

## The Prehistory of Transplantation: up to the 1950s



**J Stewart Cameron**

Emeritus Professor of Renal Medicine. Department of Nephrology and Transplantation, Guy's Campus, King's College, London

**Corresponding Author:** Professor J. Stewart Cameron  
Elm Bank, Melmerby Cumbria CA10 1HB United Kingdom;  
Tel:+44 (0)1768 881804; e-mail: jstewart.cameron2@btopenworld.com

### ABSTRACT

The “prehistory” of organ transplantation began in the 19<sup>th</sup> century, and clinical transplantation might have begun in the 1920s, decades earlier than it did. Organ transplantation required surgical vascular anastomoses, achieved in the late 19<sup>th</sup> and early 20<sup>th</sup> centuries. Guthrie and Carrel showed from 1902 that autografts could function, and along with others attempted renal xenografts. But the main result of this activity was the emergence of the idea that some “biological incompatibility” caused their failure.

Its complexity was realized as the many components of the immune reaction were identified – particularly lymphocytes. Modification of this “bio-incompatibility” using benzol, gamma radiation and nitrogen mustard were rapidly described. Thus by the early 1920s, the possibility of organ transplantation with suppression of the reaction by chemical agents and/or irradiation became possible, but in fact were delayed for another 30 years. During the 1920s organ transplantation was hijacked by dubious practices, such as “monkey gland” testis xenografts. Work in the area was shunned as career-damaging for serious scientists.

In 1935 Voronoy first realized the potential of the newly-dead as cadaver donors, but all his grafts failed. Around 1950 transplantation again became a problem which surgeons were prepared to attack, principally in Boston and in Paris. Although all the 30+ grafts in the next 5 years failed, much was learned. Then as predicted by skin transfers, identical twins were transplanted – and succeeded. For other grafts no modification was used at first, but from 1958 radiation was used, new drugs such as corticosteroids then 6-MP and azathioprine were synthesized, and transplantation was launched.

**KEY WORDS:** Renal transplantation, history of transplantation, immunology of transplantation

### Paleohistory

Two years ago I had the privilege of addressing the IAHN on the “prehistory” of dialysis, from the first ideas of fluid flow in tissues and in vitro systems in the 18<sup>th</sup> century, until the first successful clinical dialysis in the 1940s. I now have the additional privilege to address the parallel evolution of the “prehistory” of renal transplantation, from first attempts at free skin grafting in the 18<sup>th</sup> century to the first successful organ grafts in the 1950s and 60s.

The idea of organ transplantation is deeply embedded in myth, such as the legend of the elephant-headed Ganesha in India, and more recently the much-illustrated (in more than 100 churches) story of the brothers Cosmas and Damian, and their leg transplant from a (dead) moor into a sacristan (1) (Figure 1).



Figure 1 - Saints Cosmas and Damian (3rd century CE) and the miracle of the transplantation of the “black leg”. More than 80 versions of this miracle occur in churches in Europe (1). This one, from the brush of Fra Angelico (c1387-1455) dates from 1442 and is to be found in the Museo San Marco in Florence.

In reality, although skin pedicle auto-grafting was invented in India in 600 BC, subsequent attempts to make use of this

treatment in injured and burnt patients as free grafts showed that only skin cropped from other areas of the same individual would persist. Much uncertainty remained, however, because whether or not a skin graft had “taken” lacked any good criterion for judgement until the 1950s. The story of skin grafting lies outside my own remit but see Brent (2) Hamilton (3) and Woodruff (4) for details. Likewise tooth “transplantation” has a long history with had a vogue particularly in the 18<sup>th</sup> century, fuelled by John Hunter’s interest in the subject, but again there was no actual transfer of living tissue, although implantation of teeth persists today.

### Organ transplantation: the anastomosis of blood vessels

Organ transplantation in any form had to await techniques of joining blood vessels – vascular anastomosis. Advances in surgery including anaesthesia allowed attempts to do this in the second half of the 19<sup>th</sup> century. The pioneers who first attempted this difficult task included Nicolai Vladimirovitch Eck (1849-1917) a Russian physiologist (Figure 2) who in 1877 performed what may be the first vascular (venous portocaval) anastomosis in a dog, using silk sutures.

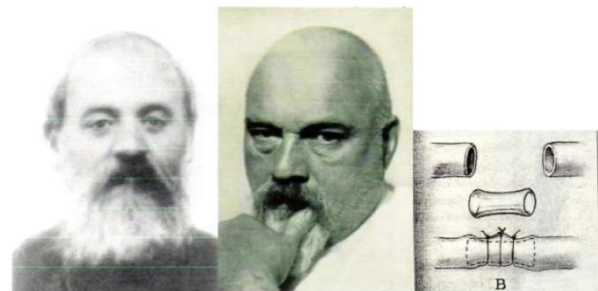


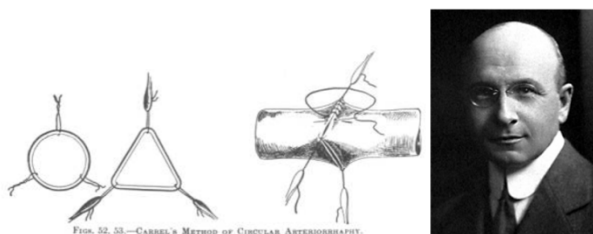
Figure 2 - (Left) Nicolai Vladimirovitch Eck (1849-1917) who performed the first vascular anastomosis in 1877 using silk sutures – a porto-caval shunt in a dog. (Centre) Erwin Payr (1871-1946) who in the 1890s used soluble magnesium stents (Right) to achieve vascular union.

John Benjamin Murphy (1857-1916) of Illinois performed an end-to-end arterial vascular repair after a femoral gunshot wound using the same technique in 1897 which was widely publicised and discussed. For smaller vessels, others in the 1890s used stents of glass or ivory, but Erwin Payr (1871-1946) of Graz in Austria (Figure 2) in the 1890s used magnesium stents which later dissolved, with success (5). Here I must stray – for not the only time – into the territory of the companion talk by Raymond Ardaillou: the talented French surgeon Mathieu Jaboulay (1860-



**Figure 3 - Mathieu Jaboulay (1860-1913)** led a fruitful team in Lyon, in the department of Surgery and not that of Anatomy, where Carrel worked alone. In parallel with Payr in Vienna, he perfected silk suturing of vessels without stents during the 1890s, using straight needles and silk (or cotton) thread. In 1906 he made the first attempt at a human transplantation for uraemia, using a pig kidney transplanted on to the arm, and a goat kidney into the thigh of two patients. Both kidneys functioned for some days! He was killed in a train accident in 1913, and his team broke up.

in Jaboulay's department, but chose continuous suturing, with the stitches only penetrating part of the vascular wall. He was also able to obtain smaller and thinner needles and cotton thread. These he retained, but later turned to Jaboulay's methods of stitching. He suggested the triangulation of a vessel with sutures still in use today, as well as the "Carrel patch", again still in use more than a century later.



**Figure 4 - Alexis Carrel (1873-1944)** a "master sewer" who perfected many techniques for vascular union still used today, in Lyon 1901-2. Not illustrated is the famous "Carrel patch" much used in renal transplantation. In Chicago, after emigrating to the USA, he did many dog transplants and, together with Guthrie (see below) postulated the "biological incompatibility" which led to graft loss. Later in life he, his ideas and life became controversial, for numerous reasons (see ref.8).

