

## HISTORICAL PERSPECTIVE

**Surgeon Yurii Voronoy (1895–1961) – a pioneer in the history of clinical transplantation: in Memoriam at the 75th Anniversary of the First Human Kidney Transplantation**

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**Introduction**

In 1933 Yurii Voronoy from Kherson in the Ukraine achieved the first human kidney allotransplant, using 6 h anoxic cadaver kidneys to be reimplanted into the medial thigh (Fig. 1). He measured kidney function using an ureterocutaneous fistula. Actually, his first patient died 2 days after with ABO incompatibility [1–6]. In the classic account by David Hume of the pioneer kidney transplants done in Boston, credit was given to the Soviet surgeon, Yurii Voronoy, as the first to perform an allograft kidney transplant in a human being. The description made by Hume of this first human-to-human transplant, referred to a short article published in 1936 by Voronoy in an obscure Spanish journal [4,7]. This original article shows that not only had Voronoy carried out a human kidney transplant from a cadaver, but also that he had some insight into the immunological characteristics of graft rejection, which is well illustrated in an article by Hamilton *et al.* [8], which was used by the authors a lot for putting Voronoy's life in the right perspective.

On April 3, 1933, Voronoy performed the first human allograft kidney transplantation. The recipient was a 26-year-old woman with acute mercury intoxication after a suicide attempt (Fig. 2). Although there had been some early attempts in xenogeneic transplantation of kidneys from monkeys or sheep to human beings, and there had been some experiments with allograft kidneys in animals without immunosuppression, no patient had received a human allograft transplant before [12–14]. On the second day after surgery, the 5th of April, the patient's condition worsened. On that evening, the excretion of urine from the transplanted kidney stopped, and at 21 h 40 min, the 26-year-old patient expired. The article published in the Spanish journal is brief in its account of the transplantation, but more details of this case were given in a recent Soviet review [3,4,6]. The reasons for Voronoy's failure with the pioneer allograft are clear. The donor kidney had a very long warm time of ischaemia and the kidney and patient were mismatched in their blood groups. The postmortem changes are difficult to understand, but probably represent a mixture of mercury damage, hyperacute rejection and anoxic damage.



**Figure 1** Voronoy YY (1896–1961).



**Figure 2** The surgical Team of the first human kidney transplantation from Voronoy (Kherson, 1933).

Organ transplantation plays a common and important role in clinical medicine of today. Its history and development have been a stony and challenging path. This article will highlight some historical aspects, failures as well as milestones, to appreciate the successes we can take for granted today.

## Short history of kidney transplantation

An important prerequisite for the clinical kidney transplantation was the development of the vessel surgery. In 1902, Carrel described a new technique for vessel anastomosis in the journal 'Prese Medicale de Lyon' which is used until today [9]. A further step to kidney transplantation was taken in 1910 when a renal failure was measured by the renal Clearance [10]. On March 13 1902, Erich Ullmann reported about the first successful experimental kidney transplantation in the 'Wiener klinische Wochenschrift'. He performed a kidney transplantation in a dog by transplanting one of the dog's kidneys on his neck vessels. Ullmann was able to show with this experiment that an autologous transplant kidney starts to function again directly after re-connection to the circulation and functions for several days [11].

Since 1902, Alexis Carrel remained involved in experimental kidney transplantation. In the following years, he performed a large number of experimental kidney transplantations [12,13]. Carrel is said to be the pioneer of kidney transplantation. For his work on vascular anastomosis, he received the Nobel Prize in 1912. The first xenotransplantation of a kidney in the human was performed in 1906 by Mattheu Jaboulay in Lyon. He transplanted a pig kidney to a 49-year-old woman with a progressive kidney dysfunction caused by Bright's disease.

The German surgeon Ernst Unger also performed a number of xenotransplants in humans. In 1909, he tried to transplant the kidney of a dead born child to a monkey but without success. In 1910, he transplanted both kidneys of a monkey to a 21-year-old female patient with progressive kidney dysfunction. The patient died 32 h after the transplantation [14].

