

Kidney transplant: history, results and perspectives
(The 50th anniversary of the first successful kidney transplant in
Russia)

S.A. Kabanova, P.M. Bogopol'skiy

N.V. Sklifosovsky Research Institute for Emergency Medicine of Moscow
Healthcare Department, Moscow

Contacts: Pavel M. Bogopol'skiy, bogopolsky_med@mail.ru

A brief history of kidney transplantation in experiment and clinic in Russia and in the world is presented. The role of Russian scientists in the solution of this problem and their research priorities are highlighted. Achievements of scientific school of academician B.V. Petrovsky, who performed in 1965 the first successful kidney transplant in Russia, are showed. Attention is paid to current problems in the field of organ transplantation. Some results of kidney transplantation in Russia are given and perspectives of its applications are indicated.

Keywords: Kidney transplantation, history of the issue, the role of Russian scientists, problems in the field of organ transplantation in Russia.

Organ and tissue transplantation is one of the outstanding achievements of world science of the XX century. The success of transplantation is predetermined by the activities of many scientists from around the world and, in particular, from Russia. Mutually enriching each other with new ideas and facts, overcoming various obstacles in its path, they contributed to establishing the building of transplantation, as it had been set up by the beginning of the XXI century.

Historical review of the transplantation in Russia confirms that its development was predetermined by a high level of the Russian medical science development. But the realization of its potential has often been slowed down in our country by a number of objective and subjective reasons.

At the turn of XIX-XX centuries, thanks to the work of some scientists, the organ transplantation with the maintained organ blood supply became possible. In 1902, E. Ullman made the first attempts of experimental heterotopic auto-, allo-, and xenotransplantation of a kidney to the neck in a dog and a goat, the vessels being united by means of Payr's prostheses. In 1905, A. Carrel performed a heterotopic transplantation of allogenic kidney into the neck, using his novel original method of vascular suture. In 1906, he was the first to perform an experimental bilateral nephrectomy in a dog and a renal allotransplantation of both kidneys with aorta and inferior vena cava segments, and achieved a good graft function within 9 days [1, 2]. In Russia, E.G.Chernyakhovsky, a surgeon from Kiev, transplanted kidneys into the inguinal region, on vascular anastomoses, as well, in his experiments on dogs in 1914. [3]. Important to note that kidney transplants made by E.Ullmann, A.Carrel, and E.G.Chernyakhovsky were genuine organ transplantations (with the blood vessels being united), and this was their significant value for the world transplantation.

Organ and tissue transplantation issues were the subject of a vivid interest of leading surgeons in our country. In 1922, P.A.Herzen organized the Department of Experimental Surgery at the Clinic he headed where various experiments in organ and tissue transplantation were performed [3].

In the late 20s-early 30s of the last century, the most important studies in this area were carried out by Yu.Yu.Voronoy, V.N.Shamov's disciple. He

first published the results of his research on animal kidney transplants in 1930. In experiments on dogs Yu.Yu.Voronoy (Fig. 1) transplanted the animal's native kidney on the right side of the neck, uniting the renal artery and vein to the common carotid artery and the external jugular vein. Dermoplasty was made by means of two flaps tailored in such a way that they covered the graft; the ureter was exteriorized. The dog's kidney autograft transplanted by Yu.Yu.Voronoy well survived, the kidney functioned properly; the post-transplant follow-up by the time of demonstration had made 6 months [3, 4].



Fig. 1. Yu.Yu.Voronoy with co-workers (1930s)

The world's first cadaveric kidney allotransplantation to a human was made by Yu.Yu.Voronoy on April 3, 1933, when he worked as the Head of the Surgical Department in Kherson City Hospital. The kidney was retrieved from the body of a 60-year-old man at 6 hours after his death from cranio-cerebral trauma and was transplanted to a 26-year-old female patient with

acute renal failure occurred as a result of poisoning with mercuric chloride. The kidney was transplanted to the anteromedial surface of the right hip in its middle third to the femoral artery and vein. The patient survived with the transplanted kidney allograft for 2 days. Reviewing this case, Yu.Yu.Voronoy reasonably believed that the short recipient and transplant survival did not compromise the kidney transplantation as a treatment for sublimate poisoning. Moreover, he believed that in case of the first kidney graft loss it should be replaced with a new, fresh kidney graft, thus prompting the necessity of kidney retransplantation to be performed. The extremely important fact clinically proven by Yu.Yu.Voronoy was that kidneys from fresh corpses were capable to come alive and function after having been transplanted to a new host. In Yu.Yu.Voronoy's opinion, cadaveric organs transplanted to a human do not induce any intoxication or anaphylaxis, and the graft non-survival is caused by a local mesenchymal and overall immunobiological reaction in the form of emerging specific antibodies [4].

