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Acad. Filatov's contribution to ophthalmology and further development of keratoplasty by his pupils and followers

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Corneal transplantation (CT) was a major 20th-century achievement in medicine. It took more than 130 years to make it a practical means of overcoming the blindness and disablement due to leukoma. Mankind should be grateful to Himley, Reisinger, Zirm, Elschnig and Shimanovskyi, who contributed to the development of CT. V.P. Filatov's research on this major problem holds a special place in the history of science. "The development of corneal transplantation is a special page in the science of ophthalmology. I became interested in corneal transplantation in 1898, when I was a young resident doctor at a university eye clinic. When asked by my bosses what topic I would like to explore, I answered without hesitation: Corneal transplantation", the academician said in his public lecture on "Corneal Transplantation in Leukoma" in Kyiv in 1949. He started his research on the topic in 1912. "After moving to Odesa, I was promoted to Chair in Eye Diseases at the university in 1911, and came back to my research on corneal transplantation in 1913-1915" [1].

V.P. Filatov performed his first (partial) CT on February 28, 1912. The case was presented at the 67th meeting of the Ophthalmological Society of Odesa, March 13, 1912, and a report of the case was published in the Vestnik Oftalmologii journal in 1913 [2]. "The World War I impaired the operation of the Department of Eye Diseases, Novorosiisk (Odesa) University, to such an extent that I could come back to my research on corneal transplantation only in 1922" [3].

In December 1922, V.P. Filatov started to work on the problem systematically. As early as October 18, 1923, he performed the first partial penetrating CT, which proved to be successful. In the beginning of his experiments with partial CT, V.P. Filatov followed von Hippel's technic, with the trephining done with von Hippel's trephine. The technique was rather difficult to perform, and was associated with some risks, primarily of injury of the lens and prolapse of the vitreous. To prevent these complications, V.P. Filatov and the engineer A.P. Marzinkowsky invented special tools (FM1, FM3 and FM4 trephines; Fig. 1) that enabled a safe surgical procedure.

V.P. Filatov designed each of the stages of the procedure in detail, improved the technique of partial penetrating CT, extended the indications for its use, and introduced brilliant green antiseptic into ophthalmological practice [4]. In 1927, he proposed to fasten the transplanted cornea with a conjunctival flap. A flap of the scleral conjunctiva was cut at the upper part of the eye. The flap with its epithelial surface was stretched over the transplant and pulled by sutures into a conjunctival incision to fasten it securely to the transplant. For stopping the prolapse of the vitreous, V.P. Filatov suggested to pass a special instrument - which could be called a "disciform retrograde obturator" - into the anterior chamber [5].

In January 1933, V.P. Filatov brought his four patients with successfully transplanted corneas to Moscow to demonstrate them at the meeting of the local Society of Ophthalmology [6]. Later he wrote: "Up until that time, no corneal transplantation had been performed, and even no successful cases of corneal transplantation had been seen in the capital of the country. Therefore, my report with demonstration of my patients attracted the attention of not only ophthalmologists, but also the whole local medical community. Physicians of various specialties attended the meeting to listen to this report" (Fig. 2).

At that time, the lack of living donor eyes with clear cornea was a major obstacle preventing the wide use of CT. The eyes enucleated at an eye-care facility from other patients due to the pathological processes not associated with corneal lesions were the major source of transplant corneas in the facility. The capacity of this source, however, was not sufficient for the needs of numerous patients requiring CT. Because the practical value of penetrating CT was threatened by an imminent crisis, the issue of a new source of transplant corneas became a major concern. V.P. Filatov considered the options for overcoming the issue of donor cornea shortage: "For sure, using cadaver eyes was an option to be considered. The using of transplant corneas from cadavers' eyes had the major advantage of a greater

