totic agent (Ishitani *et al.*, manuscript submitted). A recent report[4] has provided compelling evidence for apoptotic cell death in the postmortem brain of HD and the brain of a quinolinic acid-induced animal model of HD. Moreover, it has been shown that β-amyloid precursor protein binds GAPDH to its carboxyl terminal. In the latter context, we have found that GAPDH cross-interacts with a monoclonal antibody raised against amyloid plaques from Alzheimer's brain, and that tetrahydroaminoacridine, an anti-dementia drug, effectively suppresses the over-production of GAPDH mRNA and protein[5]. Thus, our results raise the interesting possibility that GAPDH over-expression plays a role in triggering the neuronal apoptosis found in neurodegenerative diseases. It is also possible that binding of GAPDH to disease-causing gene products is secondary to over-production of GAPDH.

GAPDH has many functions and is found not only in the cytosol but also in cellular organelles and structural elements. In humans, approximately 100 copies of the GAPDH gene have been found, and in rabbit brain, as many as 16 isoforms have been detected. Future investigation will determine which isoform(s) and which activities are involved in the neuronal apoptotic process. Our results suggest that a non-glycolytic activity may play a more prominent role in the apoptotic pathway. Moreover, the ability of GAPDH antisense oligonucleotides to rescue neurons from undergoing apoptotic cell death[3] also suggests that such oligonucleotides may be useful for treating of neurodegenerative diseases.

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Roses et al. *reply* — Many hypotheses could relate the length-dependent binding of polyglutamines to GAPDH and the mechanism of disease expression[1]. In fact, there may be multiple interacting mechanisms that are not necessarily mutually exclusive. Apoptosis has been implicated as the final pathway to cell death for various neurodegenerative diseases. However, mechanisms that trigger apoptosis in susceptible individuals may, of course, be more relevant to the selection of those individuals who develop disease.

Chuang and Ishitani are quite correct in pointing out that direct experiments are required to determine whether or not the binding of polyglutamine repeats to GAPDH actively impairs cellular energy metabolism. GAPDH (and phosphofructokinase) is believed to catalyze highly controlled steps in glycolysis in the nervous system. Therefore, modulation of the control of GAPDH might alter energy metabolism in interesting ways. Calculations based on "bag of enzymes" assumptions are difficult to interpret, particularly for GAPDH which is distributed in multiple cellular compartments. Of course, our suggestion is that the mutated protein binds GAPDH abnormally implies more complex interactions than solution stoichiometric estimates would predict[6].

Our paper focused on the paradigm of the abnormal shared protein structure of expanded polyglutamine neurodegeneration. The assertion that apoptotic cell death is a major factor in the clinical course in HD, DRPLA, SCA1 and AD is simply an alternative hypothesis that should be subject to further investigation. How this process may relate to the huntingtin and ataxin mutations and to polyglutamine repeats is unclear. We are in the early days of mutation-specific mechanism development and these mechanisms will provide targets for therapeutic intervention. Only successful prevention or treatment based on these targets will eventually validate the right hypotheses.

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Spectacles and young eyes

To the editor — In the August 1995 issue of *Nature Medicine*, an original article[1] and an accompanying News & Views[2] conclude that, like chicks,[3] the eyes of juvenile monkeys grow into focus; that is, they appropriately alter their growth to compensate for defocus imposed by spectacle lens wear. Unfortunately, alternative conclusions are possible and render premature any extension of these results to the clinical care of children.

The authors base their conclusions on refractive data obtained with tropicamide as the cycloplegic agent. In human infants, tropicamide is considered inadequate to paralyze accommodation.[3] Infant monkeys possess an accommodative capacity of some 30–40 diopters, perhaps twice that of human infants.[4] Because accurate refractions in eyes with substantial accommodative capacity require adequate cycloplegia, most workers studying the refractive status of monkeys use cycloplegic agents more potent than tropicamide. Confirming the inadequacy of tropicamide, we find in six-month old rhesus monkeys that stronger cyclopegic agents such as 1% cyclopentolate or 1% atropine can disclose up to 1–2 diopters more hyperopia than tropicamide alone (unpublished). As the monkeys in the study by Hung *et al.*[1] initially were hyperopic, the accuracy of the reported refraction data is thus uncertain.

Even if the reported refractive data are assumed accurate, the authors' interpretation of the data is still questionable. Only one of the two eyes wore a lens with optical power; and because the spectacle lenses were not matched to the baseline refractions, no two monkeys developed under identical optical conditions. Monkeys fixate with the eye requiring the least accommodation under all viewing conditions[1], and each non-fixing eye experienced chronic hyperopic defocus, as