Thus, Yu.Yu.Voronoy possesses a dual priority: the first clinical kidney transplantation, and the first use of cadaveric kidneys for clinical transplantation.

A similar surgery, the temporary allogenic cadaveric kidney transplantation to a young woman who was dying of acute renal failure was made by an American surgeon Ch.Hufnagel in 1947. In that case, Ch.Hufnagel, unlike Yu.Yu.Voronoy, transplanted kidney on shoulder vessels and immediately obtained a good graft function. Kidney continued producing urine for several days allowing the disease to be transformed into diuretic stage that was followed by a rapid recovery of the patient [1].

During the Second World War, research activities on transplantation considerably attenuated. Yet, it was in that period when an extremely important concept of creating artificial organs took its principal solution. In 1943, a Dutch scientist W.Kolff managed to implement the idea of possible using a hemodialysis for cleaning the blood from toxins accumulated in a situation of renal failure. He called his hemodialysis machine an "artificial kidney". On March 17, 1943, this machine was first used to treat a patient with uremia [1].

W.Kolff's invention played a great role in the development of kidney transplantation because the chronic hemodialysis made it possible to prolong the life of patients with kidney failure and uremia that enabled many of them to survive while waiting for donor organ transplantation.

In 40-50th of the last century, scientists in our country proceeded with their research in clinical transplantation. In 1948, V.P.Demikhov started working on allogenic kidney transplantation in dogs using several developed options. By 1955 he had performed 30 kidney transplants, half of the transplanted kidneys functioned for more than a week, and one of the operated dogs lived with a transplanted kidney for 19 days [5]. However, this wonderful experimental researcher never ceased to insist: "There is no evidence that tissue specificity is an obstacle to organ transplantation ..." [6]. In fact, V.P.Demikhov denied the existence of the tissue specificity problem in organ transplantation; however, that does not diminish the value of his outstanding scientific experiments. In 1948, A.A.Vishnevsky and V.P.Demikhov made an experimental transplantation of a dog kidney to posterior mesenterial artery in the Institute of Surgery of the USSR Academy of Medical Sciences [3].

The world's first vessel-suturing device invented by V.F.Gudov in 1947 became a great achievement of Soviet medicine. Using one of the early models of the device, G.A.Richter and N.P.Petrova performed a successful kidney transplantation on the dog's neck in 1949 [3].

The modern era of clinical transplantation began in the middle of the XXth century. In 1950, Yu.Yu.Voronoy who was then working at the Institute of Experimental Biology and Pathology named after A.A.Bogomolets in Kiev reported 5 cases of cadaveric kidney transplantation after a long (12-28 days) graft conservation. However, Yu.Yu.Voronoy did not seek to achieve a long-term kidney graft survival, but set the task of achieving a temporary favorable effect of cadaveric kidney transplantation in acute renal failure. So, the transplanted kidney was removed on the 4th day in one of two cases, and on the 7th day in the other, and soon afterwards both patients with acute renal failure recovered [7].

In the USA, a modified "artificial kidney" machine had been ready for use by 1950, and the blood transfusion techniques and antibiotic therapies widely spread in that period made the complicated surgical procedures safer. It was for the first time when on March 31, 1951, the surgeon Scola in Boston (USA) transplanted an allogenic kidney from a patient with cancer of the lower third of the ureter to a 37-year-old patient with chronic glomerulonephritis on hemodialysis. Both operations were made simultaneously in two operating rooms; the kidney graft ischemia time was 70 minutes. Unfortunately, this operation ended up with graft rejection, and the recipient died after 5 weeks of progressing renal failure despite hemodialysis. Yet, the way for clinical kidney transplantation had been opened, and in the following years 15 kidney allotransplantations were performed in patients on chronic hemodialysis in the United States. This

initial experience provided with important information supporting the necessity of removing the recipient's native kidneys affected by glomerulonephritis in order to achieve an acceptable quality of life and a more or less long-term survival of the renal allograft. Otherwise, there remains a high risk of severe complications of renal vascular hypertension, and the kidney transplant arteries in these conditions soon become susceptible to sclerosis [2, 3].

