complexity to an overregulated industry, it will have been written before anyone fully understands the impact it will have in the next decade, and it will add to the cost of a product that should be available to all.

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Nowak's article about genetic testing for human diseases raises several questions regarding the optimal approach for diagnosis, liability, regulation, and fees, especially for the rare genetic diseases. In my laboratory we have addressed the efficacy of DNA-based tests by using polymerase chain reaction and restriction fragment length polymorphism procedures for identifying specific mutations in disease-related genes, as opposed to functional tests for the gene products. This was alluded to in Richard Fishel's remarks about developing tests for the mismatch repair genes *MSH2* and *MLH1*. We have been involved in developing functional tests for the rare repair-deficient diseases xeroderma pigmentosum (XP) and Cockayne syndrome (CS) (*1*).

When there is clear phenotypic expression, functional tests are simpler than DNA tests, especially for multigenic and multiallelic diseases such as XP and CS. But functional tests for rare diseases have the disadvantage that they are often specialized, tailored to the specific disease, and difficult to transfer to a clinical testing laboratory. They require specialized knowledge, and clinicians are unlikely to raise enough money to justify their use. Such tests, therefore, may best be administered in a research laboratory specializing in the particular disease. But this raises other problems, among which insurance and liability are major concerns.

Although we have been able to produce consistent patient and prenatal diagnoses, the financial and administrative burden has become excessive. In addition, and more important, the introduction of the Clinical Laboratory Impovements Act (CLIA88) and other regulations have made it difficult if not impossible for a research laboratory to carry out the diagnostic tests it is equipped to do because the licensing procedures are burdensome and unrelated to the reliable execution of the diagnostic tests.

The development of both DNA-based and functional tests, therefore, needs to be fostered in a regulatory climate that permits research-based laboratories to develop tests for rare disorders on a patient-specific basis, and even to continue when functional specialized tests cannot be economically carried out by a clinical testing laboratory. Because of the current regulatory environment, we are already in the position of declining to carry out tests that we know to be predictive, something that is disappointing to ourselves and to patients.

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References

1. J. E. Cleaver, J. P. G. Volpe, W. C. Charles, G. H. Thomas, *Prenatal Diagn.*, in press.

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Mechanism of Scrapie Replication

The Perspective "Structural clues to prion replication" by Fred E. Cohen *et al.* (22 April, p. 530) indicates that the elucidation of the mechanism of scrapie replication is within reach. It is therefore important to acknowledge those individuals who have contributed significantly to the development of the mechanistic scheme presented therein by Stanley Prusiner and his co-workers. All of the mechanisms for the replication of a protein-only scrapie agent that have been debated over the years were first proposed by J. S. Griffith in 1967 (*1*). Since that time, Carleton Gadjusek (*2*) and others have discussed the possibility of a crystallization mechanism, and models that involve the modification of host protein by the infectious agent have also been suggested (*3*).

Two detailed and mutually exclusive chemical mechanisms have been proposed, the heterodimer model of Stanley Prusiner and co-workers (*4*) and our seeded polymerization model (*5*). The Perspective presents a general scheme which embraces our specific proposal. Despite their recent statements to the contrary (*6*), Prusiner and co-workers now seem to concede the possibility that prion formation involves a polymerization. They also seem to agree with our proposal (*5*) that unfolding of the cellular prion protein is required for its conversion into the infectious form and that pathogenic mutations may act by influencing the unfolding equilibrium. On the basis of our work on peptide models of the prion protein, we proposed that prion replication occurs via a nucleation-dependent polymerization process which resembles a crystallization and that the scrapie infectious agent is a seed for the polymerization process (*5*). According to this scenario, formation of the nucleus is the rate-determining step in in vivo aggregation, while the conformational change that Prusiner and others have studied is a consequence of the aggregation process (*5*). I look forward to the experimental elucidation of this fascinating process.

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References

1. J. S. Griffith, *Nature* **215**, 1043 (1967).
2. P. Brown, L. G. Goldfarb, D. C. Gajdusek, *Lancet* **337**, 1019 (1991).
3. D. C. Bolton, P. E. Bendheim, *Ciba Found. Symp.* **135**, 164 (1988); B. Oesch, D. F. Groth, S. B. Prusiner, C. Weissmann, *ibid.*, p. 209; J. Hope *et al.*, *EMBO J.* **5**, 2591 (1986).
4. S. B. Prusiner, *Science* **252**, 1515 (1991).
5. J. H. Come, P. E. Fraser, P. T. Lansbury Jr., *Proc. Natl. Acad. Sci. U.S.A.* **90**, 5959 (1993); J. T. Jarrett and P. T. Lansbury Jr., *Cell* **73**, 1055 (1993).
6. K.-M. Pan *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **90**, 10,962 (1993).

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Biodiversity Questions

The role of biodiversity in controlling pest outbreaks (Y. Baskin, News & Comment, 8 Apr., p. 202) receives little attention. In Southern Africa, altered biodiversity as a result of interannual climate variability helps explain a "rodent plague" that is reducing grain supplies.

Rodents annually reduce Southern African cereal harvests and stores by an average of 1.3 million tons (out of 10 million tons). Major infestations in Zimbabwe (1974–76, 1983–85, 1993–94) have often followed El Niño–Southern Oscillation warm events, data complementing the findings of Cane *et al.* (*1*). This year's infestation in Zimbabwe and western Mozambique—involving the multimammate rat [*Praomys* (*Mastomys*) *natalensis*], the house mouse (*Mus musculus*), and the giant rat (*Cricetomys gambianus*)—has been particularly severe, and seeds, maize cobs (in milky and mature stages), and some stored grain are being consumed. Once again food security in the region is threatened.

We believe the severe drought of 1991–92 reduced predators of field rodents (for example, snakes and raptors) and draft animals, which thwarted tillage and preserved burrows. With plentiful rains and grains in 1992–93, and short rains and scant predation this year, well-nourished rodents have flourished. Rodents transport many pathogens including hantaviruses (News & Comment, 5 Nov. 1993, p. 832) (*2*) and five emerging arenaviruses in Latin America that cause hemorrhagic fevers (*3*), Lyme disease, and plague.

We submit that (i) top predators (competitors and insurance species) provide resistance against the selection and emergence of opportunistic pests and pathogens; (ii) climate can impact biodiversity directly or indirectly through cumulative cascades that involve species' synchronies and time lags; and (iii) rodent (and insect herbivore) abundance and distribution are sensitive biological indicators, integrating global signals with local conditions. Meteorological forecasting and eco-