

**Authorized translation from
“Transplantology” [“Transplantologija”, in Ukraine]
Volume 3, №3, 2002, pages 116-136**

(Journal of Ministry of Public Health of Ukraine, Academy of Medical Science of Ukraine, Coordination Center for Transplantology of Organs, Tissues and Cells of Ministry of Public Health of Ukraine, Institute for Surgery and Transplantology of Academy of Medical Science of Ukraine, Association of Transplantologists of Ukraine)

TRANSPLANTATION OF EMBRYONIC STEM CELLS AT THE TURN OF THE FIRST AND SECOND WAVE OF DEVELOPMENT

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In the history of medicine, the world has not witnessed a more significant and global attention paid by society to a new scientific direction in medicine as what we can observe today towards the transplantation of embryonic stem cells (ESC).

The boom began on November 5, 1998 in the USA after publication of articles by James Thomson [1] and by John Gearhart [2] in the *"Science"* magazine and a press conference of "Geron" corporation (which funded both research studies) dedicated to these publications.

Already on December 2, 1998 the US Senate hearings of the first person in medicine of the USA, the Nobel Prize laureate Director of National Institute of Health (NIH) Harold Varmus regarding derived human stem cells and the prospects of their usage in medicine were held [3]. In February of 1999, new Senate hearings were held [4-6], and president Bill Clinton has commissioned NIH to prepare an official guidelines for development of this branch.

The said guidelines [7] approved by B. Clinton approximately one month prior to expiration of his presidential term, has been annulled within the first month of George W. Bush's presidency.

The Roman Pope John Paul II interrupted his summer 2001 vacation in order to express his reservations regarding the problem of researching and utilizing human stem cells. President G. Bush addressed the nation with the doubts regarding the problem of human ESC [8]. The parliaments of Germany, Great Britain, and France repeatedly debated the problem of researching and using stem cells.

«Why the excitement?», - Dr.H.Varmus asked at the US Senate hearings. And answered this question: «For the first time, scientists have obtained human stem cells that can give rise to many types of cells in our body.... It is not too unrealistic to say that this research has the potential to revolutionize the practice of medicine and improve the quality and length of life» [3].

In 1998 human stem cells that can give growth to many types of cells in a body were received for the first time as a result of doctor J. Thomson's experiments [1]. Stem cells of animals have been derived in the beginning of 80th years and J. Thomson used the techniques initially developed for mice [3]. «The big step which shows a possibility to grow human ESC in culture was made» [2]. At the same time, J. Thomson, and J. Gearhart have shown reserve making comments on the possible terms of the beginning of clinical application of results of the research. In their opinion, it will take 5-10 years to begin clinical application of stem cells.

Human ESC for cultivation under laboratory conditions were acquired from two sources:

- from internal cellular mass of the viable embryos after artificial in vitro fertilization at the blastocyte stage (age of embryos about 2 weeks) in J. Thomson's work, and
- from a fetal tissue - tissue of embryos from terminated pregnancies (age of embryos of 5-9 weeks) - in J. Gearhart 's work.

When grown in culture, these stem cells appear to be pluripotent and can develop into cells of the three major tissue types. [3].

Since the subsequent discussion gave rise to ethical questions, Dr. Harold Varmus determined the position assumed by NIH regarding each source of embryonic stem cells. In opinion of H.Varmus, Dr. J. Thomson's work in which cells were derived from embryos created by in vitro fertilization clearly falls within the Congressional ban on human embryo research. NIH could not, and did not, support Dr. J. Thomson's recent work developing this cell line. The same restrictions do not apply to Dr. J. Gearhart's work, who derived his pluripotent stem cells from fetal tissue from terminated pregnancies [3], although it may be governed by other laws and regulations regarding using fetal tissue.

Human stem cells can be obtained from the tissue of an adult human being (peripheral blood, bone marrow, muscles, etc.), from umbilical cord blood of a newborn, from tissues of an embryo or a fetus. The cells are called embryonic up to the eighth week of gestation inclusive, from the ninth week of gestation they are referred to as fetal cells.

For transplantation of ESC, there are two known sources of material, where the second source appeared literally during the last years of the 20th century.

The first source is a human cadaveric embryonic tissue.

After the legalization of abortions (within 12 weeks) in most civilized nations a significant legal work was conducted regarding the regulations of the utilization of cadaveric fetal (embryonic) tissue after medical abortions. At the end of 80's Recommendation 1046 (1986) and Recommendation 1100 (1989) of the Parliamentary Assembly of the Council of Europe have formulated legally and ethically acceptable approach toward the using of human cadaveric embryonic tissue (fetal tissue) [9,10], which have been accepted and acts now in most countries. This is a natural approach from a medical doctor's position. Most research regarding the problem of transplantation of embryonic and fetal stem cells in the 1970s-90s respected this approach [11-14]. With these Recommendations in view, more detailed regulations were developed, among which we would note the guidelines of the Network of European CNS Transplantation and Restoration (NECTAR), 1993 [15-17]. The legislation for research and applications of human cadaveric embryonic tissues, including the therapeutic purposes, was developed in detail by the international community and was adopted by most nations, including the United States [7, 18-21].

The second source has appeared as an attractive by-product of artificial in vitro fertilization.

«When doctors match sperm and egg to create life outside the womb, they usually produce more embryos than are planted in the mother... the additional embryos remain frozen in laboratories», - explained president G. Bush to American citizens [8]. The president pointed out two fundamental questions: «First, are these frozen embryos human life, and therefore, something precious to be protected? And second, if they're going to be destroyed anyway, shouldn't they be used for a greater good, for research that has the potential to save and improve other lives?».

The claim for usage of viable embryos, that remain following artificial in vitro fertilization, raised a protest of the society not only in the USA, but also all over the world. To tell frankly: medical community has never offered to use viable embryos – neither fresh nor preserved - as a medicine or as a source of medicine. The proposition to use embryos after artificial fertilization in the USA also does not belong to the medical community.

We do not intend this article to contain discussion of philosophical or theological issues regarding the moment of originating of life in an embryo or the moment of embodiment of a soul. But regarding the frozen embryo resulted from artificial in vitro fertilization, in our

opinion, - it is clearly a «precious human life», - just like his happier brother or sister that was implanted into a mother's womb. It will also live, if given the right conditions.

For this reason, our answer to President G. W. Bush's first question is undoubtedly "yes" - this is human life in our opinion. In this case, it is pointless to ponder the second question.

Moreover, the transference of a real possibility and of a legal right for arbitrary control of life (artificial conception) and death (destruction of an embryo) in the setting of laboratories and corporate interests with an undercurrent of financial motivations unequivocally affects interests and safety of humanity.

Commissioned by the USA government, NIH has summarized modern scientific knowledge of Stem Cells in a book «Stem cells: Scientific progress and directions of the future researches. Possibilities and difficulties: with the stress on the future applications of stem cells», published in June, 2001 [22]. This book and the publications of the last three decades (see the bibliography list) gave the basis for our evaluation of the issue, its opportunities and problems.

The English word "stem" has a wide meaning: a trunk, a stalk, a sort, a tribe, a shank, a basis, etc. Each organism develops starting from two initial cells into a complex system of hundreds of types of the specialized cells.