Further significant event took place on December 23, 1954, when Joseph Murray (Nobel Laureate of 1991) in Boston (USA) performed the world's first successful kidney transplantation in a patient with chronic glomerulonephritis from a living related donor who was his homozygous twin. The donor and the recipient matched by blood type, in addition, a preliminary tissue compatibility testing between the twins was performed by cross grafting of small skin flaps that demonstrated a complete adherence. Despite these favorable facts, the scientists were facing an important ethic problem: whether it could be justified to remove a kidney from a healthy person to transplant it to an almost hopeless patient, if the outcome of a transplant is not completely clear? But the sincere desire of the donor to sacrifice his kidney to his severely ill brother outweighed doubts of transplant surgeons. Simultaneous operations of the donor's kidney removal and its orthotopic transplantation to the recipient were successful. At 6 months after transplantation, the recipient's own kidneys were removed due to the progressive renal vascular hypertension, and soon he was discharged healthy from the hospital. Since then, a related kidney transplantation has quickly spread in clinical practice [2, 3].

In that period, the problem of organ and tissue preservation attracted the attention of researchers again. For example, in 1946 for the first time in

the USSR, a special laboratory for tissue preservation (actually the first tissue bank) was established in the Leningrad Institute of Blood Transfusion [3]. Later, similar labs were established in Moscow: in the Central Institute of Traumatology and Orthopedics (1955), and the N.V.Sklifosovsky Institute for Emergency Medicine (1956), in Rostov (1957), and then in the Institute of Traumatology and Orthopedics in Kiev (1958), Kharkov (1959), and other cities of the USSR. Special Order of the USSR Minister of Health (1959) envisaged the extension of activities in the field of preservation and transplantation of organs and tissues, including the organization of laboratories for tissue preservation (tissue banks) in 20 scientific and research institutes. All these innovations played a key role in the practical implementation of transplantation techniques because they helped surgeons to continuously expand the potential implementation of organ transplantation in clinical practice. At the same time, they were important and necessary steps for the transition to a new task, namely the organ preservation [3].

In 1956, R. Schwartz and W. Dameshek discovered the capacity of 6-mercaptopurine (6-MP) derivatives to suppress graft immunity and prolong the functioning of the transplanted kidney. Later on, an immunosuppressive effect of corticosteroids was discovered, and kidney transplantations became more frequently performed abroad, and with better results. [8]

In that period, the native medicine began using the latest achievements of scientific and technological progress, improved and technologically sophisticated devices, such as the "artificial kidney" machine created in the Research Institute of Surgical Equipment and Instruments of the Russian Federation Healthcare Ministry in 1957 [3].

In 1960, the monographs "Transplantation of Vital Organs in Experiment" by V.P. Demikhov, and "Transplantation and Replacement of Tissues and Organs" by A.N. Filatov et al. were published. These rather valuable books served for many years as reference manuals for native and foreign researchers in transplantation.

A qualitative leap in the clinical transplantation took place in our country in the mid-60s. In that period, the research on organ transplants actively involved leading scientific and research institutions, first of all, the Institute of Clinical and Experimental Surgery (Director: Boris Petrovsky), and the Institute of Surgery named after A.V.Vishnevsky (Director: A.A.Vishnevsky). Alongside the experimental research in the field of organ transplantation, preservation, and transplant immunology, the clinical transplantation was widely developing.

The obtained experience directed the efforts of scientists to a search for the ways to reduce the immunological incompatibility of allotransplants, to overcome the organ transplant rejection. The research in this field carried out in different clinics and laboratories appeared fruitful.

In April 1965, Academician B.V.Petrovsky performed the first in our country human kidney transplantation that was a success (Fig.2). It actually opened up an era of transplantation in the Soviet clinical medicine. Soon after that, similar operations started being made by G.M.Soloviev, N.A.Lopatkin, Yu.M.Lopukhin, V.I.Shumakov, V.S.Krylov, I.S.Yarmolinsky, I.A.Belichenko, and other surgeons. Surgeons B.V.Petrovsky, N.A.Lopatkin, Y.M.Lopukhin, G.M.Soloviev, and V.I.Shumakov were awarded the State Prize of the USSR for their work on a clinical kidney transplantation (Fig.3) [3].