## The life of Yuri Voronoy

Yuri Yuriyevich Voronoy was born in 1896 in the village of Zhuravka in Poltava (Ukraine), where his father was a professor of mathematics (Fig. 1). After receiving a medical education in Kiev and graduating in 1921, Voronoy spent his life working as a surgeon and researcher, either in Kiev or in the nearby major cities in the Ukraine. His formative years seem to have been from 1926 to 1931, when he was a member of the Department of Surgery at Kharkov, headed at that time by Professor Shamov. One of the department's interests was in blood transfusion and they pioneered the Soviet method of using cadaveric blood for this purpose. Another interest of the department at that time was testicular transplantation in man. The reason for this odd and doubtful project was that the Russian surgeon Serge Voronoff (with whom Voronoy should not be confused), was touring Europe and the

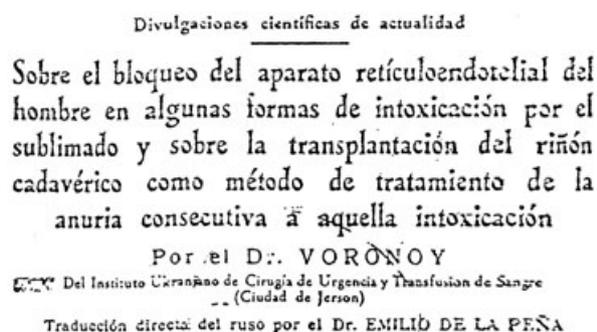
world in the late 1920s and claiming plausibly that the transplantation of the testis from monkeys to jaded or ageing humans would rejuvenate and revive them [15]. Thus, Voronoy began work in a department interested at that time in blood transfusion and testicular transplantation.

In 1931, Voronoy moved from Kharkov to Kherson and this promotion gave him new responsibilities for emergency surgical treatment and medicine. On April 3, 1933, Voronoy performed the first human allograft kidney transplant. Voronoy's understanding of the need for immunosuppression in transplantation was clear and he considered that he had found a method of sorts. In an article published in the Spanish journal *El Siglo Medico*, Voronoy describes his pioneer operation (Fig. 3); however, explicit details of this case were given in a recent Soviet review (Publications of the All-Ukrainian Institute of Surgery and Emergency Blood Transfusion, published by Surgical Archives, Dnepropetrovsk, 1934). In 1950, Voronoy became Professor of Experimental Surgery of the Ukrainian Institute of Experimental Biology and Pathology. Although Voronoy's first kidney transplantation had powerful official backing in the United Soviet Socialist Republic, his work was later ignored. In 1953, Voronoy became the head of the Kiev Research Institute of Traumatic Surgery and Blood Transfusion. He died in Kiev 1961.

**Description of the first human kidney transplantation (Original hand written records of Voronoy consisting of the patient's medical file and the operation-report from the archive of the Ukrainian Academy of Medical Sciences in Kiev which was seen during the German-Ukrainian transplantation congress)**

**General aspects**

The attached reports on the results of the first kidney transplantation from a dead donor include a series of



**Figure 3** The first publication of the first human kidney transplantation in Spanish journal *El Siglo Medico* (title page, 1936).

interesting facts which arose during the analysis of clinical and laboratory chemical data, as well as based on the analysis of experimental data regarding the immunological reaction after a kidney transplantation. Our previous work allows the overall conclusion that one of the reasons for an allograft rejection is the existence of a local mesenchymal, as well as general, immunobiological reaction, which led to the formation of specific antibodies and finally to the elimination of the allograft. Therefore, it seems to be obvious that a consideration on Isoagglutinine of the blood groups is not obligatory and decisive because it is already proven that the specific antibodies can also be formed after an auto-transplantation. On the other hand, it is known that an immunological reaction is extremely variable and can be completely absent, which allows the acceptance of an allograft. It is remarkable that under the conditions of an auto-transplantation, the immune reaction seems to be slightly reduced compared to that of a homo-transplantation. The investigation of these phenomena is an essential part in the work of different study groups. Therefore, and in the context of the knowledge about the reticulo-endothelial system and on the basis of many experimental results about the formation of antibodies, there were attempts to block the immune response through the use of different preparations in an attempt to increase the chance of acceptance of the allograft [Bogomoletz AA, *et al.*]. (This is an original citation and so we don't know, which part of Bogomoletz's work Voronoy is referring to here.) Without a doubt, the results of these researchers showed the influence of this blockade on a prolonged allograft survival. Lemann and Tammann, *et al.* showed that the allograft survival of skin was prolonged over 10 times under the mentioned blockade (from 6–7 days to 60–60 days). The hopeful results of kidney transplantations in animals allow the assumption in this context that such operations have to be performed under the condition of 'blockade'. For reasons of the fact that this method of the artificial 'blockade' in humans is not fully developed yet, we have no other choice but to make use of the condition of 'blockade' because of accidental poisoning of the organism.

