Chapter 2

Alternatives to xenotransplantation

2.1 The starting point of this enquiry was the widening gap between the demand for, and the supply of, human organs and tissue for transplantation. Xenografts are only one way of closing that gap. In view of the scientific and ethical questions to which xenotransplantation gives rise, it is important to examine other ways of meeting the demand for organs for transplantation. Three approaches will be discussed in this chapter. First, reducing the demand for transplants by promoting health and reducing disease. Second, implementing measures to increase the supply of human organs and, third, developing artificial organs and tissue.

Preventive health measures

2.2 One possible way of bridging the gap between supply and demand is to reduce the demand for human organs and tissue by introducing public health measures to prevent the conditions that currently require treatment by transplantation. For example, the major causes of liver failure in the UK are alcoholism, infection with hepatitis viruses and drug intoxication. In this context, public health measures and policies to encourage healthier lifestyles and to achieve environmental improvements are important. The UK Government published **The Health of the Nation** in 1991, in order to highlight how changes in lifestyle and environmental improvements might contribute to a reduction in the incidence of major diseases.[1] The British Union for the Abolition of Vivisection wrote in their submission: "*Concentrating on improving health and preventing disease, rather than on cures or treatments to repair the damage once it has occurred, is a vastly more sustainable approach.*"

2.3 There are formidable obstacles in the way of measures to improve health and prevent disease. It is often difficult to establish a precise relationship between a lifestyle or environmental factor and a particular disease. Whilst the relationship between excess alcohol consumption and cirrhosis of the liver is clear, the situation is more complicated for most other conditions for which transplants may be required; for example, a high blood cholesterol concentration is one risk factor in coronary heart disease, but there are many others, not least genetic influences and perhaps also environmental factors encountered in fetal life. Cholesterol levels taken in isolation are therefore poor predictors of the likelihood of coronary disease in any one

[1] **The Health of the Nation** (1991) London, HMSO Cm 1523.

individual.[2] In addition, devising policies that are effective in changing attitudes and lifestyles is extremely difficult. A study examining different methods of giving dietary advice, for example, found that whether advice was given by a dietician, a practice nurse, or presented in a leaflet, it resulted in only a small reduction in cholesterol levels compared to what might be expected, suggesting that behaviour is difficult to modify.[3] Moreover, many of the diseases currently treated by transplantation are not amenable to preventive approaches and are unlikely to become so in the near future, if at all. These include all the common causes of kidney failure and the cardiomyopathies which afflict young people. Sufferers from cystic fibrosis, an inherited disease, are unlikely to live beyond the third decade without a lung or heart-lung transplant. Finally, any gains made as a result of preventive measures to reduce disease are likely to be long-term ones. In the meantime, the demand for transplantation remains pressing.

Increasing the supply of human organs

2.4 Two recent reports have examined the factors influencing the supply of human organs, and possible ways in which the supply could be increased.[4, 5] The factors affecting human organ donation are many and complicated. Establishing that a particular policy on organ donation does indeed affect the rate of donation is difficult, and many of the factors affecting supply may be either beyond the control of specific policy measures or desirable in their own right. For example, the low rate of organ donation in the UK, compared to some other countries, is due in part to the decline in deaths from road accidents and from brain haemorrhages. Countries with a low population density may have more difficulty collecting and transporting organs and coordinating their transplantation into recipients, though this is not a factor in the UK.

2.5 The level of provision of intensive care units, from which most organ donors come, and of transplant centres also affects transplantation rates. The number of intensive care beds is lower in the UK than in other European countries and there is increasing evidence of a need to expand provision and staffing. Transplant units also suffer from a shortage of surgical staff and transplant coordinators. Increased provision on both fronts would be expected to increase transplantation rates. The National Kidney Federation believes "*there is considerable room for improvement in*

[2] Cholesterol: Screening and Treatment. **Effective Health Care**, June 1993, N° 6.

[3] Neil H A W *et al.* Randomised trial of lipid lowering dietary advice in general practice: the effects on serum lipids, lipoproteins, and antioxidants. (1995) **British Medical Journal,** 310:569-74.

[4] New B *et al.* (1994) **A Question of Give and Take: Improving the supply of donor organs for transplantation**. King's Fund Institute Research Report 18.

