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Half a Century of Heart Transplantation

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"A new heart also I will give you, and a new spirit will I put within you;
and I will take away the stony heart out of flesh and I will give you a new heart of flesh"

Ezekiel 11:19

"Transplantation is an excellent example of parallel and not mutually exclusive forces, to which investigators in basic science and scientifically orientated physicians and surgeons contribute equally while seeking answers relevant to their patients."

Rupert Billingham

The idea of sharing body parts has a long history[1]. The attributes of animals shared with those of humans are seen in Egyptian Gods (for example the four sons of Horus), Greek Mythology (the minotaur, centaur, Medusa and the iconic Chimera of Homer). Ganesha in the Hindu religion is another example.

Divine involvement in healing was assumed for centuries and saintly intervention in the form of re-implanting severed ears (Christ, after Simon Peter had cut off the ear), St Agatha's breasts (St Peter), hands (Saint Mark) and Legs (Saint Anthony of Padua).

Saints Cosmas and Damian, themselves thought to be identical twins, are reputed to have replaced the gangrenous leg of the custodian of a Roman basilica with the leg of a demised (and recently buried) Ethiopian gladiator. Although, since the twins had been beheaded about a century earlier, it is perhaps stretching credulity a little far.

Some of the most important concepts in transplantation followed the ancient art of skin grafting[2]. This had been carried out about 3000 years ago amongst the Hindu tile-maker caste to reconstruct noses amputated as judicial punishment. Skin grafting is a form of **auto-transplantation**, moving tissue from one part of a subject's body to another part of the same subject's body. Giuseppe Baronio published work in 1804 reporting the success of skin grafting in 27 animals of several species. He noted that autografts survived well, but **allografts** (from same species, but different animal) did not and **xenografts** (from a different species) were destroyed even more rapidly. The science of immunology and the understanding of rejection were still far away, but this was seminal work[3], added to by work from Bert in France in 1864, Reverdin, a French surgeon, in 1874 and Pollock in Glasgow in 1871 (see Brent Chapter 2).

As Tilney points out[1], the horrors of the 1st World War led to many attempts at skin grafting, but few clinicians questioned why allografts (often from a relative) failed, but autografts survived. It was not until 1924 when Emile Holman working in Boston, commented on the rejection of allografts "The destroying agency is specific for each set of grafts. It seems plausible to propose, thereafter, that each set of grafts develops its own antibody".

Later, James Barratt-Brown from St Louis showed that repeating an allograft in patients produced worse results; the grafts were rejected much more quickly, both he and the famous pathologist Leo Loeb were very pessimistic, and in Loeb's case nihilistic about the potential for graft survival. He refused to attend the first conference on transplantation in the early 1950s stating "the subject matter was a waste of time, the goal [of survival of foreign grafts] was impossible to attain". How wrong he was.

Brown was stationed in England during the Second World War and suggested to a young Oxford zoology student that he might study skin grafts in humans. That student was Peter Medawar, who with Frank Macfarlane Burnet went on to win the Nobel Prize for Medicine and Physiology in 1960 for their work in Transplantation Immunology. Medawar was too tall to serve in the army, and was directed by the recruitment board towards the treatment of burns. The failure to save the life of a seriously burned airman whose plane crashed near Medawar's Oxford home, led the physician caring for the patient to entreat Medawar to "lay aside intellectual pursuits and take a serious interest in real life". Medawar's studies on skin grafting in Glasgow and Oxford (with Rupert Billingham and Leslie Brent) led to the recognition that genetic variations between donor and host produced different tissue responses. This observation, and the identification of histo-compatibility genes in mice by Peter Gorer, provided compelling evidence of the involvement of the host immune system in the behaviour of grafts.

As a (crucial) aside, Landsteiner's discovery of the ABO blood groups in 1901 was one of the most important advances in medicine in the 20th century[4]. As well as making blood transfusion (a highly successful but normally transient transplant) safe, it marked the beginning of the study of immune-genetics and was fundamental to the development of solid organ transplantation.