From our point of view, the consequence of the mercury intoxication (mercury chloride) [author's remark: in those times, mercury chloride was a common disinfectant] is imitating this condition and thereby leading to a 'blockade of the reticulo-endothelial system' with a simultaneous acute renal failure. Therefore, in this clinical situation with the above-mentioned constellation, the absolute indication for kidney transplantation is given because of the lack of renal function. Mercury chloride, which is known to be

a salt of a heavy metal, causes localized lesions and after resorption, it causes damage to parenchymatoseous organs, particularly of the intestine and the kidneys. Obviously caused by the negative molecular charge and the binding to blood proteins, it results in a selective dysfunction of the reticulo-endothelial system. The histopathological analysis of the organs which were damaged by the mercury chloride (spleen, lymph-nodes, liver, heart, adrenal glands, etc.) showed that particularly the organs which are rich in reticulo-endothelial-system had degenerations, although they retained their ability to regenerate. Furthermore, the mercury elimination from the organism is prolonged because of a relative high blood level. So, in our case, the blood-concentration of mercury on the fourth day after the ingestion of 4.0 g of mercury chloride with suicidal intention was 1.5 mg%, and it was reduced by 10-fold on the next day, which was the first day after transplantation. Therefore, at a state of moderate intensity and in an early stage of the mercury chloride poisoning, after a complete degeneration of the parenchymatous organs did not already occur, the time window of the 'blockade of the reticulo-endothelial system' in a state of potential regeneration of the parenchymatous organs can be identified. In such a situation, the kidney transplantation performs the task of elimination of the poison from the organism as long as the endogenous kidneys have regenerated fairly. In summary, it can be concluded that after the question of sense and purpose of a kidney transplantation after mercury chloride poisoning was explained, we had to find an adequate organ, as we know the attempts of xenotransplantation (for example, from monkeys or domestic animals like pigs or goats) were disappointing. Particularly, in some of these experiments, a continuous anaphylaxis of the recipient animal after reperfusion of the organ which was anastomosed by vessel suture could be observed, which had a lethal result for the recipient animal. Against the background of these facts, a human cadaver seems to be the best option as a donor transplant organ because a healthy human can under no circumstances be deliberately injured by the organ removal, even if the removed organ is for transplantation. It is proven that cadaveric organs keep their sterility for some time. Furthermore, it is known from the physiology that cadaveric kidneys keep their function for some time after reperfusion with ringer-solution. Under consideration of these assessments, different groups of scientists have tried to transplant skin, joints and parathyroid glands from a human body to another human. The description of a kidney transplantation from a traumatic body to another human with the revascularization by vessel anastomosis is not yet known. So we report here about a kidney transplantation which was approved by Professor A. Belz.

