Head Transplantation: Editorial Commentary

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doi: 10.1111/cns.12434

Head transplantation and the controversy it stirs are not new. In fact, in 1908, as an application of his research on blood vessel surgery, American Physiologist Charles Guthrie transplanted the head of a donor dog onto the neck of a recipient dog [1]. In this research on blood vessel surgery, Guthrie collaborated with the French Physiologist, Alexis Carrel, and in 1912, Carrel was awarded the Nobel Prize for this work. In their book "America's First Nobel Prize in Medicine or Physiology: The Story of Guthrie and Carrel", Stephenson and Kimpton claim that the primary credit for this work should have gone to Guthrie rather than Carrel, and they suggest that the controversy surrounding Guthrie's head transplant experiments possibly influenced the Nobel committee's decision [2].

In the 1940s and 1950s Russian scientist and organ transplant pioneer, Vladimir Demikhov, developed a number of different surgical techniques for transplanting heart, lung–heart, limbs, and a head in dog models [3]. The work of these early transplant pioneers focused exclusively on developing the techniques required to surgically transplant these organs/tissues and did not consider the immunological and the ethical barriers standing in the way of performing these surgeries in humans.

The late 1950s and early 1960s brought the discovery of the first immunosuppressive agents (azathioprine, 6-mercaptopurine, corticosteroids) and allowed transplantation to move from animal experiments into the clinical arena. At this time, several teams led by the likes of Joseph Murray, Norman Shumway, and Richard Lower in the US and Christian Barnard in South Africa attempted human kidney and heart transplants. In 1954, Murray performed the first successful kidney transplant between identical twins (not requiring immunosuppression) [4], which in 1990 earned him the Nobel Prize in Physiology/Medicine for his pioneering work in organ transplantation.

Due to the primitive immunosuppression agents available at the time, these early organ transplants had poor outcomes by today's standards; however, they served to lay the surgical, immunological, and ethical foundations of organ transplantation, a treatment

now considered to be one of the greatest advancements in modern medicine [5].

In the early 1970s, Neurosurgeon, Robert White, in the US led a team that performed head transplants in monkeys [6]. Benefitting from the surgical techniques developed by their predecessors and the recently introduced immunosuppression medications, the procedure was reported to be a success with postoperative restoration of the senses of smell, taste, and hearing in the transplanted head. However, the amount of immunosuppression required to prevent the head from rejecting caused the monkeys to die 9 days posttransplant [7]. In spite of this technical success and initial immunological attempt, the ethical aspects surrounding the procedure received great criticism from animal rights activists. In spite of many remarkable achievements in his field of neurosurgery, White's head transplant research was the focus of a great deal of criticism being called "barbaric" and "epitomize the crude". White himself was called "Dr Butcher" by animal activists [8]. The effect this had on White is captured in his own words "... it is now possible to consider adapting the head-transplant technique to humans. Whether such dramatic procedures will ever be justified in the human area must wait not only upon the continued advance of medical science but more appropriately the moral and social justification of such procedural undertakings..." [9].

By the 1980s and 1990s, the field of transplantation had come into its own with kidney, heart, lung, and pancreas transplants being performed routinely in centers worldwide. In spite of this success in organ transplantation, however, at the time it was still not possible to transplant human hands or faces. This was due primarily to the high immunogenicity of the skin tissue contained in these structures. The immunosuppression medications that were being successfully used to prevent rejection in organ transplants were ineffective in preventing skin rejection [10]. Then, in the mid 1990s, a team of scientists in the US led by John Barker discovered a cocktail of 3 immunosuppression medications (tacrolimus/MMF/corticosteroid), being used at the time for kidney transplantation, to be effective in preventing skin rejection [11].

This discovery opened the door for hand and subsequently face transplantation, and in the late 1990s and early 2000, teams from the US, France, and China performed the first successful human hand and then face transplants [12,13]. Today, more than 90 hand and 30 face transplants have been performed worldwide.

The next frontier, some would say, the final frontier in transplant surgery is head transplantation. Many of the surgical, immunological, and ethical questions that will have to be answered prior to performing human head transplants have already been answered. This has been done in animal research and in the development of exiting treatments of diseases, trauma, and congenital deformities in the head and neck region.

Surgical techniques necessary to transplant a head from one body to another have been developed over many years (mentioned above) in different animal models and in human cadavers [7,14]. Perhaps the most pressing surgical question that remains unanswered is how will the cervical spinal cord be reattached between the recipient head and the donor body to restore sensory and motor function?

Immunological hurdles that must be overcome to perform human head transplants are formidable. Some of the “immunological” questions that will have to be answered before human head transplants are performed include the following: Will the same cocktail of immunosuppression medications that successfully prevent hand and facial tissues from rejecting be effective in preventing the head from rejecting? If and when episodes of acute rejection occur after transplanting the head, as they do in hand and face transplants, how will these present themselves and how will they be treated? In hand and face transplants, the hand and face come from donors and are transplanted onto the body of recipients. In these cases, it is the immune system in the recipients’ body that mounts an immunological response to reject the hand and facial tissues. In a head transplant, this will be reversed, the body, containing most of the immune system, will come from the donor, and it will be this donor immune system that will reject the recipient head. How will this dynamic affect the immunosuppression strategy? Will the much feared, and often irreversible, chronic rejection occur in head transplants? Ultimately, many of these questions will have to be answered in preclinical animal models whose immune system closely resembles that of humans. The accompanying article in this tome by Dr. Ren and his col-

leagues, “Head Transplantation in Mouse Model” describes the development of a mouse model to be used to answer some of these critical immunological questions.