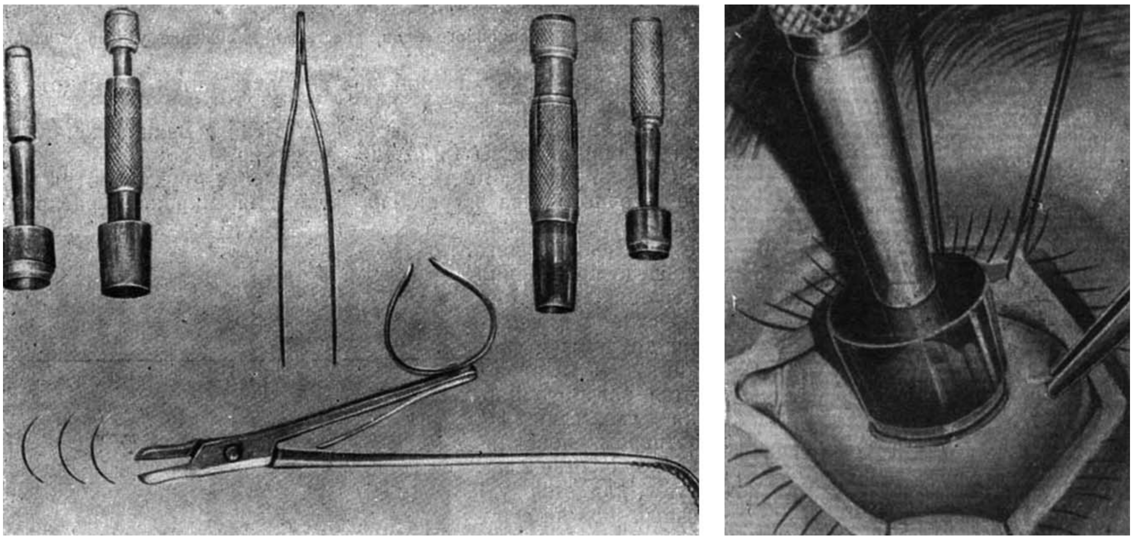

Fig. 1. Trephines and keratoplasty tools designed by V.P. Filatov and the engineer A.P. Marzinkowsky (A). Trephining the recipient's cornea with the FM-3 trephine (B)

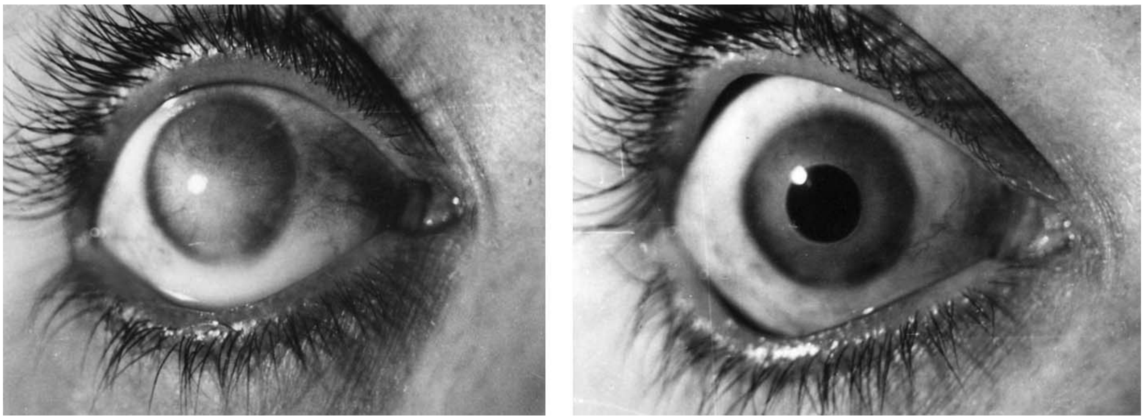

Fig. 2. Partial penetrating corneal transplantation performed by V.P. Filatov in 1928. The affected eye before (A) and after surgery (B)

number of eyes available than any other option. But are the cadaver eyes applicable for transplantation? Without a doubt, if used immediately after death, the eye of the individual that died from a non-wasting disease (cardiac disease, cerebral hemorrhage, trauma, etc.) will not be essentially different from the eye removed from the patient. In practice, however, using cadaver eyes immediately after death is possible only exceptionally. Consequently, actually, the problem of using transplant corneas from cadavers' eyes has transformed into that of using cadaver eyes after their preservation at the conditions that do not affect their viability" [1].

Before Filatov's work in the field, for some time cadavers' eyes had been employed in a few single cases by several surgeons (Fuchs and Komarovych), but their results were inconclusive, and the techniques have failed to enter wide clinical practice. Filatov based his solution on "the remarkable case reported by Morax and Magitot (1912) who obtained a permanently transparent union of the cornea removed from a living person and preserved in the donor's blood at a temperature of minus 6 ºC for eight days" [7]. The transparency of the transplanted cornea was maintained for two years.