Fig. 2. Academician B.V.Petrovsky (1908-2004)



Fig. 3. USSR State Prize Winners (1971) for the development and clinical implementation of kidney transplantation: N.A.Lopatkin, Yu.M.Lopukhin, G.M.Soloviov, B.V.Petrovsky, V.I.Shumakov

In 1966, addressing a scientific conference in Ryazan, B.V.Petrovsky said, "We are facing the start of the developments in organ transplantation, the subject that is destined to a great future. We will witness this, and a great role in the success of this matter belongs primarily to reconstructive vascular surgery owing to which all the very organ transplantation became possible. No doubt, that implementation of kidney transplantation will be followed by

transplantation of other vital organs such as the liver, intestine, and, possibly, the heart "[9].

Initially, kidneys from living related donors were used for transplantation, and later cadaveric organs became to be used. Developments in this field were actively supported by the scientific medical community, and the USSR Healthcare Ministry authorized the retrieval of cadaveric kidneys for transplantation. In 1967, the Academy of Medical Sciences of the USSR organized the Laboratory for Organ and Tissue Transplantation (headed by V.V.Kovanov) that studied the issues of overcoming tissue incompatibility, its morphological forms, and optimal methods of cadaver organ preservation [3, 10].

The first in the country Kidney Transplantation Center was established in 1967 on the base of the All-Union Scientific and Research Institute of Clinical and Experimental Surgery (VNIKiEH) of the Healthcare Ministry. In this Center, B.V. Petrovsky's followers launched a broad spectrum of studies to find the ways and means to overcome tissue incompatibility. They developed a Research Programme and identified three main areas: the selection of immunogenetically matching pairs; the suppression of the immunological resistance in a recipient; the graft management aimed at reducing the activities of incompatibility antigens. The VNIKiEH-based Kidney Transplantation Center actually took the leadership in the research and practical work on this issue in the country. The Institute formed research groups to study the possible ways of the donor organ preservation and the creation of artificial organs. The work on the issue of organ transplants was so active that demanded to create a new springboard for further developments. Assuming that need, and at the initiative of Academician B.V.Petrovsky, the USSR Healthcare Minister, the

Institute of Organ and Tissue Transplantation was established in 1969 that was the world's first specialized scientific and research institution in the field (now it has the name *Academician V.I.Shumakov Federal Research Center of Transplantology and Artificial Organs [FNCTIO]*). The Institute was headed by the representatives of B.V.Petrovsky scientific school: G.M.Soloviev from 1969 to 1974, V.I.Shumakov from 1974 to 2004. Since 2005 and to present, the FNCTIO has been headed by S.V.Gautier, its Director [11].

An important event for further progress of transplantation was the legal implementation of the brain death concept and criteria. These criteria (Harvard criteria) were clearly defined in Harvard in 1968, and since 1970, the organ retrieval from brain-dead donors has become a routine procedure in most countries of the world [3].

In 1973, B.V.Petrovsky wrote: "About 500 kidney transplant operations have been performed in our country so far (235 transplants have been made in our clinic). Approximately 25-30% were live donor transplants from close relative, and 70-75% were cadaver kidney transplants. The maximum recipient survival times have been 8.5 years for a kidney recipient from a living donor, and 7 years for a cadaver kidney recipient. Twelve Kidney Transplantation Centers are functioning in our country now (in Moscow, Kiev, Minsk, Riga, Kemerovo, Baku, Tashkent, and others); three more centers are being organized. Kidney transplantation centers were created as a single complex with the laboratories for hemodialysis, and today there are 12 such laboratories. Further advances in the transplantation of a kidney and other organs depend on the solution of multiple issues, including the organ preservation. The Institute of Clinical and Experimental Surgery of the Healthcare Ministry have developed and introduced into the clinical

practice the methods of cadaveric kidney conservation for the period of 33 hours. A number of devices have been constructed for organ storing and assessing their viability prior to their transplantation. All these make possible to transport donor kidneys to other towns of our country". [12]

The outcomes of kidney transplant surgery were rather middling at early stages of clinical kidney transplantation development. Transplanted kidney grafts functioned for over 1 year in 25-30% patients only, and postoperative recipient mortality reached 40%. The results were improving over time, but significant progress occurred only after the invention of a new immunosuppressive drug cyclosporine A (Sandimmun). In 1984, B.V.Petrovsky's followers were the first in our country who performed clinical trials and approved the drug that made a real revolution in transplantation [3, 11].