### The patient history

A 26-year-old female patient, married, was admitted to the hospital on March 3, 1933 after the poisoning with mercury chloride with suicidal intention the previous day, after a familial conflict. She ingested 4.0 g of unsolved liquid. By the patient's own statement, it resulted in convulsive abdominal pain and vomiting directly after ingestion. At the time of hospitalization, the patient complained about spastic abdominal and loin pain, and choked and vomited a gall like secretion. Furthermore, in the somnolent patient, a stomatitis, along with fibrillations of the peripheral muscles, a distinctive paleness and irregular reaction of the pupils to light could be observed. Furthermore, there was a persistent anuria and there was no diuresis after catheterization. A therapy with infusion of 5% glucose solution, rectal clyster and an adequate diet was initiated. In the further course of treatment, even on day three after hospitalization, there was a persistent anuria. Therefore, we made the decision to perform the kidney transplantation. At this time, a 60-year-old male patient with a basal skull fracture was admitted to the hospital who died of his injuries after a short time in the emergency room. The clinical examination showed no signs of tuberculosis or syphilis (although the results of the blood examinations 'wassermann's reaction' were available on the next day). The body had the blood type B, the patient with the mercury-chloride intoxication the blood type 0.

### Surgical technique

The operation was performed on March 3, 1933 by Voronoy and his team (Fig. 2). 'Under local anaesthesia (Novocain-solution) a skin incision was performed in the area of the middle ventro-medial part of the right thigh by consideration of the supposed localization of the blood vessels. Two tongue-shaped skin areas were cut in such a way that the base of each skin rag pointed to the other (length 8 cm, width 5 cm). Furthermore, the femoral artery and vein were prepared below the A. profunda femoris and above the Hunter-canal (canalis femoralis). In that area, many collaterals were found. Afterwards, the wound was covered with moist compresses. Thereupon, the explantation of the cadaveric kidney started, which took approximately 6 h. Here, after laparotomy and ligation of the renal artery and vein as well as the ureter, the right kidney together with the capsula was prepared. The organ was placed into the wound of the recipient without following with reperfusion with ringer-solution. Therefore, attention was taken on the anaerobia of the vessel lumina (the explantation was performed after the dissection of the vessels between two double ligatures). Next,

the vessel forceps were placed 1.5 cm above the ligatures of the renal artery and vein, and the vessels were cut off together with the ligatures distal to the forceps, such that the vessel lumina was now visible. Then, after putting vessel forceps on the femoral artery and vein, and after arteriotomie/venasectio, the anastomosis of the vessels was performed according to Carrel's method with little changes. The ureter was inserted through an opening in the thigh and its end was fixed by a suture of the strength 2. Directly after the release of the blood circulation, capillary bleeding began out of the visible part of the ureter and the kidney capsula, which means a proper perfusion of the organ.

Furthermore, a peristalsis of the ureter and the outflow of few drops of urine could be observed. Despite the proper pulsation of the renal artery, the little production of urine stopped at the end of the operation. However, this was not a reason for a concern because we observed this kind of phenomenon before in animal experiments (laboratory dog), which lasted up to 1 day'.

Vorony interpreted this phenomenon as a 'reflex of the allograft to the transplantation'. 'The operation was finished after the transplanted kidney was covered with the skin flaps (standard suture) and a drainage was placed. During the operation, the patient's condition did not change. Importantly, there was no appearance of an anaphylactic reaction or intoxication. The blood level of mercury was 1.5 mg%'.

#### Postoperative care and function of the kidney allograft

In the first postoperative night the patient was a bit more restful without vomiting or muscular convulsions. The skin flaps showed a regular colour without oedema. The visible end of the ureter appeared peristaltic and excreted lucid urine. A balancing of the diuresis was not possible, particularly under these circumstances in which the placement of a catheter was not possible. Furthermore, the colour of the toes on the right side was regular, but an anuria of the patient's own kidneys persisted. In the intention to intensify the blockade of the reticulo-endothelial system and to decrease the concentration of mercury in the blood, a bloodletting (700 ml) and a blood transfusion (400 ml Citratblood bloodtype 0) were performed. On the following day, the mercury concentration in the blood was 0.15 mg%. After these procedures, the production of bloody urine was observed. Shortly after, an agitation became evident, accompanied by vomiting and muscular convulsions. The patient's condition deteriorated significantly thereafter. While the anuria of the own kidney persisted, the amount of urine from the allograft was 4–5 ml. The analysis of the urine showed a proteinuria and no glucose. The creatinine concentration was

1.8 g/l. On the April 5, 1933 at 9:00 the allograft kidney showed no urine production anymore. At 9:40, 48 h after the transplantation, our patient died.