Finally, ethical barriers associated with human head transplants will be challenging. If we use past experience as an indicator of “the storm to come”, the above-cited controversies surrounding the pioneering work of Guthrie, Carrel, and White are telling. One of the main ethical questions posed in hand and face transplantation focused on risk vs. benefit. This question was “do the risks associated with the lifelong immunosuppression, required to prevent hand or face rejection, justify the benefits of receiving one of these “nonlifesaving” procedures?” In the case of head transplantation, this risk vs. benefit trade off will be more straight forward as this procedure would be “lifesaving”, and therefore, the risk would justify the benefit. Another difficult question; in the case of chronic rejection, if and when all attempts to reverse rejection fail and the head must be removed, what will be the exit strategy?

Many questions have already been answered and many remain. While several of the remaining questions can be addressed in well-planned experimental protocols in appropriate animal models, many questions will remain unknown until head transplants are performed in humans. To assure productive research that advances science and avoid destructive and unnecessary controversy that stifles progress, it is important to engage in open dialogue and debate with our professional peers [15–17], potential patients, and the general public, through public forums [18] and print and broadcast media. These conversations are difficult because of the different languages and the different agendas each community and individual brings to the table. Even so, the effort is worth it as the final result is a broader and deeper understanding of the questions, concerns, and the ultimate benefits of our research and the new treatments they generate.

Funding

FIRM is supported in part by the Friedrichsheim Foundation based in Frankfurt am Main, Germany.

Conflict of Interest

The authors declare no conflict of interest.

References

- Guthrie CC. *Blood-vessel surgery and its applications, international medical monographs*. London: Edward Arnold, Longmans, Green & Co., New York, 1912.
- Stephenson HE Jr, Kimpton RS. *America's first nobel prize in medicine or physiology: the story of Guthrie and Carrel*. Boston, MA: Midwestern Vascular Surgery Society, 2000.
- Konstantinov IE. At the cutting edge of the impossible: a tribute to vladimir P. Demikhov. *Tex Heart Inst J* 2009;**36**:453–458 PMID: PMC2763473.
- Murray J, Merrill J, Harrison J. Renal homotransplantation in identical twins. *Surg Forum* 1955;**6**:432.
- NHS Organ Donor Register Website. at: <http://www.organdonation.nhs.uk>. (Retrieved 9 June 2015)
- White RJ, Wolin LR, Massopust LC Jr, Tasltiz N, Verdura J. Primate cephalic transplantation: neurogenic separation, vascular association. *Transplant Proc* 1971;**3**:602–604.
- McCrone J. Monkey business. *Lancet Neurol* 2003;**2**:772.
- Bennett C. “Letter to the editor: Cruel and Unneeded”. New York Times (August 26, 1995) From: <http://www.nytimes.com/1995/08/26/opinion/1-cruel-and-unneeded-324295.html> (Retrieved 9 June 2015)
- From “Head transplant”. at: http://en.wikipedia.org/wiki/Head_transplant#cite_note-gem-9. (Retrieved 9 June 2015)
- Hovius SE, Stevens HP, van Nierop PW, et al. Allogeneic transplantation of the radial side of the hand in the rhesus monkey: I. Technical aspects. *Plast Reconstr Surg* 1992;**89**:700–709.
- Jones JW, Ustuner T, Zdzichavsky M, et al. Long-term survival of an extremity composite tissue allograft with FK506-mycophenolate mofetil therapy. *Surgery* 1999;**126**:384–388.
- Francois CG, Maldonado C, Barker JH, et al. Hand transplantation: comparisons and observations of the first four clinical cases. *Microsurgery* 2000;**20**:360–371.
- Devauchelle B, Badet L, Lengele B, et al. First human face allograft: early report. *Lancet* 2006;**368**:203–209.
- Discussed at: http://www.dichotomistic.com/mind_readings_head_transplant.html. (Retrieved 9 June 2015)
- Barker JH, Jones JW, Breidenbach WC. Composite tissue transplantation: a clinical reality? *Transpl Proc* 1998; (Invited Editor) **30**:2686–2787.
- Wiggins OP, Barker JH, Martinez S, et al. On the ethics of facial transplantation research. *Am J Bioeth* 2004;**4**:1–12.
- Banis JC, Barker JH, Cunningham M, et al. Response to selected commentaries on the AJOB target article “On the ethics of facial transplantation research”. *Am J Bioeth* 2004;**4**:W23–W31.
- Naked Science – Face of the Future, Public Debate on the Feasibility of Face Transplantation” London Science Museum, Dana Center. London, UK. November 19 2003