The experience gained by B.V.Petrovsky scientific school confirmed the necessity of considering many important factors contributing to the results of kidney transplantation: a correct selection of recipients, the quality of their preoperative preparation, selection of donors, the degree of donor-recipient immunological match, the duration of the donor organ preservation, an adequate management of patients in the postoperative period, and etc. [11].

Living related donors may be mostly close relatives: mother, father, siblings. Ideal match for organ donation is an identical twin. However, such transplants are naturally very rare; we can mention only one case of kidney transplant between identical twins in our country that was performed in the Russian Scientific Center of Surgery (RNCH) of RAMS. They were female twins, both being physicians, aged 33 years who were followed-up for 11 years after transplant surgery. As for the kidney transplantation between

other relatives, the experience has demonstrated the most favorable results of a kidney transplant between siblings. Unrelated donor kidney has rarely been taken. Due to an absent genetic relationship, the results of unrelated kidney transplants are roughly comparable to those of a kidney transplant from a deceased donor with brain death. For this reason, unrelated volunteers are not currently involved as kidney donors [13].

Kidney transplantation has recently acquired some important features. Thus, the feasibility of kidney transplantation with multiple arterial and venous trunks has been confirmed. So, prior to transplantation, various, often quite complex angioplasty procedures may be performed on a kidney graft in conditions of continued hypothermia, using microsurgical technique in some cases [8, 11].

The experience of B.V.Petrovsky's followers in kidney transplantation has demonstrated the importance of having the information on the kidney functional state as soon as on the operating table, especially when the graft does not produce urine. The necessary data can be obtained using the methods developed for intraoperative assessment of the graft hemodynamics [14]. A more efficient immunosuppressive therapy in combination with a more precise early diagnosis of rejection crises and better conservation methods have significantly improved the outcomes of cadaver kidney transplantation: a recipient survival with a functioning transplant at 1 year and longer after kidney transplantation has increased from 42 to 95% in related living transplantation, and up to 86% in cadaveric kidney transplantation [8, 11].

The fight against infectious complication still remains an important issue. Meanwhile, it is necessary to continue searches for new, more efficient immunosuppressive drugs, to improve methods of identifying

matching "donor-recipient" pairs. The problems of patients' rehabilitation after transplantation and a proper follow-up at the place of residence lag behind the present demands. In general, the improvement of kidney transplantation in the country requires increasing the number of dialysis centers that should become the bases for the kidney transplantation departments and organ procurement groups to be arranged [3, 8, 11].

Cyclosporine A introduced in the world clinical practice in early 80s has greatly increased the recipient and graft survival and has minimized the incidence of post-transplant complications. This contributed to further transplantation advances in developed countries. At that time, however, there was no legal or legislative base in Russia that would have regulated the issues of ascertaining the brain death and retrieving donor organs; and that impeded further development of clinical transplantation.

The breakthrough took shape in 1986 when the Presidium of the USSR Academy of Medical Sciences discussed the current state of the issue of the vital organ transplantation [15]. Order No. 236 issued by the USSR Healthcare Ministry on February 17, 1987, and the "Interim instructions for verifying death on the basis of the diagnosis of brain death" were the crucial steps that resulted in creating the conditions for further progress in the field of transplantation in our country.

However, the Resolution issued by the Presidium of the USSR Academy of Medical Science in 1986 remained rather "a protocol of intents". The reasons for this situation lie outside the professional skills of specialists (surgeons, immunologists, anesthesiologists, psychologists, etc.). The level of training and the potential skills of Russian transplant experts have been rather high, consistent with international standards and confirmed by practical results.