In 1934, V.P. Filatov published his observations on the transplanted cadaver corneas that had been kept for 2-3 days at a temperature of +2...+4°C [8]. Surprisingly, it has been found that the cadaver corneal material is not worse but better than the fresh corneal material from a random living donor. Regarding this Filatov wrote: "I have resolved the 'cadaver' issue and proved that cadaver eyes can be enucleated during the few hours after death, kept for 1-3 days in an ice box at a temperature of +3...+4°C, and used for transplantation (Fig. 3). Syphilis in the cadaver donor must be excluded by autopsy and/or by the Wasserman serological test before or after death. Eyes should be obtained from bodies of those who have not died from infectious diseases or malignant tumors, and had no ischemia, septicemia, surgical or infectious complications" [1]. The issue of the source of material for CT in keratoplasty was successfully solved. V.P. Filatov came

Fig. 3. Preservation of the cornea in moist chamber by V.P. Filatov

to the following conclusion: “Having proved that cadaver eyes can be used for corneal transplantation, I found a new and rich source of material for the transplantation”.

From 1922 till January, 1939, Filatov and his school performed 537 operations of the partial penetrating CT. Of these, 171 were operations of the living donor transplantation, and 366, those of the cadaver donor transplantation (“Scientific material of the Ukrainian Institute of Experimental Ophthalmology”, 1938).

The Ukrainian Institute of Experimental Ophthalmology was established by the Decree of the Council of People’s Commissars on April 4, 1936, and V.P. Filatov was appointed its director. The first Soviet Union laboratory for tissue preparation and preservation was established in the institute in 1936.

V.P. Filatov was the first not only to find the rich source of material for CT and formulate major contraindications for cadaver cornea tissue donors, but was also the first in the world to develop a corneal preservation method (“Filatov’s moist chamber method of corneal preservation”). The technique consists in keeping enucleated cadaver eyes in a sealed glass jar (moist chamber) without adding any preservative or other liquid. With the globe placed in a closed jar, chamber saturation occurs naturally due to the natural moisture of the eye tissue, without substantial drying out. Immediately after enucleation, the jar containing the eyes is placed in the fridge at a temperature of +2...+4°C. Under these conditions, the cornea can be preserved over 4-5 days. It is noteworthy that this corneal preservation method was widely used not only in medical facilities of Ukraine, but also in those of post-Soviet states until 2010. It has become the prototype for current hypothermic corneal preservation methods.

Fig. 4. N.S. Shulgina and V.V. Skorodynska in the tissue preservation laboratory

The following works, actions and developments were undertaken and conclusions were made on the basis of experimental and clinical studies under the guidance of Professor Filatov:

- Postoperative period after CT was described in detail, and the value of glaucoma as a postoperative complication of CT was elucidated (Velter S.L., Vasserman I.A., 1936–1938)
- Substantial transient changes in refractive error after CT were pointed to (Volokitenko A.I., 1938)
- The beneficial effect of the amelioration of leukoma on optical CT was established (Vasserman I.A., 1938)
- Tectonic CT for corneal fistulas not only resulted in good tectonic outcomes, but also provided an optical effect and a curative effect (Kalfa S.V., 1938)
- A classification of leukomas was developed, enabling (1) the prognosis of partial penetrating CT depending on the category (or characteristic) of leukoma and (2) standardization of outcomes of the partial penetrating CT depending on the quality of leukoma (Bushmich D.G., 1947) [9]
- Biomicroscopic changes in the cornea during preservation for 30 days at a temperature of +2...+4°C were described (Petrosiants E.A., 1938)
- It was established that advanced donor age is does not prevent a transparent union of the corneal graft from the eye of this donor (Kamenetska A.I., 1938)
- Methods for obtaining experimental non-complicated leukoma were developed
- Regeneration of the corneal epithelium in isolated cadaver eyes at a temperature of +14...+15˚C and at a temperature of +2...+4°C was studied (Skorodynska V.V., 1938)
- It was established that (1) drying of the cornea even to the level of threshold moisture loss does not affect its viability and (2) short-term drying of the cornea, if succeeded by corneal maceration, may result in a transparent union of the corneal graft (Bazhenova M.A., Vasserman I.A., 1937)
- The dynamics of biochemical processes in the cornea in the course of its preservation was studied (Shesterinov G.P., Gelelovych I.P., 1936–1939, Muchnyk S.R., 1952) [10]
- Corneal tissue viability under various temperature regimes was studied, and optimal temperature regimes for the preservation of the cornea were established (Velter

