically evaluated the positions that existed in immunobiology at the beginning of the 1960s and formulated his view on that issue as a biologist, physiologist and transplant surgeon based on his many years of experience in homoplastic tissue and organ transplantations.

Vorwort des Verfassers zur deutschen Ausgabe

In den drei Jahren, die seit dem Erscheinen der russischen Ausgabe dieses Buches vergangen sind, haben der Verfasser und andere Forscher bei der Transplantation von Geweben und Organen unter gleichzeitigem Studium ihrer funktionellen Veränderungen weitere Ergebnisse erzielt. Nach den Angaben der Literatur wird die nach der üblichen Methode homöoplastisch transplantierte Haut sowohl im Tierexperiment als auch unter klinischen Bedingungen am Menschen in der Regel nach einer unterschiedlich langen Zeitdauer wieder abgestoßen. Demgegenüber wächst das autoplastische Hauttransplantat in vielen Fällen an.

Diese Abstoßung des homöoplastischen *Haut*transplantats veranlaßte die Mehrzahl der Forscher zu der Annahme, daß es bei *allen* homöoplastischen Transplantationen von Geweben und Organen zu einer immunbiologischen Reaktion mit der Bildung von Antikörpern kommt, die diesen Effekt hervorrufen.

Dieser Vorgang der Abstoßung oder Resorption der Homöotransplantate infolge biologischer Unverträglichkeit wurde als ein feststehendes Gesetz aufgefaßt, das für alle transplantierten Gewebe und Organe gültig ist.

Dieses sogenannte Gesetz der biologischen Unverträglichkeit bei homöoplastischer Transplantation steht jedoch zu zahlreichen Befunden in Widerspruch, von denen *hier nur die wichtigsten angeführt seien:*

1. Außer der biologischen Unverträglichkeit, die mit größter Wahrscheinlichkeit anzunehmen ist, muß man bei allen Gewebs- und Organtransplantationen vor allem auch die physiologische Seite der Frage berücksichtigen. Nach Ansicht der meisten Forscher treten die immunbiologischen Reaktionen auf das Homöotransplantat frühestens sieben Tage nach der Transplantation auf. Bis zu diesem Zeitpunkt bestehen zwischen der Anheilung der Auto- und der Homöotransplantate keine Unterschiede.

Wenn wir jedoch von physiologischen Gesichtspunkten ausgehen, so müssen wir berücksichtigen, daß der Kreislauf und damit auch der Stoffwechsel im Transplantat bereits in den ersten Sekunden und Minuten nach seiner Entnahme vom Spender aufhört. Dieses Aufhören der Durchblutung wird von den verschiedenen Geweben unterschiedlich vertragen. Ein Kreislaufstillstand im Gehirn führt bei Körpertemperatur (nach dem heutigen Stand der Dinge) bereits nach 5—6 Minuten zu irreversiblen Funktionsstörungen. Wenn jedoch beim Warmblüter das Gehirn während der Kreislaufunterbrechung stark abgekühlt wird, dann kann es nach den Ergebnissen von W. A. Negowski auch nach 1—2 Stunden noch zu einer vollständigen Wiederherstellung der Funktionen kommen.

Etwas weniger empfindlich gegenüber Kreislaufstörungen ist die Niere. L. A. Orbeli stellte fest, daß eine Abklemmung der Nierenarterien (beim Warmblüter

Fig. 2. The author's Preface to a German Edition of the book: Demichow W. Die experimentelle Transplantation lebenswichtiger Organe. Berlin: VEB Verlag Volk und Gesundheit, 1963. (From A. Werner's Library)

The purpose of the present article was to introduce this document with our comments into the scientific circulation as an important scientific publication by V.P. Demikhov.

V.P. Demikhov's Preface to the book: Demichow W. Die experimentelle Transplantation lebenswichtiger Organ. Berlin: VEB Verlag Volk und Gesundheit, 1963

> “In the three years that have passed since the publication of the Russian version of this book, the author and other researchers in the transplantation of organs and tissues and the simultaneous study of their physiological changes came to the following results.
>
> As follows from the literature, when using generally accepted methods, homoplastically transplanted skin, both in animal experiments

and in clinical conditions, will usually be rejected in various time intervals. The opposite effect was observed in cases of autoplastic skin grafting. The described rejection of homoplastically transplanted skin grafts allowed a large number of researchers to conclude that immunobiological reactions with the appearance of antibodies are observed in all homoplastic transplants, which determines this effect.[1] The processes of the homograft rejection or resorption as a result of biological incompatibility were defined as a pattern that is valid for all homoplastically transplanted organs and tissues.

However, this so-called law of biological incompatibility in homoplastic transplants contradicts [to a number of observations], the most important of which are given below" [6].

Graft blood supply disorders, their causes[2]

"In addition to biological incompatibility, which is most likely to be present in many cases of organ and tissue transplantation, the physiological aspect of the issue must be taken into consideration. According to many researchers, immunobiological reactions might be noted in homotransplantation, starting from day 7 [after surgery]. Prior to this, there are no differences between the processes of auto- and homotransplantation. <…> From an immunobiological point of view, a transplanted organ rejection occurs between 7 and 21 days of the postoperative period.> If the rejection begins later, for example, 30 days after transplantation, then this fact does not fit into the known immunobiological patterns. <…>

From a physiological point of view, blood circulation and the related metabolism in the graft discontinue from the first minutes after its harvesting from the donor. This cessation of blood circulation is tolerated by different organs and tissues in different ways.

