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LETTERS

NIH Neural Transplantation Funding

We view with considerable interest the funding of a program of neural transplantation recently announced by the National Institute of Neurological Diseases and Stroke (NINDS) of the National Institutes of Health (NIH). This is an encouraging development in support of an increasingly vigorous field of scientific endeavor.

The $4.5-million NIH-NINDS grant is the first major award since the federal ban on fetal tissue research was lifted. It supports a double-blind study of 40 patients with Parkinson's disease; 20 patients will receive neural transplants and be compared with the remainder, who initially will undergo a sham procedure. The study is extensive and costly, and the proposed evaluation protocol is said to be impeccable. The high level of expenditure, high political profile, and probity of the funding agency are such that the results are likely to have a profound influence on the future and funding of the whole field of basic and clinical neural transplantation.

Our particular concern is that only one neural transplantation procedure from a single center is to be assessed. Since transplantation techniques are still at an early stage of development, the optimal methods of tissue procurement, graft preparation, and implantation are not yet established. Consequently the results and implications of any single trial must be considered with great caution. The same strictures apply equally to similar work performed in all other institutions throughout the world.

The Network of European CNS (Central Nervous System) Transplantation and Restoration (NECTAR), formed in 1990, comprises the clinical and basic science groups with an interest in neural transplantation in Europe, and its members have extensive combined experience in both experimental and clinical neural transplantation. Since intracerebral neural transplantation is still in an exploratory phase, the range of procedures currently used is diverse and under development in many centers around the world. We are concerned that the single large trial now funded may be viewed by NIH, NINDS, and others as the critical test of the therapeutic value of neural transplantation despite the fact that only one particular procedure is tested. Although we await the results of this particular NIH-NINDS program with interest, the outcome is unlikely to determine the optimal procedure for clinical application of neural transplantation as a treatment for Parkinson's disease.

The scientific community is acutely aware of the manifold difficulties in determining and developing an effective neural transplantation therapy. We earnestly plead that, in addition to the above study, NIH will also be seeking to explore other grafting protocols at the same time.

Håkan Widner*
Department of Neurology, University Hospital, S-221 85 Lund, Sweden

*Signed by the following members of the NECTAR board and representatives of centers participating in the NECTAR collaboration: Alberto Albanese, Rome, Italy; Patrick Aebischer, Lausanne, Switzerland; Lucy E. Annett, Cambridge, United Kingdom; Anders Björklund, Lund, Sweden; Gerard J. Boer, Amsterdam, Netherlands; Patrik Brundin, Lund, Sweden; Pièrre Cesaro, Paris, France; Stephen B. Dunnett, Cambridge, United Kingdom; Philippe Hantraye, Paris, France; Olle Lindvall, Lund, Sweden; Juan Jose Lopez Lozano, Madrid, Spain; Wolfgang Oertel, Munich, Germany; Lars Olson, Stockholm, Sweden; Marc Peschanski, Paris, France; Niall H. Quinn, London, United Kingdom; Guy V. Sawle, London, United Kingdom; Michael J. Staal, Groningen, Netherlands; Harry W. M. Steinbush, Amsterdam, Netherlands; Håkan Widner, Lund, Sweden; Erik C. Wolters, Amsterdam, Netherlands; and Jens Zimmer, Odense, Denmark.

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Alloimmunization to Prevent AIDS?

In a recent letter, "Alloimmunization as an AIDS vaccine" (8 Oct., p. 161), Gene M. Shearer, Mario Clerici, and Angus Dalgleish discuss human lymphocyte antigens (HLAs) as "a new approach for AIDS [acquired immune deficiency syndrome] vaccines. . . ." This proposal was inspired by the protective role of xenogeneic major histocompatability complex (MHC) antigens in the simian immunodeficiency virus (SIV) vaccine model (*1*, *2*). In a recent review of AIDS vaccine development (*3*), Bart Haynes also included HLA in a list of experimental immunogens, but suggested that alloimmunization might preclude future organ transplantation. Shearer *et al.* address this criticism in their letter and present several other potential advantages of immunization with HLA with which we agree. We have also been assessing the possible role of HLA in AIDS vaccines and present here experimental evidence that immunization of humans with alloantigens, as opposed to xenoantigens, can induce a potentially protective immune response to human immunodeficiency virus (HIV).

