***Transplantologiya*. 2017;9(3):192-210.**

DOI: 10.23873/2074-0506-2017-9-3-192-210

Key problems of transplantation development and the objectives of higher medical education

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Received: 24 July 2017

The article presented here as a Program lecture of the Rector of the First Saint-Petersburg State Medical University n.a. acad. I.P. Pavlov highlights the key problems of modern organ transplantation, and explores the main challenges for medical professional education in this context.

Keywords: organ transplantation, higher medical education

Bagnenko S.F., Reznik O.N. Key problems of transplantation development and the objectives of higher medical education. *Transplantologiya.* 2017;9(3):192–210. (In Russian). DOI:10.23873/2074-0506-2017-9-3-192-210

Introduction

We are facing a complex and difficult task to cover all the problem areas of modern transplantation in the format offered by an influential Russian transplant journal. It is uneasy to determine the nature of the expected report. On these pages, we will try to present our view on modern ontological problems of transplantology and the tasks they set up for the higher medical education in terms of organizing the educational process.

The main problems of contemporary transplantology

Organ transplantation that promptly burst into life just over 50 years ago currently takes a firm leadership among young medical technologies. There are well-known facts that a wide clinical application of the organ transplantation methods had been initiated by the work of Russian scientists [1, 2]. Transplantation has an exclusive medical potential as a science, because organ transplantation appears the only treatment option that made it possible to improve the quality of life of the patients with an end-stage renal disease, and to save the lives of patients who were formerly doomed to die from cardiac, pulmonary, or hepatic failure. With the development of immunosuppression strategies and regimes, the recipients' quality of life and their life expectancy that could be achieved have become actually the same as in healthy people that gives them the chance to live a worthy life and make a decent contribution to the welfare of their Motherland. However, transplantation has some features that significantly limit its therapeutic life-saving potential, and this reveals its paradoxical nature: with the maximum efficacy of this type of care it is impossible to achieve its maximum availability for all who need it. Unlike other medical specialties, its "innate" feature is rather not the high cost of equipment and medicines, or even the interdisciplinary approach (which we will discuss below) in this area of medical activity, but it is its dependence on the most unusual resource, from a traditional point of view, necessary for rendering this assistance, that is the resource of "healthy" donor organs. In general, for the first time in the history of medicine, and also in the mankind history, the material for assisting organ transplantation should be obtained from a human proper, either living or deceased. This is the very gap between the scientific-and-technical progress in medicine and the ability of a person and the society to

perceive such changes in the usual way of life and the standards of medical care that have being developed over centuries. In this article, we will present the main, in our opinion, problems of modern transplantation and the tasks that they set up for the medical education, as well as the society indirect requirements to doctors as carriers of this knowledge. The efficacy and availability of transplantation care for the population of the Russian Federation is determined by the basic professional training and the skills that the graduates from the higher medical education institutions have received and by the knowledge of the doctors who have chosen transplantology as their specialty.

In order to structure the medical education tasks, it is necessary to identify the main problems that are currently faced by the transplantation in general. The first thing to begin with is the terminology. For the most part, the terms pertinent to organ donation (we defined this very term in 2003) [3, 4] are not quite perfect translations of the definitions formulated in the West that currently do not meet the requirements of today's Russian public healthcare practice; however, the topic of terminology deserves separate studies [5-8]. It is necessary to point out once again to an undesirable use of the term "cadaverous" when discussing the problems related to transplantation; we should rather use the term "posthumous" as the one having more acceptable connotations in the context of treatment both for the general public and for the medical community. We are the initiators of changing the terminology of the past, the terminology belonging to the period when transplantation was establishing as a kind of medical activity; and paying tribute to the founders of transplantology in our country [9], we are satisfied to note a legislative acceptance of new definitions in practical recommendations and guidelines on organ donation and transplantation

issued by the Healthcare Ministry [10]. In the context of organ transplantation terminology currently forming, it would be appropriate to state the necessity of approving the term "explantation" as an acceptable euphemism of the transplantation area that is defined today as "organ removal", "organ retrieval", etc. As for the actual organ transplantation, then sharing the opinion expressed by Prof. Ya.G. Moysiuk, we believe that the term "transplantation" should be referred rather to clinical activity as describing the method of rendering care to the patients with the function loss in any organ(s), including the surgery of donor organ transplantation and subsequent immunosuppression; and the term "transplantology" should be used to describe the entire complex of scientific problems arising in the study of such treatment methods (the passport of this scientific specialty has been defined by VAK as "Transplantology and Artificial Organs", Code 14.01.24). There arise the parallels in the perception of the term "bone marrow transplantation" that is also a method to treat hematological diseases. A scientific support of this treatment method is provided by VAK specialty 14.01.21 "Hematology and blood transfusion" (Item 6 of the Specialty Passport: "Transplantation of bone marrow and stem hemopoietic cells of peripheral and umbilical blood in hereditary and acquired diseases of blood and the immune system, and also in the complex treatment of oncological diseases. The study of indications, preparation methods, transplantation and post-transplantation management, efficacy and specific features of post-transplantation hematopoiesis recovery. Typing and selection of histocompatible donors, establishing of bone marrow and stem hemopoietic cell banks"). Despite nearby positions in the VAK Listing and the use of the word "transplantation" (from Latin 'transplantare': I transfer), as well as similar methodological features of rendering medical care (donor-

recipient compatibility, immunosuppression), the organ transplantation and the bone marrow transplantation are two different types of medical activities, identified, first of all, by the source and type of donor material.

After such a terminological differentiation, it is possible to outline a scientific-practical search as to which problems of organ transplantation as a type of medical care today are the main ones. Let us quote them:

- The problem of the shortage of posthumous organ donors;
- The problem of the shortage of optimal donor organs;
- The gerontologization of donor and recipient pools;
- A rapid development of emergency and urgent neurosurgical care, leading to changes in organ donation structure;
- The problem of searching for optimal immunosuppression regimens in connection with changes in nosological and demographic characteristics of donors and recipients;
- The problem of how to prolong the allograft life span and a recipient survival.