The blood flow cessation in the brain at normal body temperature (given the current bulk of knowledge) for 5-6 minutes leads to irreversible

[1] From the very beginning of the text, it becomes clear that V.P. Demikhov took into account only the humoral mechanism of the immunity and did not touch upon the tissue one at all.
[2] Section headings were introduced by the authors of this article to structurize the text.

physiological impairments. But if the brain of the warm-blooded is extremely cooled during the interruption of blood circulation, then (according to ***V.A. Negovsky***; all the names in the text are highlighted by V.P. Demikhov. - *Auth.*) a complete restoration of its function can be expected even after 1-2 hours.

Kidneys are less sensitive to an impaired blood flow. ***L.A. Orbeli*** found that functional disorders of these organs in warm-blooded species under normothermic conditions occur at 30 or more minutes after the renal artery has been clamped.

The heart of a warm-blooded animal, cooled after the cessation of coronary blood flow, began to contract again after an increase in the body temperature after 2-3 hours since the circulation had stopped; if the heart remained cooled, then the resumption of its contractions was possible after 24 hours or more. ***S.V. Andreev*** managed to restore the rhythmic activity of the cooled, isolated heart of a child after 112 hours since it had stopped. The author of these lines experimentally restored the normal activity of the isolated heart of an adult dog after its being kept in the refrigerator for 24 hours at a temperature of +4° C.[3]

The skin, if it is cooled, may be even less sensitive to an impaired blood flow. <…> Therefore, the success of organ and tissue transplantation in warm-blooded animals at normal body temperature largely depends on the time of blood flow restoration and [hence] metabolism in the graft.> ***If the function of the graft is quickly restored after stitching the vessels supplying it with blood, we can talk about its long-term preservation in the physiological sense*** (emphasized by us. - *Auth*.).

When we transplanted skin flaps without suturing the blood vessels supplying these areas, from the moment the graft was harvested from the donor until it was fixed in the recipient for 3-4 days the formation of regenerating blood vessels was noted. At that time, the graft at a temperature of +36.5°C was practically not supplied with blood. It is

[3] We are talking about harvesting *a contracting heart of a healthy animal* with the subsequent cessations of its activity and rapid cooling. This principle is used today when transporting a donor heart to a recipient.

known that tissue damage occurs very rapidly at this temperature, which leads to irreversible maceration followed by rejection. That is why the hope for the survival of the graft engrafted without a vascular pedicle was mediated primarily by how quickly and to what extent the blood flow will be restored and, consequently, metabolism.

The restoration of the graft blood supply also depends on how quickly the recipient's regenerating vessels grow into the graft. If the regeneration of the vessels was delayed, then this led to a rapid death and rejection of a non-survived graft. If, however, at this time, the blood supply to the graft was restored, then the rejection process was slowed down. Such a shift in the rejection time during skin homotransplantation, according to the observations of many surgeons, can take from several days to many months. At present, it has not yet been fully established what are the differences in vascular regeneration during auto- and homotransplantation.

It can be assumed that a prolonged impairment of the blood supply to the graft abruptly reduces its ability to adhere. But the active regeneration per se with the formation of a dense scar between the tissues of the recipient and the donor can lead to circulatory impairments [in transplanted tissue or organ].

Ceased graft functioning without its rejection and without resorption due to impaired circulation was most often encountered in cases of inadequate vascular suture, which led to thrombosis. If the cause was a vascular suture, then the impaired trophism [of the vascular wall] was noted at the sites where the intima was damaged. When the vascular suture was perfectly made, we had never observed cases of anastomotic thrombosis. <…>

Very good results were obtained during skin grafting from one parabiotically connected animal to another. This was first shown by the outstanding German surgeon ***F. Sauerbruch***. Later, his results were confirmed by other scientists. Research by ***J. Schwind***, ***A.G. Lapchinsky*** et al. showed that in small laboratory animals (for example, rats) under conditions of parabiosis during transplantation of skin or entire limbs, a good adherence of the homograft took place within 9 days, which did not reject until the natural death of the animal. The author of these lines managed to achieve a complete adherence of the skin graft in rats that were in parabiosis, without any specific adverse reactions.

From the point of immunobiology, the observed successful skin coalescence in parabiotically connected animals is the manifestation of one organism adaptation to another or the development of the immunobiological paralysis phenomenon. The physiological aspect of this process can highly probably be explained by the fact that the blood supply to the transplanted tissues is in more favorable conditions. <…>

The second factor (after blood circulation resumption - *Auth*.) determining the graft destiny is the maintenance of sterile conditions in the surgical field. [On the one hand] it was found that additional anaerobic infection is a common cause of damage to human corpse tissues. Corpses of dogs were damaged much faster (apparently due to high infection). <…> [On the other hand] it is known that with wound suppuration, a dense connective tissue scar develops.> Moreover, due to a high pressure in the arteries, the blood flow to the graft changed insignificantly. On the contrary, the pressure in the veins is always lower due to their elasticity and compliance to compression. This leads to the difficulty in venous outflow, and ultimately to the death of the transplanted organ. If the adhesions compressing the graft veins are surgically excised, the edema is very quickly (within 1–2 hours) reduced, which leads to normalizing the transplanted tissue or organ viability.

