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THE FUTURE OF ORGAN REPLACEMENT—NEEDS, POTENTIAL APPLICATIONS AND OBSTACLES TO APPLICATION

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Abstract

The supply of organs available for transplantation is already far smaller than the demand, and the demand may grow substantially in the near future. For this reason, it is timely to consider how organ function might be replaced in the future. In this communication, we consider new technologies that might be used to replace organ function, the obstacles to applying new technologies and now those obstacles might be overcome in the developing of new strategies for organ replacement.

The future of organ replacement will be conditioned by three variables. The first variable is the need, particularly how the number of organs to be replaced will change over time. The second variable is the set of applications and new technologies that will be available to replace those organs. The third variable is the set of obstacles, biological and societal, that may hinder the replacement of organ function. This communication will summarize our perspective on how these variables may change in the foreseeable future.

The Need for Organ Replacement

The need for organ replacement may change profoundly during the next period of years¹⁻⁴. New treatments for disease, better nutrition and better approaches to public health will decrease the prevalence of some of the diseases that cause organ failure and hence the need for transplantation. For example, better diet and treatment with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-coA)-reductase inhibitors may prevent atherosclerosis and cardiac failure in some, perhaps in many. However, increased longevity brought about by improvements in medical care, nutrition and public health will subject a greater fraction of the population to diseases of aging, such as diabetes and failure of the heart or kidneys. This will increase the prevalence of organ failure and the potential demand for transplantation.

The circumstances in which organ replacement is sought may also soon change. Advances in molecular diagnostics, proteomics and other fields may allow the detection of lethal diseases long before clinical manifestations occur. A sample of blood might reveal the existence of cancer of the kidney or lung before a lesion is localized. This event will tempt the clinician and patient to replace the potentially “lethal” organs with a transplant. Such an approach is already taken in those rare circumstances in which a young infant has dysmorphism suggesting a high risk of Wilm's tumor. Preemptive transplantation as such could dramatically expand the demand for organ replacement and just as dramatically change the concept of what would constitute adequate replacement – normal function and limited or no immunosuppression would be even more prized than they are today.

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Applications

A growing need for transplantation would make the question of which new technologies could be applied to addressing that need even more compelling. Allotransplantation already fails by far to address the demand for replacing the heart, lungs, kidneys and liver^{5, 6}. Perhaps the availability of some organs can be improved by increasing cadaver donation or use of living tissues. Still, allotransplantation cannot provide vastly larger numbers of organs that might be sought. Accordingly, we have considered the merits of other technologies, including xenotransplantation, implantable devices, stem cells, tissue engineering, organogenesis and xenotransplantation⁴. We shall briefly consider this subject below.

Xenotransplantation could provide a plentiful, inexpensive and physiologically satisfactory replacement for the major parenchymal organs, at least in principle. We have discussed the potential applications of xenotransplantation elsewhere and will refer the reader to those discussions⁷⁻⁹. Much excitement has been generated regarding the potential use of genetic engineering to limit the immune and inflammatory reactions that limit the function and survival of xenografts. Despite this enthusiasm, no genetic manipulations to date have allowed organs from pigs to survive and function long enough in primates to propose using those organs in people, and no approach yet tested has allowed survival and function beyond a brief period without severe manipulation and/or immunosuppression. Below we will discuss other potential ways that xenotransplantation might be used, but for the moment we shall dismiss this approach to replacement of organ function, with the possible exception of the liver¹⁰.

Fully implantable devices are available, experimentally, to replace the function of the heart. The devices are only used in extreme conditions, and the use engenders substantial risk. However, we believe the technology will improve with use and one can envision that all cardiac replacement may one day be addressed in this way. Unfortunately, the same cannot be said for other organs. Although external devices and procedures like dialysis can replace the function of the lungs and kidneys, these devices and procedures do substitute fully and they engender serious complications. It is difficult to imagine then that devices will provide optimal replacement for organ function in the foreseeable future, particularly if that replacement is to be preemptive.

Stem cells have the capacity to proliferate and to differentiate into relatively mature cells of various types. Embryonic stem cells can become any organ in the body and do so when implanted into a blastocyst. In principle, then embryonic stem cells could be used to replace any organ in the body. However, at least two factors limit this possibility. First, embryonic stem cells and embryonic stem cell lines are inevitably different genetically from the person to be treated and their use, and use of tissues or organs derived from these cells may require immunosuppression. This problem can potentially be solved by cloning⁴, as discussed below. The greater limitation to using embryonic stem cells (or stem cells generated by nuclear cloning) is that while those cells can be grown into differentiated cells and tissues, no means are known by which those cells can be coaxed to form organs outside of the embryo. The limit of stem cell technology, thus, appears to be the fetal microenvironment.

Another technology sometimes proposed for organ replacement is organogenesis. Organogenesis refers to growing of intact organs or organ-like tissues from primitive cells. Just as organogenesis occurs naturally in the fetus, it can also occur when tissues or cells from a primordial fetal organ are placed in culture or implanted in living animals. For example, fetal kidney tissues grown can generate maturing glomeruli *in vitro*¹¹ and organs in mature mammals¹². Fetal tissues and cells can also be used to generate engineered structures¹³. Application of organogenesis is limited however by the source and immunogenicity of fetal tissues. Human fetal tissue is not suitable for this purpose. Some have proposed that fetal tissues

from animals might be used instead¹⁴. However, organogenesis of a xenogeneic organ is impaired by immunity against that organ, and this barrier probably equals the barrier to allotransplantation, with certain exceptions¹⁵.

A Combination of Technologies

We have proposed that the obstacles of organ replacement might be addressed if various technologies could be pieced together in a way that exploits the advantages of each technology^{2, 4}. Thus, nuclear cloning (the transfer of a nuclei from mature cells of the individual to be treated into primitive enucleated cells, allowing the reprogramming of DNA) could be used to generate embryonic stem cells. To avoid the ethical problems of nuclear cloning and the potential immunogenicity of proteins encoded by foreign mitochondrial DNA, one might envision treating mature cells with “cloning factors” obtained from xenogeneic sources that would partially reprogram nuclei without transfer¹⁶. The stem cells obtained in this way might be coaxed to mature by placing them in a suitable location in a xenogeneic fetus⁹. For example, we have shown that human stem cells introduced into the fetal pig can mature in normal, histotypic ways at appropriate locations in the pig fetus^{17, 18}. The tissues that begin to mature in this xenogeneic system might then be harvested, and the human cells isolated and transferred into the person to be treated so that full maturation and vascularization (i.e., organogenesis) could occur.

Concluding Remarks

The strategy discussed here is complex and may never be realized. However, every step has been accomplished in one experimental system or another, and what is lacking is the piecing together of the steps. Regardless of whether this concerted strategy succeeds, we believe the efforts made in testing it may generate new knowledge and new visions about how organs may be replaced in the future.

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