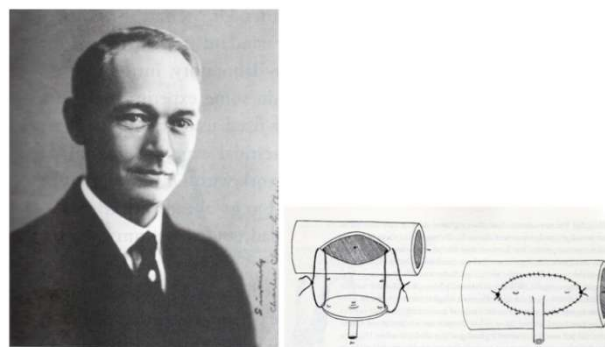
In 1953 Comroe wrote: "Between 1901 and 1910...Alexis Carrel performed every feat and developed every technique known to vascular surgery today.."

1913) (Figure 3) and his colleagues in Lyon returned to careful interrupted silk anastomoses on everted ends of the vessel(s) in 1896, without a stent (6). Working in Lyon also – but in the anatomy, not the surgical department – was the subsequently famous and controversial figure of Alexis Carrel (1873-1944) (7, 8) (Figure 4) who is often credited alone as having solved the problems of vascular anastomosis and vascular transplantation.

Clearly Carrel, besides being a brilliant technician was also an original, imaginative and highly creative surgeon. He must have been aware of the work

He was aiming to transplant endocrine glands which were at that time, together with their "hormones", then a "hot" new topic. The need for his techniques was brought forcefully to the fore when in 1894 an Italian anarchist stabbed the French President Sadi Carnot in Carrel's home town of Lyon, and severed his portal vein. Carnot bled to death because the surgeons in whose care he was could not suture the vessel, which Carrel could only lament – and did. In 1902 he published his work in a seminal paper in the journal *Lyon Médical* (7).

The difficulty is that he did not work alone, as so many accounts of his work imply. In 1904 after failing to obtain a senior surgical post in Lyon (we can speculate why), he emigrated to French Canada, then to on the United States. There after a period he entered the surgical laboratory of George Stewart in Chicago, to work under Charles Guthrie (1880-1963) (Figure 5), seven years younger than he (9).



**Figure 5 - Charles Claude Guthrie (1880-1963)** was assigned Carrel as his assistant in Chicago. The two had a successful but later contentious partnership, and published a shoal of papers on vascular anastomosis in 1905-6. They included the description of the "Carrel patch" (right) - which should have been called the "Carrel-Guthrie patch".

But meanwhile interest in vascular anastomosis and organ grafting in Europe intensified: in 1902 (Imre) Emmerich Ullman (1861-1937) (Figure 6), a Hungarian from Pécs working in



**Figure 6 - Imre (Emmerich) Ullman (1861-1937)** did autotransplantation of the kidney in the dog in 1902 in Vienna, and later in the year a dog-goat xenograft which worked for some hours, but he did no more work in the area.

Vienna (10), using Payr's stents, autotransplanted a dog's kidney from loin to its neck, with some function surviving: the first autotransplant – alongside Carrel and Guthrie's similar work, also in 1902 (see below). That same year Ullman went on to transplant a kidney from a dog into a goat, which amazingly functioned for some hours, but he did not pursue this research further. Also in Vienna in 1902 in another (the Second Medical) Clinic, Alfred von Decastello-Richtwehr (1872-1960) did similar dog-dog grafts using stents (11). Unappreciated at the time, he also showed a great fall-off in lymphocytes following tying-off

the thoracic duct. Again there was no follow-up to either observation. Decastello also described blood group AB in 1904, and myeloma kidney in 1909, and deserves to be better known. Another less well known observation was that of the Romanian N Floresco (12), who in 1905 used hirudin to prevent clotting, and implanted the transplanted ureter into the bladder of his dogs for the first time. But his allograft data are suspect as one native kidney was left in place, although one graft continued to

secrete urea-containing urine for a week. In 1907 Rudolf Stich of Breslau (1875-1960) used the pelvic position for his autologous kidneys, as is now standard, as did Jacobus Henricus van Zaaier (1976-1932) of Amsterdam the following year.

Work in Lyon went on – “*la transplantation des organes sont à l'ordre du jour*”. In 1906, Jaboulay made the first attempt at *human* transplantation (13). Reasonably he sought a donor organ from an animal – in two cases from a pig and a goat, the pig kidney being transplanted into the arm using the brachial artery, using a stent this time, in a patient with terminal uraemia. It functioned producing normal amounts of urine until the artery clotted on the third day. The goat kidney transplanted into the thigh of the second patient and similarly did well. Subsequent experiments in the next few years never duplicated these initial successes.

This work in Lyon was followed in Berlin by further trials of more than one hundred renal transplants conducted by surgeon Ernst Unger (1875-1938) (14) (Figure 7) working in his own privately-funded clinic and laboratory, with support from the Countess Bose foundation. Most of these were in dogs, but In 1910 he did a modern-looking experiment, using both kidneys of a pigtailed macaque *en bloc* into the thigh of his recipient, a young woman in advanced renal failure. It did not function however, despite having a short warm time, and she died two days later in pulmonary oedema. Unger’s paper contains the first illustration of a human renal graft (14). Fascinatingly, the post mortem histology of the kidney showed abundant lymphocyte infiltration – another first.

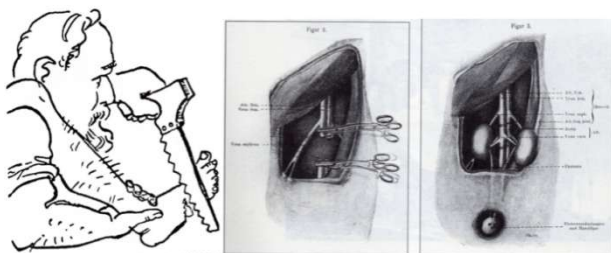


Figure 7 - (left) Ernst Unger of Berlin (1875-1938). This cartoon was all I was able to find by way of an illustration of him. Unger worked alone in a privately-funded laboratory clinic, and in 1910 he used the two kidneys of a macaque pigtailed monkey transplanted *en bloc* into a young woman in advanced renal failure (right). This technique is used for young paediatric donors today.

We must turn back from this European work to review the activities of Carrel and Guthrie in Chicago. Despite the huge difference in character, between the shy, rural and quiet Guthrie, and the bold, thrusting and confident Carrel the two co-operated productively in 1905-6, refining techniques of arterial suturing, and published 21 papers in a single year! – plus 5 more under Carrel’s name alone.

Some of these papers concern autografted kidneys, which Carrel had first performed in 1902 in dogs in Lyon, with success. With Guthrie, Carrel did a number of allografts and xenografts in – and between – cats and dogs from 1904 to 1906. But in 1906, Carrel moved to the Rockefeller institute in New York, and only 6 years later in 1912 was awarded, alone, the Nobel Prize for his work in vascular surgery and transplantation (8). Not for the first time, the prize was awarded in a fashion which others disputed. At that time however the prize was only awarded to individuals, so a joint award was beyond the remit of the current Nobel committee (the rule was changed shortly afterwards and now awards to several individuals are almost inevitable). They had preferred the charismatic Carrel to the

unworldly Guthrie. The latter’s only reply was major work on vascular surgery in 1912 (9), which along with the author were rapidly forgotten. Carrel’s subsequent stormy career and political philosophy and involvement has ensured continued interest in this strange, complicated but immensely talented man (8) with a penetrating gaze amplified by two different iris colours.

But all this early work on transplantation of organs has brought to the fore the idea, to quote Carrel and Guthrie, that there was a “biologic incompatibility” between species which precluded successful transplantation, which was to dominate events down to the present day. Carrel was again at the forefront, and his colleague at the Rockefeller Institute, James Baumgardner Murphy (1884-1950) (Figure 8), even more so (15).