S.L., 1936; Bazhenova M.A., 1936–1940; Puchkovska N.A., 1940)

- Morphological changes in the corneal tissue during preservation of the cornea were established (Pupenko D.O., 1936–1938)
- Histomorphological structure of the corneal transplant in various types of CT was studied in humans and animals (Voino-Yasenetskyi V.V., 1952–1957) [11]
- Efficacy of pediatric CT was studied, and it was demonstrated that all types of keratoplasty (partial penetrating, subtotal and reconstructive keratoplasty) must be widely used to eliminate blindness due to leukoma (Barkhash S.A., 1958) [12]
- Mechanisms of transplant union were studied (Voino-Yasenetskyi V. V., 1953–1958) [13].

Filatov's studies reflect his powerful gift for research, great erudition in the field of biology and medicine, and the desire to alleviate suffering of patients. Subsequent clinical studies demonstrated that the rate of transparent union of the corneal graft was higher for grafts preserved at a low temperature than for fresh corneal grafts. This supposed that, in the course of corneal preservation at low temperatures, cornea accumulates substances beneficial for a transparent union of the graft. V.P. Filatov had noted that a considerable clearing of the leukoma surrounding the transplant may occur several months after a partial penetrating transplantation [14]. However, when he began to use the cadaver cornea preserved at a low temperature for CT, considerable clearing of the leukoma surrounding the transplant became more frequent, and this clearing became more pronounced. V.P. Filatov associated the phenomenon of leukoma clearing with the best results of transplantation of a preserved cadaver cornea, and concluded that corneal preservation at low temperatures results in the accumulation in the transplant of the substances that trigger regenerative processes both in the transplant and in the host leukoma.

Postoperative clouding of a corneal transplant was a complication affecting CT efficacy. While looking for a way to combat this complication, V.P. Filatov turned his attention to the science of tissues. He used the fact that, with a small piece of new tissue placed near the ageing tissue that has stopped growing, the latter tissue will recommence growing. He tried to cut superficial layers of the leukoma near the opacified graft, and place small pieces of human cornea into the defect, which was found to have a beneficial effect on the opacified graft. This method was published in 1933 and became a starting point for the development of tissue therapy. Since then, V.P. Filatov began using the corneal material preserved at low temperatures and placed close to the graft in an attempt to clear the opacified graft. Subsequently, he began treating a number of corneal disorders, and, for this purpose, he cut a piece of pathological host cornea near the periphery, and covered the defect with a cut piece of superficial cornea of a cadaver eye. Placing the preserved corneal tissue on the defect had a curative effect, with a prompt resolution of symptoms of even a prolonged inflammation.

After the World War I, many of the wounded required plastic reconstructive surgery.

Facial defects are especially difficult to treat, because the potential for the transfer of local soft tissues can be limited, and the use of pedicle autografts is not always effective due to limitations in their movement and/or their insufficient blood supply. In 1917, V.P. Filatov proposed to use a round (also known as tubed) pedicle flap in plastic procedures not only in ophthalmic surgery, but also in other surgical disciplines [15]. That is why the tubed pedicle is referred to in the literature also as the Filatov's pedicle. A good blood supply of the pedicle enables its union at the areas with insufficient blood supply and is beneficial for forming the anatomical structures e.g., the eyelid [16]. The Filatov's walking pedicle technique is important in surgery, because abnormalities of the anatomy of the facial structures due to congenital or acquired defects cannot always be managed with the transfer of local soft tissues. The original method of plastic surgery for closure of tissue defects which was proposed by V.P. Filatov 110 years ago is still relevant, especially for the tissue defects associated with abnormal blood supply.

Development of tissue therapy and science of biogenic stimulants

Clinical and experimental studies conducted by Filatov demonstrated that any human or animal tissue can be used for curative purposes [17]. Such a tissue should not necessary be similar in histology to the tissue of the organ affected, and it was even not necessary to transplant this tissue to the site near the patient's affected tissue or organ. V.P. Filatov began using human cadaver skin preserved at low temperatures for seven days for transplantations aimed to treat skin disorders. A piece of such skin was transplanted into the skin defect made near the host skin area affected with the disease. The success of curative skin transplantation (even for such a severe process as lupus tuberculosis) was beyond expectation. Preserved tissues have been widely used for the treatment of various eye diseases such as keratitis, corneal and vitreous opacities, vitreous hemorrhage, choroidal inflammatory disease, optic nerve atrophy, retinitis pigmentosa, etc [18]. Tissue preparations have been successfully used for the treatment of system disorders, gastric ulcer, lupus erythematosus, chronic furunculosis, torpid skin ulcers, bronchial asthma, neuritis, etc [19].