There would be no effective transplantation if it was not for the work of these pioneers. A deep understanding of the processes involved in rejection and its manipulation is critical. There is neither space nor time to discuss this complex and fascinating field of transplantation immunology, but I refer you to Leslie Brent's book on the subject for a detailed and brilliant review[5]. The important practical points are these;

- We are different from each other and unique
- This difference is manifest by different molecules (antigens) expressed on the surface of cells
- If another's cells are transplanted to our own body, then they are recognised as 'non-self' and an immunologic process of rejection), both acute and chronic, begins, potentially destroying the transplant.
- The antigens have been studied extensively and classified so that it is possible to identify patients with very similar sets of antigens using **tissue typing** to 'match' recipient and donor. The closer the match, the milder the rejection.
- The immune response of rejection can be modified by the use of drugs.

Technically, the transplantation of skin, whilst biologically important, is considerably less complex than transplanting a solid organ such as the kidney, liver or heart. Essential to the ability to perform such procedures was the development of the ability to join together (anastomose) blood vessels. The basic methods of such surgery were developed by Alexis Carrell in Lyon at the end of the 19th century. He took sewing lessons from an embroidress (Mme Laroudier) and successfully repaired vessels using fine, oiled silk sutures on equally fine needles. Using similar techniques in 1904, Ullmann in Vienna moved the kidney of a dog from its flank to the neck, where it produced 'a liquid resembling urine'. One of Ullmann's students, Nicholas Floresco, in Bucharest, developed the surgical techniques used in modern kidney transplantation, placing the kidney in the pelvis and attaching the ureter to the bladder.

Carrell, meanwhile, left conservative Lyon for the 'freer' Chicago where he continued to develop vascular techniques for many organs, including the heart. He became interested in renal transplantation, until he became more involved in the vascular trauma of war. In St Louis, Guthrie, with whom he worked, even transplanted the head of one dog onto another! Transplantation was effectively 'born' and experimentation continued throughout the 20th century.

The history of heart surgery is one of attempts to repair the heart. But sometimes repair is either not possible or fails. It would be wonderful, then, if the failing organ could be replaced by a healthy heart no longer needed by another, altruistic person. Several developments needed to come together to be able to perform a human heart transplant. These were;

1. the ability to maintain the circulation to the rest of the body whilst operating on the heart; cardio-pulmonary bypass
2. the ability to preserve the heart (myocardial preservation) either for repair or for transportation; cardioplegia and hypothermia
3. an appropriate set of techniques both to remove the donor and recipient's hearts and to insert the replacement
4. an understanding of tissue-typing, anti-rejection therapy and intensive care
5. excellent organisational skills and dedicated teams
6. an infrastructure to identify potential donors and manage logistics
7. ethical, scientific and social acceptance

I have discussed bypass and myocardial preservation in previous Gresham lectures https://www.gresham.ac.uk/lectures-and-events/heart-surgery-for-congenital-heart-defects-science-or-art , but to remind you, cardiopulmonary bypass became possible in the early 1950's as a result of pioneering work by John Gibbon and his wife Mary in Philadelphia and by C Walt Lillehei and his extraordinary team of innovative and brave surgeons in Minnesota.

Lillehei trained or influenced many cardiac surgeons who achieved fame in their own right, but four of them are crucial to this story. They are Norman Shumway, Christiaan Barnard, Richard Lower and Adrian Kantrowicz. These surgeons were the main players in what Donald McRae called "the extraordinary race to transplant the human heart"[6]. McRae's excellent book makes fascinating reading, bringing a journalist's eye to the personalities, politics and rapid progress of the time. And he is right, it was a race, and it was extraordinary. It coincided with what became known as 'The Space Race', and indeed a Russian called Vladimir Demikhov is credited[7] with performing many 'firsts' in transplantation, notably the first heart and heart lung transplants in dogs in 1946. Survival was short, but technical solutions advanced. He became infamous in 1954 after performing head transplants in dogs. Shumacker suggests[7] that his contribution is underestimated, perhaps because of his work being carried out behind the Iron Curtain.