What tasks do these problems set up for transplantology as a science? They are the following:

- The scientific search and development of optimal administrative and organizational solutions in the field of rendering the emergency medical care, anesthesiology, postmortem donation, and transplant coordination;
- The development and implementation of organ-saving technologies implying a widespread use of extracorporeal circulation in situ and ex vivo;
- Ensuring the efficacy of organ transplantation through optimizing the immunosuppression regimens (minimizing and eliminating calcineurin blockers);

- The development of new legal norms and the substantiation of the need to adopt them by state regulatory authorities (for example, justification of a living non-genetically related donation between spouses, by guardians, adopters, and foster parents, children);

- The identification of social and humanitarian problems in transplantation and organ donation, the development of recommendations on the interdisciplinary search for solutions on the major limiting factor in transplantology, i.e. the shortage of donor organs, the rationale for the necessity to conduct broad socio-cultural and ethico-philosophical studies in this field;

- Seeking a dialogue with representatives of the traditional religious confessions in the Russian Federation to create optimal humanitarian conditions to come to an agreement in the field of the efficiency and accessibility of transplantation care.

From surgery to an interdisciplinary approach in the development of transplantology

The main surgical techniques of the explantation and transplantation of donor organs from the deceased and related donors were developed at the turn of the 20th and 21st centuries. [8, 9, 11, 12]. The efficacy of transplantation as a medical care having its main sense in being available for all who need it, rather than demonstrating the surgical art of high-class surgeons or surgical teams, lies in the plane of strategic decisions, which will be discussed below.

One should emphasize that surgical procedures for organ explantation and transplantation should be standardized and unified (from Latin "unus" one, "facio" I do, unite), because a technical error of one surgeon can lead

the work of a team of several dozens of specialists and their assistants to failure, because the success of transplantation depends also on skilled explantation. Organ transplantation combines the basic techniques of general surgical training and comprehensive knowledge in the field of vascular surgery, general topographic anatomy and operative surgery. It is necessary to introduce special training hours (up to 8 hours) in the curricula to provide such knowledge to medical students and to prepare them for mastering these disciplines, as well as to arrange 16-hour (2 day) master classes with the subsequent certification and permission to perform transplantation and explantation for the physicians who improve their knowledge in a chosen specialty. *The First Saint-Petersburg State Medical University* was the first in the country to have gained and integrated the experience of such postgraduate education [13].

The clinical development of organ transplantation demands a serious reorganization of routine clinical practice and care. In early years and decades of establishing organ transplantation as a routine practice, it was wholly managed by clinical transplantologists, usually surgeons. Later, we came to the conclusion that the tasks of surgeons would most appropriately include the technically competent performance of the surgical procedures on actual explantation and transplantation, and the provision of postmortem donors should be the task of emergency hospitals, specifically, those units that render urgent neurological and neurosurgical care. Starting from the mid-1980s, there have been transplant coordinators performing these tasks at hospital, regional and state levels in the countries having well-developed transplantation care systems [14].

The first legal Act that gave rise to the development of transplant coordination in the Russian Federation was St. Petersburg Government

Instruction No. 323p "On the Staff Structure of an Organ Donation Center" that was the first to introduce the position of a Hospital Coordinator in the staff structure of the Center for Organ Donation at I.I.Dzhanelidze Research Institute of Emergency Medicine in St. Petersburg, the oldest donor coordination center in Russia [15]. For 10 years (2003-2013), 12 training programmes for transplant coordinators were arranged in close cooperation with the *First Saint-Petersburg State Medical University* and the Association of Transplant Coordinators; the concepts and principles of transplant coordination had been developed and they were recognized by the scientific community, the Russian Transplant Society, and healthcare authorities at the regional and levels [16].

In the opinion of Professor Ya.G.Moysiuk, the first model of transplant coordination in the form similar to the European one was adopted in St.Petersburg in 2006. The search of efficient organizational solutions in this area is still under way; the establishing of a nationwide donation and transplantation system, and its Registry is on the agenda. The structural components of such a system have been developed by the Ministry of Health of the Russian Federation and their implementation led to an increased efficacy of transplantation programs in Moscow and Russian regions. Thus, it was the introduction of innovative elements of transplant coordination, rather than any new surgical innovations that led to extending the transplantation care over the past few years, according to the Registry of the Russian Society of Transplantologists (created on the initiative of Ya.G. Moysiuk) [17]. In 2015, there were 36 centers for kidney transplantation, 17 for liver transplantation, and 10 for heart transplantation in the Russian Federation. The waiting list for kidney transplantation in 2015 included 4,167 potential recipients, accounting for approximately 13% of the total

(31,500) patients receiving dialysis. The donor activity level in 2015 amounted to 3.0 per 1 million of population, while the rate of multiple organ donations was 57.8%, and the average number of organs harvested per one effective donor was 2.7. In 2015, the transplantation rates per 1 million of population were 6.5, 2.2, and 1.2 for kidney, liver, and heart transplant, respectively.

The number of liver and heart transplantations is increasing in the Russian Federation. In 2006, there were only 11 heart transplants performed, and in 2016, V.I.Shumakov Federal Research Center of Transplantology and Artificial Organs became the world leader in heart transplantation: 132 successful cardiac transplants were performed for a year with the outcomes comparable to those in the world. Moreover, heart transplantation is currently performed by the Russian medical centers in Moscow, St.Petersburg, Krasnoyarsk, Belgorod, Ufa, Kemerovo, Yekaterinburg, Novosibirsk, Krasnodar. In 2016, total 220 such transplantations were performed. The first place in the country by the number of organ transplant performed belongs to Moscow and Moscow region that have 10 functioning transplant centers where almost half of all kidney transplants and more than 65% of all liver and heart transplantations are performed [18]. An absolute leader in kidney and liver transplantation is the N.V.Sklifosovsky Research Institute for Emergency Medicine where up to 70 liver transplants and up to 120 kidney transplants are performed annually.

All this proves the necessity to arrange the educational curricula of the undergraduate training in the specialty "Public Health and the Organization of Public Healthcare" in a way that would include the studying of the organizational principles of a high-tech care through the transplantation of organs and tissues in order to develop transplantation in the Russian regions.