Stem cells are non-specialized cells which are able to reproduce themselves and create a more specialized offspring. There are various types of stem cells, united in a hierarchy of stem cells of different levels of specialization.

Progenitor cells, which are categorized between the stem and specialized cell types, produce only specialized offspring and do not reproduce themselves in their original form. [22].

Specialized cells are tied to a particular function - in this sense, they are different from the stem cells from which they are created.

Stem cells of adults are non-differentiated (non-specialized) cells; they can occur in differentiated (specialized) tissue, can reproduce themselves, and can also specialize in order to create any specialized type of cell of a tissue from which they descend [22].

A widely accepted classification of stem cells does not yet exist. Several modern classifications of stem cells are incomplete, they contain contradictions and temporary agreements [7, 22].

It is a known fact that cells that exist within a body for the least period of time (first of all – blood and epithelium cells), are provided with stem cells for replenishment of the appropriate cell population during human lifetime. As for other types of cells, there is less clarity of understanding now. For instance, it used to be believed that the nervous tissue of an adult human lacks any stem cells. The results of research studies during the past few years allow us to view the reparative abilities of human body more optimistically [23] due to recent discoveries of new stem cell types (nervous tissue, muscle tissue, and other) in the organism of an adult human being. Moreover, certain types of stem cells exhibit a great level of plasticity and can contribute into a recuperation not only of inherent for them tissue, but also into tissues of other types [24, 25].

Among the stem cells, the haematopoietic stem cell has been studied the most [22].

Sources of the haematopoietic stem cells are as follows: bone marrow, peripheral blood, embryonic blood, and the fetal hematopoietic system. The quantity of stem cells is 1 for every 10 - 15 thousand cells in bone marrow and 1 for every 100 thousand in the bloodstream [22].

There are still no developed exact methods allowing to distinguish stem cells from blood cells or other cells within bone marrow. Stem cells appearance and behaviour in the tissue culture resembles that of ordinary leukocytes. The only "golden standard" of distinction stem cells in a transplant is the following: the transplant is injected into a sub-lethally exposed mouse and, if the regeneration of all three blood growth is observed, it is concluded that the transplant contained stem cells [22].

However, in the review of stem cells' clinical applications, the authors [22], limited themselves to application of stem cells only from bone marrow and cord blood for the purpose of treating blood diseases (leukemia, lymphomas, aplastic anemia, hereditary blood diseases), and for restoration of haematopoiesis after a chemotherapy in the course of treatment of oncologic diseases. The experience of clinical transplantation of fetal (embryonic) stem cells from a fetal liver in human for the very same purposes, which has a thirty-year history in a dozen nations, is not mentioned in the book [22].

Thirty-years experience of clinical embryonic stem cells transplantation

At the same time, transplantation of stem cells [27, 28] from a cadaveric liver of human embryos (fetal liver transplantation, further - FLT), was developed namely for regeneration of a haematopoiesis - as an alternative to a complex and expensive method of a bone marrow transplantation [26]. Transplantation of haematopoietic stem cells is the essence of both these methods. This scientific branch was not mentioned in the review [22].

By 1958 there have been shown fetal stem cells' ability to restore devastated immune system of rodents [29].

By 1961 remission was achieved in two out of four patients suffering from chronic pancytopenia who were treated by the transplantation of human fetal cells [30]. There is an array of existing publications issued at the end of 1970s and the beginning of 1980s that describe successful treatment of hematological patients and patients suffering from immune deficiency [31-38]. It is important to note that such work began simultaneously in several nations: the USSR [39-46], the USA [47, 48], India [49-52], Japan [53], France [54, 55], Italy [56-59], China [60-66], Poland [67, 68], Hungary [69] and more.

In 1985 there was held the first international conference on FLT, in which experience of clinical application of this method was presented [47, 49, 50, 56, 63, 65, 70, 71]. Most approaches in these researches were based on experience of bone marrow transplantation, including the use of patient conditioning by means of irradiation or chemo preparations, as well as post-transplant immune suppression to facilitate engraftment of transplanted cells. Both fresh and cryopreserved embryonic tissue was used. The characteristics of a tissue were limited to a summary cell count of transplanted cells. The issue of infection precautions was practically not addressed. Some individual very good results were observed. At the same time, overall clinical results and patient survival rates were disappointing. This proved the perspectives of the method, and lack of elaborated technique for its performance.

In 1987 in New Delhi the second conference on FLT problem was held, and the materials were published in the journal *"Thymus"* (1987, 10) [51, 52, 72-76]. In the report, which summarized the world's experience on the matter, the leaders of this scientific branch Gale R.P (USA), Touraine J.L (France) and Kochupillai V. (India) indicated that there were over 300 people that were treated with FLT in cases of aplastic anemia, leukoses and genetical immune diseases [74].

Gale R.P. [77] analyzed international experience of FLT application in cases of severe hematological diseases. According to his data, around the world, FLT has been administered as treatment for at least 122 patients suffering from aplastic anemia and 39 transplants to treat acute leukemia. The improvement of the patient's state was observed in 54% of aplastic anemia cases. In 41% of acute leukemia cases engraftment of a transplant was observed [77]. At the same time, the treatment results were not always a success, and were sometimes accompanied by significant complications related to immune suppression and patient conditioning. The author's recommendations bore a reserved character: FLT was recommended in situations where there was no appropriate bone marrow donor.

Several publications about unsuccessful treatment of Chernobyl accident victims by means of FLT appeared the next year [78-80].

A large number of publications were issued all over the world, dealing with the use of FLT as a tool in regenerating the immune system of patients suffering from severe hereditary diseases [31- 33, 36, 53, 54, 81-84].

Under J.L.Touraine's (France) leadership over the course of 18 years 202 FLT for treatment of 58 children with severe immune deficiencies (24), severe aplastic anemia (2) and inherited metabolic diseases (27) were performed. The good results of treatment during the observation period of 1-16 years were noted in about half of the cases [55, 71, 85]. A unique procedure of ESC transplantation to inutero patients (unborn patients - 12-28 week old fetuses) was developed, and considerable curative effect was achieved [86, 87].

The authors [22] expressed a predisposition that transplantation of ESC would allow the successful treatment of an entire array of autoimmune diseases. Theoretical outlines that indicate the possibility of successful treatment, particularly, type 1 Diabetes Mellitus were developed. However, there are no references to scientific literature providing appropriate clinical results of treatment of Diabetes Mellitus type 1 by means of ESC .

Authors [22] stress the significant progress regarding the recently developed understanding of recuperative possibilities of a brain in the last years: "Just a decade ago neuroscience textbooks held that neurons in the adult human brain and spinal cord could not regenerate... That dogma that brain tissue could not be regenerated is history" [22, p.77]. Preliminary studies show, that stem cells improve the motion of the paralyzed mice. Since the mid-1980's clinical researches with use of tissues of 7-9 weeks embryos were conducted in several centers of the world, and have shown encouraging results [22, p.81]. Although not all patients improved, in the best cases patients after fetal tissue transplantations have shown clear reduction of their symptoms. In postmortem investigations of such patients whose death was not related to the Parkinson's disease, living neurons were revealed. They were integrated into the normal frames of a striatum.

«A major weakness of these initial studies was that they were all done "open label" », without the double blind control [22, c.81].