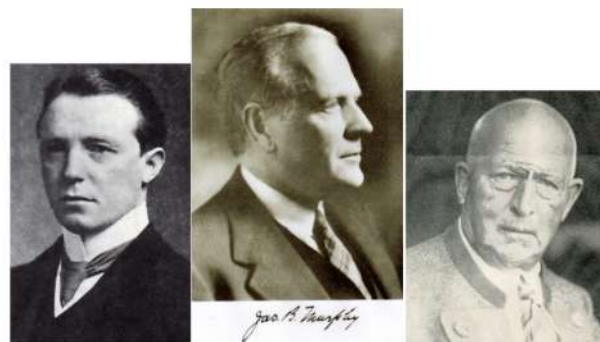


Figure 8 - Immunologists important in the dissection of the “biologic incompatibility” of Guthrie and Carrel. Left, Ernest Bashford (1873-1923) of the MRC in London, whose career was limited by his alcoholism, (Centre) James Baumgardner Murphy (1884-1950) of the Rockefeller Institute on New York a key player in the field. (Right) Erich Lexer of Vienna (1867-1937). All attributed graft loss principally to the action of what are now known as lymphocytes around 1912. (Courtesy Wellcome library, Rockefeller Institute and Wikipedia commons).

### The immune system and the transplantation barrier in 1910-20

What was this “biologic incompatibility”? During the early, technical, years of kidney transplantation from 1902-1912, major advances were made also in understanding what we now call Immunity. The history of this subject is vast and I will note here only ideas and facts strongly related to organ transplantation. It needs to be said here that the relevance of a large amount of work done from 1860 onwards using skin served only to confuse, right up to some of the data of Gibson and Medawar in the 1940s (see below). In large part this resulted from difficulties in assessing whether skin grafts had “taken” or not, and many deceived themselves on this point. More rewarding for organ transplantation was a huge amount done on the transplantation of various tumours from one animal to another.

Details of the genesis of protection against disease by prior exposure was developed over 200 years from the mid-1700s, and continues today (2, 16). The discovery of the various components of the reaction accelerated greatly in the early 20<sup>th</sup> century, after phagocytic white blood cells as defensive agents had been described by Ukrainian Ilya Metchnikoff (1845-1916) in the 1880s, and then antibodies by Paul Ehrlich in Germany (1854-1915) in the 1890s and 1900s which led to unnecessary but productive rivalry, since both groups were correct – as so often happens when two opposing views, both with excellent data to support them, and in opposition. In addition on 1902 Viennese Karl Landsteiner (1868-1943) described human blood groups, and Hans Buchner (1850-1902) of Munich and then Belgian Jules Bordet (1870-1961) working in Paris unlocked alexine, later called by Ehrlich “complement”. All

these factors turned out to be important as aspects of recognition and elimination of foreign antigens, including those important in transplantation. All the investigators mentioned in this paragraph were awarded a Nobel Prize.

Thus by only the second decade of the 20<sup>th</sup> century the idea that organ and tissue grafts were destroyed through mechanisms important in defence against foreign organisms had emerged, but details remained scanty. Georg Schöne (1875-1960) born in Berlin trained with Ehrlich, and did work on skin and tumour transplantation. In his book of 1912 (17), his observations led him to the first use of the term *transplantations immunität*. He described accelerated loss of second grafts between the same individuals. His contemporary Erich Lexer (1867-1937) of Vienna (18) (Figure 8) had the same idea, describing a “reaction” to the graft, which resulted in destruction of all unmodified homografts. In his book he described also for the first time the longer survival of grafts between close relatives, and most severe and rapid across race differences. In London yet another brilliant pupil of Ehrlich, Ernest Bashford (1873-1923) (Figure 8) (19) confirmed Schöne’s observation of accelerated second-set grafts, and made careful histological studies showing invasion by lymphocytes and plasma cells, whilst no circulating antibody was detectable in the same individuals. He retired, and died young, of alcoholism.

But Bashford was forgotten, as less forgivably was James Baumgardner Murphy (1884-1950) (15), a pupil of Rous working at the Rockefeller Institute, who showed that transfusion of adult spleen cells (mostly lymphocytes) would prevent the taking of tumours on to the yolk sacs of chicken embryos (a technique he pioneered). Only recently since the 1950s has the scope of Murphy’s work on transplantation been rediscovered. But at that time lymphocytes were viewed as static cells, despite several suggestions to the contrary in previous decades, which long handicapped understanding of their crucial importance in graft destruction. Also, a now obscure embryologist John Beard (1857-1924) (20) working in Edinburgh had described in 1899 that the thymus was the origin of lymphocytes (21), but yet again this work was forgotten and the function of the thymus considered a “mystery” for another half-century.

Most surprising of all was the rapid acquisition in this early era of information on how to modify the immune system. Murphy was a lead figure in this, with the clear idea that removal or inactivation of lymphocytes would improve graft survival in tumours. X- irradiation had been described from 1895, but was quickly seen to have effects in suppressing bone marrow and the lymphoid system. Ludwig Hektoen (1863-1951) (Figure 9) in Chicago showed that antibody levels were depressed by X rays (22), and Murphy showed they prolonged the survival of rat tumour grafts, with Hektoen. But easier agents were at hand. Glanville Yeisley Rusk (1875-1943) (Figure 9).

In California in 1914 showed that benzol would depress antibody formation (23). This agent had been available since 1890s and proved toxic, leading to a selective marrow depression, principally of white cells. Murphy used this agent as well, and splenectomy.

It is tempting to speculate what exchanges of ideas and experiments there may have been between Murphy and Carrel in adjacent labs at the Rockefeller prior to WW1. David Hamilton (3) trawling the reports of the Rockefeller Institute, discovered a statement by the director, Simon Flexner, from

1914 that Carrel *had* taken up Murphy’s ideas, and “*found that in animals damaged [by irradiation or benzol (see below)] transplantations could be accomplished which in healthy animals were absolutely unsuccessful*”.

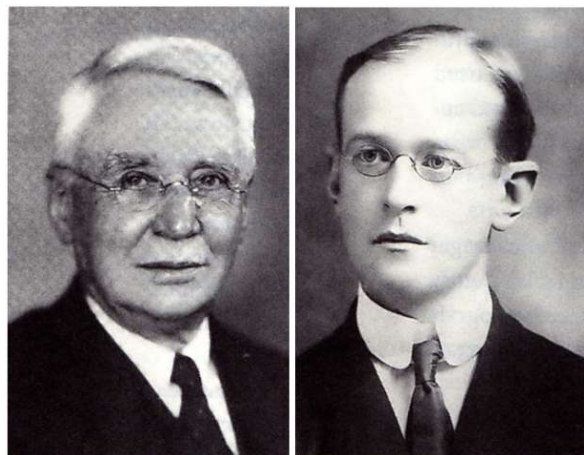


Figure 9 - Two pioneers of modulation of immunity. (Left) Ludwig Hektoen (1863-1951) of the John McCormick Institute in Chicago (now the Hektoen Institute), who studied irradiation, benzol and nitrogen mustard, and (Right) Glanville Yeisley Rusk (1875-1943) of California who first noted that benzol depressed antibody formation.

Benzol was not the only chemical immunosuppressant available. Studies by the husband and wife team of Edward and Helen Krumbhaar at the front in World War 1 from 1915 onwards showed that soldiers exposed to mustard gas developed marrow depression and reduced white cell blood counts (24). In 1921 Hektoen followed his work on benzol with similar studies of nitrogen mustard.

Hamilton (3) describes a major surgical meeting held in New York on the eve of World War 1 in Europe, one of whose three main subjects was – transplantation of organs and tissues. This meeting was attended by Ullman, Morestin from Paris, Lexer, Villard from Lyon – and Carrel, who presented a “road map” of where studies in the area would go. The New York Times (3) reported the meeting extensively, finishing:

*“all our efforts must now be directed towards the biological methods which will prevent the reaction of the organism against foreign tissue and allow the adapting of homoplastic grafts to their hosts...”*

Clearly transplantation as a clinical technology was about to take off – in 1914. The “gap” in advancement of transplantation studies which followed has been highlighted and described in detail by David Hamilton (3, 8).

