Letters

Potential Use of Nerve Growth Factor to Treat Alzheimer's Disease

In light of proposals to use growth factors to treat neurodegenerative diseases associated with aging, the National Institute on Aging organized a workshop on 30 August 1988 to discuss the potential use of nerve growth factor (NGF) in clinical trials involving patients suffering from Alzheimer's disease (AD). The workshop was held to examine the scientific rationale for and the methodological problems associated with clinical testing of NGF and to determine whether further basic investigations are necessary before controlled human trials are initiated. A more complete report of the workshop will appear elsewhere (*1*).

Alzheimer's disease is characterized by a progressive loss of cognitive function associated with degeneration of basal forebrain cholinergic neurons. Studies in animals indicate that NGF may normally act to support the viability and function of these neurons. Treatment with NGF can prevent injury-induced degeneration of these cells and may improve cognitive function in rats with memory impairments. Because of these and other findings (*1*), the participants in the workshop agree that there is a convincing rationale for the use of NGF in the treatment of AD. However, there is also strong agreement that important methodological and basic research concerns need to be addressed before human trials can begin. These include (i) identification of a reliable source of well-characterized human NGF with known activity in sufficient quantity for a comprehensive program of research; (ii) a method for delivery of active NGF over a period of at least several months; (iii) animal dose-response evaluations to establish the minimal dose of NGF that has an effect on cholinergic function; (iv) short- and long-term studies of human NGF to identify toxicity and, if possible, long-term effectiveness in at least two animal species; and (v) demonstration that human NGF has an effect on cholinergic neurons in a nonhuman primate.

When these concerns have been addressed, human trials should be planned in the following sequence: (i) open toxicity studies in a small number of AD patients with the use of a dose-escalating paradigm; (ii) a short-term (3- to 4-month) study of a separate cohort of AD patients to determine whether NGF can induce improvement in cognition (this study should be short enough so that any change in cognition is not obscured by natural progression of the disease); and (iii) a full-scale controlled trial with a sufficiently large AD patient sample to determine whether long-term treatment with NGF alters the rate of decline of memory and other cognitive functions.

While there is urgent need for an effective treatment for Alzheimer's disease, we have the moral and ethical responsibility to endorse only those treatments that have been subjected to rigorous and thorough examination with the use of the methods and procedures of controlled preclinical studies and clinical trials.

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REFERENCES

1. C. H. Phelps *et al.*, *Neurobiol. Aging*, in press.

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Petition on Dugway Facility

Some 4 years ago, the U.S. Army asked Congress for the funds to construct at Dugway Proving Grounds, Utah, a facility at the highest level of biological containment for the testing of aerosolized pathogens. This request, rescued from obscurity by Senator James Sasser (D–TN) (*1*), brought to public attention the tip of an iceberg of as yet unknown proportions. The following text of a petition, signed in August 1988 at Salt Lake City by more than 140 biological professionals with M.D. or Ph.D. degrees, outlines the various concerns engendered by the Army's request.

The undersigned physicians and biological scientists petition our representatives to review DOD's [the Department of Defense's] Biological Defense Program in general, and in particular their plan to build at Dugway Proving Grounds a Biological Aerosol Test Facility at the highest level of biological containment. Their request for such a high containment facility anticipates the testing of genetically engineered biowarfare agents. We biologists are committed to using the new genetic technology for diagnosing, curing and preventing disease, not causing it, as well as for such purposes as the improvement of agricultural crops, reversal of genetic disease, provision of rare biochemicals and the unravelling of biological mechanisms. We abhor the use of biological agents as offensive weapons by any nation, in accord with the many nations who signed the 1972 International Convention banning the use or stockpiling of biological weapons.

Although we recognize DOD's responsibility to provide defense against possible biological attack, we find their program to be flawed, hazardous and likely to break the constraints of the 1972 Convention. In the first place, any use of actual pathogens, particularly in aerosols, will present a hazard to workers, their families and the community at large; even endemic agents of such diseases as anthrax, tularemia and plague, normally poorly transmissible, will become highly dangerous when aerosolized. In the second place, an infinite variety of potentially lethal agents already exists or could be produced by genetic engineering; engineered organisms raise the specter of epidemics that can be neither diagnosed nor treated. In view of the variety of agents possible, it is essential that defense be general rather than specific, if it is to provide protection of wide scope that will not soon become obsolete. On both counts DOD's need to provide detection, protection and decontamination will best be served by testing with harmless simulant organisms. In any case it is unconscionable that DOD be allowed the capacity to develop new pathogens in order to test our defenses against them.

To allay all suspicion and to reduce worldwide the vulnerability to biological warfare, it will be most valuable to make the DOD program open: *reviewed and subject to approval* by a nonmilitary committee of physicians, scientists and citizens. By renouncing military research on genetically engineered organisms, while conducting defensive research in full view, DOD will contribute to reducing rather than escalating the risk of biological warfare.

As reported by Colin Norman (News & Comment, 30 Sept., p. 1749), the Army has now backed down a little from its request, settling for a laboratory at a containment level of BL3. That helps, but it leaves the iceberg for us to ponder. Particularly alarming is the involvement of the military in research using genetic engineering to study pathogens. It seems to us that relatively harmless simulants would suffice for the testing of protective shielding against invasive aerosols. Since the Army is unwilling to settle for the use of simulants, there remains the suggestion that they contemplate the aerosol testing of actual candidate pathogens as agents of biowarfare.

Some will argue that the Army does an invaluable world service by its vaccine development research, carried out at Fort Detrick, Maryland, in BL4 facilities. If the object of that research is *health*, it would seem appropriate for it to be conducted without secrecy under the auspices of the National Institute of Health. Such a proposal (HR 3241) has been submitted to Congress by Utah's Representative Wayne Ow-