[5] **Report of the British Transplantation Society Working Party on Organ Donation**. (1995) British Transplantation Society.

medical/nursing training in organ donation. In a study by the Federation in 1991, only 1.5 per cent of undergraduates and 4 per cent of postgraduates described their training in recognition of potential donors as 'good'."[6] Again, improved training would be expected to increase transplantation rates. Spain, which has a well-developed network of transplant coordinators, has seen a steady increase in transplantation rates.[7]

2.6 Efforts could also be made to increase the use of organs from donors whose hearts are no longer beating. Recent studies have suggested that transplantation of kidneys from such donors can be almost as successful as transplantation using heart-beating donors,[8, 9] although another study has questioned this view.[10] Another source of kidneys (and, to a lesser extent, livers) is live donors. In Norway, the high kidney transplant rate is due to the high number of live donors giving kidneys, and recent reports have recommended that kidney donation by live donors should be encouraged in the UK.[11, 12]

2.7 Opinion polls consistently show that, while 70 per cent of UK citizens are in favour of donating their organs after their death, willingness to register as an organ donor is fairly resistant to publicity campaigns, and only about 25 per cent of the population carry organ donor cards.[11] The cards are valuable in that they give a clear indication of the donor's intention to relatives. This is important, since 30 per cent of relatives refuse permission for removal of organs from a potential donor. In an attempt to increase registration, in 1994, the Department of Health introduced a national, computer-based register of potential organ donors.[13] It is too early to determine the effectiveness of this initiative, but, however effective, it is unlikely that it can meet the existing demand for human organs, much less cope with any expansion in that demand.

2.8 One possibility would be to change the law so as to remove the right of relatives to withhold consent to the removal of organs from someone who before dying expressed a wish to donate. A more radical change would be to operate a system of presumed consent in which people who did not wish to have their organs removed would sign a dissent register. Such changes are controversial. Some argue that, given

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6 Submission to the Working Party.

7 Matesantz R and Miranda B (1995) Letter to **Lancet**, 346:53.

8 Wijnen R M H *et al.* (1995) Outcome of transplantation of non-heart-beating donor kidneys. **Lancet**, 345:1067-70.

9 Andrews P A *et al.* (1995) Letter to **Lancet**, 346:53.

10 Chang R W S (1995) Letter to **Lancet**, 346:322.

11 New B *et al.* (1994) **A Question of Give and Take: Improving the supply of donor organs for transplantation**. King's Fund Institute Research Report 18.

12 **Report of the British Transplantation Society Working Party on Organ Donation**. (1995) British Transplantation Society.

13 For information about the NHS Organ Donor Register, freephone 0800 555777.

the sensitivity of potential organ donors to adverse publicity, more contentious measures to obtain human organs might backfire. Advocates of such changes argue that such legal frameworks have been successful in increasing the supply of human organs in Belgium and Singapore. Yet, establishing that specific policy changes have led to increased transplantation is not easy. In Belgium, for example, an important factor may have been the simultaneous improvement in transplant coordination.

2.9 Another procedure for increasing the supply of human organs is elective ventilation. Elective ventilation involves placing a patient for whom death is inevitable on a ventilator in order to maintain their organs in a suitable state for transplantation. This procedure was used with eight patients in Exeter, between 1988 and 1990.[14] Elective ventilation is contrary to the principle that treatment should be in the best interests of an incapacitated patient, however, and the Department of Health has issued guidance that it is unlawful.[15] This conclusion was supported in a recent report of the Law Commission.[16] A number of bodies, including the British Medical Association[17] and the British Transplantation Society,[18] have concluded that elective ventilation would not be unethical, however, and have recommended that the law should be changed to make it legal. Thus, the issue remains controversial.

2.10 Since 1990 the number of human organ donors has levelled out at about 950 a year.[19] Increased provision of intensive care and transplant facilities, and increased use of donors whose hearts are no longer beating and live donors would go some way to improving transplantation rates. Other measures, such as changing the consent law or introducing elective ventilation, are more controversial and would be regarded by some as unacceptable. Even if all human cadaveric organs were somehow made available for transplant, the supply would still not meet the potential demand.[20] So it is necessary to consider how far the use of artificial organs and tissue may provide an alternative to human organ transplantation.

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[14] Feest T G *et al.* (1990) Protocol for increasing organ donation after cerebrovascular deaths in a district general hospital. **Lancet**, 335:1133-5.

[15] Acute Services Policy Unit (1994) **Identification of potential donors of organs for transplantation.** London: Department of Health (HSG(94)1). The situation has been criticised as being unclear due to the existence of another, previously issued, code of practice (Departments of Health of Great Britain and Northern Ireland (1983) **Cadaveric organs for transplantation: a code of practice including the diagnosis of brain death.** London: HMSO). The guidance in this code of practice is ambiguous (Francis R (1995) A legal comment. Letter to **British Medical Journal,** 310:718).

[16] Law Commission Report No 231 (1995) **Mental Incapacity.** London: HMSO. pp 94-5.