Changing the structure and demographics of posthumous organ donation as a challenge to modern transplantation

A "competitive" position of organ transplantation in reference to related medical specialties has become a new and, to some extent, unexpected problem. At initial stages of the transplantation development, in the 60-70s of the past century, it seemed evident that patients who died from diseases and injuries of the central nervous system became a "natural" source of organs for potential recipients. Many years had passed before the problem of legitimizing the brain death diagnosis was solved; the first instruction on stating the fact of brain death was adopted in 1987, and that option was legislated in our country only in 1993. All that allowed the initiation of extrarenal transplant procedures that were performed only sporadically until the beginning of 2010 [19, cit. p.p. 0-67]. However, over those years, the organization of neurosurgical care and patient delivery to hospital were significantly improved [20, 21]; these innovations took place in our country as well. According to the database of St. Petersburg Bureau of Forensic Medicine, the number of deaths among people with brain traumatic injury aged from 18 to 60 years [20] decreased five-fold between 2003 and 2009; and currently the main source (90%) of donor organs in St. Petersburg comprise the patients who died from generalized vascular diseases manifested in the form of an acute cerebro-vascular accident of an ischemic or hemorrhagic type.

Timely diagnosis and timely life-saving surgical or therapeutic interventions have led to the fact that such patients do not develop a classic clinical pattern of brain death, as they used to before. C.L.Sprung et al. (2003) reported that the number of patients with brain death in Europe does

not exceed 8% [23]; 2-3 cases of diagnosed brain deaths per month as common for ICU were reported by E. Wijdicks (2011); 1-2% of all deaths from the central nervous system conditions were indicated by S.D. Shemie (2015) [24, 25]. Similar data were reported by Dr. S.K.Sergienko, the Head of the Neurological ICU (of 12-bed capacity) in Mariinsky Hospital, St.Petersburg. In 2014, 648 patients were treated there, 219 of whom died making the mortality rate of 33.8%; the brain death diagnosis was ascertained in 25 death cases (11.4%) and 6 of them became donors. In our opinion, the situation in St. Petersburg looks like a "model" and it will only aggravate as the emergency medical care system is developing, paradoxically deepening the crisis in organ donation. What conclusions should we draw of this?

At the stage of undergraduate training, the students should be taught the basic concepts of diagnosing brain death and the principles of donor management in the framework of training the specialists in neurology, anesthesiology and critical care. As for postgraduate training, it is necessary to deepen the knowledge through postgraduates' attending master classes, possibly with subsequent certification. Our University has a positive experience of such activities, the same as the case with rotations in Transplant Surgery. In St. Petersburg, it took only 10 years to reach a certain consensus thanks to the annual Schools of Transplant Coordinators arranged from 2003 to 2013. Now these events need to be assigned a certain status in the system of continuous medical education.

Another, especially important aspect of the donation system development is the need to search for new sources of donor organs, taking into account the advances in cardiac surgery and resuscitation technologies, especially such as the extracorporeal membrane oxygenation. At early stages

of transplantation development, a favourable outcome of transplants could be guaranteed only if the ideal quality of the donor organ and the donor proper was provided. Since the mid-90s, the struggle of the transplantation community for increasing the number of donor organs has started; the criteria for the selection and acceptability of transplants have been changing, as well as the strategy of their pre-operative evaluation, harvesting, distribution, and preservation. A general reduction of brain-dead donors in number and a critical shortage of donor organs have created the prerequisites for using alternative sources of donor organs. Such sources are the organs obtained from expanded criteria donors (ECDs), as they are termed in literature, as well as the organs from donors with an irreversible cardiac arrest, or asystolic donors (ASDs) [26-29]. The viability of grafts obtained from ECDs is mainly limited by the ischemic-reperfusion injury associated with explantation. This injury also reduces the recovery potential of such organs already affected by the age-associated degenerative changes (e.g. interstitium fibrosis, glomerulosclerosis, atherosclerotic arteriolar lesion) that preceded the death of the patient who became the organ donor.

The first reports on the successful use of renal perfusion system for the kidneys from ASDs raised the interest to the prospects of using the instrumental perfusion techniques for other organs [30-35]. In this regard, we should note that currently used techniques of organ preservation considerably differ from the concepts existed in 1960s and 1970s; now the instrumental methods enable us to prolong the organ storage times, and also to select and diagnose organs, to control the organ vascular system. Both the advantages of instrumental perfusion, and its new tasks became obvious [36, 37]. The innovative perfusion technologies create the prerequisites for increasing the period of graft storage, and also for pharmacological and

instrumental "repair" of the donor organ damaged in the ischemia period (from the moment of donor cardiac arrest to the moment of graft reperfusion at transplantation).

Like cardiac surgery, whose role was limited only to occasional extraordinary procedures prior to the routine use of heart-lung machine; transplantology, as a science, expects a possible quantitative and qualitative breakthrough with the practical implementation of tools and devices for resuming perfusion and preserving donor organs. After the heart-lung machine had become an integral component of the operating room, the number of surgical interventions went to tens of thousands all over the world, making them available to almost everyone in need, and not just for those patients who could undergo a cardiac surgery "on a beating heart only". The innovative extracorporeal technologies (heart-lung machine), new for surgery of that time, made it possible to overcome a seemingly unavoidable contradiction, namely to save a human life with a non-functioning heart. So today, the main problem of transplantology (the contradiction between the demand for transplantation and the number of operations performed), the search for a sufficient number of optimal donor organs, can be solved by routine means of mechanical life support in the organs and organ complexes of a deceased person, which obviates the problem unsolvable by the traditional approaches, namely, the vulnerability of donor organs to ischemic injury, specifically in suboptimal donors and ASDs [36]. Since 2009, we have consistently developed the concept of "perfusional recovery of donor organs and keeping them viable" [37]. The main idea of the concept is graphically shown in Fig. 1.