This result clearly shows that the limb edema often observed during auto- and homotransplantations has physiological rather than immunobiological genesis" [6].

From this section of the Preface it is clearly seen that in 1963 V.P. Demikhov considered the main conditions for the homotissue and homo-organ survival to be their blood flow resumption and, as a result, the functional recovery of these tissues and organs. Therefore, he still considered the primary (and main) cause of homotransplantation failure (without denying, however, immunobiological reactions per se) being an inadequate blood supply to the homograft (an impaired vascular suture technique, anastomotic thrombosis, scar-induced graft venous compression, etc.), after which the graft, as a rule, rejected. The second cause of unsuccessful homotransplantation, in V.P. Demikhov's opinion, is the infection that contributes per se to biological tissue dying or leads to the formation of a dense scar that impairs blood circulation in the graft (mainly, the blood outflow through the veins). Therefore, according to V.P.Demikhov, the main conditions for long-term survival (adherence, viability) of transplanted tissues and organs included: minimized trauma to a transplanted organ and its vessels, optimal vascular anastomosing and strict following the aseptics rules (Fig. 3).

Fig. 3. V.P. Demikhov is operating. From the funds and on the permission of the National Museum of the History of Medicine. P. Stradins, Riga, Latvia

We also note that if earlier (in 1959 and 1960), V.P. Demikhov explained the success of skin homografting under conditions of artificial parabiosis by mixing the blood of the donor and the recipient with the formation of a single blood circulation and, accordingly, a single metabolism with the loss of hereditary properties, later he explained that by the fact that in parabiotically connected animals "*the blood supply to* *the transplanted tissues was in more favorable conditions*".

The next topic of his criticism was humoral immunity.

Immunobiological reaction to alien proteins and bacteria

"Based on the "Biological Incompatibility Law", many researchers have been convinced that antibodies are formed during homotransplantation. In fact, most of the colleagues (including us) could not confirm this even on a large array of transplantations performed. Such a situation can be explained by the imperfection of the applied modern immunobiological methods.

In immunobiology, the principal position is known, according to which *the donation of a large protein mass does not lead to the formation of antibodies* (hereinafter the author's italics. − *Auth.*). These provisions were formulated in the Manual on Immunobiology edited by ***N.F. Gamalei***. The exception is a human body, where blood groups are clearly differentiated. Clinical cases in which autoantibodies have been detected speak in favour of the provision on the genesis of antibodies. We refer, for example, to the studies on a burn disease by ***N.A. Fedorov***, who found the autoantibodies in the *burn scab*[4], which were contacting with the protein structures of intact skin.

It is also known that when transplanting tissues without a vascular link, individual cells are destroyed, as a result of disturbed trophism, and will be resorbed. In response to the *resorption* of damaged cells, an appropriate amount of antibodies is produced. But in this case, the antibodies are the *consequence*, rather than the *cause*, of the graft rejection.

Obviously, the protein structures of dead and living tissues are biochemically different. Therefore, the antibodies that appear during the resorption of dead tissue are not specific for living tissues. However, if we consider that antibodies are generated during damage to living cells, then we must admit that any damage to the skin should lead to general damage

[4] In the 1960-1970s the employees of the All-Union Burn Center of A.V. Vishnevsky Institute of Surgery of the USSR Academy of Medical Sciences found that the proteins of burn scab are involved in the etiopathogenesis of burn disease.

of healthy skin. This does not really happen.

Transplantation of organs and tissues on a vascular pedicle prevents the death of individual cells and tissues due to circulatory disorders. Hence it follows that the detection of antibodies during transplantation of an entire organ while preserving its vascular link indicates *an error in* immunobiological studies.

Some immunobiologists see a similarity of the reactions observed during organ and tissue transplantation with the reactions that develop when higher bacteria enter the body. This key biological point of the "alien" identification logically follows from the pattern, according to which the reaction of the warm-blooded organism to alien blood is similar to the reaction to the pathogenic bacteria extract.

However, the protein structures of pathogenic bacteria, the organisms between plants and lower animals, cause a more pronounced effect compared to effector reactions to the blood of another group or other tissues [6]".

We draw attention to the fact that V.P. Demikhov spoke only of the general humoral reaction of the warm-blooded body to alien proteins (production of antibodies) and overlooked the local lymphocytic reaction.

The issue of tissue immunity in organ transplantation was developed very poorly in the USSR in the early 1960s. Things were different in other countries. It was precisely to suppress the reaction of tissues to alien proteins that immunosuppressants were aimed, which were used in oncology in those years, and began to be widely introduced into transplantology since the early 1960s.

Reaction to transplanted tissues in the form of their resorption and replacement

In his works, V.P. Demikhov often referred to periods during which, according to the authors of the sources available to him, the rejection of transplanted homotissues or homo-organs occurred. Exceeding these periods in his experiments gave him the right to defend his point of view on the effect of transplantation. For example, if the transplanted kidneys in his experiments functioned for longer than 21 days, then he believed that the immunological barrier was overcome and the kidneys took root, and the subsequent cessation of their function was due to thrombosis or infection.