#### Statement about operation and autopsy

The autopsy showed massive degenerative alterations of the parenchymatous organs, especially of the native kidneys, liver and spleen. Furthermore, signs of inflammation in the mucous membrane of stomach and intestine without substantial necrotic areas were observed. The myocardium was dark red and without change of its consistency. The heart cavities contained fluid blood without the persistence of emboli. The inspection of the operation field showed unsuspecting skin. The allograft was adherent to the preformed cave without the existence of pus. In the area of the kidney poles, there were irrelevant haematomas. The renal pelvis contained a bloody secretion and the vessels in the area of the anastomoses were porous. The microscopic examination of the allograft showed a slightly enlarged glomerula whose surface was adherent with the Bowman's capsule and filled with masses of fibrin in most slices. However, there were some slices in which the gap was intact. Furthermore, in the vasa efferentes of the glomerula, single red blood corpuscles were found. The intestine of the allograft was slightly extended and wall adherent thrombi were observed in the vessels. The histological assessment of the patient's own kidneys showed glomerula with an edematous endothelium, as well as nuclei of the cells with extensive mitosis. In summary, with the results of the autopsy in hand, it can be diagnosed that the organs, which were mostly affected by the intoxication, were the patient's own kidneys; however, the regenerative processes were detectable. Furthermore, the reticulo-endothelial system suffered under the intoxication, as was seen by the pathological assessment of the spleen.

How can the described changes in the allograft kidney be described? Obviously, in the first line stands the toxic effect of the mercury. Furthermore, the postoperative blood transfusion seems to have had a toxic effect because the relatively high mercury concentration in the blood might have had a haemolytic effect on the transfused erythrocytes. These changes and particularly the consequence of a haemolysis could be seen in the postmortal preparation obviously. Also, the partially incompatible constellation of the blood type between the donor and the recipient should not be ignored, although the macro haematuria which did not occur simultaneously, but in a time interval after the transplantation, speaks against this point. It is obvious that even a short survival of the patient – in our case 2 days after kidney transplantation – does not compromise this operation for this indication in

any way. The clinical consequence from this case is that the performed blood letting therapy has to be accompanied by an infusion therapy and not by a blood transfusion therapy. In the case of a nonheart beating donor kidney transplantation, the technique, indication and contra-indication as well as the immunological mechanisms of the rejection should be overworked in detail.

Voronoy performed five more nonheart-beating donor kidney transplantations in the following years and summarized his results in a symposium in 1950. The time in which the kidneys were producing urine was between 24 h and 7 days. His idea was not to cure a kidney insufficiency because of a kidney transplantation as a final solution, but more a bridging therapy in patients with temporary kidney insufficiency until their own kidneys would work properly again. Two cases are described. The one is a 47-year-old female patient with a chronic nephritis and acute deterioration of the kidney function. The transplanted kidney stopped functioning on the fourth day after operation and was removed. The patient survived and was discharged from hospital after 2 months.

The other case is a 23-year-old female patient with anuria after left nephrektomy. Here, the transplanted kidney lost its functioning 7 days after the transplantation and was removed. This patient survived too and was discharged from hospital after 2 months [6].

A search in the contemporary literature published in the Russian language, primarily taken from the archive of the Ukrainian Academy of Medical Sciences in Kiev and consisting of Voronoy's original work as well as of congress reports and reviews of other authors about Voronoy's work, shows a uniform picture: the first human nonheart-beating donor kidney transplantation in the world in an anuric patient was performed by Voronoy *et al.* on the third of April in 1933 in Kherson, Ukraine [6,16–19]. This certainty is found in the serious world literature as well, although the description of what happened was sometimes different from the original description by Voronoy [7,8,20–22]. In this article, next to our ambition to show the relevant facts, we are also concerned about the pictures and illustrations which were not known in the western medical society until today. Furthermore, we tried to resolve the differences between the international cited and the original literature. A question which was not answered in the western world until today is why Voronoy decided to transplant the kidney of a donor with blood group B to a recipient with blood group O even though he was aware of the different blood groups. The answer is given in his documentation which is also published in a Russian biography by Mirskii MB [1]. Voronoy thought that the reason for a rejection was the formation of specific antibodies in the mesenchym of the transplant. Furthermore, he was aware of the