Filatov wrote: "The tissues separated from the body preserve their vitality for some time if the conditions of their preservation (e.g., high temperatures) do not kill them at once. If the tissue separated from the body is kept at a low temperature and is vital, one has to suppose that it undergoes biochemical rearrangement with the formation of some substances that stimulate its vital processes under unfavorable conditions. Biogenic stimulants, when being introduced into the ill body, strengthen vital reactions in the body, and it is this that leads to recovery. Fresh tissues, when transplanted into the body, also may exhibit a curative action, but this action will be significantly weaker than that of the tissues preserved at low temperatures" (1951). Subsequent observations demonstrated that other isolated tissues of animal origin also acquire curative properties after being subject to a low temperature for some time. Various homologous and heterologous tissues of animal origin may serve as a source of biogenic stimulants after being kept at a temperature of +2...+4°C for 6–7 days [17]. Tissue preservation techniques have been developed and preserved tissues (like cornea, sclera, choroid, retina, placenta, peritoneum, etc.) have been successfully used. Instructions for methods of preparation and applications of tissue preparations for treatment with biogenic stimulants according to the method of Academician Filatov were issued in 1946.

Filatov's achievements in the discovery and development of CT and his works on curative tissue transplantation in 1933-1939 were highly appreciated by the government, and the Council of People's Commissars issued a decree, awarding him the highest state prize, in March, 1941.

Subsequent studies on CT established the value of immune reactivity of the body in graft union formation and the role of allergic reactions in CT (Voino-Yasenetskyi V.V., 1956–1963). Additionally, they investigated immune properties of the cornea in health and disease (Shul'gina N.S., 1961), transplantation properties of the cornea in various types of preservation of the cornea (Savchuk L.N., 1961) [20], and transplantation properties of dehydrated corneal tissue (Popov G.P., 1965) [21]. Moreover, they investigated various techniques for trephining the leukoma and secondary glaucoma in leukomatous eyes before and after keratoplasty (Gorgiladze T.U., 1960, 1974) [22, 23].

The research and practical applications in CT to which V.P. Filatov devoted his life were continued and further developed by his followers. The advent of immunological studies allowed for HLA antigen-based donor graft selection for keratoplasty, which was reflected in studies by professors T.U. Gorgiladze and N.S. Shul'gina and the Bulgarian post-graduate student T.V. Mitov [24]. The effect of the selection of donor-recipient pairs on the basis of erythrocyte characteristics (blood type and rhesus factor) and human leukocyte antigen (HLA) system antigens on the dynamics and type of graft union were studied (Puchkovska N.O., Gorgiladze T.U., Shul'gina N.S. and Mitov T.V. 1982) [24]. A bank of HLA-typed corneas preserved in liquid nitrogen was for the first time established.

In subsequent studies, V.L. Ostashevskyi investigated the effect of protease inhibitors in the treatment of purulent ulcerative keratitis [25]. Additionally, O. V. Ivanovska described the clinical characteristics, diagnosis and classification of anterior segment cysts and the method of their cryogenic treatment [26]. Moreover, O. I. Kochkariova examined the relationship between the transplantation features of donor cornea and the outcome of penetrating keratoplasty [27]. Techniques for the preservation and storage of silica-gel dried cornea, and preservation of the costal cartilage, sclera, dura mater and labial mucosa were developed at the tissue preservation laboratory.

Filatov school of corneal transplantation today

CT remains a priority area of work for the institute. Department of Corneal Pathology, SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine", a leading research, diagnostic and treatment center in Ukraine, has been dealing with pressing issues of CT for more than 89 years. Additionally, it has been dealing with congenital, hereditary and acquired disease of the cornea and anterior segment. The department conducts studies in cooperation with the Institute of Molecular Biology and Genetics, National Academy of Sciences of Ukraine (research on the spectrum of mutations in TGFBI in patients with hereditary corneal dystrophy, candidate susceptibility genes for keratoconus, etc.), Institute of Cell Therapy, Kyiv (research on the impact of the viable cryopreserved amnion on the clinical course of corneal inflammation in the developed model of bacterial keratitis and in the clinical setting in keratitis of various etiology), and university eye clinic, Köln, with the leading German specialists in keratoplasty and treatment of severe corneal disorders (research on the clinical manifestations of rare corneal disorders and their treatment).