Norman Shumway joined Lillehei's team as a resident in 1949. Shumway was tall, witty and 'engagingly laconic'. An extremely accomplished technical surgeon, he was also the 'cleverest and funniest' of Minnesota's residents' according to Claude Chabrol[6]. Famous though Shumway became, he always gave the impression of being a reluctant occupier of the limelight, and indeed quite shy. I have strong memories of his dry and ironic sense of humour, and his put downs delivered with a winning smile. He was charming. But he was also a driven, careful, thorough researcher. During the 1950's he worked in Minnesota to develop the method of topical hypothermia (directly cooling the heart) to give them time to repair its internal valves and any defects.

Richard Lower, a modest and caring man harbouring an ambition to be a GP, arrived in Stanford in 1957 to gain surgical expertise. Six years younger than Shumway, they met within weeks and immediately hit it off. Lower was soon inveigled into working in the lab with Shumway, first on kidney machine research and then on topical hypothermia. Norm and Dick made a good team; the skills of one amplifying those of the other. Through 1958 and 1959, as they waited with the cold heart stopped for periods of up to 90 minutes, they began to question whether they might be able completely to remove the heart and re-implant it. This they did. It was a short step to attempt to transplant a heart from dog to dog. These produced technical success with early survival, but the dogs soon died of rejection. Perfecting the technique of transplantation and evolving methods for managing rejection drove Shumway, Lower and their teams for the next decade.

Meanwhile, in Brooklyn, a surgeon called Adrian Kantrowicz was also making waves. An incredibly creative man, described by his superiors as 'difficult to work with', he had moved in 1955 to Maimonides Medical Center in Brooklyn from Montefiore in New York, where he had been working largely on stray cats to develop ways of repairing the mitral valve and mechanical support of the heart. In 1959, he used diaphragm muscle to create what he called a 'booster heart', the contraction linked electronically to the beat of the native heart. He too began to consider the possibility of heart transplantation.

Christiaan Barnard, went to Minnesota to train in oesophageal surgery in 1955. After being introduced to the heart lung machine, he transferred to Lillehei's service and became fascinated by cardiac surgery. He was regarded by his fellow residents as aggressive, self-absorbed and rather over-bearing, and perhaps unsurprisingly soon began a rivalry with Norman Shumway, a few months his junior, who preceded him as Lillehei's senior resident. Barnard worked hard, cramming a normally long training into the relatively short time he had in the USA. He was helped by an excellent memory and huge drive. He returned to South Africa in 1958 as Head of experimental surgery at the Groote Schuur Hospital in Cape Town.

The 1960's saw all four of these men develop a growing interest in the potential for being able to transplant the human heart, building on the work of Shumway and Lower on hypothermic preservation of the heart in dogs. After spending the first 5 years of the decade in Stanford working with Shumway, Lower moved in 1965 to head up cardiac surgery in the Medical College of Virginia where David Hume (a renal transplant pioneer) was based. Kantrowitz remained in Brooklyn. Each team painstakingly increased their experience with the techniques and management of heart transplantation in hundreds of dogs, many of which survived for over a year. They became increasingly confident of their readiness to attempt it in humans.

In 1963, James Hardy in Jackson, Mississippi performed the first human lung transplant. Hardy was committed to innovation, and in 1964 attempted a chimpanzee to human heart transplant. The heart beat for over an hour before the patient died. He received much criticism for this attempt.

Kantrowitz came close to performing the first human transplant in a child with severe congenital heart disease in June 1966. A baby had been born with anencephaly in Portland Oregon and the parents agreed for it to be flown to New York to act as a heart donor for the operation. Anencephalic babies have no realistic chance of survival because of the absence of almost all the brain. Kantrowitz considered them ideal donors ("there is no brain, there is no life" he declared)[6] because the heart could be removed in perfect condition. Yet at that time, there was no definition of 'brain death'. The heart had to be observed to stop before death could be confirmed. Neither the board of the hospital nor Kantrowitz's anaesthetists were willing (appropriately) to break this rule, and after support was withdrawn from the donor, it took a long time for the heart to stop beating by which time it was not suitable for transplant. A second donor became available in July of the same year, and this too proved an unsuccessful process.

