Development Of Organ Transplant

Organ transplantation is important to the patient. The idea of taking a faulty body part out and replacing it with a healthy version has been around for a century. The organ cannot be chop and sew without some understanding of science. So, the road to the first successful organ transplant was full of challenges, discoveries, and need a whole lot of work specially related to tricking the recipient’s immune system.

As early as the 2nd CE, the stories of leg, nose, and even heart transplants can be found across the globe. With the technology and medical understanding around the time, the patients probably did not have great outcomes. Still, this only the guess we can make. Historians do not have much concrete evidence because these early attempts were not well-documented. That changed in the ate of 16th CE with the Italian surgeon Gaspare Tagliacozzi. He performed skin grafts, taking skin from one area of the body, and transplanting it onto another. As he developed surgical skills, he made sure to document everything. In 1597, he published an illustrated book with a title that roughly translates to 'On the Surgery of Mutilation by Grafting.' Besides showcasing his techniques, these records may have been some of the first to hint at the science behind skin graft rejection which is when the recipient's immune system attacks the newly transplanted tissue. In particular, Tagliacozzi noticed that tissue from the patient's own body was generally rejected less than allografts, or tissue from other people's bodies. He attributed this to 'the force and the power of individuality' which now we understand it as an individual immune system.

For the next few centuries, not much happened in the field of transplantation. But then, two technologies set the stage for bigger breakthroughs. The first was anesthesia which is anything that interacts with the brain and blocks the sensation of pain. Some anesthetics had been used for dubious recreation for centuries. But the first ones that were widely used in medicine hit the scene in the early 1800s. Early anesthetics were chemicals that patients inhaled like nitrous oxide, which we may know as laughing gas, or diethyl ether. These chemicals gave surgeons more chances to practice because more patients will choose surgery when it did not feel like someone are cutting them open with a knife

The other big innovation was antiseptic surgery which was formally documented by surgeon Joseph Lister in 1867. Around that time, microbiology was gaining more traction. Lister credited Louis Pasteur's work with microbes as his inspiration in attacking gems. Early antiseptic surgery involved handwashing and sterilizing wound dressings, instruments, and operating rooms with the microbe-killing carbolic acid. These techniques let surgeons operate with a smaller risk of infection, which led to fewer people dying.

With clean, painless surgery available, doctors started attempting more simple transplants. Their main goals were to make healing times faster and increase long-term survival. For instance, skin graft had been performed for a long time and became a more popular treatment in the mid-1800s. They could be used to cover up amputations or burns, prevent infection in larger injuries or even repair sagging eyelids. However, it is not just cutting and pasting. Skin is responsible for a lot of things, from temperature regulation to preventing infection. Thu, surgeons had to consider factors like blood supply, nerves, and sweat glands. They ended up

experimenting with skin from different body parts of the patient, but also skin from dead bodies. Around this time, doctors also became interested in transplanting other body parts like the cornea, the clear tissue that helps protect the front of the eye and focus light. The first few surgeries involved xenografts or body parts taken from other species especially pigs. The cornea does not have a blood supply, so doctors could just lay the pig cornea on a human eye like a contact lens, suture it up and let it heal.

The early transplant was far from perfect. A lot of people's bodies were rejecting foreign tissues, breaking down and absorbing them. Still, all these experiments were steps toward more complicated surgeries. In the late 1800s, the Swiss physician Emil Theodor Kocher operated on hundreds of patients with goiters, which are swollen thyroid glands. His strategy was just to cut into the neck and completely remove the thyroid, but he noticed that afterward, the patient developed a condition that now we recognized as hypothyroidism. The thyroid gland produces some of the hormones that run your metabolism. When it's removed, there are symptoms like sluggishness and trouble regulating the patient body temperature. To try and fix that, in 1883, Kocher transplanted thyroid tissues back into a patient. Which may count as the first organ transplant.