By these remark the authors [22] concluded overview of the clinical application of human fetal stem cells in neurology. Though, in our opinion, the history of fifteen-year international experience of clinical ESC application for treatment of Parkinson's disease, - which began in Sweden [88-92] and fell on fertile ground in many other countries (Great Britain [93], the USA [94-96], China [60, 97], USSR [98-100], Czech [101], Poland [102], Canada, France, Spain, Cuba (see [11]), etc., - deserves more attention.

Moreover, at the beginning of the 90's there was established the European Network of the Transplantation and Regeneration of central neural system (NECTAR) [15-17, 103] which quickly united the researchers in this scientific branch and is currently active (see a workshop of 2001 «Neural transplantation in neurodegenerative disease» [104-106]). In 1992 the experience of 120 patients treatment using intrastriatal implantation of mesencephalic tissues from embryos of 6-12 weeks gestation (using from 1 up to 16 embryos in each transplantation) was summarized. The majority of patients experienced a positive change in their condition. There were no cases of a negative/unfavorable change in any of the patients [11].

Over the course of fifteen years, enough material has been accumulated to state a significant prospect of the given direction. Transplanted cells survive in the recipient's brain and produce dophamine, which is deficient in patients suffering from parkinsonism [105]. Over the course of 6 to 12 weeks, symptoms of parkinsonism are reduced, reaching a minimum level in 4 to 5 months. For a year-long period following the transplantation, relative stability of the symptoms [107] is observed. In cases of one-sided implantation, more explicit clinical effects were contralaterally observed[108]. The most part of transplanted neurons (80-95%) dies within 1 to 3 weeks after the transplantation procedure. For this reason, for one transplantation, the mesencephalitic tissue of 3 to 5 embryos [109] is used. Functions of the transplanted growth exceed the boundaries of simple dophamine supply. It is functional integration of transplanted neurons in a brain of the recipient needed to obtain clinical convalescence of the patient [110]. The engraftments of transplanted tissue into recipients' brain "without a seam" are remarkable [111]. The two

basic preconditions of engraftment are stated: the transplanted tissue should contain both neurons and glial cells; and the second, - there must be the damage of a brain [106].

Thus, over the period of thirty years scientific institutions of the USA, UK, Sweden, Russia, China, Japan, France, Poland, Ukraine, Canada, and more, clinical studies of ESC transplantation were conducted. Basically, there were used embryonic (fetal) stem cells of haematopoietic and nervous tissue - for treatment of patients with disorders of immune system and diseases of haematopoiesis, congenital and inherited diseases, and also Parkinson disease. Results were published in the most prestigious international scientific medical journals [33, 35, 42, 43, 62, 94, 97, 113-126]. The publications provided the analysis of curative action of stem cells from a human cadaveric embryonic tissue, results of a considerable number of successful transplantations. The most complete review of the FLT problem by the beginning of the 90's was made by A. Fine [11, 112]. However, some publications on the matter, a lot of which were published in the USSR, were not included. The regeneration of haematopoiesis, which was observed in the studies - according to " the golden standard " [22], - testified the presence of ESC in transplanted suspensions.

Nevertheless, this significant international clinical experience was mostly omitted in the review publication [22].

Methodical problems of ESC transplantation

Publications on the problem of stem cells transplantation refer to the following major unsolved scientific problems, methodical limits and technical obstacles:

- tissue incompatibility [5, 6, 127-136];
- necessity of a large quantity of embryonic material for transplantations [43, 104, 106, 109];
- infectious safety of transplantation material [137, 138];
- long-term preservation of the material (conservation, cultivation) [39, 116, 139-144];
- methods of administering the transplant (some of which are very sophisticated) [107, 108, 125, 145, 146];
- long-term preservation of vitality and activity of a transplant in recipient's body (including, a problem of engraftment).

In addition to the abovementioned items , certain issues have not yet been established in scientific literature at all, in spite of their importance. These include the following: specifics of embryonic material for various forms of pathology [130, 147-149]; the issue of combined utilization of several different types of ESC; the issue of correlation of ESC transplantation with standard methods of treatment; long term maintenance of clinical effects, including repeated transplantations of ESC, etc.

Without solving these issues, ESC transplantation would not be able to become a routine clinical method.

These serious unresolved problems considerably reduced initial enthusiasm of the 80's, caused skepticism in the leaders of this scientific branch, and led to absence of the special conferences on a problem in the 90's. From the beginning of 90's, there can be observed the decrease of activity in the area of clinical application of ESC according to reduction of number of appropriate publications in the scientific literature. Only five such clinical works on ESC application were presented at the 4-th Congress of the International Cell Transplant Society in 1999 (Montreux, Switzerland), [150, 151]. Only one such work was presented at the first European Conference on cellular therapy in 2000 in Pasteur Institute in Paris [152].

Experience of clinical embryonic stem cells transplantation at Embryonic Tissues Center "EmCell"

On the background of general decrease of scientific activity in the area of clinical ESC transplantation caused by methodical and scientific obstacles, in the 90's there appeared a scientific school that managed to practice daily clinical application of ESC transplantation, having overcome the majority of the mentioned problems. Worldwide, it is known as Center "EmCell" (www.emcell.com) [153].

Since the beginning of the 1990s, clinical effects of ESC transplantation are regularly studied at the Cell Therapy Clinic of National Medical University and Embryonic Tissues Center "EmCell", Kiev, Ukraine, under supervision of Prof. A.I.Smikodub. Among the first patients, under the influence of J.L.Touraine [126] and Gale R.P. [47, 48], there were patients with serious haematological diseases [154], immunodeficiency [155, 156], Diabetes Mellitus [150]. Encouraging results were received in treatment of aplastic anemia [154], agranulocytosis after chemotherapy in patients having leucosis [157] and solid tumors [158], AIDS patients [159, 160], Diabetes mellitus patients [161, 162], etc.

The development of transplantology of ESC was supported by the Academic Council of National Medical University. In 1994 a specialized Cell Therapy Clinic of National Medical University and Embryonic Tissues Center "EmCell" was established.

In 1994-2001 post-graduate Medical Doctors of National Medical University have carried out six multiyear studies on clinical problems of ESC transplantation for Ph.D. degree. The application of ESC transplantation was studied in treatment of immune and hematological disorders, in patients who suffered from Diabetes Mellitus [160, 162], from cytostatic myelodepression [157, 163], cancer of pancreas, complicated with a mechanical jaundice [164], AIDS [155, 156, 165], complex treatment of oncological diseases [156, 158], nonspecific ulcerative colitis and Crohn's disease [152].

By the end of 2001 the doctors of the Cell Therapy Clinic of the National Medical University and Embryonic Tissues Center "EmCell" have published about 100 scientific works in journals, materials of international congresses and conferences. Eleven patents were granted, including five patents of Ukraine and two patents of the USA. Guidelines for treatment of several diseases and conditions using ESC transplantation were developed and approved in a due course by Ministry of Health of Ukraine and Academy of Medical Science of Ukraine for wide practical use [167-169].

At present, Ukraine apparently possesses a higher level of preparedness for wide-scale use of ESC transplantation than any other country. Clinical experience of application of ESC transplantation exists for a wide range of diseases and states, and due legislation is in place.