In October 1967, Shumway addressed the American College of Surgeons in Chicago and said; "after eight years of laboratory experience we are now quite convinced that cardiac transplantation is perfectly feasible from the technical as well as the physiological standpoint…..the time has come for clinical application". His team had acquired an international reputation for careful and thorough research. They had shown that rejection could be reduced by the use of azathioprine and corticosteroids, and most of the cardiac surgical world thought Shumway's team in Stanford would be the first to do the transplant.

Meanwhile, back in Cape Town, Barnard had become increasingly interested in organ transplantation. In 1960, he visited Demikhov in Moscow and in 1966 he spent three months with Richard Lower in his lab in Virginia. Barnard apparently announced to Lower's lab technician that he planned to go back to South Africa and perform the world's first human heart transplant. Lower apparently simply said "how can he"[6], knowing that practice and rejection management were likely to be critical to success. In Cape Town, Barnard transplanted 48 hearts into dogs, many less than hundreds performed by Shumway or Lower, with survivors of over a year. None of Barnard's dogs had lived for more than 10 days. Barnard, though, thought he was ready.

In November 1967, Louis Washkansky, a 54-year-old diabetic with severe heart failure after three heart attacks, was dying in kidney and liver failure in Groot Schuur Hospital. He was considered a possible transplant candidate, and Barnard agreed, suggesting a, subsequently much criticised, 80% chance of success. In late November, a young black man fell off a truck and had a catastrophic head injury. Politically, the idea of a black man's heart going into a white man was considered a huge political and PR risk, and the chief of cardiology was against it, arguing in favour of only using white donors. The potential donor's heart deteriorated rather quickly and the transplant was not done; for medical rather than political reasons.

On Saturday 2nd December, the Darvall family were in Cape Town, when mother and daughter were hit by a drunk driver killing the mother, Myrtle, immediately and causing catastrophic brain damage to 25-year-old

Denise. Astonishingly, the consequences of the accident were witnessed by Ann Washkansky who was driving by. Denise was transferred to Groot Schuur, but although her heart was beating, there was no brain electrical activity. She was what we now call brain dead. She was blood group O-ve, and suitable to donate to Louis Washkansky.

Denise's father, Edward, agreed that Denise could be an organ donor. But the criteria for brain death (the Harvard Criteria) were not developed until 1968; in 1967 South Africa, all function, including the heart, had to have stopped before anyone could be considered dead and their organs donated. But with consent, Barnard could go ahead and perform the transplant. He was assisted by his brother Marius, and a large team. Perhaps including his black laboratory technician, Hamilton Naki.

The donor and recipient were taken to adjacent operating rooms and surgical teams prepared the patients and both hearts were exposed. Denise's ventilator was switched off and without oxygen her heart would gradually fail and stop. As Donald McRae records[6], for forty years Marius kept secret the fact that rather than wait for the heart to stop beating, and at Marius ' urging, Christiaan injected potassium into the aorta and hence coronary arteries to paralyze it, protect it and fulfil the whole body death criteria. Routine practice now, with clear definitions of brain death, in those days it might even have been considered criminal.

The heart transplant went on through the night, until at 0543 am the new heart was re-perfused with Washkansky's own warm blood and after a DC shock from a defibrillator, began to beat in a normal rhythm. The heart lung machine was disconnected at 0613 with the heart beating well. The race to the first heart transplant had been won, and the media world-wide went crazy. Charismatic Barnard became a celebrity overnight, and he was born for it.

It was a technical success, but as all those who had spent so much time in the lab with their transplanted dogs knew, the problems were just beginning. Five days into recovery, a decision was made to give massive immunosuppression to prevent any rejection, but such severe suppression brings with it an increased risk of infection, and Louis Washkansky died of pneumonia just eighteen days after surgery.

Only 5 days after the first human heart transplant, Kantrowitz performed the first transplant in a child (aged 17 days), from an anencephalic donor. The baby lived for just a few hours.

Christiaan Barnard did the 3rd transplant in January 1968 controversially (at the time) transplanting the heart of a 24-year-old "mixed blood" male into Dr Philip Blaiberg, a dentist. Blaiberg died of in August 1969 hepatitis and severe coronary artery disease in the donor heart, probably rejection-related. Blaiberg's autobiography makes fascinating reading, and paints a picture of a man whose life, and fulfilment, were restored by the transplant.[8] He was well aware of the nature of the 'experiment' of which he was a part.

