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Information for Contributors appears on pages 112–114 of the 6 January 1995 issue. Editorial correspondence, including requests for permission to reprint and reprint orders, should be sent to 1333 H Street, NW, Washington, DC 20005.
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LETTERS

NIH Review of Gene Therapy Protocols

Eliot Marshall's informative News & Comment article about the National Institutes of Health's (NIH's) efforts to review its activities in the area of gene therapy (17 Mar., p. 1588) merits some minor clarification.

First, the review activities were designed to involve more than one external committee. The panel described in the article, chaired by Inder Verma, is charged with evaluating the process by which human gene therapy protocols are approved by the NIH Recombinant DNA Advisory Committee (RAC). A second group, now being formed, will have a much broader mandate to examine research activities, especially those funded by NIH, in the gene therapy arena.

Second, I am not, as stated in the article, the first NIH director to defer a decision about a human gene therapy protocol after it was approved by a majority of RAC members. For example, in 1988 the RAC approved the first gene-marking protocol, submitted by Stephen A. Rosenberg, R. Michael Blaese, and W. French Anderson, by a vote of 16 to 5. James Wyngaarden requested that the proposal be reconsidered by the Human Gene Therapy Subcommittee after provision of additional data.

Third, important information is missing in the discussion of the protocols proposed by David Curiel and by Jeffrey Schlom. At the time Schlom proposed to conduct a "cancer vaccine" trial involving the use of a vaccinia vector encoding carcinoembryonic antigen, vaccines were defined in the *NIH Guidelines for Research Involving Recombinant DNA Molecules* in a manner that did not mandate review of such a protocol by the RAC. Subsequent to that time and before the submission of the Curiel protocol, the RAC deliberately changed the definition of vaccines so as to require review of the so-called "cancer vaccine" protocols. The fact that the Schlom protocol was not reviewed and the Curiel protocol was reviewed has nothing to do with the merits of either, but simply reflects a policy change made by the RAC.

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Alzheimer Tangles and Abnormal Phosphorylation

The excellent and thought-provoking article "Protein studies try to puzzle out Alzheimer's tangles" by Wade Roush (Research News, 10 Feb., p. 793) describes recent experiments by John Trojanowski, Virginia Lee, and their colleagues at the University of Pennsylvania and by Gerald Fasman at Brandeis University. The research focuses on the events leading to the hyperphosphorylation of the microtubule-binding protein tau and the subsequent accumulation of this abnormal form of tau in the characteristic Alzheimer tangles. It is stated in the article that "Researchers turned first to kinases, enzymes that add phosphate groups to proteins. But no one could definitively catch a particularly active kinase in the act." I believe we did just that.

In 1991, H. M. Roder and I reported (*1*) that we had discovered a protein kinase that could convert tau in vitro into the hyperphosphorylated form found in Alzheimer tangles. This kinase, which we called $PK40^{erk2}$ because it is a member of the ERK family, was strongly inhibited in vitro by adenosine triphosphate (ATP) uncomplexed with Mg^{2+} in the millimolar range. We proposed that the expected decrease of ATP concentrations in the brains of patients with Alzheimer's disease might upregulate the kinase, leading to hyperphosphorylated tau and therefore tangles. We have recently demonstrated (*2*) the hyperphosphorylation of tau (and of neurofilament proteins) in vivo, that is, in differentiated PC12 cells that were depleted in ATP by uncoupling oxidative phosphorylation or by inhibiting ATP synthesis. At the same time, and unexpectedly, protein phosphatase PP1 was found to be upregulated by an unknown mechanism, producing dephosphorylation of tau in one specific site, while the upregulated kinase hyperphosphorylated tau at some other site or sites. One supposes that the ability of tau to interact appropriately with microtubules depends on a precise distribution of phosphorylated and dephosphorylated sites.

The mechanisms are probably more complicated than those set out in the article. Active protein phosphatases might be one factor, but upregulated protein kinases are another. We need to look for explanations that would include both Trojanowski and Lee's and also Fasman's observations, as