#### What went wrong?

Undoubtedly the world war on a scale unprecedented had major effects, destroying especially the German economy and institutions, meetings and international exchange of ideas and people. German innovation had been central to the field, as the account above shows. Carrel, although in his 50s, returned from the USA and became an officer in the French Army at the Front during the war, and changed his interests completely in the following decades. Except in the United States, economies such as those of France and Britain were in a poor state, and research declined in quantity.

Also, the continued defeats by rejection of other than autologous grafts, from skin to whole organs, hung heavily over the field. Rather than the successes of the pre-war years in transplantation, these ideas now became dominant. In the

increasingly important United States, it was not a field in which to be involved – especially in the light of many scandals which emerged in the 1920s. What little science was done in that decade was confused, with no attempt to build on the fertile

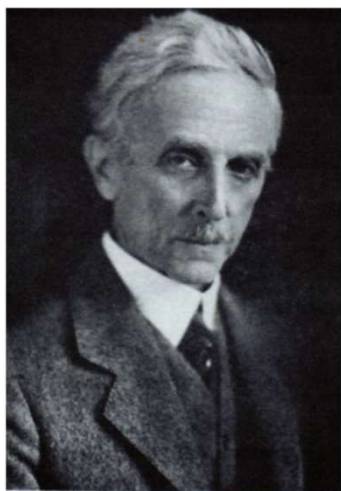


Figure 10 - Leo Loeb (1865-1959) of St Louis, one of the few serious scientists who continued to study transplantation immunology in the 1920s. He established and related the key concepts of cellular immunology.

Finally, there had been a general shift of emphasis and funding from clinically-oriented research to basic biology.

Even worse, the major events of the 1920s in the transplantation field were the quackery and scandal of gland transplants, particularly involving slices of human testis, and whole testes from apes into humans. This field was led by the work of the Russian Sergei Voronoff (1866-1951) with the object of returning sexual potency, or even of a general rejuvenation. The gland or tissue slices were placed within the scrotum and excellent results reliably obtained, if the propagators were to be believed – which they were. Ovarian grafts were also popular. A large amount of effort and money was dissipated, and the reputation of the idea of “transplantation” effectively destroyed as science. By 1930 the field was a career no-go area for young investigators. I will not waste space or time detailing this shameful period in surgery, when so many deceived themselves, as well as others. Even into the 1950s there persisted proponents of spurious ideas that various glands (thyroid, parathyroid, ovary, testis) were capable of avoiding an immune reaction, if suitably manipulated by culture, storage, cooling or other treatments.

#### A revival in the 1930s and 1940s?

The next event of importance was a series of human transplants done in an unlikely site, and unknown to almost all surgeons and physicians outside Russia until the 1950s. The major importance was that this surgeon used a new source of potential organs – the newly deceased cadaver. The question of where one could obtain human kidneys (or other organs) for transplantation had never been properly explored, and the idea of living donors had never arisen publicly.

The surgeon was Yuri Yurevich Voronoy (1895-1961) (Figure 11), a Ukrainian surgeon with a good training in surgery in the clinic

idea of modifying the now well-developed reaction to allografting using chemical agents. A few individuals in America kept the flame alight, particularly German immigrant Leo Loeb (1865-1959) in St Louis (25) (Figure 10), and Frank C Mann (1887-1962) at the Mayo clinic working on lymphocytes, but neither moved knowledge much beyond what that been attained before and during the war. However Loeb was convinced that the tissue reactions to foreign grafts was a fundamental inbuilt reaction of importance, and involved cell infiltration. Its basis must be some individual set of markers which could be recognised as foreign by the host, exemplified by his work on interfamilial grafting (25).

of Vasili Shamov in Kharchiv. In April 3<sup>rd</sup> 1933 he anastomosed a cadaver kidney into the right thigh a woman with acute renal failure from mercuric chloride poisoning for four days, with anuria (26). He wrote:

*“transplantation of primate organs and above all domestic animals... have failed utterly. The only source of grafts is cadavers, since the donor does no suffer a loss.”*

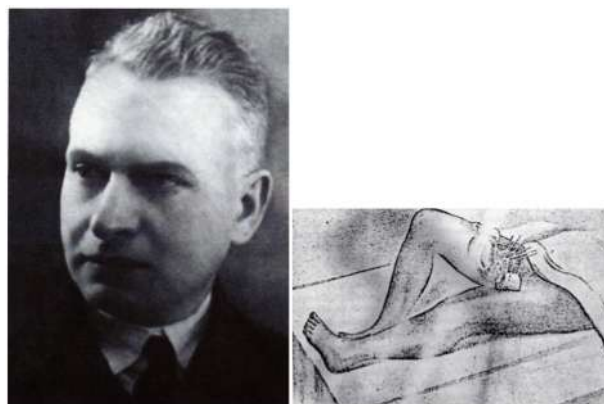


Figure 11 - Yurii Yurevich Voronoy (1895-1961) of Kherson, Ukraine who in 1934 performed the first human-to-human renal graft, from a cadaver donor, which he advocated as the only possible source “since the donor does not suffer any loss”. The illustration on the right is taken from the German re-publication of his paper attributed to “Ú Woronoy”.

Voronoy may well have got this idea from the frequent employment of cadaver blood for transfusion in the Ukraine by Sergei Yudin (1891-1954), a pioneer of blood transfusion – the first civilian blood bank. Voronoy moved to Kherson in Southern Ukraine in 1931, where he planned renal transplantation as a temporary measure at least for patients with mercury poisoning, usually taken to procure abortion or for suicide, but sometimes accidentally. He had observed splenic and lymph node shrinkage in such patients, and reasoned they might better accept a graft. He had also done transplantation in dogs previously.

This first human-human transplant and its course are meticulously described (25): the donor was a 60-year old man dead for 6 hours; the donor blood group was noted to be B, and the recipient O, i.e. incompatible. The kidney barely worked and an exchange transfusion of citrated group O blood was given, in part to remove some mercury. The patient died after 2 days (sadly, as she had wished). The operation was done under local anaesthetic into the right thigh; the ureter was left free.

His work was published in Russia, Germany and even Spain, but did not come to general attention in the West until a search by David Hume of the literature in 1954 (see below). Voronoy did another 5 kidney grafts up to 1949 back in Kiev, but detailed results are not available and none seem to have succeeded for any length of time. This not surprising, since politically-dictated Soviet biological dogma forced the organs to be stored from 1 to 20 days before transplantation!

In retrospect, the next major event was the publication in 1943 of a landmark paper (27), from Tom Gibson (1915 -1993) a surgeon and head of the Glasgow burn unit, and Peter Medawar (1915 -1987 (Figure 12). In the UK, World War II resulted in an input of money and energy into the treatment of the hugely increased number of major burns casualties, fuelling in turn a resurgence of interest in skin grafting.



Figure 12 - (Left) Peter Medawar (1915-1987) immunologist and Nobel laureate and (Right) Tom Gibson (1915-1993) plastic surgeon of Glasgow. Their observations on skin grafting established that these were rejected by an immune mechanism, but misled in suggesting that antibodies were principally responsible for this (Courtesy Wikipedia commons and Glasgow University).

A badly burned young woman received multiple pinch skin grafts from her brother, and the results became a classic paper, showing finally, and conclusively, that allografted skin did *not* survive indefinitely, and confirming that second-set grafts rejected more quickly. Odd things had appeared, in that the grafts rejected later than expected, and that they contained little or no cellular infiltrate – leading the pair to the conclusion that rejection depended on antibody rather than lymphocytes. Also they still believed that these were local cells, as they still thought that lymphocytes did not move much or at all, as Gowans destroyed this idea for good only in 1959. The patient was ill and may have had poor immunity, and the donor may have been tissue compatible, accounting for the lack of infiltrate. Medawar's successor in Oxford, Avron Mitchison (1928- fl.) restored emphasis to the Murphy-Loeb model of lymphocytes as the main mediators of tissue reaction to grafting, whatever their origin might be.