Nowadays, we see the change of the organ donation paradigm on the agenda: instead of the traditional hypothermic conservation (the Russian

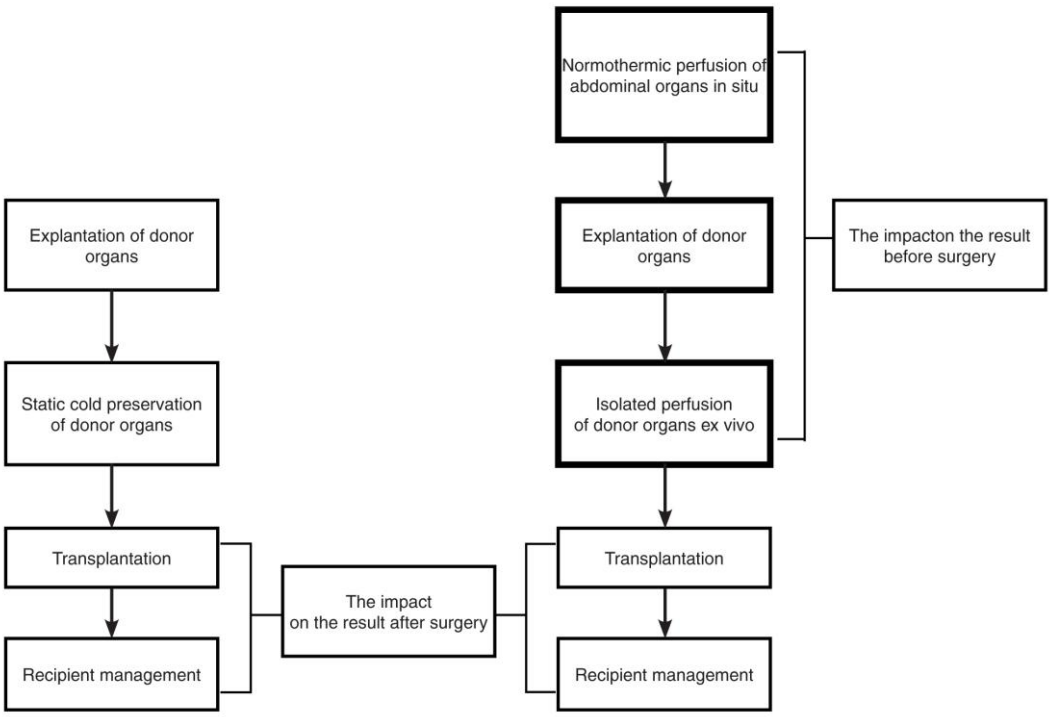

Fig. 1. The scheme reflecting the perfusion approach advantages in organ donation. The right part of the scheme reflects the possibilities of influencing the graft quality before the transplantation has been performed

term itself seems a misleading interpretation from English since it is rather the "preservation" of organs than the "conservation" that is actually the "conservation" of ischemic organ damage in the context of the problems under discussion), it is necessary to implement a continuous normothermic organ perfusion at all stages of explantation and transplantation (artificial life of organs?), which would both expand the donor pool and prolong the organ survival. We are aware of the necessity to adhere to the anticipatory organ-preserving tactics in organ management (organ – to be – transplant) at all stages of the explantation process: from donor conditioning to organ transplantation, since the entire spectrum of probable events of the graft

survival in the recipient's body has been programmed before the organ is removed and transplanted to the recipient. In practice, outside the context of the terminological clarity expectation, this means the current need for a speedy development and implementation of systems for the perfusional preservation and recovery of donor organ viability, i.e. the need for the equipment and devices to be used at all stages of donor organ movement from the expanded criteria donor to the recipient in the operating room.

An evident proof of our concept validity has been demonstrated by a 5-year kidney graft survival achieved using the normothermal perfusion in situ, and by a 5-year survival of these graft recipients, the outcomes being comparable to the recently recognized "golden" standard of the donor resource, i.e. the donors with ascertained brain death [38]. Of note, we were the first in the world clinical practice to prove that the renal grafts do not lose their quality even after absent blood circulation in a deceased patient body for one hour (i.e. within an hour of the so-called primary thermal ischemia time); however, it is important when we use *a posteriori postmortem* the perfusion protocols including streptokinase, anticoagulants, and the leukocyte filters incorporated in the extracorporeal membrane oxygenation circuit [39]. The results have been so encouraging that the First St. Petersburg State Medical University in cooperation with the RF State Research Center "Central Research and Development Institute of Robotics and Technical Cybernetics" (St. Petersburg) and I.I.Dzhanelidze Research Institute of Emergency Medicine supported by the grants from the Ministry of Education and Science of the Russian Federation and the Government of St. Petersburg have conducted a 3-year scientific research to create an original device for a therapeutic perfusion of the donor liver ex vivo [40].

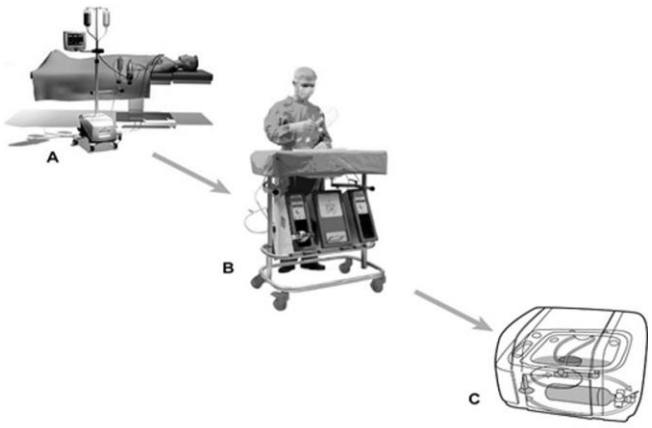

Fig. 2. The scheme of applying the perfusion approach to organ donation: Module A: the perfusion in situ in donor's body (restoring the viability before explantation); Module B: testing, selection, "treatment", and modification of donor organs ex vivo; Module C: preserving the organ viability at the transportation stage