Clinical results of two completed and published scientific researches ended by approval of the elaborated methods are reviewed below.

ESC Transplantation in treatment of oncological and hematological patients

During 1994-2001 the research on application of ESC transplantation for treatment oncological and hematological diseases were conducted by Embryonic Tissues Center "EmCell" jointly with National Medical University, Institute for Oncology and Radiology of Ministry of Health of Ukraine, Institute for Hematology and Transfusiology of Academy of Medical Science of Ukraine, Central Army Hospital of Ministry of Defense of Ukraine, Republican children's hospital " Ohmatdet" and the Kiev Medical Academy for Postgraduate Education. About 200 patients were studied during this period.

It was determined, that ESC transplantation in complex treatment of oncological and hematological diseases is indicated in all phases of the disease, and at all stages of the treatment process [151, 157, 163, 166, 167, 170, 171, 172].

In the initial phase

Transplantation of ESC facilitates preparation of patients in critical condition for surgical treatment, in particular: provides a considerable improvement of general state, reduces asthenia, fatigability, depressions. The transplantation allows regain body mass of emaciated patients; it is possible to stabilize weight of patients with cachexy. Anemia disappeared in 94% of cases during 2 weeks. The risk of complications resulting from a hemorrhage is reduced. Postoperative recuperation proceeds more rapidly.

ESC transplantation was observed to have a positive influence on the immune system, which consisted of significant 1-month-long growth of the quantity of CD4+ lymphocytes and a tendency toward the increase of the total population of lymphocytes and CD3+, CD8+, CD19+ sub-populations, as well as natural killer cells within 2 months [171].

The improvement of immune protection of patients results in lower risk of postoperative infectious complications, reduction of dissemination of tumor cells and metastasizing. Patients who received ESC transplantation prior to the operation had less difficulty tolerating chemotherapy and radiotherapy treatments.

In the Process of Chemotherapy and/or Radiotherapy

In oncological patients with myelotoxic agranulocytosis, ESC transplantation allows for much more rapid regeneration of peripheral blood count.

It is especially important to note, that following ESC transplantation the time of neutrophils level regeneration sharply shortens to a 5-7 day period [170], compared to the typical 30 days in a control group (Fig.1). During febrile neutropenia, clinical improvement is observed almost immediately - for the duration of 1-3 days, still prior to a significant increase of neutrophils in the blood formula. The body temperature is normalized, intoxication syndrome is diminished, and manifestations of stomatitis are reduced [172].

Rapid exit from agranulocytosis guarantees a significant (2 or 3-fold) reduction in the quantity of complications related to infection [163]. The gravity of such complications is also significantly diminished (Fig.2). The rapid regeneration of the quantity of thrombocytes (Fig.3) facilitates the reduction of manifestations of hemorrhagic syndrome, risk of cerebral haemorrhages, and other complications associated with thrombocytopenia. Transplantation of ESC allows to effectively conquer even a persistent thrombocytopenia.

Rapidly bringing the patient out of the risk zone in cases of cytostatic disease and expressed agranulocytosis, thanks to ESC transplantation, allows one to conduct a more aggressive chemotherapy treatment, with lower risk to the patient's life. This significantly increases effectiveness of chemotherapy courses in treatment of oncological diseases, as well as in prophylaxis of metastasizing and relapses [167, 171].

Fig.1a RECOVERY DYNAMICS OF TOTAL LEUKOCYTES AND OF NEUTROPHILS IN HAEMATOLOGICAL PATIENTS WITH SEVERE POST-CHEMOTHERAPY NEUTROPENIA AFTER EMBRYONIC STEM CELLS TRANSPLANTATION (N=16). Abs.num.