During the 1940s in particular are rumours of several human kidney transplants done under irregular circumstances, details of one of which are preserved (3, 4). This was the placement of a kidney in Boston in 1945, obtained from a deceased relative of a staff member, on to the arm of a woman with acute renal failure (there was then no dialysis available). The graft functioned for 4 days until the patient's own kidneys recovered function and she went home. Sadly however she died not long afterwards from hepatitis. The surprise is that this clandestine transplant was done by three interns: David Hume, later a leading transplant surgery, Charles Hufnagel equally a well-known cardiac surgeon, and Ernest Landsteiner, urologist and son of Kurt Landsteiner – at the Peter Bent Brigham hospital. Another "clandestine" transplant is mentioned by Hamilton (3, p. 168).

### The 1950s – clinical transplantation emerges

For reasons that are now hard to discern, around 1950 surgeons began to ignore the pessimism of the immunologists that allografts simply could not survive immune attack, and started doing human renal transplants nevertheless. They accepted in their collective ignorance that they knew of no agent which they could modify any immune reaction to the graft – even though they might from the start have used at least irradiation, and perhaps benzol or nitrogen-mustard-related drugs. They *hoped*, not knowing of all the work done around 1910-20, that at least *some* grafts would be successful without any immunotherapy. This period is rich in testimony from the participant surgeons physicians and immunologists and thus is a field which can be explored by historians.



Figure 14 - On the left is Ruth Tucker (1906-1954) doing her housewife duties, recipient of a cadaver kidney transplanted by Richard Lawler (1895-1982) in Chicago in 1950 (Right). Lawler intended to "start something", and he certainly succeeded, as another two dozen grafts were done in the following decade, most without any immune modification save corticosteroids in small doses in some cases. In 1958-1962, irradiation was used to modify recipients and a number survived long-term.

One of the earliest to do this type of unmodified transplant was Richard Lawler (1895-1982) in Chicago in 1950 (28) (Figure 14), who performed a cadaver kidney transplant into a woman of 44 called Ruth Tucker, with advanced polycystic kidney disease and severe symptoms, of a kidney from a cirrhotic patient who had just died; as he said "I was only trying to get it started". Forty-five people packed in to watch the operation. One cystic kidney was removed, and the blood group-compatible kidney placed in its bed. The kidney functioned for about 50 days, then decreased in size, and was subsequently removed – but with the patient retaining her superior health and lived further 4 years. The remaining cystic kidney must have increased its renal function. Lawler achieved his aim, as his attempt encouraged teams in Boston and Paris.



Figure 15 - The French teams in 1951. Above left Charles Dubost (1914-1991) of the Necker Hôpital, and Marceau Servelle (1912-2002) of Strasbourg. Below left, René Küss (1913-2006) of the Hôpital Cochin then Hôpital Foch, below right Jean Hamburger (1906-1986), the "godfather" of French Nephrology, who had dreamed for years of successful renal grafting. A dozen grafts were done in France in 1951-2 using "free" kidneys and cadaver donors.

Thus the centre of attention turned to France, as Raymond Ardaillou discusses in a companion paper, proposed and carried through principally by Jean Hamburger (1909-1992) (Figure 15) who had planned transplantation from the late 1940s. A good

summary of this work, at different sites, is given in Table IV of Woodruff's book (4, pp. 521-5). In early January 1951, Charles Dubost (1914-1991) in the Necker hospital in Paris, and Marceau Servelle (1912-2002) a vascular surgeon in Strasbourg (Figure 15) obtained the two kidneys of a condemned prisoner who had just been guillotined, which were placed in blood group- matched recipients, into the pelvis. Both patients died at 20 and 17 days of complications – but with functioning kidneys, and at post mortem neither showed much cellular infiltrate. Later in that same month René Küss (1913-2006) (Figure 15, Figure 19) then at the Hôpital Cœchin, performed the first of 6 mostly cadaver transplants (29) but on this occasion using a “free” kidney, subject to nephrectomy for ureteral problems, as a donor. He also used kidneys from the guillotine, an experience he described later as “*extrêmement pénible*”. After all this work, in one of his papers in 1952 he made the following prescient statement “... *in the present state of knowledge, the only rational basis for kidney replacement would be between monozygotic twins*”. He perfected the pelvic placement of the kidney still current today, and the tricky anastomosis of the ureter into the bladder.

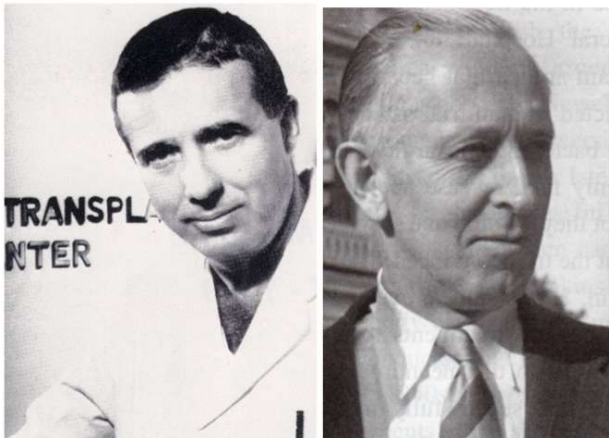


Figure 17 - (Left) David Hume (1917-1973). Encouraged by Francis D Moore chief of surgery at the Peter Bent Brigham hospital he began in 1951 a series of more than a dozen unrelated cadaver transplants, most done without any modification. Unlike the Paris transplants, which were placed in the pelvis, these were grafted into the thigh with a cutaneous ureterostomy. One functioned 5 ½ months, but all were rejected. (Right) Gordon Murray (1894-1976) of Toronto, a solitary and secretive, but brilliant and innovative cardiac surgeon who had developed and used an artificial kidney. He transplanted more than 4 uraemic patients in 1951-2. One of them was apparently well when lost to follow-up about 2 years later. Whether she made a spontaneous recovery from her nephrotic syndrome or not, is unclear.

Next up was Gordon Murray (1894 -1976) (Figure 17) of Toronto, Canada (30), primarily a cardiac surgeon but who did research on heparin, built and used for several years a static coil artificial kidney from 1946. He performed, after much work in dogs, four, maybe more human cadaver renal transplantations in 1951; but few details (as was usual for Murray) are available. It appears that irradiation was used in at least one of these cases, showing that Murray had been in the library as well as the OR. One of his patients was reported to be at work and well 15 months after transplantation but we know nothing of his residual function of her own kidneys. Murray did further grafts of which no account exists.

Back to Paris in 1952, and Hamburger's team at the Necker hospital were presented with an agonizing problem (31): a 16 year old carpenter, Marius Renard, fell off a scaffold at work, and ruptured a kidney which continued to bleed. It was removed, as was normal under such circumstances. But he was now anuric; he had had only a single kidney: what to do? –

dialysis was not available at the Necker at that time, in any form. Then his mother made an offer: “*give one of my kidneys to my son, who is dying before my eyes*” (Figure 16). Jean Hamburger and his team replied in the affirmative. The operation itself, the first living donor kidney graft [done using the Küss technique by urologist Louis Michon (Figure 13)] went faultlessly; the kidney functioned immediately and went on functioning until 21 days, when it faltered and stopped on the 22<sup>nd</sup>. Marius died in uraemia. But so much was learned from this attempt (31). The histology of the kidney showed an intense infiltration of cells. The Küss surgical technique worked; the local and systemic signs of a rejection were observed and recorded, and the histology studied. And one hopes that Mme Renard felt that all had been done to help her son, as she wanted – but she probably did not know about the lack of dialysis, although this would only have postponed the inevitable a week or two because of the then inevitable access failure.