[17] BMA's Ethics, Science and Information Division (1993) **Medical Ethics Today: its practice and philosophy**. BMJ Publishing Group.

[18] **Report of the British Transplantation Society Working Party on Organ Donation**. (1995) British Transplantation Society.

[19] Information supplied by United Kingdom Transplant Support Service Authority.

[20] Caplan A (1992) Is xenografting morally wrong? **Transplantation Proceedings,** 24:722-7, quoted in Tania Woods' submission to the Working Party

Artificial organs and tissue

2.11 Artificial body parts, from glass eyes to wooden legs, have been used for centuries and offer a possible means of addressing the shortage of organs and tissue for transplantation. Technological advances and modern materials have increased the range and sophistication of artificial implants, but many difficulties remain in replicating the complicated functions of certain human organs. Artificial implants currently under development range from totally mechanical devices to organs consisting of a combination of artificial materials and human cells. The rest of this chapter describes the latest developments in producing artificial organs and indicates where they may become a viable alternative to xenotransplantation.

2.12 The human body is a demanding and hostile environment for artificial tissue and organ replacements: blood has a tendency to clot, it is in constant motion and can be corrosive; tissues may need to bend or stretch and can be subject to sudden shocks; organs may need to adjust their function and output according to the changing demands of the body. The human immune system has evolved to reject substances it recognises as foreign, causing inflammation and blood clots. In addition, artificial devices are susceptible to infectious organisms: even organisms which are not normally dangerous can become deadly when they colonise a foreign object implanted inside the body. Faced by such difficulties, it is perhaps not surprising that most devices currently in use perform fairly basic mechanical or cosmetic functions, and are often located where the blood supply is limited. However, researchers are attempting to develop artificial organs capable of carrying out more sophisticated functions in more difficult environments.

Kidneys

2.13 The longest established procedure for replacing the function of a failing organ with an alternative is dialysis of body fluids in patients with kidney failure. A synthetic membrane, or the peritoneum, is used as a dialysing medium across which the blood can be freed of toxic waste products normally excreted by the kidneys. Patients spend several sessions a week having dialysis, and can live relatively normal lives between treatments, which is not the case when most other organs fail. There has been little research into developing implantable artificial kidneys because patients can be successfully kept alive by dialysis while awaiting transplantation. For many patients, however, dialysis is far from ideal, because it requires lengthy sessions of treatment, restrictions in diet and cannot prevent a general decrease in overall health. As the length of the waiting list for kidney transplants testifies, dialysis does not offer a complete solution to the shortage of kidneys for transplantation.

Heart

2.14 Of all implantable mechanical organs, most progress has been made with artificial heart devices.[21] This is because the operation of the heart is fairly simple (it is basically a pump) and, unlike many other organs, it performs only limited biochemical or metabolic functions. Two types of artificial hearts are being developed: ventricular assist devices and total artificial hearts.

2.15 Ventricular assist devices (VAD) are at a more advanced stage of development than totally artificial hearts. Ventricular assist devices support but do not replace the heart, which remains in place and continues to perform some functions. Left ventricular assist devices (LVADs) are the most common type and help the left ventricle of the heart pump blood around the body. Since 80 per cent of the work of the heart is done by the left ventricle, LVADs are the most important type of artificial heart. Right ventricular assist devices (RVADs) help pump blood to the lungs for oxygenation, and can be used in conjunction with LVADs.

2.16 Most LVADs are implanted in the abdomen. A small lead through the skin attaches the LVAD to batteries, which are carried in a pack on a belt. The LVAD can keep time with the natural heartbeat and a computer adjusts the pumping action to cope with changes in activity. Patients have lived with the aid of an LVAD for up to two years. Currently, LVADs are used on a short-term basis, to keep a patient alive until a human organ is available. Supported by an LVAD, the heart can rest and, in some cases may recover sufficiently to allow the device to be removed after which the patient's condition can be managed with drugs. Thus, LVADs could in principle be used as an early form of treatment for heart disease before the condition becomes life-threatening. Also being developed are intra-ventricular artificial hearts which are so small they can be implanted into the heart itself. These devices have the potential to be used on a long-term basis as an alternative to human organ transplantation.

2.17 Total artificial hearts are designed to carry out all of the main functions of the heart. Several designs have been tried, but all follow the same basic principles, in which chambers pump blood to the lungs for oxygenation and then around the rest of the body. In 1982, a patient was kept alive for 112 days with a total artificial heart. Development continues and the devices have potential for short-term use in patients suffering from biventricular heart failure who are waiting for a human organ.