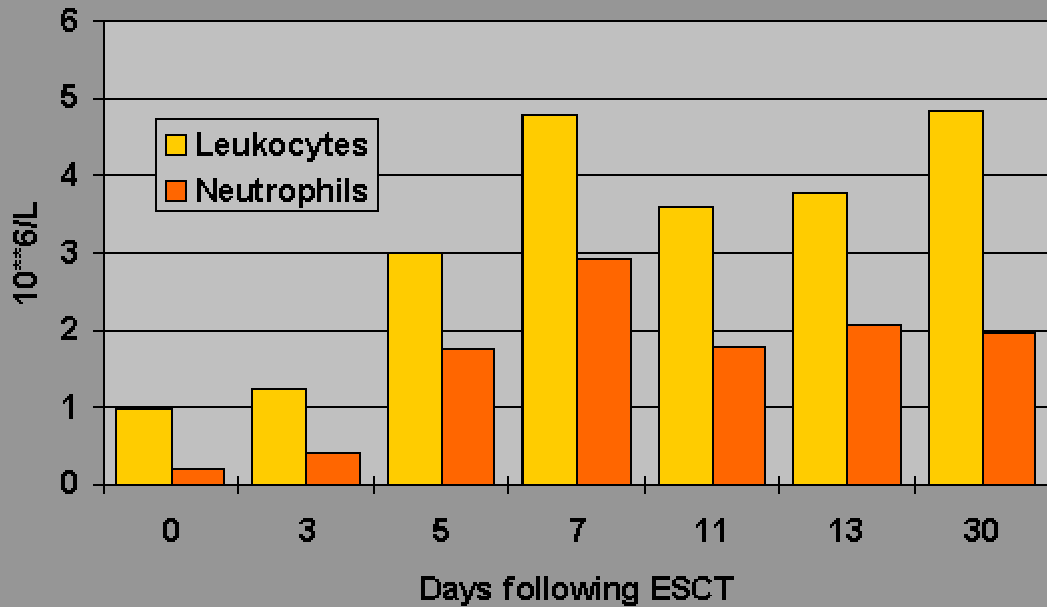
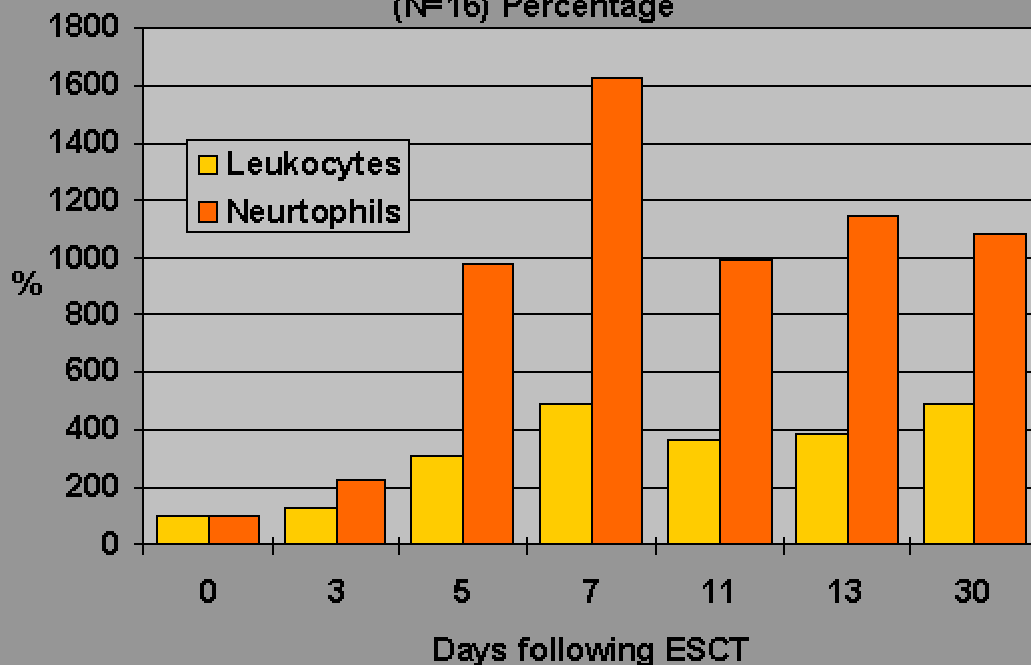
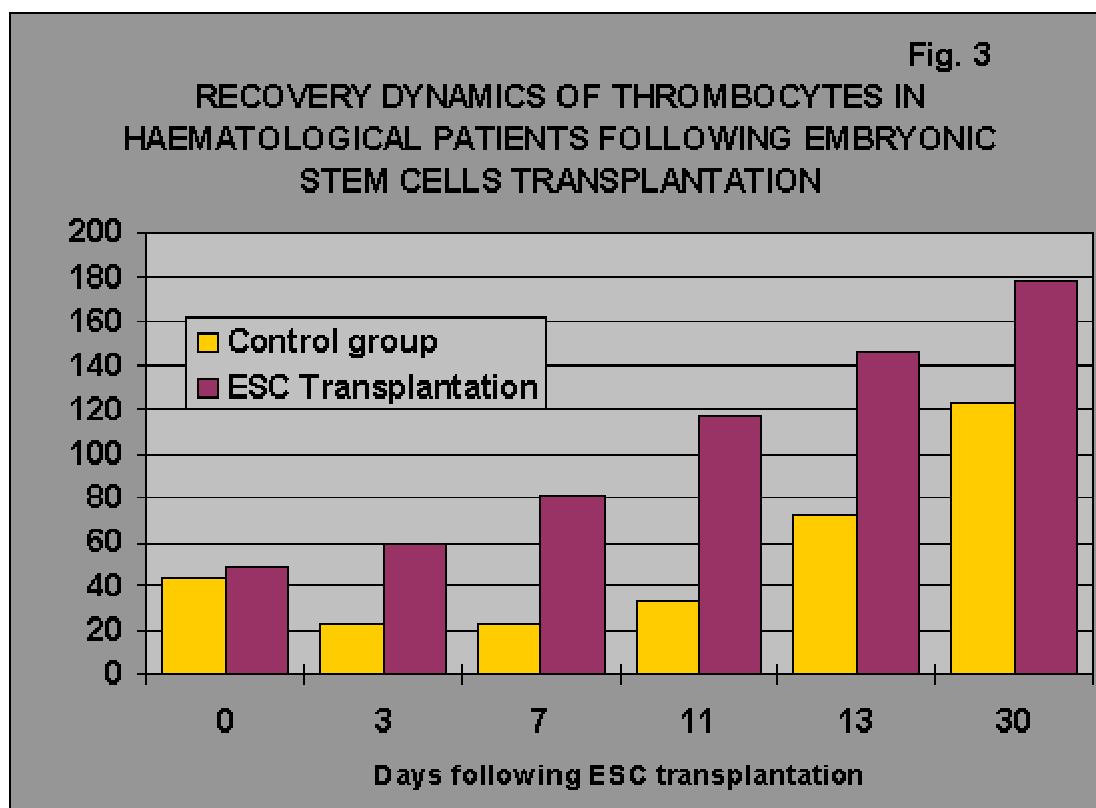
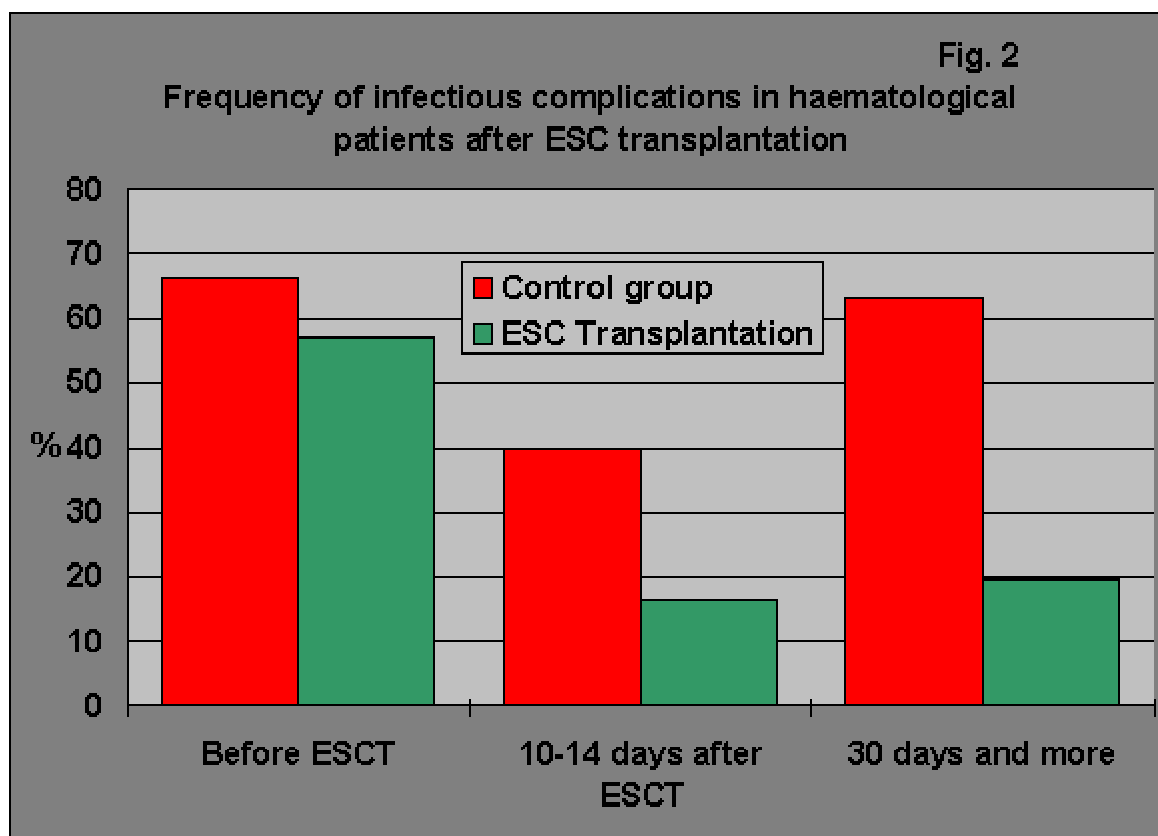


Fig.1b RECOVERY DYNAMICS OF TOTAL LEUKOCYTES AND OF NEUTROPHILS IN HAEMATOLOGICAL PATIENTS WITH SEVERE POST-CHEMOTHERAPY NEUTROPENIA AFTER EMBRYONIC STEM CELLS TRANSPLANTATION (N=16) Percentage





In the final stage of treatment

After completing chemotherapy or radiotherapy courses, there is still a remaining problem of regenerating activity of the patient's immune system, which insufficiency, in fact, allowed for the development of tumoral disease [173, 174]. In patients with a manifested secondary immune deficiency after radical treatment of solid tumors, the CD4+, CD8+, CD3+ and CD19+ lymphocyte quantity indices, due to the transplantation, showed increasing amounts during a two month period, with the total doubling by the end of the period. Although the quantities did not reach normative levels, the reached amounts remained at the new higher levels for approximately one year of observation [171].