In our opinion, the implementation of the proposed concept would be possible through the creation of a technologically new donation model (Figure 2) that would imply the establishment of specially designated units in transplantation centers (donor centers, donor coordination centers) responsible for carrying out the tasks on "resuscitation and repair" of donor organs, as well as their selection and treatment. And, as early as in 2009, we already stated that "... the evolution of immunosuppressive drugs turned the immunosuppression from stiff unvaried schemes of patient management, to the "palette" (as expressed by Prof. Ya.Moysiuk) of professional solutions. The same approach will be justified when choosing the organ preservation algorithm from the existing arsenal of methods. This would legitimate all forms of donation, without the subdivision into ideal, marginal, optimal, and suboptimal grafts. The only necessary step here would be to individualize

the "schemes of donor organ preservation" (in a similar way as it has been done with immunosuppression schemes) with regard to explantation conditions, and an adequate selection of the recipient. We believe the following probable scenario of actions could be justified when working with an expanded criteria donor. After the cessation of blood circulation in the donor (with brain death or with irreversible circulatory cessation), a "therapeutic" (from θεραπεω - I serve, I care) extracorporeal perfusion of the entire organocomplex to be explanted can be performed. After the optimal parameters of organ perfusion have been achieved, the surgical stage of explantation is performed with the perfusion of donor operating field being continued. That may be followed by the stage of an isolated organ-specific perfusion to evaluate organs, make their selection, undertake management and repair. In the near future, the concept of perfusional repair of donor organs can lead to establishing specialized units in transplantation centers (donor centers) that would be engaged in "resuscitation" and "repair" of donor organs in the way similar to conventional ICUs for patients; meanwhile, the perfusional preservation schemes will be chosen on individual basis depending on the type of the organ obtained from one and the same donor. The strategy and tactics of transplant organ repair would allow the outcome and quality of organ transplantation to be controlled even before the transplantation has been performed, and could lead to a partial solution of the problem of donor organ shortage. The realization of the proposed concept seems promising and requires further study "[37].

Such projects did not met understanding in the Russian transplant community; almost 8 years have passed since the publication of this strategic paper, but today such Regional Organ Assessment and Repair Centers (ARC's) ("reconditioning" seems a "weak" term for us in its semantic

meaning) have already been established in the USA and Canada [41, 42]. After the explantation, a normothermic perfusion of the isolated organ(organs) ex vivo should be performed in the device based on the rotary or roller pumps (see Figure 2, Module B), thus offering the possibility to evaluate the organ, to improve its condition by using filters, and medications for the prevention of undesired ischemia-reperfusion consequences, and to apply new biomedical technologies, such as a targeted delivery of antibodies, siRNA [43, 44]. And, finally, the third stage of the proposed methodology implies the organ transportation to the transplantation center in a portable device (see Figure 2, Module C) providing an ongoing flow perfusion. The perfusion solutions must provide oxygen delivery, which allows the synthesis of ATP de novo (based on an erythrocyte suspension, artificial hemoglobin, perfluorocarbon emulsions, nutrient components, and energy substrates in cells).

The strategy and tactics of the graft repair would allow the outcome and quality of organ transplantation to be controlled even before the transplantation has been performed, and could lead to a partial solution of the problem of donor organ shortage by using the grafts that are considered hardly suitable today. Over time, the transplantation of almost all organs from asystolic donors will be feasible, as shown by the first pioneering works in this area, i.e. transplantation of the lungs, the liver, and even the heart [30-35].

It is quite obvious for us that the creation of the above-described "park" of perfusion machines is possible through the combined efforts of several universities, both technical and medical, since the interdisciplinary nature of transplantology, as a scientific knowledge, is a universally recognized, starting approach. The availability of university educational

platforms will ensure an inter-regional scientific integration aimed at creating a high-quality original product in our country for solving the problem of donor organ shortage as the main task of transplantation. This assumption was confirmed by the creation of the "Consortium for Organ Preservation in Europe" (COPE) in the European Union 3 years ago. The COPE Consortium is funded through the EU's 7th Framework Programme on research, technological development and demonstration and is the official organ preservation task force of the European Society for Organ Transplantation (ESOT). "The Consortium brings together academic institutions, clinical and scientific experts from across Europe to work together on advancing organ preservation techniques. The COPE Consortium aims to advance and develop organ preservation technologies by performing clinical and translational studies with on-going experimental refinement. Through testing quality and safety, increasing the efficiency and refining preservation strategies we set out to bring technologies from the bench to the bedside". [45]. It is amazing that all these approaches represent the development of the brilliant ideas put forward by S.S. Bryukhonenko 90 years ago [2]. At national congresses, conferences, and scientific events on Transplantology, we stated many times the need for such cooperation between our Russian universities. In our country, after the "perestroika catastrophe" that resulted in the loss of a significant part of the scientific and technical potential, not so many teams remained whose members could have developed perfusion devices for transplantation (critical care, pulmonology, cardiac surgery). They are the Moscow Institute of Physics and Technology (MIPT), the Experimental Units in V.I.Shumakov Federal Research Center of Transplantology and Artificial Organs, LLC "Dona", and LLC "BIOSOFT-M", the Zelenograd Innovation Center, the above mentioned

Institute of Robotics and Technical Cybernetics, and I.I.Dzhanelidze Research Institute of Emergency Medicine. Their cooperation and the coordinated role allocation between the developers and the "donors of ideas" could play a constructive role in the process of seeking the support from the state to implement the projects.

New immunosuppression regimens

The problem of using suboptimal donor organs inevitably forces the clinician to seek the ways for the optimization of immunosuppression schemes. And here, we are planning a revolutionary turnabout. As noted above, the main problem of modern kidney (and not only kidney) transplantation has been the change in the nosology profile of postmortem donors, being mostly the patients who died as a result of vascular diseases. The functional resource of the renal graft is compromised by a general atherosclerotic process, so such a graft is more sensitive to the toxic (vasoconstrictive) effect of calcineurin inhibitors (CNIs); all this requires an individual approach to immunosuppression regimens. The use of schemes involving mTOR inhibitors (rapamycin, everolimus) for transplantation of the kidney from an ECD allows the level of cyclosporine (CsA) to be decreased, thus minimizing its nephrotoxicity. At present, there is no clear algorithm for using combination of CsA in various clinical situations. However, we have our own unique experience of using new immunosuppression regimens with the dose reduction and withdrawal of CNIs [46]. Having summarized our 5-year experience, we are convinced that the early administration of mTOR inhibitors is indicated in all cases of transplantation of renal grafts from ECDs. We have developed an original scheme that allows a CNI dose minimization, which leads to the decrease of

the drug-related nephrotoxicity manifestations without compromising the overall therapy efficacy, and ensures a stable renal transplant function in the long-term after ECD kidney transplantation [47]. The presented data convincingly demonstrate the need for graduate medical students to get as much knowledge as possible on the pathophysiological and immunological processes in recipient's and donor's body; and this knowledge should be provided at appropriate stages of basic education, so that when obtaining clinical skills they could have a clear idea of the immunosuppression role and place in the life of organ transplant recipients.