2.18 Artificial hearts may eventually provide an alternative for patients waiting for a human organ and they do not require the use of immunosuppressive drugs. But there are various problems to be overcome with the use of artificial hearts:

[21] Reviewed in Westaby S (1996) The need for artificial hearts. **British Heart Journal,** in press.

- since blood tends to react with nearly every artificial substance, clots can form inside the devices and may cause strokes if they dislodge and travel through the circulation to the brain. Researchers are attempting to produce materials that reduce the tendency of blood to clot. One approach is to use the patient's own endothelial cells to line the surfaces of the device that are in contact with blood. In the meantime, patients are treated with anticoagulant drugs to reduce the tendency of the blood to clot;

- artificial hearts tend to damage blood cells, causing anaemia and sometimes liver and kidney problems. Such damage is reduced by designing devices which allow a less turbulent blood flow;

- the power supplies are bulky and inconvenient, and need frequent recharging; often the person must be connected to a recharging unit at night. Because of their size, and the heat they generate, the power units cannot be implanted. The lead connecting the heart to a power supply outside the body can cause problems with infections;

- the devices are very expensive, costing about £30,000 each.

Thus, for the foreseeable future at least, mechanical hearts are unlikely to satisfy the demand for heart transplants.

Lungs

2.19 The first artificial lung capable of oxygenating blood and eliminating carbon dioxide was developed in the 1950s.[22] These devices were located outside the body and were used for periods of up to five hours to support patients during heart surgery when it was necessary to bypass the function of the heart and lungs. In 1992, a patient survived for 45 days with the aid of extracorporeal membrane oxygenation in which blood is removed from the body, oxygenated and returned to the body. This technique is now in clinical use for treating lung failure, especially in infants, but it remains a short-term measure.

2.20 Trials of implantable oxygenating devices are now in progress. The intravascular oxygenator is a miniature membrane lung which can be placed inside the body. The heart pumps blood through the device (unlike external devices which require external pumps) and gas is exchanged through microporous polypropylene fibres. The efficiency of the gas exchange depends greatly upon the surface area of the membrane, and therefore on the size of the devices. Thus, small implantable devices are not as efficient as external artificial lungs.

[22] Goldsmith M (1993) After two decades Penn State researchers may be near perfecting replacement hearts and lungs. **Journal of the American Medical Association**, 269:966-973.

2.21 Infection is a major problem with artificial lungs, since they are in constant contact with the atmosphere and do not have the natural protection mechanisms found in human lungs. Blood clotting is another problem that must be overcome before artificial lung implants become a realistic option.

Bioengineered organ and tissue replacements

2.22 As indicated above, reproducing the complicated functions of the body in a purely mechanical way is extremely difficult. This has led to the development of artificial organs incorporating living cells, tissues or organs which can perform some of the functions of the tissue or organ that needs replacing.

Liver

2.23 The liver performs a wide range of important functions including the processing of the products of digestion, the control of the metabolism of proteins and carbohydrates, the manufacture of essential proteins such as blood clotting factors, the removal of toxic substances absorbed from the gut, the excretion of the breakdown products of red blood cells and the secretion of bile. It is impossible at present to begin to replicate all of these complicated functions by wholly artificial means, so research has focused instead upon bioengineered livers. The intention is to use them on a short-term basis to keep patients suffering from liver failure alive while they wait for a transplant or to give their own liver a chance to regenerate. At the simplest level, the patient's blood is passed through an animal liver: at best this can keep patients alive for a very short time.[23]

2.24 Implantable artificial livers are a long way off, but clinical trials are under way for artificial livers which function outside the body. One such device is the extracorporeal liver assist device, which has been used successfully in small numbers of patients.[24] The device filters blood through thousands of tiny porous tubes. Human liver cells are packed around the tubes to process the passing blood and to get rid of waste. The liver cells are immortalised (they have the ability to keep reproducing) and can be grown in the laboratory. It is important that the liver cells do not enter the blood, as there is a chance that if they passed into the body and became established in an organ or tissue, they might develop into tumours.

[23] Chari R *et al.* (1994) Brief report: Treatment of hepatic failure with *ex vivo* pig-liver perfusion followed by liver transplantation. **New England Journal of Medicine**, 331:234-7.

[24] McNair A N B *et al.* (1995) Recent advances : hepatology. **British Medical Journal,** 311:1351-5.

2.25 Other devices contain pig liver cells. The person's blood is separated before treatment, with the cells being removed and only plasma entering the device. Eliminating the cells reduces the risk of blood clot formation, but the lack of red blood cells means that the liver cells in the machine suffer from a lack of oxygen. Alternative methods of supplying the liver cells with oxygen have been tried, but so far the cells have died within eight hours or so.

