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The Royal College of Surgeons of England
35-43 Lincoln's Inn Fields
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Dear Mr Kerr

Thank you for inviting me to participate in this exercise.

I have divided my predictions into the different areas of transplantation, and confined myself to abdominal organ transplantation.

1. The patients
The population is getting older and greater, and therefore the demand for transplantation will increase. At the moment we ration access to the transplant waiting list for all organs, stipulating that patients should have an expectation of 2 to 5 years of life following transplantation of the kidney and liver respectively. Inevitably that excludes some patients who would benefit, and it is notable that the longest UK survivor following a liver transplant would not be considered acceptable by today's criteria. I can see this situation being challenged, particularly once opting in becomes law, with everyone having the expectation of being offered a transplant where there is a possibility it may prolong life.

For renal transplantation, in addition to increasing age, the increase in prevalence of diabetes is likely to be a major contributor to the increase in demand.

For liver failure, non-alcoholic fatty liver disease (NAFLD) is becoming the leading indication for a transplant and is likely to be so for the next 10 years, after which I imagine some form of targeted therapy will be introduced such that it is managed medically. Hepatitis C will remain an indication in the context of hepatocellular carcinoma for the next 5 years or so, but transplantation for HCV will be dramatically reduced in the same way as it has for Hepatitis B.

Some metabolic diseases may be best managed by hepatocyte transplants or gene therapy

Pancreas transplantation is primarily offered to type 1 diabetics, not type 2. While I do not see a significant change in the numbers of type 1 diabetics, there will be more type 2 diabetics in renal failure. However, the number coming forward for pancreas transplantation will be less due to the advent of closed loop insulin delivery devices, with continuous glucose monitoring and accurate insulin delivery algorithms. This change will occur over the next 5 years, and be routine within 10.

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2. Organ Donors
The number of organ donors in the UK has increased steadily since the first Organ Donor Taskforce report in 2008, and when opting out legislation is increased it will further increase. A significant proportion of deceased donors donate follow circulatory death (DCD), rather than brain death (DBD) - currently 42% are DCD donors.
Organ retrieval networks will need to be expanded, and will be an increasing challenge to staff. For DCD donors, the use of *in situ* normothermic regional perfusion will be commonplace within 5 years – at present it is only a few centres. Research on deceased organ donors to improve transplant outcomes will also be commonplace, something that has been lacking to date.

3. Organ preservation
We are currently seeing a resurgence of interest in organ preservation outside the body prior to transplantation, and in reducing the magnitude of reperfusion injury that greets a new transplant.

Normothermic perfusion technology will allow us to evaluate organs *ex situ*, identifying those which can and should be safely transplanted while also allowing others to be treated *ex situ* to improve them prior to transplantation. While the utilisation of technology for viability assessment will become routine for marginal grafts over the next 5-10 years, it will take longer (10+ years) to be able to come up with treatment strategies that enable resuscitation of unusable organs to make them usable. I see the ability to defat a steatotic liver as the biggest challenge. I can see organ assessment and resuscitation taking place in centres of excellent, perhaps 2 or 3 in the UK, were marginal organs are taken to be evaluated and managed

Reperfusion injury in the context of myocardial infarction and post stroke is receiving considerable attention and transplantation will benefit from this research such that the initial outcomes will improve, with concomitant improvement in long term graft survival. I believe we will see widespread adoption of strategies to minimise reperfusion injury within 10 years, be that an intervention in the donor, the organ or the recipient.

4 Robotic transplantation
My personal view is that for most patients undergoing deceased donor kidney transplantation there will be little benefit in robotic surgery. It may have a role in the more obese patient, and in living donation. However, most transplant surgeons have little exposure to robotic surgery, and are not trained in it, and I do not see this taking off within 5 years, but it may be more common at 10 years. I cannot see robotic surgery having a place in liver transplantation.