Just a few days after Dr Blaiberg's operation, Norman Shumway (the man who had done so much of the groundwork to make transplantation possible) performed his first transplant on Mike Kasperak in Stanford. This proved to be complex, required 3 additional operations (and 210 units of blood) and sadly Mr. Kasparak died just two weeks later.

The media storm which followed these early transplants was astonishing. Barnard cannot be described as a shrinking violet, and he was photogenic, charismatic and confident. The media loved him, and Barnard and the topic, were everywhere. It was a heady mixture of celebrity, ethics, politics and science. Unsurprisingly, those surgeons who had lost out in the race to be first to this relatively inexperienced South African upstart were, to say the least, not happy.

Tilney quotes[1] Shumway's alleged response to a colleague who asked him for his reaction to Barnard's transplant "*Does anyone know who was the second person to fly across the ocean?*". Shumway need not have worried about his legacy. The profession recognised his key role and I remember being in awe of his achievements when the Stanford team published, in 1979[9], their experience of 150 transplants over the initial decade of experience. I was one year into my own experience of cardiac surgery; it was humbling. A fascinating video interview with him is available here
https://www.library.vanderbilt.edu/biomedical/sc_diglib/exhibits/cardiac_surgery/shumway.php

In 1968, another South African, Donald Ross, who had been a student with Barnard in Cape Town, performed the UK's first transplant (and the world's tenth) at the National Heart Hospital in London. You can read a wonderful commentary on early heart transplant surgery in the UK as part of the Wellcome Witness Series on the History of Modern Biomedicine[10] http://www.histmodbiomed.org/witsem/vol3.html. It was a controversial procedure. The donor was transported to the recipient's hospital for the operation and there was a heavy media presence. Francis Moore, a famous American surgeon, was present at the time and recalled[1, 11]

> the surgeons, in full operating regalia, appeared on the steps of [the hospital]to the shouts of cheering crowds, bands playing "Britannia Rules the Waves" and "God Save the Queen" with the waving of flags, guardsmen in bearskin busbies hovering around on horseback. British reserve was cast into the waves as Britannia rules.

The public did not take to this 'hullabaloo'[1] and organ donation reduced dramatically. Further, a group of transplant surgeons advised the government that intact donors should never again be transported to the recipient hospital. This has remained the case. The first British transplant patient, a man of 45 lived for 46 days before succumbing to overwhelming infection.

It was difficult to find donors. There was no definition of brain death at the time, and even physicians thought that heart transplantation "almost amounted to cannibalism"[1]. Ross performed two more transplants, but public and medical opinion was against him, and there was a moratorium against heart transplantation in the UK. In 1977, opinion was beginning to shift and the Department of Health set up a Transplant Advisory Group to agree criteria for the operations to go ahead. In January 1979, Terence English performed a heart transplant at Papworth Hospital (just outside Cambridge) on a patient who died 17 days later[12]. There was local controversy, particularly relating to whether transplants should be performed at Papworth or at Addenbrooke's where kidney transplants were performed. We will hear more about this time from Sir Terence himself, and get some of the flavour of the determination and toughness needed at that time.

The technical plumbing problems had largely been resolved, and have not changed much since. But the problems of rejection and immune-suppression, in those days largely with steroids and azathiaprin, remained profound. Tissue matching techniques were relatively simple and there remained a large element of 'luck' in getting a perfectly matched organ. The drugs were both toxic and only partially effective and excessive treatment increased your risk of severe infection. Early success rates were relatively poor as a result. The 1970's saw a widespread move by researchers to sort out the intricacies of the immune mechanisms associated with rejection and by drug companies to identify drugs which might, more effectively, reduce the risk of rejection.