An important effect of ESC transplantation is the rapid and stable improvement of psychological, emotional, and psychophysiological nature. The patients' condition changes within a few hours after the transplantation procedure: patients experience a better mood and a sense of willpower, strength of mind, followed by an improved emotional and mental condition. Subsequently, depressive tendencies are significantly reduced, emotional stability is increased, etc. [156].

Phobias, apathy, depressions, general weakness, insomnia are typical in critically ill oncological and hematological patients. Positive psychological and psychophysiological changes after ESC transplantation assist such patients to go through many trials related to a disease. The improvement of psychoemotional state of patients in grave conditions, including incurable ones, is the important contribution to improving the quality of perhaps the last period of life of these patients.

After ESC transplantation a frequency of relapses considerably diminishes. In particular, patients suffering from cancer of the neck of the uterus, the percentage of relapses was reduced by more than one-half of incidents after transplantation (23% in a control group and 10% after ESC transplantation) during a 2-year-long observation period [163, 174]. There was noted a significant increase of survival period of incurable patients, who underwent the palliative operations to treat cancer of pancreas, complicated with an icterus [164].

Prophylaxis of oncological diseases

There are no factual clinical data regarding prophylaxis of oncological diseases by means of ESC transplantation. At the same time, theoretical consideration and experimental results [158] suggest a significant preventive effect of ESC transplantation in case of oncological diseases. So, experimental results of ESC transplantation in mice with Lewis's carcinoma prove a considerable (approximately three-fold) reduction of a risk of metastasizing: their numbers (1.2 ± 0.2 compared with 4.5 ± 0.3 in the control) and masses ($1.1 \pm 0.4 \text{ mm}^3$ compared with $3.7 \pm 0.5 \text{ mm}^3$ in the control)) [158, 174].

Thus, application of ESC transplantation in treatment of oncological patients allows for preparation of critically ill patients for the operation, provides for a higher tolerance of chemotherapy and a more rapid recuperation after chemotherapy treatments, allows for the regeneration of an antitumoral immunity, and lowers metastasizing and relapsing [171].

ESC transplantation in treatment of Diabetes Mellitus

Publications of the 80's expressed assumptions of the probable curative influence of ESC transplantation in cases of Diabetes Mellitus I type. However there were no publications with the actual clinical results of such treatment.

An original method for Diabetes Mellitus treatment with the use of ESC transplantation was developed [150, 161, 162, 169]. According to the method, transplanted cell suspensions do not contain β -cells, which appear in later stages of embryogenesis. Analysis of the patent applications in patent offices in Washington, Hague and Moscow have shown complete novelty (level A) of this method. The method proved to be effective in treatment of Diabetes Mellitus of type I, as well as of type II. EmCell's experience of successful application of ESC transplantation covers 150 patients having Diabetes Mellitus.

ESC transplantation is especially effective in complex treatment of patients suffering from an initially manifested insulin-dependent diabetes and leads to stable compensation of the disease [162]. Practically all patients, after undergoing ESC transplantation, experienced a decrease in the required daily dose of insulin (by 20-100%, by 40.8% on average) for the duration of 2 - 3 months (Table 1, Fig.4). The return to initial required dose of insulin was not observed within at least a year. ESC transplantation allowed to slow down development of the diabetes mellitus type 1. The course of the disease became gentler, the periods between relapses grew to 5 - 14 months [162].

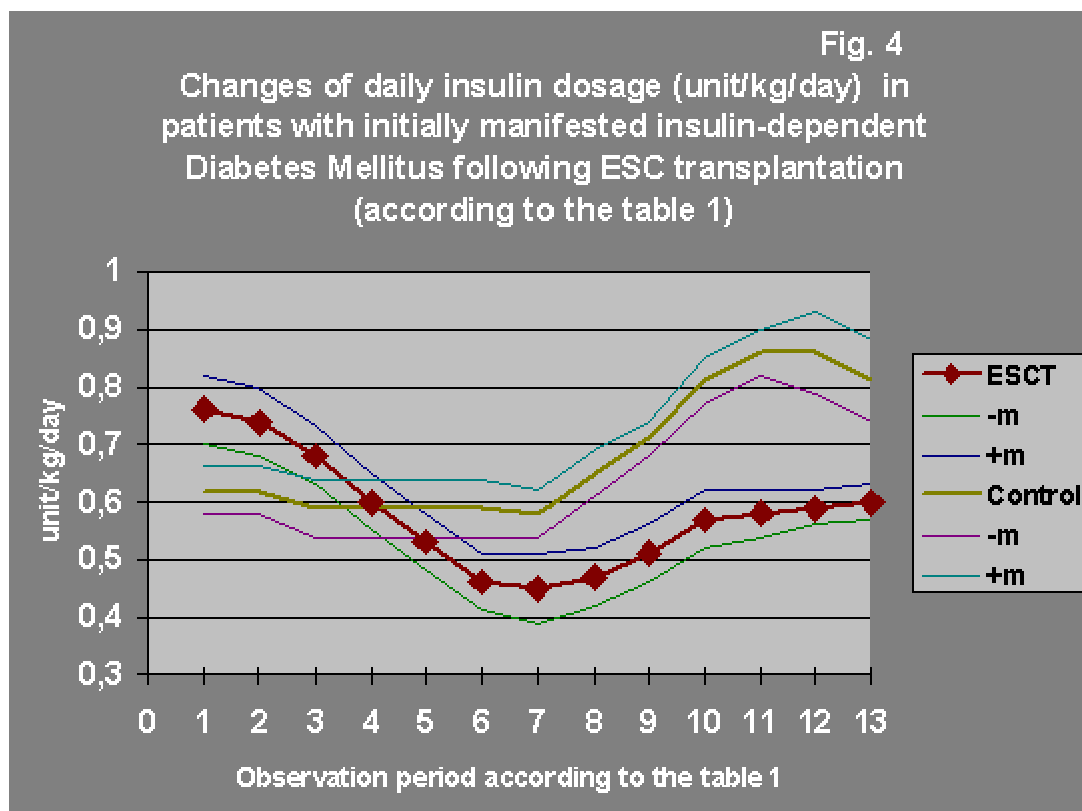
Apparently, the most important curative action of ESC transplantation in the initially manifested Diabetes is essential weakening or interruption of autoimmune aggression resulting in discontinuation of insulinitis and partial reparation of insulin production. The probability of this very mechanism is hinted at by the reestablishment of specifically immune indicators of the patient after the transplantation procedure. This way, after 14 - 28 days, the researchers observed an increase in the absolute quantity of lymphocytes (on average $35.9 \pm 10.7\%$), quantity of T-lymphocytes: CD3+ cells – by $58.1 \pm 17.2\%$, CD4+ cells – by $54.9 \pm 24.2\%$, CD8+ cells – by $57.7 \pm 13.1\%$. This effect was retained in repeat observations held 2-3 months after the transplantation: quantity of CD3+ cells – by $43.0 \pm 12.7\%$, CD8+ cells – by $56.2 \pm 15.4\%$. The quantity of B-lymphocytes was reduced: CD22+ cells – by $28.4 \pm 13.9\%$.