> “According to [currently existing] immunobiological views, the rejection or resorption of transplanted organs and tissues is observed on the 7th, 14th, and 21st day [after their implantation in the host’s body]. In fact, like many other researchers, we did not encounter these processes. On the contrary, if the transplanted organ was well supplied with blood, then at 8–10 days after surgery, it adhered well to the surrounding tissues. <…> In the 1950s, in a series of our attempts to transplant lung lobes, we observed a complete resorption of the graft after 2-3 weeks.> However, at that time, we did not use antibiotics in the postoperative period.
>
> ***Since 1962, we have improved the*** *[transplantation]* ***technique, prescribing a wide range of antibiotics simultaneously. So far in none of the nine cases*** *[of lung lobes transplantation]* ***did we observe resorption, although the postoperative follow-up period lasted up to 5 months*** (emphasized by us. − *Auth.*)[5].
>
> These results allowed us to conclude that the resorption of the homograft and the death of its cells were the result of either tissue trophism impairments due to disturbed blood supply, or the impact of the bacterial flora. With the rejection of skin homotransplants, a similar pattern of behavior of other tissues was often observed. With hundreds and thousands of successful homoplastic transplants of cartilage, cornea, bones, blood vessels, and fascia in humans, the described processes were observed under clinical conditions.

[5] It is unclear whether V.P. Demikhov observed the transplanted lobe functioning for "*5 months*" or only the absence of its resorption.

For example, it has long been established that when transplanting blood vessels, the latter are resorbed and replaced by the recipient tissues. Numerous studies by ***A.D. Hristich*** showed the absence of differences in this process during auto- and homotransplantation of blood vessels. In histological studies, ***T.A. Grigoryeva*** and her colleagues found that the transplanted homo-vessels were changed in the same way as the auto-vessels during denervation.

For a long time, the assertion prevailed that homoplastically transplanted tissues could not regenerate, and would eventually be replaced by recipient tissues. Numerous experiments of ***F.M. Lazarenko*** and his employees showed, however, a good ability of this type of transplanted tissue to regenerate." [6].

Here V.P. Demikhov again discussed the destiny of donor homotissues and homo-organs that were rejected or resorbed (meanwhile, he did not see a difference between these phenomena) due to impaired blood supply or added infection, and were also replaced by similar tissues. And even were able to regenerate.

Let us draw attention to his remark that from 1962 he began to use (obviously, in the pre- and postoperative periods) *a "wide range of antibiotics*", which immediately increased the survival time of the transplanted organs to several months.

Considering the blood group of the donor and recipient in organ and tissue transplantation

"Frequent, successful cases which have already counted in millions, of homoplastic transplantations (transfusions) of liquid tissues, such as blood, indicated the need for compliance with the group compatibility [of the donor and recipient], as well as the possible consideration of other factors. It has been established that blood cells in a new organism die due to their incompatibility with the blood cells of the host. Labeled atom experiments indicate that homoerythrocytes live in the new body for about

100 days. <…> Blood is the universal tissue of the body.> In addition to cell populations, it contains soluble substances that penetrate the body's tissues in the form of antigens.

Therefore, we may take into account that the reactions to blood groups and its other factors during blood transfusions will be similar to reactions during homoorgan transplantation (emphasized by us. − *Auth*.).

In addition to the “group” properties, hundreds and thousands of other additional factors were found in the blood, according to which the blood of different organisms may be incompatible. However, during the transfusion of single-group blood, they did not have clinical significance, and in the same way, they may not matter during a tissue transplantation” [6].

In this part of the Preface V.P. Demikhov brilliantly noticed the similarity of recipient's body reaction to transfused donated blood with the reactions to transplanted organs. And since blood is a universal tissue, then considering the compatibility of blood groups of the donor and the recipient when transplanting organs, one can expect a minimal reaction of the recipient's body to donor organs[6].

How dog Grishka “put a bomb under immunity”

The most impressive V.P. Demikhov’s experiment for all his many years of practice, was the one with transplanting an extra heart into the chest of the dog Grishka. Having received a second heart in July 1962, Grishka lived with two hearts until November 7, 1962, after which he was withdrawn from the experiment. Today this fact can be explained both by coincidence and by V.P. Demikhov's following his originally developed rules for organ transplantation: (1) the donor-recipient selection

[6] Today, the issue of mandatory compatibility of blood groups in a donor and a recipient is debatable when transplanting a number of organs, for example, kidney. - *Ed*.

considering the blood groups, (2) meticulously applied vascular anastomoses, (3) prophylactic antibiotics therapy.

In our translation of the text from German, V.P. Demikhov first told about Grishka's destiny, who, as contemporaries said, "*put a bomb under immunity*".

> “In 1962, we improved the technique of heart-and-lung transplantation in experiments in dogs, which allowed us to maintain the viability of the transplanted organs for a long time. One of these animals operated under new conditions was the East European Shepherd dog named Grishka that lived for 141 days. We transplanted the heart and part of the left lung to this dog. The donor was an adult mongrel dog of a smaller size.
>
> Despite the difference between the breeds of Grishka and the donor dog, no incompatibility reaction to the transplanted organs was noted. The donor and biological hearts functioned normally and showed a regular rhythm (Fig. 4). With an increase in motor activity (running), a transplanted (denervated) heart responded with increased heart contractions. After 10 minutes of the load cessation, the rhythm of the transplanted heart returned to its original rate that was faster compared to the recipient-dog's heart.
>
> On day 141 after surgery, the transplanted heart tones could not be heard. On the ECG, irregular signals of low voltage were noted. An hour after the intravenous administration of heparin, the sounds of the second heart reappeared, and a distinct cardiac impulse began to be felt. A repeated ECG taken by ***V.M. Goryainov*** showed the resume of cardiac activity. However, the next day, the contractions of the transplanted heart stopped, and the dog was withdrawn from the experiment.
>
> At autopsy section, we found an obstructing blood clot in the right atrial appendage of the donor heart, which was the mechanical cause of the low cardiac output syndrome. The detected thrombus could have formed as a result of circulatory disorders at increased physical activity (running) and as a result of external trauma, given the anatomical position

of the right atrium in dogs near the anterior chest wall.