Organ transplantation, biobanks, and personalized medicine

The brief description of a relevant scientific search for new immunosuppression therapy regimens logically leads to the necessity to describe the processes occurring in a donor organ. There are still a number of ongoing studies on ischemia-reperfusion injury mechanisms in donor organs. And the molecular mechanisms that would actually limit and regulate the viability of donor organs are still unknown. The coming era of personalized medicine dictates the necessity for individualized approaches to solve these and other problems. The creation of transplantation biobanks followed by various studies on their base on them may be a key solution. Biobanks are an essential component of the personalized medicine, which allows large-scale population studies, the discovery of new biomarkers and therapy targets, the development of new drugs. The significance of this relatively young industry has increased many-fold in recent decades, making its way from small national collections of biological specimens to large national and international biorepositories. Biobanks are the complex systems for the storage of human biological specimens and associated clinical

information. Over the recent 20 years, biobanks and related scientific activities have become an integral part of personalized medicine, which has provided impressive advances in understanding the mechanisms of a disease development, in working up the methods for the prevention, diagnosis, and treatment. The main goal of the educational programs in medical universities should be the training of specialists for the implementation of biobanking in clinical practice and the related scientific research. This is of special scientific interest in transplantology where the main means of rendering care is another person's organ with a different genetic structure, that is to be "imported" into the body of a new host. The molecular basis of its "life span" has not yet been studied. The creation of transplant sample tissue banks where each step is recorded and tracked starting from donor tissue collection and throughout its storage till the end of its life span will open up unprecedented research opportunities. [48].

Transplantologist and the society

The main problem in transplantology development seems the perception of organ donation and transplantation by society and the medical community. The donor organ shortage has deeper, essential causes than simply the medical ones described above. As we have already noted, the entire technological process of transplantation involuntarily addresses the human body as a resource, as a medication that becomes available when a person either dies or voluntarily surrenders his body or its part as a means of saving someone else's life. The issues of organ donation and transplantation affect the very essence of a human, because when discussing this type of help as acceptable, one immediately refers to the reflection on one's own demise and the posthumous fate of the body. We should admit that today the

issues of the end of life are not discussed within the framework of secular society; this issue has been completely delegated to the Church and the philosophical and ethical communities of thinkers. Today's secular man lives as if there were no death. According to the definition of Priest A.D.Shmeman, there is a "conspiracy of silence" in secular society around the problem of death [49]. Therefore, the issue of postmortem donation seems excessive, unnecessary, and unpleasant for a layperson. On this basis, there is some kind of a conditional confrontation between the transplant cohort and the rest of the society.

What does this seemingly speculative confrontation lead to? To a definite technical ability available in the modern medicine arsenal to assist by organ transplantation, and, nevertheless, to an actual inability of the organ transplant "workshop" to provide the assistance to all those in need. Meanwhile, there is easily identified problem of an adequate knowledge transmission, namely, the ethical, educational, and medical knowledge transfer from the transplantation community to the general population and entire medical community as a whole; whereas an obvious disagreement between an expert (doctor) and a layperson arises. This, in turn, brings predominating "sub-medical" prejudices into mass media leading to a failure of national transplantation programs, simply saying, to the inability of a "healthy" majority to protect an "unhealthy" minority.

Let us address to some available illustrative examples. The results of extensive and detailed public opinion survey that was made by Levada Center with the support of the Presidential Grant in 2013 and demonstrated that only 21% of Russians do not object against their being postmortem organ donors , 41% of respondents were not ready to be postmortem organ donors, 38% had not formulated any personal attitude to organ donation;

and, surprising were the opinions, sounding like: "I'm basically against organ transplants to other people" from 3% of responders, or "...in general, it is inadmissible to use the organs of one person to treat another" from 14% of 1,630 respondents. Moreover, when answering the question "Do you think, the illegal trade in human organs is extended in Russia?" more than a half of the respondents (urban and rural residents) gave the affirmative answer, and only 3-7% of the respondents believed that there was no trade in human organs in the Russian Federation [50].

Significant is also the fact that some ignorant views on the nature of transplantation care are often prevalent in the medical community, as well. Thus, the Polish Survey of 2006 reported the opinions of directors and chief physicians of 159 medical institutions in Poland, including 68% of municipal hospitals. Seventy one per cent of these hospitals were involved in organ donation procedures. It turned out that in 48% of cases, the head managers of the institutions did not have a clear idea of how a patient with terminal brain damage becomes an organ donor [51]. The data of the Physician Opinion Survey made in St.Petersburg in 2011 demonstrated that 82% of Anesthesiologists and Critical Care Physicians consider organ donor management a routine practice. Meanwhile, among neurologists, 40% reported their unbelief in legal provision of the work with organ donors, 20% were unaware of the existence of the Transplantation Law, and 40% had never heard about the issued Instruction on the Diagnosis of Brain Death; 83% had never had to work with transplant teams [52]. All that means that there are significant gaps in the general and special training of the doctors who are expected to keep the stability of donor supply.

Higher medical education and transplantology

The educational tasks in transplantology need to be addressed, keeping in mind its main problem: the shortage of donor organs. It is universally recognized that new medical technologies have been developing so rapidly that they acquire an interdisciplinary, synthetic character, posing complex tasks for modern higher medical education. Before, we were used to "grow" a specialist, gradually providing him with the opportunities to gain knowledge of his chosen specialty. Thus, the traditional, pre-industrial way to update medical knowledge was the state of affairs where a doctor could master the top professional skills without resorting to a wide involvement of related specialists, since rendering medical care was akin to mastering the craft personalized by tasks and types of performance; roughly speaking, the doctor himself was the carrier, store, and source of both knowledge and method(s) of rendering care.

In transplantology, such approach can not be justified. The top of the transplant art is organ transplantation in the operating room and the stable health status of the recipient discharged after such surgery. But for this to happen, the work of dozens of specialists from different institutions is necessary both on the day of surgery, and afterwards, in the postoperative period when the knowledge of surgeons and anesthesiologists, intensive care specialists comprising the transplantation teams is strongly required. A lifelong follow-up of organ transplant recipients requires a deep understanding of unusual clinical and pathophysiological processes occurring in the recipient's body (as compared to "classical" patients). All this may be said about the basic transplantation process: keeping the recipient waiting list, as well. This broad clinical concept comes down to the need to support the life of patients by using all available means and facilities

of modern medicine, until they receive a donor organ. An on-going psychological assistance to the patients before and after organ transplant surgery is a mandatory requirement today. The same requirement can be referred to the need for infectious care of the patients at all stages of their life. Even a brief description of transplantology problems demonstrates that they can not be solved within the competence of a single Medical University Department or Faculty; and, to be efficient, the transplantation needs other principles of education and training. There is a need for a "distributed" acquisition of sustainable knowledge with the involvement of various groups of medical experts.