The most important role in solving the problem of organ transplantation belongs to the RF Federal Law "On transplantation of human organs and(or) tissues" enacted in 1992. In accordance with the WHO principles, and the RF Federal Law of 1992, the organ retrieval from the donor is applicable if the donor is in a family relationship to the recipient. Nevertheless, some controversial issues still remain in the problem of donor selection for cadaveric kidney retrieval. This applies, above all, to defining the age limits. Although there are literature reports on the use of kidneys from donors over 60 years old; yet, according to B.V. Petrovsky's followers, the donor age should not exceed 45-55 years. [11]

In Russia, kidney retrievals from non-heart-beating donors have been practiced, and, the Law of 1992 allows a kidney retrieval from donors after brain death. The latter term refers to an irreversible functional and morphological brain damage while maintaining the heart beating and the gas exchange provided by continued mechanical ventilation. The USSR Healthcare Ministry authorized a comparatively small number of health care facilities possessing appropriate resources to undertake the organ retrieval from brain-dead donors [3, 11].

The Center for Organ Procurement and Typing was established in Moscow in 1997. It is responsible for the selection of donors and recipients, and for coordinating the allocation of deceased donor kidney transplantations among Moscow Transplant Centers. To date, more than 15,000 kidney transplantations have been made in Russia. Annually all centers of the country made 500-600 transplantations, meanwhile, the estimated demand for kidney transplantation approximates 5,000-7,000. A comparatively low number of kidney transplants in our country may be explained by some objective factors, specifically, by an inadequate provision

of healthcare facilities with "artificial kidney" machines, but what is most important, by an acute shortage of cadaveric organs. However, a donor organ shortage has been evident in other countries, as well. Overall, the annual number of kidney transplants makes 12,000 in Europe (excluding the former socialist countries), more than 15,000 in the United States. In Asian countries, the rate of related donor transplantations is 80-90%. In Russia, such operations are limited to approximately 10% of all organ transplants.

Experience in kidney transplantation gained by B.V.Petrovsky scientific school has been presented in a number of monographs: "Kidney Transplant" (1969), "Transplantation" (1995), "Fundamentals of Nephrology" (1972), "Introduction to Clinical Transplantation" (1993), "Clinical Transplantation" (2004).

In the XXI century, the kidney transplantation has become nearly a routine surgery. Currently, kidney transplantations are performed in 35 of 41 active transplant centers of the Russian federation, and new centers are emerging. Among the latter, the Kidney Transplantation Department established on the base of the N.V. Sklifosovsky Research Institute for Emergency Medicine may be considered the most successful one that has rapidly taken a leading position in this field. In 2013, total 935 kidney transplants were performed in Russia (6.5 per 1 million population), including: 112 transplants in *Academician V.I.Shumakov Federal Research Center of Transplantology and Artificial Organs (FNCTIO)*, 91 in N.V.Sklifosovsky Research Institute for Emergency Medicine, 55 in Moscow Region Scientific and Research Institute named after M.F.Vladimirsky, 50 in the Urology Research Institute, 46 in B.V.Petrovsky Scientific Center of Surgery, 33 in the Republican Children's Clinical Hospital (RCCH). Related kidney transplants were performed in FNCTIO

(n=48), the Urology Research Institute (n=32), B.V. Petrovsky Scientific Center of Surgery (n=24). Fifty seven kidney transplants were made in children, including 47 in B.V.Petrovsky Scientific Center of Surgery, and in RCCH. In 2013, the waiting list for kidney transplantation enumerated 4,172 potential recipients (16% of total 26,000 patients being on chronic hemodialysis). The mortality on the waiting list was 3% (n=124).

In the Russian Federation with a population of 143.3 million, total 1,400 organ transplants were performed in 2013 or 9.8 per 1 million population (compare: 1,345 organ transplants in 2012, or 9.4 per 1 million). The number of patients in the waiting list for transplantation in Russia is 3 times lower than in Western Europe and the United States. Donor programs have been implemented in 20 of the 83 Russian Federation Constituent Entities (Federal Subjects), meanwhile, 61 Federal Subjects have no transplant centers. As for the availability of transplant centers per unit of population, Russia lags behind Western Europe and the United States by twice or thrice. As estimated, 82-104 kidney transplant centers should be an optimal number for the Russian Federation. [16]

Thus, an allogenic kidney transplant that opened up a new era of vital organ clinical transplantation in the mid-twentieth century, currently goes on in its successful development. The kidney transplantation prospects for Russia in the XXI century should be directed to coping with the donor organ shortage, improving the system of organ procurement and allocation, and establishing new transplant centers well-equipped with modern facilities for diagnosis and treatment of severely ill patients.

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