This led to more attempts to replace deficient hormone-producing glands with working ones, especially thyroid transplants. Yet, over time, these allografts eventually failed. As surgeons experimented with more organs, they ran into trickier problems. For instance, they learned that it was crucial to hook up a patient's blood supply to keep newly transplanted organs alive with oxygens and nutrients. In the early 20th century, the French surgeon Alexis Carrel invented new techniques for anastomosis or suturing 2 tubes together. In this case, blood vessels. In fact, he got so good at it that he successfully transplanted many different organs. Even hearts between dogs and they stayed alive, at least for a little while. In all of his surgeries, he noticed that allografts and xenografts always failed given enough time.

As transplantation became more accepted in the medical community, rejection became the biggest challenge. Scientists offered a bunch of explanations like, maybe rejection had to do with different nutrients or proteins in different bodies. Doctors tried a bunch of fixes, like soaking the donor organ in the recipient's blood but it did not do anything. Over the course of all these experiments, they did notice something which is animals that were battling some kind of infection during transplant usually had better results. They figured that the host's immune system was too busy dealing with the illness to deal with the transplanted organ. So, the researcher started weakening animal immune systems on purpose before transplantation.

This technique is called immunosuppression. Initially, the scientist tried radiation, certain drugs, or even removing the spleen. The spleen is an organ that filters blood and makes white blood cells, which are key for immune responses. Unfortunately, radiation was the only effective immunosuppression treatment. Doctors hoped it would make rejection less likely, but it was way too dangerous for clinical use. So progress stalled as a scientist tried to nail down how the immune system worked. By the early 1900s, a few researchers stumbled upon a discovery. They knew that if a patient got a skin graft from a donor, it would usually be rejected after a few days but if they took a tissue from the same donor and grafted it to the same patient again, it was rejected much faster.

This pointed to some kind of adaptive immune response that they called the second set phenomenon. They do not really know what to do with this information yet, but it helps them

understand how the human body recognizes foreign stuff with antibodies. Around the same time, a biologist named Peter Medawar made discoveries too. Supposedly, while Medawar in a party, a colleague asked him if he could tell different types of twin cows apart and Medawar said that skin grafts between two fraternal twin cows would be rejected, but two identical twins would not. It was an important distinction. Identical twins develop from one sperm and one egg cell and may share a placenta while fraternal twins are made from two separate sperm and egg cells with separate placentas.

Now, they ended up testing this experiment and what they found was surprising. Most skin grafts between twins worked, even fraternal twins which is not what they expected. A few years earlier, research had shown that fraternal twin cows shared blood and another cell while developing in the uterus and as adults, their bodies made two types of red blood cells instead of just one. With that discovery on top of their own, Medawar and his colleagues realized twin cows were probably making multiple types of immune cells too which is why they are not rejecting skin grafts from their twins. Basically, the cows' bodies did not recognize their twin's cell as foreign, because of how their immune systems developed. Then, these researchers attempted to cause the same phenomenon in mice. The team took spleen cells from a donor mouse, then injected those cells into mouse fetuses. If those babies grew up, skin grafts from the donor mouse were not rejected. After all this time, they had proven that it was possible for a host to accept an allograft. Even though we could not necessarily apply this technique to humans.

The skin was one thing, but a fully functioning organ would be more difficult, and perfect storm factors made one organ ideal candidate to test in humans; the kidney. Back in the 1900s, we did not have many effective treatments for end kidney stage disease. So taking a shot at transplantation seemed like the best option. In 1933, a doctor performed the first-ever human-to-human kidney transplant, but the kidney came from a 6-hour-old cadaver and the transplant patient died less than 22 hours later. This probably because of mismatch and damage that had been done to the kidney from ischemia, a lack of blood supply.

Then in 1954, an American doctor named Joseph Murray had the opportunity to use a patient's identical twin a kidney donor. Similar to the cow and mouse studies, he was able to bypass the issue rejection because their immune systems were a pretty straightforward match. This 1954 event is usually credited as the first organ transplant in humans. The recipient went to live for another 8 years, which is significant. This surgery mostly reinforced what scientists knew. The researcher continued to study histological compatibility, finding matches for organ donors and recipients based on aspects of their immune system and there were still plenty of kinks to work out to get modern organ transplants.