5. Xenotransplantation
Xeno-transplantation was said to always have a promising future, that is, it is unlikely to be realised as a clinical entity in the near future.
There are three main issues that need resolving. The first is xeno-rejection. This comes in two forms. The first relates to circulating natural antibodies that cause the equivalent of hyperacute rejection. Genetic manipulation has been shown to be possible and may overcome this. However, the main immunological barrier results from indirect presentation of antigen and is more aggressive than had ever been envisaged. Research in novel immunosuppressants for transplantation has dramatically reduced over the last 5 years as adequate immunosuppression is now available from generic medicines such that there is little profit for Pharma. The breakthroughs in immunosuppression in the future will be spin offs of discoveries for cancer and autoimmune disease.

The second issue relates to endogenous retroviruses. In the case of the pig these are called PERVs, but it is likely that other species have these as well. It may be possible to engineer pigs such as these viruses are no longer in their genome, but I do not foresee this in the next 10 years.

The final issue relates to the physiology of the animal. Even if you can overcome the differences in histocompatibility and the presence of endogenous retroviruses there are significant physiological differences between animals and man that make xeno not a long term option. For example, the body temperature of the pig is 38°C, its blood pressure is lower, the levels of factor V in the blood are 20-fold higher, and so on.

6. Diverse transplants

I can see these coming to be more routine. Hand and upper limb transplants are already being performed. The indications for such transplants are not many, but they will be offered increasingly to amputees in the future. Similarly face transplants will be offered in the UK. At present there have been proposals but there has not been a take-off in a programme of transplantation. The recipients will be few in number, reflecting the incidence of disfiguring conditions. The need for limb and face transplantation may increase substantially if we are drawn into a major conflict where mass casualties occur.

Uterine transplants are already occurring outside the UK in small numbers, and there is a proposal from a group in London to start a programme in the UK. While there have been great advances in assisted conception, this will be another treatment offered routinely. The uterus will be transplanted and left in place for long enough to have a couple of children, following which it will be removed and immunosuppression stopped. The numbers will not be great, but it will be offered as a treatment. I think it will become routine in 5 – 10 years, probably at 2 or 3 centres in the UK.

7. Cell therapies

I would include gene therapy in this as well. Cellular therapies are already proving their worth, best exemplified by the recent publication concerning the treatment of haemophilia. These will take off over the next 5 years and beyond. It will take some time to assess the correct dose of such interventions, but this is the area where I see the biggest gains, largely for inherited diseases such as haemophilia but also other metabolic diseases affecting children.
Hepatocyte transplants are already used in the treatment of some inborn errors of metabolism, and hold promise for others, and they may have a role in the management of acute liver failure. However, they are currently limited by shortage of donor organs, difficulties in achieving engraftment, and lack of sustained effect; similar problems face islet transplantation for diabetes, and 17 years after the landmark paper on islet transplantation from Edmonton there has been little progress. However, I imagine that in 10 years that many of these problems will have been surmounted, and such transplants will be more common place.

With respect to stem cells, I have to admit to being a bit of a sceptic. It is very impressive that stem cells can be produced and their differentiation steered in the direction of the desired tissue, but there seems to have been limited success. For example, one might expect the ability to differentiate into a beta cell to produce a regulated amount of insulin would be relatively straightforward, yet it remains elusive as a clinical treatment. I suspect there will be more success in steering a patient's own stem cells to repair their own damaged tissues in a way that they do not at the moment, but it will be 10 to 20 years before we see this sort of advance.

8. Training the future surgeon

There are several areas to think about here

i) Increasing numbers of patients being referred for transplantation, predominantly older and less fit. More surgeons needed.
ii) Increasing numbers of organ donors – how can these be managed and will donor management and organ retrieval become a specific consultant role, or will we develop

centres around the UK where donors are transferred for organ recovery, as they do in parts of the UK. I think it is unlikely, but not impossible.

iii) Familiarity with newer perfusion techniques, some of which are more familiar to cardiac surgeons, is challenging. It will require a change in the way we train the surgeons, with a greater understanding of biochemistry and physiology being required to interpret the readouts of the varying perfusion devices.

iv) Anti-social hours. At present organ donation and transplantation are nocturnal activities. This is making the specialty less attractive to junior doctors and I think there is a real danger that transplant surgery is heading for a serious man-power crisis

I hope these thoughts are of use

With best wishes

Yours sincerely

C. J. E. Watson