The intensity and the duration periods of between relapses depended on the time between initial manifestation of diabetes mellitus and ESC transplantation: in cases where the transplantation was completed within a maximum of 2 months after the detection of the disease, treatment results were significantly superior to those achieved with a longer waiting period of 2-5 months between detection and ESC transplantation. This also supports the supposition that ESC transplantation interrupts autoimmune insulinitis and protects the patient's pancreatic β -cells, which survived until the time of ESC transplantation, from destruction.

The given result exceeds the boundaries of problems associated with diabetes alone - in fact there is no available method for discontinuation of an autoimmune aggression in any autoimmune disease now (chemotherapy and hormone therapy, which are applied now to suppress activity of autoimmune process, are palliative methods with severe side effects).

Effect of correction of immune system behavior in autoimmune diseases was revealed in treatment of several other diseases with autoimmune genesis (unspecific ulcerative colitis [152, 176, 177], multiple sclerosis [153], rheumatoid arthritis, etc).

Period of observation		Quantity of patients	M	m	P (P<0.05)	
1	Before transplantation >	20	0.76	0.06		
2	Days following transplantation	1-7	20	0.74	0.06	0.85
3		7-14	20	0.68	0.05	0.37
4		14-28	20	0.60	0.05	0.06
5		28-45	20	0.53	0.05	0.01*
6		45-60	20	0.46	0.05	0.00*
7		60-90	20	0.45	0.06	0.00*
8		90-180	20	0.47	0.05	0.00*
9		180-270	19	0.51	0.05	0.00*
10		270-365	15	0.57	0.05	0.03*
11	Years following transplantation	2	9	0.58	0.03	0.06
12		3	6	0.59	0.03	0.13
13		4	5	0.60	0.03	0.20



In patients suffering from Diabetes Mellitus complicated by diabetic I-II stage nephropathy, from chronic kidney insufficiency of I-II degree, or from anaemic syndrome - ESC transplantation allowed for regeneration of red blood cell indices within 30-45 days with a subsequent stable period that lasted 2-11 months. Within the same time frame, the oppressed cellular immunity also experienced significant regeneration: the absolute quantity of leucocytes – on average by $50.7 \pm 14.5\%$; of T-lymphocytes – CD3+ cells by $72.3 \pm 11.5\%$, CD4+ cells by $62.7 \pm 11.9\%$, CD8+ cells by $84.3 \pm 21.2\%$. Within the next 2-3 months the abovementioned indices rose by an additional 5 - 12% [162].

The kidney function in this group of patients following ESC transplantation either improved or stabilized: the patients experienced a significant reduction in the daily proteinuria with the maximum level of reduction being reached by 2 months; additionally, the creatinine level stabilized; finally, there was a marked improvement of protein metabolism with a higher content of albumins and a higher protein coefficient after 1-2 weeks.

Stabilization of hemodynamics was noted, specifically the decrease of blood pressure - first on the initial dose of hypotensive medications and later also in view of their lowered dose or partial cessation of medication. Duration of the hypotensive effect following ESC transplantation was 5-9 months in patients suffering from diabetes with I degree chronic kidney isufficiency and 2-4 months in patients suffering from diabetes with II degree chronic kidney isufficiency.

Glycemia indices showed lowed levels and were stabilized. Following ESC transplantation, the daily dose of insulin was lowered by almost 20% for the duration of 2-3 months in this group of patients.

The patients having diabetes experienced the reduction of dystrophic symptoms; the working capacity [161, 162] has increased.

Thus, the ESC transplantation appeared to be an effective treatment of diabetes and its numerous complications.

The specific medical action of ESC transplantation in Diabetes Mellitus patients is hypoglycemic effect, which is manifested by decrease of a glucose level in blood, of glucose contents in urine and allows for one to reduce doses of hypoglycemic medication, including insulin [150, 161, 162].

ESC transplantations in patients suffering from Diabetes Mellitus provide the complex curative effect [162] consisting of:

- immune status correction,
- decreasing or interruption of autoimmune aggression,
- improvement of protein, carbohydrate and mineral metabolism,
- improvement of haematopoiesis,
- improvement and stabilization of hemodynamics,
- decrease of micro- and macroangiopathy manifestation
 - o diabetic trophic lesions,
 - o diabetic neuropathy,
- improvement of kidney function,
- improvement of vision,
- decrease of frequency and depth of infectious complications,
- improvement of general state of health,
- improvement of mental and physical capacity,
- optimization of psychoemotional condition.

The ESC transplantation provides a significantly milder course of Diabetes Mellitus longer and deeper remissions, lower rate of the disease's progression, prophylaxis of complications, and more favorable life prognosis. The repeated ESC transplantations provide a possibility of long-lasting maintenance of abovementioned ESC curative effects.

Conclusion

The clinical experience of Cell Therapy Clinic of National Medical University and Center of embryonic tissues "EmCell" allows to conclude, that the essential scientific and technical obstacles, which were indicated by researcher of ESC transplantation, have been successfully surmounted. In particular: problem of a graft rejection, danger of contamination of the patient, a possibility of long cryopreservation of cell suspensions, rational ways of delivery of the transplanted cells to the lesion, the possibility of repeated (sometimes, multiple) transplantations, ensuring the long-term survival of a transplanted material in the recipient, and long-lasting clinical action of provided curative effects, etc. [168, 169, 207].

It should be stressed, that in absence of a methodical solution for any of the abovementioned issues, ESC transplantation would not become possible and the presented results could not have been achieved.

We consider, that cadaveric embryonic tissue may completely cover the current demand for ESC needs for investigations and clinical application at the present stage of ESC transplantation development as a scientific clinical branch.

The legislation, which allows and regulates using of cadaveric embryonic material in scientific and therapeutic purposes, is accepted in the majority of the developed countries of the world [3, 9, 10, 20, 21, 177, 178]. The use of this material demands very delicate ethical approach. The mostly complete and elaborated ethical guidelines for ESC transplantation, in our opinion, were developed by NECTAR [15], and may be recognized, accepted and respected worldwide .

Thus, we are the witnesses and participants of the birth of a new branch of transplantology – clinical Embryonic Stem Cell Transplantation. It allows

- essentially extend clinical means for treatment of many diseases,
- considerably contribute into prophylaxis of many diseases (cancer, cardiovascular, etc.),
- retard premature ageing,
- increase quality of life of elderly and ill people.

The peculiarity of ESC transplantation, is the fact that transplanted is a small amount of rather universal cells (stem cells may have different degree of specialization), and the curative effects are provided by their specialized posterity. Differentiation and multiplying of this posterity is guided by systemic regulation of the recipient's body, in regard of maintaining its weakened or impaired, ill or lost functions.