Microscopic examination revealed no abnormalities in the donor's heart myocardium. Its pericardium, as well as the pleura of the transplanted lung, were firmly fused by connective-tissue indurations with the relevant recipient's tissues. Grishka's pleura and pericardium were free of adhesions and visible changes.

Transplant fragments were removed for examination by ***I.A. Chervova,*** the Assistant Professor of Histology Department of the 2nd Moscow Medical Institute (2nd MGMI) named after N.I. Pirogov. - *Aut*.) and Professor ***N.K. Permyakov,*** the Head of the Pathology and Anatomy Department of N.V. Sklifosovsky Institute. Several samples were sent to Boston (USA), at the request of Dr. Matlow from the Clinic of Professor R. Deterling, "*the American colleagues of the dog Grishka*" (text by V.P. Demikhov. − *Auth.*), who observed the dog during life[7].

Histological examinations of the myocardium conducted by ***I.A. Chervova*** showed that the muscle fibers of the graft were intact. Part of the conduction system cell population died, another part remained intact. Epicardium contained residual inflammation signs. However, there were no alterations in the endocardium. The qualitative alterations in the transplanted heart were identical to those that the Department staff had previously revealed in denervated hearts.

Similar alterations were found at heart autopsy in 14 previously operated dogs who survived for 1 to 30 days after surgery. All histological studies in these animals were also performed at the Histology Department of the 2nd MGMI named after N.I. Pirogov.

In most cases, epicardium alterations were noted while the endocardium was intact. Meanwhile, it was the endocardium, being under the constant impact of a new body bloodflow, which could have been exposed to the most damaging effect of antibodies. However, that did not happen (emphasized by V.P. Demikhov. − *Auth.*).

The observed inflammatory reaction *in the epicardium* was the result of either surgical trauma, or the consequence of postoperative

[7] Unfortunately, the results of this histological examination are unknown to us.

infectious complications, or the result of aseptic inflammation, which had been well-proven so far.”[6].

Fig. 4. Grishka the Dog. Summer 1962. Photo by M.M. Razgulov. On the author's permission

As V.P. Demikhov expected, I.A. Chervova, being an experienced histologist, did not find any morphological changes that would have indicated the rejection of the second heart transplanted to Grishka. In V.P. Demikhov's opinion, the cause of the donor heart's activity cessation was the technical defects of transplantation that led to thrombosis of the right atrium appendage.

This is paradoxical, but the endocardium intactness and the epicardium damage due to aseptic or septic inflammation, as V.P. Demikhov believed, were convincing him that there was no immunological reaction to transplanted hearts[8].

Differences in immunobiological reactions in animals and humans, and in various animal organs

“The biological incompatibility phenomena at the morphological level in animals and humans have their own specific features. It is known that blood transfusion from one individual to another without taking into

[8] According to up-to-date information, one of the causes of thrombosis in organ transplantation is humoral immunity. - *Ed*.

> account the group compatibility leads to recipient's death. In dogs, neither heterogeneous blood transfusion, nor the transfusion of known amounts of blood from a human to the animal bring damage. In our laboratory, ***E.A. Zotikov*** transfused up to 500 ml of human blood to a small dog. The dog developed pollakiuria and hematuria at 30 minutes after transfusion. In the following days, the dog felt normally and remained healthy further.
>
> We also used large amounts of human blood (obviously cadaveric. − *Auth.*) in a functioning isolated heart-lung preparation of a dog. The heart showed a normal contraction rate, and the lungs performed their function of saturating the blood with oxygen, despite the human blood circulating in their vessels. These observations showed that not only different organisms, but also different organs of the same organism responded differently to transfusion of apparently incompatible blood.
>
> We also noted differences in the functioning of transplanted organs. While at 2-3 weeks after homoplastic kidney transplantation, the renal tissue was significantly changed in a number of animals, the transplanted heart and lungs of the dog Grishka after 4 months (141 days) were subject to only a slight change. Probably, the kidneys that function as a filter and serve as reliable protection for the body are more susceptible to changes during surgical trauma, denervation, and infectious processes" [6].

The necessity to compare immunobiological reactions to transplanted organs in animals and humans, in our opinion, was prompted by the fact that all V.P. Demikhov's experiments, and particularly those made in 1962−1963, were specially focused on the implementation of homo-organ transplantation to a human in clinic.