The most hard-to-treat patients from all over Ukraine come to the Filatov institute to have corneal surgery. Nowadays, the institute receives many individuals with combat-related injuries (including those with mine-blast related injuries) who require combined anterior-and-posterior segment interventions involving keratoplasty. It is the proficiency in various keratoplasty techniques and the experience of surgeons that allow choosing the most effective type of CT for each particular case. One of various types of keratoplasty – superficial, deep lamellar, "biological dressing" of the cornea by Puchkovska, intralamellar, penetrating and its subtypes (posterior, step-by-step and mushroom penetrating keratoplasty), reconstructive, keratoplasty with two grafts or exchange keratoplasty – is performed depending on the severity and depth of the corneal lesion. Therapeutic keratoplasty (including urgent keratoplasty) accounts for more than 78% of keratoplasty cases. The major goal of this surgery is to eliminate the focus of inflammation, restore the damaged cornea (closure of fistulas and other corneal defects) and preserve the eye [28].

For the first time in Ukraine, G.I. Drozhzhyna initiated and implemented molecular genetic studies of hereditary corneal stromal dystrophy, described the types of stromal dystrophy found in this country, and studied mutations in the genes causing the disease. Additionally, the efficacy of lamellar keratoplasty in patients with hereditary corneal stromal dystrophies was studied [29, 30].

T. B. Gaĭdamaka studied the efficacy of various types of keratoplasty in the treatment of patients with recurrent herpetic keratitis. Lamellar keratoplasty was found to be a recipient cornea-sparing and the most effective treatment of the disease [31].

L. F. Troichenko studied the efficacy of treatment of persistent epithelial defects (including graft defects) and torpid corneal ulcers including autologous serum. With this in mind, the criteria for the severity of the pathological process and reparative properties of the cornea were determined [32].

K.V. Sereda used a model of bacterial keratitis to study the features of the amnion that had undergone cryopreservation using a new technique. Additionally, she demonstrated the efficacy of transplantation of thus cryopreserved amnion in the treatment of patients with various corneal disorders (bullous keratopathy and bacterial, herpetic and neurotrophic keratitis) [33].

The results of our experimental and clinical studies on the efficacy of amnion transplantation using the amnion prepared and cyopreserved at the Institute of Cell Therapy, Kyiv, have allowed to obtain an approval for its use in clinical practice from the Coordination Center for Transplantation of Organs, Tissues and Cells (Approval reference Number: 8, Approval Date: October 32, 2019).

As a result of these studies, a specially prepared high-quality domestic amniotic membrane has become available to Ukrainian ophthalmologists for the treatment of inflammatory, neurotrophic and post-traumatic corneal disorders.

The gap between the demand and availability of donor cornea makes us look for the way of its rational use. A technique for the rational use of donor cornea was developed at the Department of Corneal Pathology. The technique consists in the use of the whole area of the donor cornea and enables cutting out two or more grafts of the required size and shape for performing various types of keratoplasty (lamellar, penetrating or biological dressing) if small-diameter grafts are in need (Patent of Ukraine No. 111373, 2016). The technique enables using one donor cornea for two recipients [34].

In 2024, for the first time in Ukraine, we performed successful transplantation of the Boston keratoprosthesis on a single eye in a patient that had a severe mine blast injury with wounds to the face and eye and a corneal lesion unsuitable for conventional penetrating keratoplasty; this transplantation resulted in the restoration of vision in a single eye [35].

The keratoplasty school established by Academician V.P. Filatov and his talented pupils and followers lives on and develops further.

The name of Academician V.P. Filatov has been written in gold letters in the history of CT. He was the first to demonstrate that human cadaver eyes can be used for CT. At present, human cadaver cornea is the best and single donor material for optic keratoplasty. V.P. Filatov was the first in the world to develop a hypothermic corneal preservation method ("Filatov's moist chamber method of corneal preservation"). The method has become the prototype for new hypothermic corneal preservation methods currently used in European tissue banks. In 2014, the late Academician V.P. Filatov was honored for his contribution to the field of ophthalmology, and inducted into the American Society of Cataract and Refractive Surgery (ASCRS) Ophthalmology Hall of Fame.

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Disclosures

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