For instance, researchers developed immunosuppressant drugs to treat patients before surgery and as a method of anti-rejection in the long term. Healthcare teams also had to figure out how to get organs to patients. They developed cold storage chains to preserve organs for as long as possible because ischemia gets to work quickly. But figuring out where to get organs sparked many ethical dilemmas. Now entire systems and committees are dedicated to figuring it all out.

Xenotransplantation

For the last fifty years, we've been replacing damaged human heart valves with pig valves. So, if we can transplant heart valves from pigs, why not entire hearts or kidneys or livers or lungs?

How come you can walk around with a pig's heart-valve inside of you but you reject a kidney from another human? Out of all the creatures in the world why pigs? Transplantation of organs from one species to another is known as Xenotransplantation. It turns out to be pretty bizarre but since there's a shortage of human organs figuring out how to get a steady supply of animal organs and tissue that we could use is something we might want to figure out.

Transplantation from human to human is tricky enough. Much more difficult than matching blood types. The new organ is often rejected by the recipient because of a protein called human leukocyte antigen (HLA). Almost every type of human cell has different kinds of these proteins on its surface and normally, they are the immune system's undercover agents, making a target for it to attack. So if you transplant an organ from one person to another, and the recipient's immune system recognizes the donor's HLA as foreign, it'll attack the transplanted tissue. This can lead to severe blood clots, failure of the new organ, and all kinds of painful symptoms that, put together, amount to transplant rejection.

The problem with these HLAs is that they are incredibly diverse, with thousands of variants, which makes it very hard to find a donor whose chemistry matches a recipient. Some people spend years on the waiting list. Others never get a match at all. However, there are few ways around the problem, and one of them is to skip human and move to a pig.

People might find this too flattering but we have a lot in common with a pig. Our immune system functions in a similar way and our organs mostly do the same things. Shockingly, pigs are the right size. We absolutely would not want a heart valve transplant from a mouse or beluga whale. The main thing is that s heart valve does not need to be alive to do its job. It's really just a piece of tough, flexible connective tissue that acts as a glorified piece of plumbing to direct blood flow.

Blasting the pig valve with a chemical called glutaraldehyde, the pig valve can be preserve while killing all its cells in the process. Dead cells can not produce those HLA proteins, so there is much less risk of rejection. The risk is not zero, though. These heart valves can wear out over tie since they are dead and unable to replace damaged cells. Sometimes the patient's immune system still gets nervous about having this foreign thing in the body. The dead cells still have some antigens on their surface, and patients especially those with stronger immune systems can react to them. The valve may eventually fail. So scientists figured out how to minimize even that small risk. They identified as the main antigen that our immune system attacks in pig tissue, galactose-alpha 1, 3-galactose, or alpha-Gal for short.

Then, they genetically engineered pigs not to express alpha-Gal, so the human immune system can accept a pig valve much more readily. But why it's stopped? Why pig is not used to grow not just heart valves but whole heart, or anything else people might be needed? That could solve the organ shortage. Well, the scientist is working on it. Knocking out alpha-Gal is not enough to convince the human body to accept a whole organ from a pig, but some more extensive genetic engineering could help. For example, the gene that tells the cell to produce some of its other antigens could be removed, or throw in some human genes to make the tissue seem more familiar to the human immune. The scientist has tested these genetically engineered pig organs in non-human primates like baboons, which only for a short time. Still, technology is advancing quickly.

There the downsides from xenotransplantation. Some people are not comfortable with the idea of genetically engineering pigs to express human genes, even if it is only to trick the human

immune system. Plus, cloning enough pig cells for the technique to work is mega-expensive. For now, these genetically engineered pig organs would be too costly to reach any patients.