Technical features of organ transplantation

> "After conducting a large number of experiments, we were convinced that the vascular suture, which can hardly be absolutely reliable, does not solve the problem of the transplanted organ survival either. Careless suture tightening, ligature cross-twisting or "blocking the

knot" (expression of V.P. Demikhov. − *Auth*.) can result in bleeding. If the ligature had been too extremely tightened, that could lead to intima damage, and as a result, to thrombosis, entailing an impairment of blood circulation in the transplanted organ.

With the prophylactic heparinization or fibrinolysin administration within a month after surgery, it is likely that we can talk about an appropriate control over thrombus formation at the sites of vascular anastomoses and ligature of large vessels.

However, for technical reasons, such procedures in dogs are difficult to perform" [6].

Here, V.P. Demikhov, most likely, was cunning. Of course, this was not about the "*technical causes of such procedures in dogs*," but about the lack of control over blood coagulation in dogs under the conditions in which he worked. Many-day administrations of heparin to prevent thrombosis, as well as the fibrinolysin use in increased blood coagulation in the 1960s were rather expensive procedures not only for the animal clinic, but also for the human clinic. The time of widespread use of fibrinolysin for the treatment of coronary artery thrombosis and the treatment of myocardial infarction came much later, in the 1980s. (E.I. Chazov et al.)[9].

But we consider particularly interesting the final section of the text, containing V.P. Demikhov views to the future of transplantology.

Prospects of organ transplantation in human

"If we look at the foreseeable future of organ transplantation, and in particular, heart transplantation, it is clear that the time will come, and an additional, parallel-functioning heart or its ersatz will be transplanted in a

[9] For the first time, intracoronary thrombolysis was undertaken in the USSR on June 5, 1974, at the Institute of Cardiology named after A.L. Myasnikov, the USSR Academy of Medical Sciences, under the leadership of E.I. Chazov (Lenin Prize 1982.).

human for preventive purposes[10].

The space for a cardiac graft in the chest will no longer require removing a part of the lung, as we have shown it in our numerous experiments. In order to provide an appropriate receptacle for an extra heart without removing a part of the lung, we placed the heart, which vessels inside the chest had been already stitched, in a transparent plastic bag. Monitoring the function of the heart prepared for transplantation through the transparent wall of the bag was uncommonly interesting and important.

It is known that at the end of surgery, the thoracic cavity is sutured tightly, after that the air is pumped out. We performed the same procedure when transplanting a heart placed in a bag. We found that the reaction to the complete air removal and achievement of low negative pressure in the bag was the development of cardiac activity weakness, up to the low cardiac output syndrome. Meanwhile, the right ventricle expanded at first, and then its wall lost its contractile capacity. But as soon as the negative pressure was minimized by introducing a small amount of air into the bag, we could observe the resume of cardiac activity.

From the physiological point of view, the essence of these processes is understandable. The heart seeks to minimize negative pressure, attracting external force, when a decrease in ventricular volume entails a decrease in its contraction. The right ventricle wall is thin, easily compliant to compression, and only a third or a quarter stronger than the same parameter of the wall of the left ventricle. Therefore, its activity decreases rapidly as the external pressure rises.

The phenomenon of a cardiac arrest during an increase in external pressure is as exciting as the false century-old idea that the suction action of the chest causes blood flow to the heart [7]. In contrast, it is understood that high negative pressure in the thoracic cavity, which determines the described mechanism, leads to a cardiopulmonary failure in chronic pulmonary emphysema. The same mechanism is observed in chronic bronchitis, when breathing-in is difficult due to increasing negative

[10] It is not clear what was at stake, but it is possible that V.P. Demikhov had in mind an artificial heart.

pressure in the thoracic cavity. Due to this increment in negative pressure, the right ventricle has to increase its contractility, overcoming the external resistance, which leads to hypertrophy of its wall. Thus, in our opinion, hypertrophy of the right ventricle wall in cardiopulmonary failure is a morphological manifestation of negative pressure in the chest.

In our multiple early experiments on isolated heart transplantations (without a pulmonary complex), we were always surprised that the air removal from the pleural cavities often led to a deterioration of the transplanted heart activity. Watching the heart in a plastic bag led to an explanation of this mystery.

Placing a viable human heart and lungs in a plastic bag and then connecting to the femoral vessels is the first and actually safe step to transplanting the heart and lungs. If a viable cardiopulmonary preparation connected to blood vessels and located in a plastic bag functions normally for one or two months, then you can proceed to the second stage of the surgery: its transplantation to the thoracic cavity. Using our originally developed two-stage principle, it will be possible to transplant other visceral organs.

In this state, namely, under sterile conditions at a temperature of +37°C and with ensured blood circulation with oxygenated blood, the viable organs can be preserved [for a long time] until they are transplanted. Similarly, the viability of physiological systems can be determined in stillborn children when their brain is damaged. If an organism with irreversible brain damage is viable, then its tissues and organs can be grown and stored until their transplantation is made to a sick person.

We also believe that in future medicine, a two-stage transplantation of organs with the possibility of their long-term function in conditions of cross blood circulation between a young and relatively old body will eliminate the significance of the age factor" [6].

We emphasize that, speaking of heart transplantation to a human, V.P. Demikhov suggested transplanting an *additional, rather than* *isolated, heart functioning parallel to human's native heart,* either in the chest (experiments of 1940-1950s) or extracorporeally (experiments of 1960s). Today, this is performed using various intra- and extracorporeal devices (implantable and external artificial ventricles of the heart, LVAD). Based on the fact that the use of ventricle-assist devices of the heart today is conceptually a continuation and evolution of V.P. Demikhov's idea, we believe that the concept of assisted blood circulation experimentally developed by him should also be attributed to his priorities we described earlier [8].

