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LETTERS

Open eyes

An investigator in New Zealand describes events that led up to a clinical trial for testing the safety of gene therapy for patients with Canavan disease. Two authors discuss research about the *eyeless* gene in *Drosophila* fruit flies (ectopic eye on antenna, right) and its significance to evolutionary theory. Concern is raised over the availability of nonhuman primates for use in AIDS research in the United States. The value and difficulty of maintaining a shipshape oceanographic fleet is noted. And the future of linear accelerator–based free electron lasers is pondered.

GEHRING *ET AL.*

Gene Therapy in New Zealand

I would like to respond to the News & Comment article "New Zealand's leap into gene therapy" by Eliot Marshall (15 Mar., p. 1489).

I was not a visiting professor at Yale University, as Marshall states, but a full-time associate professor of surgery and medicine and director of a gene therapy laboratory for 8 years. I accepted a position to return to New Zealand in April 1995, at about the same time I agreed to take on the Canavan project.

Canavan disease did not figure in the movie *Lorenzo's Oil*, which was a story about adrenoleukodystrophy. Although both are genetic diseases that affect the brain's white matter, they differ in terms of their inheritance (autosomal versus X-linked), the gene involved (aspartoacylase in Canavan disease), and in the rate of progression, with Canavan disease untreatable and fatal within the first decade of life.

In my press release, I stated, "The best we can hope for is that the procedure is safe; anything over and above that will be a bonus." I specifically avoided stating that this study would save the children's lives or alter the disease process.

It is not correct that I did not notify regulatory agencies either in New Zealand or the United States. The first individual I suggested that Roger Karlin (the father of one of the children with Canavan disease) speak to in March 1995 was Nelson Wivel, director of the U.S. Recombinant DNA Advisory Committee (RAC), to discuss regulatory issues. Yale was well aware of my research from an early stage, as the families together with the Yale Development Office had a major public campaign to generate research support; I submitted the protocol to the Yale Human Investigation Committee (HIC) in November 1995, as soon as we had amassed sufficient preclinical gene expression and safety data. Moreover, at the time of my accepting the position in New Zealand, I had asked New Zealand authorities to establish a gene therapy advisory committee in time to review a protocol that I had hoped to submit by December 1995.

The Yale HIC chairman, Robert Levine, was made aware of the Canavan project in June, not October, 1995; the project had only gotten under way in April 1995. I had always intended to submit the project to the Yale HIC and moreover had openly discussed the project with several members of the RAC, including the director. In my discussions with Wivel, he endorsed my decision to bypass the RAC, as long as an analogous committee would review the proposal in New Zealand.

It is true that I did try to expedite the review process. I believed that, although the study was ultimately presented as a Phase I safety study, any possible therapeutic effect would only be possible if the procedure was not delayed. The children were becoming increasingly and rapidly moribund, and delay would also mask the primary outcome measures of toxicity and evidence of gene transfer.

I am happy to state that both children appear well, and we plan to assess indirect measures of gene transfer within the next few weeks.

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Eye Evolution

The beautiful work on the *eyeless* gene by Walter Gehring and his colleagues (Reports, 5 Aug. 1994, p. 785; 24 Mar. 1995, p.

1788) (*1*, *2*) certainly merited publication in *Science*, but we would not have chosen it to epitomize the standards for aspiring contributors (Editorial, 12 Jan., p. 127). Among the criteria given in the editorial are "results [that] . . . justify conclusions" and "interpretive excellence." The interpretation of the *eyeless* gene goes well beyond known facts in at least two respects; and the resulting confusion has been amplified in many secondary reports (*3*) (M. Barinaga, Research News, 24 Mar. 1995, p. 1766), including *Science*'s "runner up" nomination for "Molecule of the Year" (22 Dec., p. 1903).