blood-group system (1928, Kiev: the first complication-free postmortal blood transfusion between the deceased Prof. S. Judin and Voronoy's teacher, Prof. W.N. Shamov in a heroic self-experiment). Voronoy's theory in the planning process of the first kidney transplantation was as follows: he thought the reticulo-endothelial system to be a filter which is blocked by a poisoning. Therefore, he thought that a universal recipient for a transplantation would be a poisoned individual. In such cases, he wanted the kidney transplantation just as a bridging therapy.

Voronoy was aware of the blood-group incompatibility of the transplantation (donor blood group B, recipient blood group O). But he thought that 'the universal donor blood of the recipient (O) would perfuse the transplanted organ and so by the transplantation rules by Landsteiner cause no agglutination' [1].

### Complement to the biography

Supplementary to the previously known biography of Voronoy, we can note that he worked in the Ukrainian corpsmen battalion as a volunteer in the year 1915 during World War I. At that time, he was a medical student. In the year 1921, Voronoy earned a medical degree from the medical faculty of the Ukrainian medical institute. He became a junior professor at the faculty for surgery and was responsible for the efficient education of the students and younger colleagues. Voronoy's first successful heterotopic kidney transplantation in the animal model was performed in the year 1930 [17]. This case, where the allograft kidney was transplanted to the neck of the recipient animal, was presented at the third Congress for physiologists (Soviet Union, 1930) and, in the same year, at the 4th Ukrainian Congress for surgeons in Charkow. Voronoy lived in a flat on the clinic campus in Kherson together with his wife and two children (a son, born 1918 and a daughter, born 1926). During World War II, Voronoy worked as a surgeon and treated wounded soldiers as well as civilians. After the war in the years 1953–1961, he worked as vice-director of the institute for blood transfusion and haematology in Kiev where he died in the year 1961 of coronary heart disease. Voronoy was buried at the Baikowo cemetery in the Ukraine.

### Review of the literature (1930–2005) in Soviet Union to first kidney transplantation

The publications of Mirskii und Korol *et al.* uncover several imprecise elements of Voronoy's biography [1–3,23,24]. Particularly, the date of the performed kidney transplantation was claimed as 1930 by some authors, which is incorrect [25]. This date represents the time of the third Congress for physiologists where Voronoy

presented his experimental work in the dog. Furthermore, Korol *et al.* pointed out the fact that the first human kidney transplantation was not performed by Voronoy in the year 1934 in Paris, but in 1933 in Kherson (Ukraine) [26]. These corrections are based on Voronoy's original work, which was published in a Spanish journal in 1936, and in 1934 in the Russian language [4,27].

### Conclusion and summary of discussion

In 1933, the soviet surgeon Voronoy performed the first human allogenic kidney transplant. In his introduction to the article, which appeared in a Spanish Journal in 1936 describing this pioneer operation, Voronoy referenced earlier transplant operations of animal kidneys to human beings. More details of this case have been given in a recent Soviet review [4,6,16]. Voronoy decided that the mass of recipient's blood flowing into the tissues of the transplanted kidney would not be agglutinated, as the blood type of the recipient was that of the universal donor. The reasons for Voronoy's failure with the pioneer allograft are clear. The donor kidney had a very long warm ischaemic time and the kidney and patient were mismatched in their blood groups. It is interesting to speculate what would have happened had Voronoy used a fresh, blood group-matched kidney. After the transplant operation with the new transplanted kidney, the patient survived slightly over 48 h [4,6,7,16,27]. Voronoy was not discouraged in attempting further transplants, although the opportunities for these were infrequent. In 1949, he reported upon five such transplants. The use of a stapling machine in performing vascular anastomoses is described first by Voronoy 1940 and it must have been one of the first uses of this important Soviet invention. Thus, Voronoy has a major place in the history of transplantation. In our opinion, Voronoy has a solid state in the history of transplantation because he was the first to perform the technically demanding kidney transplantation in a human.

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