In 1970, two new strains of fungi were identified in soil sample from Wisconsin and Norway. Both strains produced *cyclosporins*. They were soon identified by Sandoz (now Novartis) employees as having immune-suppressive action, confirmed in rat heart transplantation by Roy Calne in 1977[13]. In 1978, Powles and Barrett in London reported[14] that Cyclosporin A reduced graft-versus host disease in man and Calne and colleagues reported[15] its successful use in renal transplantation. Cyclosporin A proved a highly valuable adjunct to anti-rejection therapy, and its use considerably improved the outcome of heart transplantation.

Sadly, as with many drugs it has significant side effects, ranging from gum enlargement and hirsutism (hair growth), through to convulsions, kidney and liver damage, high blood pressure and high blood cholesterol levels. Thus, much of the transplant physician's time was spent identifying the lowest possible dose of the drug that minimised rejection. Fortunately, another Brit called Philip Caves, working with Shumway, had developed a method[16] of being able to take a tiny biopsy of the heart using a catheter passed through a vein allowing the biopsy to be examined for signs of rejection. The method is routinely used and is safe and reproducible.

Three more agents have emerged which have also improved our management of rejection. These are tacrolimus, sirolimus and mycophenalate mofetil. Used alone or in combination with cyclosporine, they have also improved short-term results of transplantation by reducing the risk of acute rejection. But rejection, and accelerated coronary artery disease in transplanted hearts, remain huge challenges. New techniques have emerged better to diagnose both. Donor-derived DNA identified in recipient blood may prove to be an

[1] https://www.theguardian.com/theguardian/2010/may/04/first-heart-transplant

excellent method of detecting rejection, and intravascular ultrasound is excellent at identifying narrowing in the coronary arteries.

As well as the scientific, technical and therapeutic advances in transplantation its integration into the wider medical services has been an organisational triumph. When transplantation started, the logistics were handled locally, organ donor lists were embryonic and transport was often done by the teams themselves helped by altruistic emergency services or private citizens. This is now all integrated though a central service UK Blood and Transplant https://www.nhsbt.nhs.uk/what-we-do/transplantation-services/organ-donation-and-transplantation/ and there is a national organ retrieval service http://www.odt.nhs.uk/retrieval/national-organ-retrieval-services/ to facilitate the harvesting and safe, prompt delivery of organs. UKB&T integrates closely with Eurotransplant https://www.eurotransplant.org/ and other national bodies to facilitate international organ matching. Improved publicity of the benefits of transplantation led to a 50% increase in the number of donors on the organ donor list between 207/8 and 2012/13, and there are now six centres in England and Scotland performing adult transplantation and two performing paediatric transplantation.

The current survival rates for adult heart transplantation are around 80% at 3 years, 55% at 10 years and 10% at 30 years. Individual patients lucky enough to have well match organs can live well for long periods.

Despite all this progress, the number of heart transplants performed around the world has remained relatively static, hovering around 4000 per year since the early 1990s. There has been a small recent uplift as a result of donor campaigns and countries outside US and Europe performing more transplants. But it is nowhere near enough to cope with demand, and currently around 250 people waiting for a heart transplant in the UK, with only around 200 transplants performed per year. Patients die waiting. And only people in real need get onto the list. Further, many patients are now bridged to transplant on mechanical support https://www.gresham.ac.uk/lectures-and-events/the-artificial-heart-a-new-ending, as we will discuss with Stephen Large later. It is not a *primary* treatment.

It is not surprising that there is so much investment into research in to mechanical assistance and heart replacement https://www.gresham.ac.uk/lectures-and-events/the-artificial-heart-a-new-ending , stem cell treatment for heart failure[17] and new ways to increase donor supply, particularly after donor circulatory death[18]. Laws relating to whether you should opt out rather than opt in to organ donation have been passed in several countries (including Wales) and mandatory choice with prioritisation of donors for subsequent transplantation has proved effective in California and Israel[19].

The innovative drive and drama of 50 years ago has resulted in many lives being saved, and in significant scientific advances which have impacted in many other fields. The collaboration and cooperation which emerged from those early highly competitive early days is a tribute to all those who have worked behind the scenes, without the glory given to the surgeon. But the real credit must go to the donors, who altruistically in advance have thought of what they can do for others, and to their families who at a time of huge sadness have allowed the organs to be shared. None of it would have been possible without them, and all of us who do this work recognise that.

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Further Reading

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