Figure 16 - The first living related renal transplant. Left, Marius Renard, 16 year old carpenter whose single kidney had been removed after rupture in a work accident, and right, his mother who volunteered to donate him the kidney in 1952 which prolonged his life by just 22 days, in a ward of the Hôpital Necker in Paris. (Pictures courtesy of Gabriel Richet).

Meanwhile in 1951, the team in the Peter Bent Brigham hospital in Boston, supported by chief surgeon Francis D Moore and led by David Hume (1917-1973) (Figure 17), had rapidly done 6 of a series of grafts (9 were included in their paper of 1955 (32) after preliminary note in 1952). All the remaining kidneys were done during the next two years, together with another probable half dozen, who one imagines may have done worse than those in the publication. The Peter Bent Brigham team had the advantage over the team at the Necker in that had on site John Merrill and his modified Kolff dialysis machine, which could be used before transplantation (as in their first transplant), and for a while at least after graft failure. All these early grafts were placed in the thigh with a free ureter, as Voronoy had done. The most exciting thing about this series was that one graft lasted 5 ½ months in a young physician from South America. The others failed from immediately to a week or two only. One patient with polyarteritis had recurrence of his disease in the graft – an ominous sign of a future problem. Much was learned from this series despite the failure of all the grafts, and some would consider it right to stop the “prehistory” clock with this paper, and that discussed in the next paragraph published about the same time. But I believe that the invention of immunosuppression is part of prehistory.

In 1954 a new patient with uraemia Richard Herrick, aged 23, was referred to the Boston team by a Chicago physician Dr David C Miller, who pointed out that Herrick had an identical twin Roland, and maybe the twin could provide a kidney, as Küss had suggested could avoid an immune reaction (Figure 18). The new divisional head surgeon after David Hume left, Joe

Murray, was a plastic surgeon, and familiar with the work on identical twins and skin grafts from the 1940s. At Christmas 1954, after some regular haemodialysis supervised by Merrill, Herrick was ready to receive his brother's kidney; acceptance of a skin graft and fingerprinting had demonstrated their identity. After preliminary haemodialysis to improve Richard's condition, the kidney was placed in the pelvis and the ureter implanted in the bladder in the Küss method (33), and maintained Richard for 8 years, when it failed because of recurrent glomerulonephritis. Roland survived until 2010. Some other of half a dozen twins referred as a result of the huge publicity did even better (34); the Helm twins Edith and her donor Wanda were operated on in May 1956 in Boston, and after having had a baby on the way, Edith survived to die in 2011, aged 76. Wanda survives. Also the Valentine twins, transplanted in 1960 aged 12 years, were still both alive in 2017, 57 years later.



**Figure 18 - Real success at last 1954 in Boston. Top: on the Left, sitting are the two Herrick identical twins, Richard (recipient) (1931 -1962) who lived 8 years, and Roland (donor) (1931 - 2010). Behind them are (left to right) Joe Murray (1919-2012) plastic surgeon, John Merrill (1917-1986) physician, and J Hartwell Harrison (1909-1984), urologist. Right, Joe Murray who (unlike the others - and Jean Hamburger in Paris) alone survived to receive the Nobel prize in 1990. René Küss (died 2006) was ignored, to fury in France.**

**Below, on the left Edith Helm (1935-2011) who received a kidney from twin sister Wanda (right) in May 1956, which served her well for 55 years. She also was the first transplant recipient to have a baby, in 1958.**

But the blunt fact remained in 1954 that it was known that kidneys behaved just as skin had eventually been proven to: autografts or isografts survived long-term, allografts only days or at most weeks. William (Jim) Dempster (1918-2008) (Figure 13) in London, and Morten Simonsen (1921-2002) in Copenhagen and the UK studied this "rejection" phenomenon in detail in the early 1950s, detailing (35, 36) that it was a cell-mediated phenomenon, depended on recognition of individual-specific antigens, and re-discovering the studies of the "lost years" of 1910-20. Dempster believed strongly that the operation had to be proved in animals, before doing any clinical experiments throughout the 1950s: in this he was wrong as species reactions are so different. Dempster was also the first to



**Figure 13 - Surgeon William (Jim) Dempster (1918-2008) of the Hammersmith and St Marys hospitals in London is on the right in this picture. He studied rejection from 1951 to 1957 at the RC Surgeons lab at Downe in Kent, UK. He published more than 100 papers on the subject, confirming that the reaction was cell-mediated, although antibodies were still allowed a role. On the left is Urologist Louis Michon, who performed the first living donor transplantation, in Paris in 1952 (see below). (Picture courtesy of David Hamilton).**

re-discover irradiation as a tool to modify the process, but in dogs this was rarely successful. Despite his scepticism, he took part in the first renal transplant in the UK in 1956, organized by Ralph Shackman (1910-1981), urologist at the Hammersmith hospital, who later ran the successful programme of renal transplantation there. The key question was now whether in humans could chemical or other methods depress this mechanism of "rejection"; or even, could tolerance be induced in adult humans, as Medawar and colleagues had achieved in neonatal mice in 1953?

#### Immunosuppression and tolerance

In retrospect it remains surprising, now that attempts to do unmodified transplants in human recipients had begun around 1950, that the earlier data from the 1910s and 20s on radiation and chemical immuno-suppression were not mined earlier. It took until 1958, when about a dozen or more unmodified grafts had been done in non-twins (4), for these ideas to be exploited again. However in this field, just as skin grafts had proved different from kidney grafts, now dogs proved to be different from humans in their reactions to both irradiation and to immunosuppression. This obscured progress and thought in important ways. Eventually empirical trials in humans proved most important route of progression.

**Radiation** was the first approach to be resurrected in transplantation, now that atomic bombs had been used and nuclear power plants built – but not until 1958. These events, awful and potentially transformational, gave sad but vital data on irradiated humans which re-demonstrated that the bone marrow was suppressed and circulating cells reduced in number, antibodies diminished, and in animals allograft survival prolonged. Protection of the spleen and bone marrow led to survival, but with lymphocytes still pictured as sessile cells until 1959, humoral factors were postulated to explain this. But by 1956 a Kuhnian paradigm shift had occurred, and the idea of migratory immune cells became accepted by nearly all, although not proved until 1959 by Gowans. What had been a search for radiation protection turned into a strategy for inducing tolerance. John Merrill was forward-looking and projected that marrow infusions could lead to tolerance, which was supported by work using donor marrow infusions in irradiated, skin-grafted mice by John Main and Raymond Prein at the National Cancer Institute (37). But how much irradiation should be used? – too much would simply kill the recipient, and too little would be ineffective.





**Figure 19 - The "other" team in Paris, who often are forgotten: the Hôpital Foch. Above left, Marcel Legrain (1923 -2003), Nephrologist, above right, René Küss (1913-2006), surgeon. Below, in July 1960 the first unrelated living donor transplant. Mme Gen. stands centre with her brother-in-law donor just behind her on her left, and flanked by Küss (right) and Legrain (left) and members of their team of doctors and nurses. She had been irradiated before grafting. (pictures courtesy of Marcel Lagrain and René Küss)**

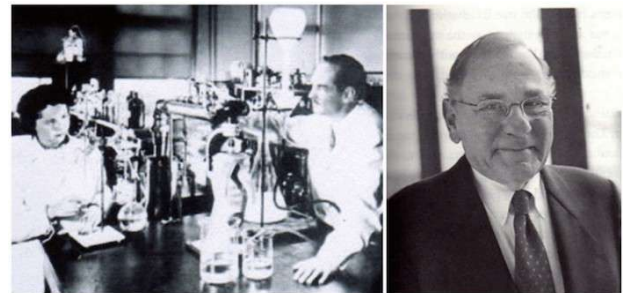
A "fortunate" accident with a nuclear reactor in Yugoslavia led to six patients being treated in Paris by bone marrow transplantation by haematologist Georges Mathé (1922- 2010), which gave data suggesting a dose limitation of about 400-450 rad (the unit then in use) for relatively safe irradiation to allow bone marrow infusion. But the first patients treated in Boston in this fashion, using "free" kidneys from nephrectomy as donors in 1958, both died. The protocol was changed to lower doses of irradiation without marrow transfer- complete tolerance would have to wait (and is still waiting). Grafting re-started in both Boston and Paris using irradiation alone – five more grafts were done beginning in Boston in 1958-62, followed by a dozen in Paris from 1959 also, divided equally between Jean Hamburger's unit at the Necker, and Küss and Marcel Legrain's unit at the Hôpital Foch (Figure 19), with survival of some recipients in all three series, and a single functioning graft functioning more than 15 years (3, 4, 38-40) A few grafts were done even from unrelated living donors with success (Figure 19), but the majority were either "free" kidneys removed for surgical reasons (which source now more or less disappeared as surgery of the ureter changed, and the Matson operation became obsolete) or cadaver kidneys.