Being unable to observe, including with laboratory methods, the reactions of the heart placed in the chest[11], V.P. Demikhov developed an original way of observing an organ by placing it in a transparent plastic bag and locating it outside the host body. This model served him both as a physiological one aimed at studying cardiac hemodynamics, and as the first stage of a safe heart transplantation in humans.

On the one hand, explaining the effect of changes in chest pressure on the activity of an isolated heart, V.P. Demikhov described the effect of the heart function on its structure: with an increased load on the myocardium, the latter undergoes hypertrophy. He tried to extend this provision to a transplanted heart, as we said earlier: the recovery of the donor heart function in the host's body, in his opinion, will inevitably lead to organ survival.

On the other hand, V.P. Demikhov believed that observing the isolated organs functioning outside the body, one can both determine their biological compatibility with the recipient's body, and also maintain them in a viable condition for transplantation to another human, if they are not

[11] In 1955-1957, N.P. Sinitsyn from Gorky developed a method for monitoring the heart transplanted by implanting a transparent "window" made of plastic ~~it~~ in a tortoise *shell* (Sinitsyn NP. Homotransplantation of a turtle's heart. *Experimental Surgery.* 1957;2:16–23) and into the chest wall of a *dog* (Sinitsyn NP. Heart transplantation in experiment. *Bulletin of Surgery named after I.I. Grekov*. 1956;77(7):28–37).

suitable for that very patient.

Model of a physiological organism

“Based on successful experiments on revitalizing and maintaining the viability of the heart and lungs of corpses delivered by ambulances, and also, based on the results of colleagues, we have developed a method that enabled us to save viable organs and to prepare them for transplantation.

In practice, this may look as follows: a corpse will be delivered to a medical institution in the first minutes after death as a result of trauma that has caused irreversible injury to the brain, while the vital functions of other organs, including the heart, can be restored. In this case, having established the mechanical lung ventilation and artificial nutrition, placing the body in a sterile environment with a temperature of +37.5° C, we will be able to maintain a viable condition of this “physiological organism” for a rather long time.

Then we can connect the organs of another corpse in an artificial container with the femoral vessels of this organism, thereby supporting their viability. In the same way, we can connect the body of this subject without a head to stillborn child's body, which is still viable, with the exception of the brain. <…> And the number of such attachable “units” can be arbitrarily large.> This connection to a child’s viable body which brain functions are irreversibly impaired will enable this body to grow and develop, thereby allowing the organs to be grown for transplantation.

Connecting the people who are in a state of agony to such a physiological system by using long vascular prostheses (mandatory considering the compatibility of blood groups, providing oxygen, hormones and nutrients) will allow their treatment to be performed until normal life functions are restored.

If this method is developed further, then it will allow a relatively safe connection to the described young physiological body of the bodies of the elderly for their rejuvenation. It is known that during prolonged storage of isolated organs, the so-called "tissue cultures", in a viable state their natural aging occurs. The addition of embryonic tissue to such culture can lead to its rejuvenation.

This method, in principle, is also applicable to humans if cross-circulation between a relatively elderly organism and the system of viable organs of a young organism or the whole body is established for a long time. It is also possible to obtain grown organs from young bodies for their subsequent transplantation, taking into consideration possible immunobiological reactions after transplantation.

In addition, ***R. Medawar*** and ***M. Hašek*** were able to show that by introducing a certain amount of blood from a future recipient into the donor embryonic material, its tolerance can be changed, and the biological incompatibility during transplantation be minimized. These results can be used for future reproduction of organs from human embryonic structures" [6].

The described method of using a "decapitated" organism with viable organs could be taken for science fiction if today similar methods have not been used everywhere in critical care and intensive care units. Truly to say, however, instead of such a physiological organism, the cardiopulmonary bypass machines, mechanical ventilation devices, and extracorporeal oxygenation and detoxification (artificial kidney and liver) apparatuses are used.

V.P. Demikhov also believed that with the help of such an organism it would be possible to store organs until transplantation (organ bank), as well as to grow young organs for future transplantation, taking into consideration their immunological compatibility, using the results of experiments by foreign scientists[12].

Conclusions

"Thus, the positive results of homoplastic organ and tissue

[12] This refers to the aforementioned work of P. Medawar and M. Hašek on the study of acquired immunological tolerance.

transplantation with long survival periods obtained so far ***do not require further discussions about biological incompatibility*** (emphasized by us. − *Auth.*).

Given this fact, we must begin to develop scientific and practical methods applicable in human clinic, which prerequisite is the preservation of viable organs, their reproduction from fetal materials, etc. It is in this direction that surgeons, physiologists, immunobiologists, therapists, doctors of other specialties, and also engineering and technical personnel should work hand in hand. According to press reports, such a direction already exists, in particular, in Leeds (UK), where British colleagues, transplanting cadaveric kidneys, save the lives of patients.

Scientists from the German Democratic Republic have also contributed to solving organ transplant problems. I especially want to note Professor ***Petros Sokratos Kokkalis*** (Fig. 5), who devoted all his strength, skills, and his tireless spirit to arranging the scientific research [in the field of transplantology] in the GDR.

