is quite closely related to that operating in Alzheimer disease. Indeed, their study provides the first molecular evidence that links these two common neurodegenerative disorders—a fascinating advance, given the large literature that has grappled with the possible relationship between these diseases[12]. While mutation of the α-synuclein gene is likely to be responsible for only a small fraction of PD cases, the presence of this protein within amyloid plaques in AD raises major questions. Is α-synuclein present in Lewy bodies isolated from familial or sporadic PD patients? Is the association of α-synuclein with APP in amyloid plaques from AD brains central to the pathogenic mechanism of AD? While the answers to these questions await further experimentation, the properties of α-synuclein and its deposition into insoluble protein aggregates suggest at least one mechanism of pathogenesis in PD and AD that has not received a great deal of attention: sequestration of α-synuclein within the cell could represent a dominant negative loss of α-synuclein function. Given the circumstantial evidence that suggests involvement in synaptic function, and the impaired cognitive function that is characteristic of AD and PD, it may be that a defect in synaptic function results in the absence or dysfunction of α-synuclein at the presynaptic terminal.

A previous attempt to organize facts concerning general properties of neurons and the characteristics of neurodegeneration into a framework for further discussion led to an analogy with oncogenesis and cell cycle control[13]. Incorporated into this idea are three key elements: the involvement of neurodegenerative disease genes in the activation of inappropriate signal transduction events; the integration of these aberrant metabolic signals by intracellular mechanisms akin to cell cycle checkpoints; and the activation of programmed cell death in response to these signals as the sole effector pathway downstream from these metabolic integrators. While the ectopic activation of programmed death in neurodegenerative disease and the existence of cell death 'checkpoints' as natural regulatory mechanisms for the initiation of apoptotic death are now established, involvement of the identified neurodegenerative disease genes in abnormal signal transduction events is not immediately apparent. It is clear, however, that aberrant synaptic function can directly lead to neurodegeneration, that impaired communication between synaptic terminals and the cell body may be directly relevant to neuronal loss in a variety of situations and that alterations in nuclear protein function can be directly relevant to neurodegeneration (Fig. 1). Although the pathogenesis in all neurodegenerative disorders caused by CAG repeat expansions is most likely mediated through the polyglutamine tract (longer repeats lead to a more severe phenotype), a clear-cut mechanism has not been delineated. However, as indicated in Fig. 1, recent data point to the nucleus as the primary site of pathogenesis.

Thus, Huntington-disease transgenic mice display neuronal nuclear inclusions containing huntingtin and ubiquitin prior to any detectable neurological symptoms[14]. In spinocerebellar ataxia type 1 and type 3, the mutant gene products, ataxin-1 and ataxin-3, lead to the formation of novel subnuclear structures (H. Orr & H.Z, unpublished data; H. Paulsen, pers. comm.). Given robust signal transduction between the synapse and the cell nucleus that is at the heart of neuronal function, it will be fascinating to decipher the pathways through which each of the major classes of neurodegenerative genes lead to neuronal death. The discovery of α-synuclein as the central molecule in familial PD, and its possible involvement in sporadic PD and AD, provides a powerful new tool to advance our understanding of the pathogenic pathways in these most common and devastating neurodegenerative disorders. □

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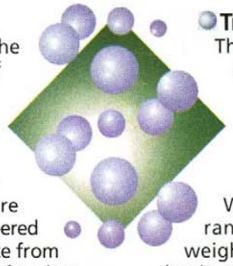
TOUCHING**base**

Sailing into freedom

The divorce of the year—between J. Craig Venter of The Institute of Genome Research and William Haseltine of Human Genome Sciences—was announced on June 24th. Despite the large sums of money involved (TIGR is losing $38 million over next five years) both parties agree that after almost five years of collaboration, they are better off going their separate ways. The freedom to publish is "worth every penny" to Venter (here depicted at the helm of his yacht *Sorcerer* which he just steered to win the Atlantic Challenge Cup, a 3000 mile sailing race from New York to Cornwall, England). TIGR celebrated its new freedom by making 40 million base pairs of DNA sequence from 11 microbial genomes available on their web site. HGS, on the other hand, states that its resources are better spent on the development of new products for the prevention and treatment of disease. At the same time, HGS is busily sequencing its own favourite bug genomes; completion of the sequence of *Streptococcus pneumoniae*, the most common cause of bacterial pneumonia, was announced just two weeks after the divorce from TIGR.



Trials and tribulations

The eagerly awaited results from Amgen's phase I leptin trial have been released in abbreviated form. 165 people of various sizes were divided into three groups and given either a placebo, or a single, daily dose of leptin (two groups received two different concentrations) over the course of three months. All participants also received counsel on diet and exercise. While the trial was designed to monitor efficacy and dose range, there were statistically significant differences in weight loss between the groups that did and didn't receive leptin, according to David Kay, the company's press officer. Exciting news, given the surprising nature of the results—data suggests that brain leptin levels appear to be more important than serum levels in regulating obesity in rodents, obese people have high serum levels of leptin, and many looked long and hard before an obese person with leptin deficiency was found. As Jules Hirsch of Rockefeller University put it, if he "were an *ob/ob* mouse, he'd be keen to get some leptin, and given improved understanding of molecular events, an effective agent may be around the corner, but it's hard to believe that leptin is the one". To what extent leptin promises to be efficacious for the majority of obese people should become evident soon. In the meantime, it's reassuring to note that the old-fashioned way of losing weight still works; the controls lost an average of 1.5 kilograms, in contrast with the 2–4 kgs lost by their counterparts.