2.26 A different approach is to try and produce a true replacement liver grown in the laboratory.[25] An artificial scaffolding rather like a sponge is produced, made either from biodegradable or from tough and inert material. Blood vessels and liver cells are encouraged to grow onto the scaffolding. If successful, organs made in this way could then be used for transplantation. All these methods of liver replacement, however, are far from becoming routine clinical procedures.

Pancreatic islet cells

2.27 Like the liver, the pancreas performs complicated biochemical functions which are difficult to replicate by artificial means. Efforts have been made to improve the success of transplantation of living islets of Langerhans, the pancreatic cells that produce insulin.[26] This would be used to treat patients suffering from diabetes. The islet cells are encapsulated in a porous membrane that does not cause an immune response. Blood passes through the membrane, and the trapped pancreatic cells produce insulin and help regulate the level of blood sugar. Since the islet cells remain separate from the blood, and from the cells of the recipient's immune system, there is no immune response to the transplant. This suggests that the pancreatic cells could be supplied by non-compatible human donors or by other animals.

Bones and joints

2.28 Techniques for repairing bones and joints using artificial materials are well established, and have become more successful with improvements in the materials used. These must be tough, lightweight, corrosion resistant and they must not cause an immune response. Stainless steel, used in hip replacements, and bone cements, however, shield the surrounding bone from stress and lead to wasting of the natural material. Thus, there is considerable interest in developing bioengineered bone in

[25] Miller S K (1992) Cells and sponge support failing liver. **New Scientist,** 1 August 1992, p 20.

[26] Soon-Shiong P *et al.* (1994) Insulin independence in a type 1 diabetic patient after encapsulated islet transplantation. **Lancet**, 343:950-1.

which an artificial framework or matrix is transplanted into the body.[27] This encourages surrounding cells to enter the matrix and leads to new bone growth. Alternatively, cells can be seeded onto the matrix before transplantation. Since the patient's own bone marrow cells can be used, rejection is not a problem.

2.29 The shortage of bone for transplantation is not as acute as the shortage of organs and some other tissue. This is partly because autografting, in which bone from one part of the body is used to repair bone in another part of the patient's body, is a relatively common technique. Human bone can also be stored for long periods which makes it easier to maintain a supply for transplantation. Nevertheless, there is some interest in xenotransplantation and limited use has already been made of transplant material derived from cow bone.[28]

Skin

2.30 Rapid advances have been made recently in producing skin grown from human cells.[29] This can be used to treat burns and ulcers. Cells from one of the skin's layers, the dermis, are grown on a biodegradable matrix to produce a sheet of dermis cells. After transplantation of a dermis layer to cover a wound, the patient's own outer layer of skin (the epidermis) grows over the transplanted dermis. Another method takes skin from corpses and treats it to remove the cells, leaving a weave of protein fibres, including collagen. When this protein matrix is grafted onto a wound, it is quickly colonised by the recipient's own skin cells and blood vessels. Because the transplanted matrix does not contain cells, it does not provoke an immune response and is tolerated well by recipients.

2.31 Like bone, a number of strategies are available to replace skin. Autografting, in which skin from one part of the body is grafted elsewhere is possible. Skin can be stored for up to three years, making its collection from corpses, and after operations such as cosmetic surgery, possible. Xenotransplantation of pig skin to treat burns patients has been used in the past but is no longer common. Should the development of transgenic pigs allow transplantation of pig organs and tissue without a strong immune response, then interest in xenotransplantation of pig skin may revive. Recent developments have involved the growth of skin cells on three-dimensional supports.[29] This raises the possibility of replacing complicated three-dimensional structures such as the ear. Ultimately it is hoped that these techniques will permit the production of bioengineered heart valves and even organs.

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[27] Crane G M *et al.* (1995) Bone tissue engineering. **Nature Medicine**, 1:1322-4.

[28] Poumarat G and Squire P (1993) Comparison of mechanical properties of human, bovine bone and a new processed bone xenograft. **Biomaterials**, 14:337-40.

[29] Dickman S and Strobel G (1995) Life in the tissue factory. **New Scientist**, 11 March 1995, pp 32-7.

Conclusion

2.32 There are problems in closing the gap between the demand for transplantation and the supply of donor organs. Preventive measures may go some way towards meeting the demand but are necessarily long-term and of uncertain effectiveness. Increasing the supply of organs from human donors is difficult and, in some cases, not without ethical complications. Mechanical and bioengineered organ replacements, while offering future promise, remain problematical for the time being. This means that attention has turned to the use of animal organs as one potential method of satisfying the demand for transplantation. The next chapter assesses the progress that has been made towards developing successful xenotransplantation.