We have taken advantage of unrelated studies (*4*) in which women were alloimmunized as a therapy for unexplained recurrent spontaneous abortions. Women with three or more unexplained miscarriages were immunized with peripheral blood lymphocytes from their husbands in a double-blind trial with autologous lymphocytes used as a placebo. While none of the control group developed antilymphocyte antibodies (ALAs), 85% of the alloimmunized women developed ALAs, and full-term pregnancy correlated with high amounts of ALA in their blood (*4*). There were no immediate or delayed side effects from the immunizations, no evidence of graft-versus-host reactions, and no production of autoreactive ALAs. In addition, sensitive Food and Drug Administration–approved HIV-1 antibody assays showed no evidence of reactivity with viral antigens, which might be expected on the basis of molecular mimicry by gp120 and earlier mouse experiments (*5*).

One out of 12 women who were successfully alloimmunized had an unusually high titer of ALA in her serum and also demonstrated the ability to neutralize the MN strain of HIV-1 in vitro (50% inhibition at a dilution of 1:300). The serum sample from this person was also particularly reactive with uninfected H9 cells, the cell line used to propagate the MN virus. The neutralization was unlikely to be explained by steric inhibition of viral attachment by the anticellular antibodies, because preincubation of antibody and target cells followed by washing resulted in no inhibition of a subsequent virus inoculum. In addition, the neutralization of free virus was complement dependent, which suggests direct virolysis. Finally, mixtures of an HIV^+ neutralizing serum sample and this alloantiserum showed largely additive neutralization, which suggests independent effects directed at both viral and nonviral target antigens present on the virion (*6*). A second patient, with an above-average amount of ALA in her blood, also showed a weak but significant neutralization titer (1:20).

These findings demonstrate that alloimmunization can be performed safely and can induce antibodies that neutralize HIV. However, the significance of these observations for vaccine development remains unclear because most of the alloimmunized women showed no neutralization of HIV-1. It is conceivable that there is significant ALA-mediated neutralization that is not detectable in this particular in vitro assay. Alternatively, cell-mediated responses to HLA might be the more important determinant of protection in vivo. In experiments with macaques, anticellular antibody titers were associated with protection but SIV neutralization was not (cell-mediated responses were not assessed) (*1*). It is also possible that critical neutralization-specific HLA epitopes, or the HLA-linked ability to recognize them (*7*), were present only in the two women with alloimmunizations that resulted in neutralization. Thus, additional studies are needed to determine the specific antigens involved and the relative contribution of humoral and cell-mediated responses.

Finally, Stott *et al.* observed only partial protection using cells alone (*8*), which suggests that immunization with both viral and cellular antigens may be necessary for efficient protection. The additive neutralization by ALA and antibodies against HIV that we observed also supports this concept. In addition, studies by Shearer and Clerici themselves have attributed "natural resistance" in high-risk seronegative individuals to HIV-specific cellular immune responses (assayed with the use of synthetic peptides that correspond to the HIV-1 envelope, excluding regions of known HLA homology) (*9*). Taken together, these observations may provide a stronger rationale for an AIDS vaccine that contains both cellular and viral antigens (for example, whole killed virus or fixed infected cells). The corresponding animal experiments, using allogeneic material for both vaccination and challenge, have not yet been reported and should provide additional insights into the utility of alloantigens in the formulation of a prophylactic AIDS vaccine. In the meantime, alloimmunized patients and high-risk seronegative individuals are the subjects of ongoing studies to determine which cellular antigens are targets for neutralizing antibody and to assess the antiviral effects of cellular responses to alloantigens.

Dobri D. Kiprov
California Pacific Medical Center, San Francisco, CA 94118, USA
Haynes W. Sheppard
Carl V. Hanson
California Department of Health Services, 2151 Berkeley Way, Berkeley, CA 94704, USA

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Astronomy: Of Fundamental Value

The assertions in the recent editorial "High-energy astrophysics" by David Lindley (7 Jan., p. 11) suggesting that astronomy is a "singularly useless endeavor" with no special claim to fundamentality, cannot