In the most general terms, it is possible to outline potential options for the university education in the section "Transplantology and Artificial Organs", the educational programs for undergraduate medical training, the educational programs for postgraduate and advanced training of doctors, and the educational programs designated for the general public and implemented in conjunction with trained students, doctors, professional medical communities, and public organizations of patients.

Pre- and post-graduate training in this field should be planned, based on the likely jobs of future doctors. The general and specialized transplantation education to ensure organ donation in the healthcare system requires pre-graduate training for all categories of students. For this purpose, the lectures and practical sessions should be arranged and conducted by Transplantology Department teachers of a conditional medical university in the amount of 2 to 8 academic hours in all faculties of basic medical education (anatomy, pathophysiology, histology, immunology, infectious diseases, gastroenterology, cardiology, cardiac surgery, general and thoracic surgery, nephrology and dialysis, anesthesiology and critical care medicine,

neurology, public health, emergency medicine, etc.). In our opinion, such "throughout" training must be completed with an 18-hour "consolidating" course in the specialty "Transplantology and Artificial Organs" in the sixth year of Medical University. With such training, the graduates of the university, even if they do not become transplantologists, will carry the knowledge that can ensure competent decisions on organ donation issues and refer the patients with end-stage diseases to transplantologists for being placed on the waiting list for transplantation.

The emphasis in the field of the advanced postgraduate education should be made on a 36-hour subject-specific training at the Transplantology Department and specialized training in general, clinical, and legal issues of brain death diagnosis and donor management for certain categories of doctors having primary specialization. Special education and training of doctors for transplantation departments (for example, surgeons, anesthesiologists, nephrologists, endocrinologists, gastroenterologists, cardiologists, etc.) should include subject-specific advanced training and residency programs for graduates in their chosen specialty.

The description of these educational problems only partially covers the request of the transplantation community (and hence the request from potential recipients of donor organs) to institutions of higher medical professional education. The subject matter of training specialists in transplantation (and today the circle of such specialists is expanded owing to the laboratory "wing", namely, the diagnostic laboratory specialists, geneticists, biologists, immunobiologists, bioinformatics specialists) should include the issues of educational cooperation with other faculties and departments competent in training specialists with fundamental knowledge on molecular biological basics in clinical practice, the departments involved

in the training of specialists in "-omics" diagnostic techniques (proteomics, metabolomics, epigenomics) and verification of clinical conditions.

Today's medicine, as a field of scientific and practical activities, is actually facing the changes in the classical model of the surrounding reality realized on the principle of "a man and an instrument". It has been substituted for the combination of "a man and a machine" where the physician becomes an element of the recognition and decision-making system. On the one hand, this requires the engineering and technical competence from future medical specialists, and the consequent need to change the classical system of medical education; but on the other hand, the requirements to moral and ethical aspects in the training of modern doctors are increasing. It would be important that technologization of the treatment process and the increasing trend towards semi-automatic decision-making based on the established clinical algorithms and standards would neither have brought the alienation of the treatment process from a patient nor posed the confrontation between τέχυη (Ancient Greek: craft, skill, ability) and βίος (life, existence); all that should not separate the doctor's direct mission to bring healing, or consolation (if cure is impossible) from the medical diagnostic process, which today is more of a technical or even a high-tech task, the transplantation being an obvious example of it. That could have resulted in the patient's feeling of being "abandoned", being in artificial situation, if not saying the patient's would perceive oneself as the "victim" of high medical technologies capable of both giving life and taking away the feeling of a full life. All this applies to organ donation. The ethical problems of innovative medical technologies are nowhere as clearly defined as in the established donation and organ transplantation practices. Actually, no country has the legislation in this area that could be considered quite

universal and comprehensive. Laws can not cover the intellectual-sensitive sphere of reflections of ordinary people and medical professionals in the challenges predetermined by scientific and technical progress. However, the efficacy (availability) of the transplantation care for the population depends precisely on the attitude of the population proper to postmortem organ donation, and transplantation. At the same time, we cannot demand the sympathy from the society when its members are not aware of the practice of transplantation; we have to "talk" with society, share knowledge. The delicate balance of opinions that arises around the problem of posthumous organ donation is based on the ethical assumption and even desirability of this type of medical care, provided that the society traditional requirements to the norms of behavior and morality of both ordinary people and medical professionals have been maintained.

The posthumous organ donation practice after euthanasia legally approved in the Netherlands and Belgium has convincingly illustrated the importance of ethics in medical activities on donation and transplantation for the Russian society. Today, the arguments for such practice could be the sufferings from severe malignancies and also from long-term depressive conditions [53-55]; the existence of such a practice will inevitably lead to the attempts to increase its acceptability and to the emergence of such organ donation models that would have threatened the very essence of a human. W.Glannon (2013) recommended a protocol for organ harvesting that does not require a necessarily wait for the death of a patient with an incurable disease if there is a lifetime patient's consent to posthumous donation [56]; in such case, the researcher considers anesthesia and pharmacological "shutdown" of the future donor's consciousness to be the most important steps. The informational impact of such intentions can shake the traditional

society trust towards transplantation and, consequently, deprive the patients awaiting for organ transplantation of the last hope.

As we have just tried to show, the advances in transplantology, more than in any other medical specialty, depend both on scientific and technical progress, and also on the society's acceptance of the breakthrough medical technologies. Today, the mentality of common people is largely determined by the mass media that present complex problems in a reduced, simplified form [57], which maximally accentuates the predominant role of medical education both for the efficacy of transplantation programs, and for the meaningful perceptions of the medical community and whole Russian population on the transplantation as on the means of saving the lives completely dependent on the views in the society.

