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-

ens (D). It would relieve the concerns of scientists to be assured that genetic engineering will not be applied to the construction of highly dangerous biological warfare agents.

We look forward to further discussion of this issue at the session scheduled for Tuesday, 19 January, at the 1989 AAAS Annual Meeting.

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REFERENCES

1. R. J. Smith, *Science* **226**, 1176 (1984).

*Co-signers include the following members of the University of Utah faculty: Cedric I. Davern (deceased), David Goldenberg, Mario R. Capecchi, Theodore Gurney, Elizabeth Gurney, and Tulle Hazelrigg, Department of Biology; Sherwood R. Casjens and Glenn S. Herrick, Department of Cellular, Viral, and Molecular Biology, School of Medicine; Elvera Ehrenfeld, Department of Biochemistry, School of Medicine; David Low, Department of Pathology, School of Medicine, Kenneth N. Buchi, Department of Medicine, School of Medicine; John F. Ash, Department of Anatomy, School of Medicine.

Energy Options

David Bodansky (Letters, 21 Oct., p. 348) appears to miss the point of the earlier letter by my colleagues Bill Keepin and Gregory Kats (26 Aug., p. 1027). Energy options are not to be chosen like dishes from a Chinese restaurant menu—one from column A and one from column B—but rather by marginal costs and benefits. In this marginalist calculus, whenever nuclear power costs more than efficient end-use of electricity, buying nuclear power instead of efficiency increases carbon emissions and worsens global warming compared to what least-cost investment of the same dollars would have achieved.

Specifically, if displacing a coal-fired kilowatt-hour costs seven times as much with a new nuclear plant as with a new superefficient light, motor, window, and so forth (the actual ratio might arguably be between 2.5 and 25 and is very probably 7+ today), then every dollar spent on the nuclear plant results in releasing six times more carbon than if the same dollar had been spent on efficiency. Bodansky's recommended nuclear exploitation "to the fullest extent practical" is thus not "prudent" but dangerously counterproductive (*1*).

Efficiency holds the edge in speed as well as cost. During 1973–1986 (1979–1986) inclusive, Bodansky's reference 1 (*2*) shows that energy savings increased U.S. energy supplies by 7.1 (12.7) times as much as nuclear expansion (*3*). Merely continuing historic rates of savings would thus yield the same climatic benefits as an order-of-magnitude scale-up of nuclear programs (*4*)—yet is much cheaper, safer, easier, and surer. Again, why keep diverting scarce resources from a winning option to a losing one?

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REFERENCES AND NOTES

1. A paper by B. Keepin and G. Kats [*Energy Policy* **16**, 538 (1988)] further shows that even if nuclear plants can be built twice as fast as they now can in the United States, then even in a low-energy scenario (a 2025 global primary energy demand of only 1.1 times the 1988 level), the sixfold nuclear expansion required to displace all coal-fired electricity by 2025 would require 1600 gigawatts (GW) of nuclear plants. These would have to be built at a rate averaging one 1-GW plant per 7.5 days (3.1 times the 1970–1985 global rate), yet they would reduce global warming by only ~15%. This suggests the question, Wouldn't it work even better to invest the nuclear plants' $1.6-trillion cost (at $1 per watt, a third the actual U.S. cost today) in efficiency instead?
2. Energy Information Administration Report, *Monthly Energy Review* [DOE/EIA-0035 (88/05), Department of Energy, Washington, DC, May 1988].
3. This comparison generously counts nuclear output at its primary (steam) value; in terms of delivered energy, efficiency's speed advantage was about three times larger still. Most of the savings were in oil and gas, not electricity, but for artifactual reasons unrelated to the feasibility, availability, or economic advantages of electric end-use efficiency [A. B. Lovins, "Eleven reasons why we're saving electricity more slowly than direct fuels" (Rocky Mountain Institute, Old Snowmass, CO, 1988); *Negawatts for Arkansas* (Rocky Mountain Institute, Old Snowmass, CO, 1988).
4. C. K. Komanoff, "Greenhouse effect amelioration—efficiency vs. nuclear" (Memo, KEA, New York, 24 August 1988).

FDA Approval of HTLV-I Tests

I would like to set the record straight regarding the Food and Drug Administration (FDA) approval process for clinical studies aimed at estimating the prevalence of HTLV-I antibodies among random U.S. blood donors. Deborah Barnes' Research News article (21 Oct., p. 312) states that "none of the companies strictly adhered to FDA regulations for using their unlicensed assays in a large-scale study. This meant that the FDA had not approved the study before it was started."

The clinical study described was a large-scale, nationwide study conducted by the national headquarters of the American Red Cross. Gerald Sandler of the American Red Cross contacted our firm in late 1985 to discuss the possibility of our participation in the study. We discussed the study protocol, and I described to Sandler how we would first be required to file the appropriate applications at the U.S. FDA. Neither Sandler nor I were willing to bypass the FDA review process. Accordingly, our firm filed the required Application for an Investigational Exemption (IDE) on 26 December 1986, and we did not initiate the study until official notification was received from the FDA indicating that the study had been reviewed and approved.

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Response: The statement from my article that is partially quoted by Montagna—"Enzyme-linked immunoassays from Du Pont, Cellular Products, and, later, Abbott were used to test for antibodies against HTLV-I in the blood samples, but none of the companies strictly adhered to FDA regulations for using their unlicensed assays in a large-scale study"—is correct with respect to Cellular Products but incorrect with respect to Abbott. FDA officials have reaffirmed that Cellular Products was in technical violation of FDA regulations by distributing unlicensed investigational assay kits for diagnostic purposes prior to formal receipt of FDA approval. However, the FDA did not consider it serious. The inclusion of Abbott in the same sentence is incorrect because Abbott did not distribute its assay kits until after it had obtained FDA permission to do so.—DEBORAH BARNES

Retraction

I have decided to retract the paper "Virus-specific splicing inhibitor in extracts from cells infected with HIV-1" by D. Gutman and myself published in the 16 September 1988 issue of *Science* (volume 241, p. 1492). The data in that paper should no longer be considered reliable.

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Erratum: Jean L. Marx, in her article "The 1988 Nobel Prize for Physiology or Medicine" (Research News, 28 Oct., p. 516) referred on page 517 to "the late James Ahlqvist" as one of the pioneers in the development of β-blocker drugs. The investigator's correct name is Raymond Ahlquist. He was on the faculty of the Medical College of Georgia in Augusta.

Erratum: In the News & Comment article "Soviet-based global foundation takes shape" by Constance Holden (25 Nov., p. 1122), Frank von Hippel was incorrectly identified. He is at Princeton University and is the co-chairman of the International Security Committee with Roald Sagdeev.

Erratum: The fourth sentence of the abstract of the report "The *elav* gene product of *Drosophila*, required in neurons, has three RNP consensus motifs" by S. Robinow *et al.* (16 Dec., p. 1570), should have read, "DNA sequence data presented in this report suggest that the *elav* gene product is an RNA binding protein, based on the presence of RNP (ribonucleoprotein) consensus sequences."