The brief era of irradiation for allograft immunosuppression of 1958-1962 was superseded by the chemical immunosuppression still with us, which brings us to the end of "prehistory" around 1960, as we enter the full history of widely-performed and increasingly successful renal transplantation. As with irradiation, the early data from around 1920 had been forgotten by transplant surgeons and immunologists alike. It was the emergence of these drugs as anti-cancer agents, and their unwanted marrow suppression, which brought them back to attention.

Following the First World war with deliberate use of nitrogen mustard, accidents also occurred, and in both circumstances the immunosuppressive and marrow effects were studied. But there was no more interest until the Second World War, during

which further disasters occurred. The incident in Bari harbour in 1944 during the Italian campaign was particularly horrifying, as 500 tons of Allied liquid mustard aboard the USS *John Harvey* escaped after German bombing, killing about 700 sailors and a thousand civilians. The military started reinvestigating nitrogen mustard, and the idea it might kill active malignant cells as well as active bone marrow arose and was tested, and it was used with some success to treat human leukaemias subsequently. An oral mustard, cyclophosphamide, became available in 1959 but was only used occasionally in transplantation, although the few data available suggest it was effective.

The talented and productive pair of Trudy Elion (1918-1999), working in George Hitchings' (1905-1988) lab at Burroughs Wellcome (Figure 20), synthesised a number of purine antimetabolites (a new concept for which they received the Nobel prize) the first of which was 6-mercaptopurine (6-MP) in 1953 – aimed as a cancer treatment. It took time, however for the concept of long- term continuous treatment to induce and maintain what came later to be called immunosuppression (in 1963 by the Boston group) to emerge. In the meantime, however, Robert Schwartz (1928- fl.) (Figure 20) and William Dameshek (1900-1969) in Boston showed suppression of antibody formation in rabbits in 1957 with 6-MP, and prolongation of survival of allografted skin again in the rabbit, in 1959 (41).



**Figure 20 - (Left) George Hitchins (1905-1988) and Trudy Elion (1918-1999) at Burroughs Wellcome labs in Tuckahoe NJ. Picture courtesy Burroughs Wellcome) (Right) George Schwartz (1928- fl.) who studied their first purine antimetabolite, 6-mercaptopurine (6-MP) an analogue of hypoxanthine, in the 1950s and showed it depressed immune responses. Hitchins and Elion received the Nobel prize for their work on antimetabolites to treat cancer.**

For subsequent events we have a rich testimony of events from participants in the subsequent explosion of ideas and actions, and only a summary is presented here at the end of our trail. In London, personal experience of this work with 6-MP was transmitted to a young surgeon who was to have great influence on the field subsequently, Roy Calne (1930- fl.), (Figure 21) by pathologist Ken Porter (1925-2013), who had just returned from time in Boston. Calne, having unsuccessfully tried irradiation, used 6-MP in dog allografts, achieving some success (42) which led on, with his new mentor John Hopewell at the Royal Free hospital in London, to trials in three human recipients in 1959-60. However all three patients, two cadaver and one living donor died without renal function, so these results were not published until later (43).

Calne visited Paris, and gave Küss some 6-MP which he used for graft "rescue" in irradiated recipients, with success. David Hume, now in Virginia, and his colleague Charles F Zukowski (1926-1983) were also using 6-MP in dogs, with much better results than in London (44). Calne then went to Boston on a grant, visiting the Burroughs Wellcome lab in New York on the way, obtaining 6-MP and a new orally active compound Elion and Hitchings had synthesised, then called BW57-322 but now

known as azathioprine. In dogs, it worked (45), but in humans almost all the several patients treated in Boston and elsewhere died usually of infection, with one notable exception. Only Hume had slightly more encouraging results, but few grafts were done anywhere in 1962-3. In retrospect, the doses of azathioprine given to most of these early recipients were far too high, and this remained so for some years.



**Figure 21 - The end of prehistory and the future of clinical transplantation. Roy Calne (1930- fl.) (left) after using 6-MP in dogs and man, showed in 1962 that imuran, a thiazole derivative of 6-MP absorbed orally, would successfully prolong renal grafts in dogs whilst on a scholarship in Boston. Thomas Starzl (1926-2017) in Colorado combined corticosteroids and imuran in 1962, starting and rapidly did 30 transplants, more than three quarters of which functioned and the recipients survived long term. Both men were at heart more interested in the challenges and biology of liver transplantation (courtesy Roy Calne and University of Pittsburgh).**

Long-term-prednisolone is today being phased out from transplantation because of its many side-effects, but a number of the grafts done in the 1950s were variously treated with cortisone, following a series of contradictory papers in animal and human skin grafts. But eventually, steroids put grafting on the road to success, despite apparently negative results in Boston in four early patients (32). However, Willard Goodwin (1915-1998) in California, during a brief series of half a dozen grafts, used high doses of cortisone to reverse acute rejection in 1960, but this was not published until 3 years later (46).

## REFERENCES

- Zimmerman K (ed.) One leg in the grave revisited. The miracle of the transplantation of the black leg by the saints Cosmas and Damian. Groningen, Barkhuis, 2013. This book gives illustrations of all the 100 –odd pictures of the miracle, and its re-appearance in modern iconography.
- Brent L. A history of transplantation immunology. San Diego, London etc. Academic Press, 1997.
- Hamilton D. A history of organ transplantation. Pittsburgh, University of Pittsburgh Press, 2012.
- Woodruff MFA. The transplantation of tissues and organs. Springfield ILL, Charles C Thomas, 1960 (available on request printing LiteraryLicensing.com 2017).
- Payr E. Weitere Mitteilungen über verwendung des Magnesiums bei der Naht der Blutgefäße. Archiv f Klin Chirurg 1901; 64: 726-740.
- Jaboulay M, Briau E. Recherches expérimentales sur la suture et la greffe artérielles. Lyon Méd 1896: 81; 97-99
- Hamilton D. The first transplant surgeon. The flawed genius of Nobel Prize winner, Alexis Carrel. New Jersey, London etc. World Scientific, 2017.
- Carrel A. La technique opératoire des anastomoses vasculaires et la transplantation des viscères. Lyon Méd 1902; 98: 859-884.
- Guthrie CC. Blood vessel surgery and its applications. New York, Longmans Green, 1912.
- Ullmann E. Experimentelle Nierentransplantation. Wien Klin Wschr 1902: 15: 281-282.
- Von Decastello, A. Über experimentelle Nierentransplantation. Wien Med Wschr 1902;15: 317-318.
- Floresco N. Recherches sur la transplantation du rein. J Physiol Path Gen 1905; 7: 47-59.
- Jaboulay M. Greffe de reins au pli du coude par sutures artérielles et veineuses. Bull Lyon Méd 107; 1107: 575-577.
- Unger E Über Nierentransplantationen. Berl Klin Wschr 1907; 47: 1057-1060; ibid Nierentransplantationen. Verhandl Berliner Med Gesellschaft 1909; 40: 198-208.
- Murphy JB. The lymphocyte in relation to tissue grafting, malignant disease and tuberculosis. Monographs of the Rockefeller Institute 1926: 21: 1-168.
- Silverstein AM. A history of Immunology. 2nd Ed. London, Academic Press, 2009.
- Schöne G. Die heteroplastische und homoöplastische transplantation. Berlin, Springer, 1912. Recently an original copy of this book was advertised at a price of almost 1000 Euros.