The evolutionary interpretation advanced in the original articles and elaborated in many commentaries does not consider convergence (analogy) as an alternative to conservation (homology) in attempting to account for the strikingly similar roles, in eye development, of *eyeless* in *Drosophila* and its homologs in vertebrates. To rule out convergence requires much more than pairwise comparisons of sequences and functions. When regulatory genes and their products evolve new functions, homologous molecules may appear in nonhomologous structures (*4*). Thus the fact that two structures are similar in many respects (including reliance on homologous genes) does not necessarily indicate that the structures themselves are homologous. Convergences of this kind, in which homologous gene products are recruited to analogous functions, may be more common than most biologists would imagine. Consider the function of *hedgehog* homologs in wing development of flies and birds (*5*). The parallels are as striking as those involving *eyeless* homologs, but no one suggests that bird and insect wings are homologous structures. Even if the proposed *eyeless* homologies should stand up to more rigorous analysis, the ancestral structure would undoubtedly turn out to have been a simple photoreceptor, not an image-forming eye. Homology at such a level has long been implied (although not proved) by the homologies of photoreceptor molecules. Because the proposed *eyeless* homologies add little to this picture, it is hard to see how they challenge "traditional" models of eye evolution (*6*).

The assertion that *eyeless* represents a new class of "master control gene" seems overstated. Like other homeotic genes, its function depends on context, consistent with combinatorial models that have been current for at least two decades (*7*). *Eyeless* is normally expressed (and required) in cells that do not contribute to the eye, and global expression under control of a heat-shock promoter does not convert the entire embryo into eye structures. We agree that "*ey[eless]* function is [probably] universal among metazoa" (*2*), but we take this to imply that it originally served some basic developmental process other than eye induction.

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Response: It was to be expected that our two papers (*1*, *2*) about the homology of *eyeless*, *Small eye*, and *Aniridia* and the induction of ectopic eyes would stir up a debate about

evolution, as they go against the dogma of eye evolution that can be found in most textbooks.

We not only presented sequence comparisons, but also found the conservation of splice sites that argue strongly in favor of the hypothesis that *eyeless* in *Drosophila*, *Small eyes* in the mouse, and *Aniridia* in humans are true homologs. We can now extend this list to the *Pax*-6 genes of squid, ascidians, nemertines, nematodes, and plathelmints. However, the much stronger argument for true functional homology comes from the fact that we can induce ectopic eyes with the mouse gene in *Drosophila*. Meanwhile, we have shown the same for the squid and ascidian genes. Evidence of this kind is not easy to obtain and is entirely new. Already, on the basis of our first paper, Stephen J. Gould has proposed (*3*) that our finding challenges the traditional model of eye evolution, which assumed that primitive eyes evolved separately in more than 40 different phyla (*4*) and that the prototypic eye might have evolved only once in evolution. We were holding back on this interpretation until we had carried out the crucial experiment, which was to induce ectopic eyes with both the *Drosophila* and the mouse gene. On the basis of these experiments, we are proposing now that the prototypic eye arose only once in evolution and that subsequent convergent evolution gave rise to the image-forming eyes of vertebrates and cephalopods, whereas the compound eyes of insects resulted from divergent evolution. The main difference from the "traditional" view is the assumption of a single, rather than more than 40, prototypic eyes. Our hypothesis is much more compatible with Darwin's theory, because the prototypic eye evolved before the time when selection was effective as a driving force, as stated by Darwin himself.

We have not implied that *eyeless* only functions in eye morphogenesis. To the contrary, we stated clearly (*2*, p. 1791)

> In addition to eye morphogenesis, *ey* controls other functions in the developing nervous system, because null mutations are lethal, and the loss of eye structures alone is not the cause of lethality.

The reason for proposing a new type of master control gene comes from the observation that the loss-of-function mutation leads to a loss of eye structures rather than a switch in cell determination, as in the previously described homeotic mutations.

We do not think that we have overstated the conclusions drawn from our experimental data. Of course, it is difficult to prove an evolutionary hypothesis, but we continue to accumulate evidence in favor of our admittedly revolutionary idea.

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NIH Regional Primate Centers

Of particular interest in Jon Cohen's News & Comment articles about changes in AIDS research control at the National Institutes of Health (NIH) (2 Feb., p. 590; 15 Mar., p. 1491) were statements relating to AIDS research at the seven NIH Regional Primate Research Centers (RPRCs).

As the former director of the RPRC program I addressed two subgroups of Office of AIDS Research Director William Paul's advisory committee on the subject of usage of the RPRCs by AIDS researchers. At that