As an example, we can cite the fact of the recent past. It is no exaggeration to say that the most important event in Russian transplantology was the First Scientific and Practical Conference "The Role of an Anesthesiologist in Organ Donation" that took place in St. Petersburg in 2003. That was the first joint event dedicated to the problems of organ donation, and attended by the previously existing two opposing cohorts representing the medical community: anesthesiologists and ICU doctors, on one part, and transplantologists, on the other. The consensus reached at that Conference served the basis for the development of the regulatory documents that were adopted by the Healthcare Committee of St.Petersburg Government in 2004-2006. Their coming into force led to a 4-fold increase in organ donation over 3 following years, the establishment of the programs of multi-organ donation and heart, lung, liver, and pancreas transplantation in St. Petersburg. As we see, the key factor was the problem of education and knowledge exchange [58].

Throughout the world, transplantation originated as the art of single-player enthusiasts, existed as "cottage industry", according to T. Mone's saying (2002) [59]. With the increasing number of transplants, with achieving impressive results of organ transplants, there arose a tendency to change medical education. The request for medical education originated from the practical activities of the physicians of various specialties, which led to the emergence of the science of "Transplantology and Artificial Organs" (as we termed at the beginning of this paper). Scientific knowledge of transplantation creates the methodological basis for teaching this kind of knowledge; the trained specialists improve the organ donation and transplantation daily practice, and thus there is a natural "double helix" for the development of this effective type of medical care. When any of the components in this process of knowledge reporoduction falls out, a crisis of "personnel" reproduction naturally arises; and the signs of this crisis can be seen even now [60].

Similar to the above described process of establishing a "transplant" professional dialogue between representatives of different medical groups, it is necessary to carry the same process with representatives of the clergy. There is a distinct tendency towards clericalization of public life in the Russian Federation (Latin: "clericalis" ecclesiastical; Ancient Greek κλήρος: destiny, "clergy". In Christianity: the clergy as a special community in the Church, different from the so-called laity), which certainly exerts a stabilizing effect on the moral and ethical sphere in general, especially in the postmodernism era. The search for cultural and religious norms that promote the development of organ donation and transplantation is a direct task of transplantologists ("no one else than us") who defend the interests of their patients. The Russian Orthodox Church in her Basis of Social Concept

recognizes the extremely important role of organ transplantation as a life-saving medical technology: "XII.7. The modern transplantology (the theory and practice of organ and tissue transplantation) makes it possible to give effective aid to many patients who were earlier doomed to inevitable death or severe disability ... The most common of all is the practice of taking organs from people who have just died. In such cases, any uncertainty as to the moment of death should be excluded. It is unacceptable to shorten the life of one, also by refusing him the life-supporting treatment, in order to prolong the life of another... The posthumous giving of organs and tissues can be a manifestation of love spreading also to the other side of death. Such donation or will cannot be considered a duty... XII.8. The practice of the removal of human organs suitable for transplantation and the development of intensive care therapy has posed the problem of the verification of the moment of death. Earlier the criterion for it was the irreversible stop of breathing and blood circulation. Thanks to the improvement of intensive care technologies, however, these vital functions can be artificially supported for a long time. Death is thus turned into dying dependent on the doctor's decision, which places a qualitatively new responsibility on contemporary medicine." [61, 62]. A wide discussion in the scientific community was raised by the recent state recognition of the scientific specialty "26.00.01 Theology", which was discussed at the First All-Russian Scientific Conference "Theology in the Humanities Educational Space" that took place in MEPhI on June 14-15, 2017. The Conference was attended by Russian Minister of Education and Science O.Yu.Vasilyeva. A greeting message on behalf of the Head of the RF President Administration A.E. Vaino was read out by the Assistant to the President of the Russian Federation A.A. Fursenko who stated: "I consider the recognition of

Theology as an integrated scientific educational discipline to be an important significant result ..., as well as a powerful stimulus for the development of humanitarian knowledge, the promotion of traditional moral and intellectual spiritual values in society." [63]. Despite the above given principles of the Social Concept Basis of the Russian Orthodox Church, there is a disapproving attitude towards transplantation among priests and their flock, which occurs not only from the ignorance of priests and their parishioners about the medical basics of this kind of medical activity, but also from their being ignorant of the Church's attitude to transplantation. This situation reminds us early 2000s, when despite the existed legitimate grounds establishing the legal norms at regional and federal levels, the majority of doctors in St.Petersburg considered the practice of postmortem donation and transplantation illegal. Therefore, we believe it important to involve future priests, regardless of their religious affiliation, in understanding the transplantation problems, and, while forming the attitude of their parishioners, in helping future recipients through the life of the Church's Community whose members may also be patients with end-stage diseases of vital organs. The Scientific Theological Conference "Comprehension of life and death problems in Intensive Care, Transplantology, and Theology" arranged by the First Saint-Petersburg State Medical University n.a. acad. I.P. Pavlov on December 9, 2016, was conducted in accordance with the main guidelines of the state policy in education. The conference was held in St. Petersburg Theological Academy, the oldest religious educational institution of Russia that, despite being nearly 300 years old, has only recently received the state accreditation by the Ministry of Education [64, 65].

Conclusion

Here we present the conclusions in the form of separate program provisions necessary for the development of transplantology in Russia:

- One can not help admitting the fact that so far there has been no other effective help to patients with end-stage organ diseases than organ transplantation;

- The Russian federal regulations and the legal base must be continuously improved; their components and structure need not necessarily resemble completely the standards adopted in the European Union and the United States;

- The perfusion technologies should be necessarily implemented into routine practice, just in the same way as it happened in cardiac surgery, in order to enhance the availability of transplantation care to the population of the Russian Federation;

- Organ transplantation is peculiar in its intention and ability to give life to a doomed patient thanks to organs of a deceased person who is not dependent on the person in need for a graft. Such a posthumous opportunity keeps a high altruistic potential for every person, and this potential can be disclosed thanks to humanitarian, rather than medical knowledge of a human. A broad, open dialogue with all representatives of society is needed to create an atmosphere of trust and altruism in the context of donation and transplantation;

- The main goal of the university medical education in transplantology is to combine the basic medical and humanitarian knowledge on a human, finding a way to spread this knowledge in the context of the transplantation development among both the medical community and the general population.

The authors state there is no conflict of interests to declare

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