Another huge contributor to transplantation, Tom Starzl (1926-2017) (Figure 21) must have credit for showing in 1963, when working in Colorado, that prednisolone combined with moderate doses of azathioprine could be the answer to long-term **chemical immunosuppression** in grafted patients (47), reporting 20 survivors from 27 rapidly-performed\* transplants, in a National research Council meeting in Washington in 1963, when 244 living-related and 68 cadaver grafts were presented by 25 units worldwide. The advance was “*essentially empirical*” he stated.

At this meeting (which for me marks the end of prehistory and the beginning of history), the Human Kidney Transplant Registry was started: the combination of corticosteroids and azathioprine was used as routine (sometimes with additional drugs) until the early 1980s, and transplantation was truly on the road: “pre-history” was over. Led by Murray, Starzl (48) and Calne (49) and then hundreds of others all over the world, renal transplantation was established as a useful treatment, even though the toll of complications during and from rejection and its treatment was huge, and survival figures still dismal at the end of the 1960s. Starzl’s papers and book (48), after Calne’s initial lack of success (and poor, at that time unpublished results at St Mary’s Hospital London) were a major factor in my own conversion to starting an integrated dialysis plus transplant unit at that time. Ironically Starzl as early as the 1950s, and also Calne, were most interested in technically more demanding liver transplantation, but realized that rejection and its treatment could be worked on more easily in the setting of renal transplantation

But in humans tolerance was nowhere on the horizon, and although spontaneously arising in long-term immunosuppressed survivors, its induction remains as elusive even today, 64 years after it was achieved in mice.

\*This was in part possible because Starzl (49) at that time had an “arrangement” with the nearby Canon State Penitentiary, whereby prisoners might offer to donate organs, and on occasion as many as 50-60 might be considered, using primitive tissue typing of the era. This arrangement ceased a year or two later (I have not considered the history of tissue typing here as it was not used in practice until the 1960s, after the end of the “prehistory” period as defined here).

18. Bashford EF, Russell BRG. Further evidence of the resistance to the implantation of new growths. *Lancet* 1910 (Mar 19): 175; 782-787.
19. Moss RW. The life and times of John Beard, D Sc (1858-1924). *Integr Cancer Ther* 2008; 7: 229-251.
20. Beard J. The true function of the thymus. *Lancet* 1899 (Jan 21): 153; 144-146
21. Hektoen L, Corper HJ. Effect of injection of active deposits of radium emanation on rabbits. *J Infect Dis* 1922; 31: 305-312.
22. Gay FP, Rusk GY (cited in Hamilton (3)) Studies on the locus of antibody formation: the effect of benzol intoxication. University of California Publications in Pathology 1914; 16 no 2: 139-145.
23. Krumbhaar EB, Krumbhaar HD. The blood and bone marrow in Yellow Cross Gas (Mustard Gas) poisoning. *J Med Res* 1919; 40: 497-507.
24. Loeb L. Transplantation and individuality. *Physiol Rev* 1930; 10: 547-616.
25. The Russian original of Voronoy's paper is almost impossible to obtain, but a translation in full is to be found in reference (3) on pp 163-166, with an illustration of the femoral placement of the graft (Figure), a technique later used in Boston during 1951-4. See also: Hamilton D, Reid WA. Yu.Yu. Voronoy and the first human renal allograft. *Surg Gynecol Obst* 1984; 159: 289-294.
26. Gibson T, Medawar PB. Fate of skin homografts in man. *J Anat Lond* 1943; 77: 299- 310.
27. Lawler RH, West JW, McNulty PH, Clancey EJ, Murphy RP. Homotransplantation of the kidney in the human. *JAMA* 1951; 147: 45-46.
28. Küss R, Teinturier J, Milliez P. Quelques essais de greffes de rein chez l'homme. *Mém Acad Churg* 1951; 77: 755-764.
29. Murray GDW, Holden R. Transplantation of kidneys, experimentally and in human cases. *Amer J Surg* 1954; 87: 508- 515.
30. Michon L, Hamburger J, Oeconomos N, Delinotte P, Richet G., Vaysse J, Antoine B. Une tentative de transplantation rénale chez l'homme. *Presse Méd* 1953; 70: 1419-1423.
31. Hume DM, Merrill JP, Miller BF, Thorn GW. Experiences with homologous transplantation in the human. Report of nine cases. *J Clin Invest* 1955; 34: 327-382.
32. Merrill JP, Murray JE, Harrison JH, Guild WR. Successful homotransplantations of the human kidney between identical twins. *J Amer Med Ass* 1956; 160: 277-282.
33. Murray JE, Merrill JP, Harrison JH. Renal transplantation between seven pairs of identical twins. *Ann Surg* 1958; 148: 347-353.
34. Dempster WJ. Homotransplantation of organs. Lectures in the Scientific Basis of Medicine 1956-8; 6: 13-27.
35. Simonsen M. The acquired immunity concept in kidney homotransplantation. *Ann NY Acad Sci* 1955; 59: 448-452.
36. Main JM, Prehn RT. Successful skin homografts after the administration of high dosage X radiation and homologous bone marrow. *J Natl Cancer Inst* 1955; 15: 1023-1029.
37. Merrill JP, Murray JE, Harrison JH, Friedman EA, Dealy JB, Dammin GJ. Successful homotransplantation of the kidney between non-identical twins. *N Engl J Med* 1960; 262: 1251-1260.
38. Hamburger J, Vaysse J, Crosnier J, Tubiana M, LaLanne CM, Antoine B et al. Transplantation d'un rein entre jumeaux non-monozygotes après irradiation du receveur. *Press Méd* 1959; 67: 1771-1775.
39. Küss R, Legrain M, Mathé G, Nedey R, Camey M. Homologous human kidney transplantation; experience with six patients. *Postgrad Med J* 1962; 38: 528-531.
40. Schwartz R, Dameshek W. Drug-induced immunological tolerance. *Nature* 1959; 183: 1682-1683.
41. Calne RY. The rejection of renal homografts. *Lancet* 1960; 275: 417-418.
42. Hopewell J, Calne RY, Beswick I. Three clinical cases of renal transplantation. *BMJ* 1964; 411-413.
43. Zukowski CF, Lee HM, Hume DM. The effects of 6-mercaptopurine on renal homograft survival in the dog. *Surg Gynecol Obst* 1961; 112: 470-472.
44. Calne RY, Murray JE. Inhibition of the rejection of renal homografts in dogs by Burroughs Wellcome 57-322. *Surg Forum* 1961; 12: 118-120.
45. Goodwin WE, Mims MM, Kauffman JJ. Renal transplantation III: technical problems encountered in six cases of kidney homotransplantations. *Trans Am Ass GU Surgeons* 1962; 54: 116-123.
46. Starzl TE, Marchioro TL, Waddell WP. The reversal of rejection in human renal homografts with subsequent development of graft tolerance. *Surg Gynecol Obstet* 1963; 117: 385-395.
47. Calne RY, Evans DB, Herbertson BM, Joysey V, McMillan R, Magainn RR et al. Survival after renal transplantation in man: an interim report on 54 consecutive cases. *Brit Med J* 1968; 2: 404-406.
48. Starzl TE. My thirty-five year view of organ transplantation. In Terasaki PI (Ed) *History of transplantation: thirty-five recollections*. Los Angeles, Tissue UCLA typing laboratory. pp.147-179.