His premature death was a very serious loss for science and for the author of these lines, who, with the death of Professor Kokkalis, lost his best friend, colleague, and co-author of a number of scientific works, which makes this loss even more painful".

V.P. Demikhov,
Head of Organ Transplantation Laboratory
of the Sklifosovsky Institute for Emergency Medicine (Moscow),
Honorary Doctor of Medical Faculty
of K. Marx University (Leipzig).
Moscow
February 1963. [6]

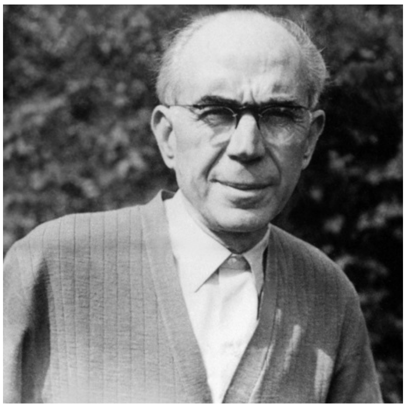

Fig. 5. P.S. Kokkalis (18.09.1896–15.01.1962). Available at: https://digitaltvinfo.gr/news/watch-on-tv/item/19999-o-ellinas-protoporos-tis-xeirourgikis-petros-kokkalis-to-epomeno-prosopo-tou-aftoi-pou-tolmisan

Concluding his address to German-speaking readers, V.P. Demikhov made, as he apparently believed, a logical conclusion that the results he obtained were quite enough to stop "*further discussions about biological incompatibility*" in homoplastic tissue and organ transplantations, and urged his German colleagues to start implementing the experimental results into clinical practice.

However, time has shown that, most of his achievements in the field of organ transplantation (for example, two-stage transplantation, preservation of organs outside the host body, etc.) were not put into practice, with the exception of a few ones (specifically, an anatomical heart transplantation[13], *the concept* of assisted blood circulation − transplantation of the second heart to assist patients; etc.); and his views on overcoming immunological incompatibility by means of biological methods (immunological paralysis, cross blood circulation, artificial parabiosis, etc.) were abandoned after the implementation of pharmacological immunosuppression in transplantology.

[13] In our country, several anatomical heart transplants were performed by S.L. Dzemeshkevich (Personal message).

Nevertheless, following the principle of historicity and considering this text in the chronological framework of his time, we present the “Cover message” to the German Edition, in fact, its first review, from Professor M. Herbst, the Director of the Cardiovascular Surgery Clinic of the University of Leipzig, who noted V.P. Demikhov's merits in world transplantation and emphasized the physiological peculiarity of V.P. Demikhov's views on homoplastic organ transplantation.

Cover message to the German Edition

"In his book" Die experimentelle Transplantation lebenswichtiger Organe" V.P. Demikhov described his numerous experiments.

No doubt, the issue of live tissue transplantation is relevant in contemporary surgery. Transplants of arteries, bones, and corneas mastered by many surgeons and successfully performed, have been widely used. In fairness, we note that these tissues belong to the so-called "bradytrophic" ones in which the metabolism is slow. They survive well in an alien organism, undergo dissimilation over time and are subsequently replaced by the tissues of recipient's organism.

Significantly different conditions determine the success of homoplastic transplantation of the tissues with a high level of metabolism, for example, such as skin or whole organs.

Having developed numerous surgical techniques, V.P. Demikhov gained exceptional famousness and authority. It is him to whom the priority of heart transplantation as organ *per se*, and in combination with parts of lungs belongs. In this book, the dynamics of his work and the improvement of surgical techniques have been described in an exciting manner, which ultimately led to the development of truly safe transplantations of the heart, heart and lungs or whole parts of the body, such as the dog’s head, into another body. With his experiments, V.P. Demikhov contributed to the development of scientific research in the field of transplantation of whole organs, organ complexes or parts of the body.

The methods designed by V.P. Demikhov are relatively simple and understandable, and his technique is captivating and may well be mastered if one wants to repeat the operations he developed. Impressive are the described in the book specific features of physiological and pathophysiological processes in the cardiovascular system during transplantation of the heart and other organs, as well as various technical skills and provisions.

The results of the experiments performed justify their publication for a wide range of readers and predetermine the scientific success of the book.

The most important upshot was V.P. Demikhov's belief that it is possible and necessary to evaluate the results of transplantations through the function of the transplanted organ (emphasized by us. - *Auth.*). The same applies to his work on parabiosis and transplantation of body halves.

In conclusion, I would like to welcome V.P. Demikhov's publication containing a significant number of scientific achievements and defining new starting points for subsequent fruitful work in the field of organ transplantation.

I wish certainly deserved distribution and attention to this book, and further professional successes to the author and his research team.

Professor
M. Herbst, Ph.D.
Director of the Cardiovascular Surgery Clinic,
Leipzig" [6]

Our research has shown that book reviews were also published in (1) Budelmann G. *Fortschr d Med.* 1964;14:506. (In German); (2) Bucherl E. *Chirurg.* 1964;7:331. (In German); (3) Bussi L. *Minerva Med.* 1963;54(956):3672. (In English); (4) Fuchsig P. *Klin Med.* 1965;1:50. (In German); (5) Gruber UF. *Zbl allg Pathol.* 1965;107(1):115–116. (In

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