Main curative effects observed in patients following ESC transplantation encompass all levels of organization and functioning of human body [153], and are arranged in a systemic way:

- Rapid and substantial improvement of volitional, mental and physical activity of patients, stabilization and improvement of mood, positive psychophysiological changes, particularly in such areas as attention, memory, and mental performance;
- Restoration of suppressed haematopoiesis (normalization of erythrocyte, leukocyte, lymphocyte, and thrombocyte counts);
- Stimulation, correction, or suppression of immune system (depending on what is beneficial for the patient in his/her current condition, or stage of the disease);
- Stimulation of trophic functions in tissues and organs, marked improvement in cases of deteriorated tissues, impaired functions, processes of ageing (vivid effect of functional "rejuvenation");

- Normalization of homeostasis (normalizing of glycemia, lipidemia, creatinemia, protein, carbohydrate, mineral metabolism, blood pressure, improvement of blood circulation, etc.).

Not all these effects are revealed in each case.

Embryonic Stem Cells of each type perform their specialized curative effects. Sufficient results of treatment can be achieved mostly by combined use of different kinds of Stem Cells, depending on mechanisms of pathological processes, current patient's condition, individual problems of treatment, stage of disease, phase of treating process and particular tasks of treatment in certain case.

Modern fashion for cell therapy and certain simplicity of technical procedures of ESC transplantation cause, some time, careless attitude to the ESC transplantation. At the same time, the simplicity of ESC transplantation should be related rather to an idea of ESC transplantation, than to the actual clinical methods for treatment specific diseases.

You may recollect the similar history of blood transfusion, which despite an obvious idea took about two millennia to develop a clinical method. It was used occasionally in Europe from the middle of XVII century, but being deadly dangerous was prohibited, until breakthrough in XX century, when it became routine effective clinical method. Less than a hundred (!) years ago.

Among all components of ESC transplantation, embryonic stem cells are the most available one. The most scarce and demanded component, from a point of view of a reputable doctorial community, - is the knowledge, elaborated and approved methods for ESC application in particular clinical cases in different diseases.

During recent years two waves of interest toward ESC transplantation were observed.

The first wave developed more than 30 years ago when ESC was investigated as the possible alternative for bone marrow transplantation in cases of irradiation injuries and diseases related to haematopoiesis. The pioneers of these studies were G. Lucarelli in Italy [109-111], J.L. Touraine in France [27, 85-87, 179], K.M.Abdulkadyrov in the USSR [180, 181, 183], Wu S.T., Ye G.Y., Meng P.L. in China [37, 65, 69, 76], R.P. Gale in the USA [47, 48, 77, 80, 182], etc.

The peak of the first wave occurred in the 70-80's. A. Fine's review [11] provides the most complete analysis of studies and results of this branch during the first 20 years of its development. Investigations on ESC transplantation started, practically, simultaneously in about 20 countries. Haematopoietic stem cells first among stem cells attracted the main interest (fetal liver transplantation). Later it involved nervous system ESC (since O.Lindval in Sweden [183-189]). During this (first, initial) wave of interest the basic clinical results were gained. High curative potential of ESC transplantation was confirmed. Major scientific and technical obstacles were revealed.

During the same period - the end of 80's beginning of 90's - the progress concerning ethical and legislative problems of the use of cadaveric embryonic human tissues was achieved [9, 10, 15, 20, 21, 123, 190, 191].

At that time complex solution for major scientific problems of ESC clinical application was not available, including histocompatibility, infectious safety, amount of applied material, age of embryonic tissue, etc., though the ways for overcoming most of these obstacles were found during that initial period.

To make a successful transition toward a routine daily clinical practice it was necessary to solve not only one or several problems, but all (!) these scientific problems-obstacles simultaneously. The absence of the complex solution of these problems retarded development of ESC transplantation as a scientific clinical branch. The number of publications on this scientific direction has sharply declined by the second half of the 90's.

The second wave of interest to ESC emerged in 1998 after publication of the research on the possibilities of human embryonic stem cells cultivation in laboratory conditions, [1] which evoked a hope for receiving embryonic tissue in unlimited quantity [2].

Anticipation of medical consequences of fantastic curative promise of ESC elicited acute reaction from society. However, world community reacted not only to the medical side of this issue, but also to the ethical facet. For the first time mass media arose and debated permissibility of using human viable embryos as a source for production of a medicine.

The scientific and popular literature of the second wave provides an important theoretical basis of potential curative action of ESC concerning different diseases in relation with specificity of their etiology and pathogenesis, but there are no attempts of treatment and even of analysis of experience of the ESC clinical application received by researches of the first wave in the 70-80's.

The potential solution of a remote marketing problem (a huge supply of embryonic tissue for ESC transplantation) hindered the top-priority problem of creation, elaboration clinical methods for ESC application.

The basic result of the second wave for clinical purposes so far was the significant attention of the society to the development of a new branch of transplantology.

It is necessary to mention, that the first wave of ESC research did not pass away completely, and its further development brought forth certain scientific and practical results. In particular, clinical research of ESC transplantation were conducted in a Cell Therapy Clinic of National medical University and Embryonic Tissues Center "EmCell" in Kiev, Ukraine [153] from the beginning of 90's. ESC transplantation was applied for treatment of hematological, oncological diseases, Diabetes Mellitus, AIDS/HIV-infection and several other diseases and conditions. Different clinical models facilitated better understanding of mechanisms of ESC curative actions and clinical results.

Over the course of ten years almost 2000 transplantations were performed for treatment of a wide range of diseases. The clinical research were done in the leading scientific institutions of the country on each of the diseases, with the participation of the recognized experts in particular medical field. During these years about 100 scientific works were published, materials were presented at 12 international and 8 domestic conferences and congresses, guidelines for treatment of several diseases and conditions with the use of ESC [167-169] were elaborated and approved in due course by Ministry of Health of Ukraine and Academy of Medical Sciences of Ukraine.

Granted were 11 patents for methods of treatment with the help of ESC transplantation, including two USA patents (in 1998 and 2001) [155, 156]. Patent offices in Washington, Hague and Moscow gave the highest possible assessment of their novelty. For this reason, it is not a surprise that many physicians know little of such methods - these techniques are only now becoming the property of medical community.

The methods of treatment with application of ESC transplantation have a high level of potential. They would, probably, have much in common for embryonic tissue from both sources – directly from human cadaveric embryonic tissue, and also from embryonic tissue that will be cultivated under laboratory conditions.

ESC from human cadaveric embryonic tissue can already be used in clinical practice. Currently human cadaveric ESC serve as the only source for development of clinical methods for treating various diseases with the use of ESC transplantation in human.

There is a long way to be completed from the defining a source of ESC, elaborating a method for their manufacturing - up to creation and approval of an efficient clinical method for treatment of a certain disease. For several diseases and conditions such work have been already completed in Ukraine.

At present, the recognition and distribution of the developed methods of treatment using ESC transplantation will proceed more effectively given organization of joint research

studies of Ukrainian specialists (who possess clinical expertise of using ESC transplantation and several approved guidelines) with Western colleagues who would like to appropriate these progressive methods. Cooperative work will allow to widen the methodical and financial foundation for such scientific research studies. It will also help to acquire new data that will guarantee a greater level of confidence in the study data achieved earlier and will open the road to the world recognition of a clinical ESC transplantation in treating of a wide range of disease and condition, prophylaxis of certain diseases, improvement of life quality and longevity.

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