DARPP-32 is found only in neurons with the D_1 type of receptor. It does not appear to occur in nerve cells with D_2 receptors. The cells that contain DARPP-32 include the medium-sized spiny neurons in the caudatoputamen region of the brain, which deteriorate in patients with Huntington's disease. These same neurons are targets of the dopamine-releasing cells that degenerate in Parkinson's disease.

As a consequence of dopamine binding to D_1 receptors, the cyclic AMP concentration increases, resulting in activation of the cyclic AMP–dependent kinase, which is the enzyme that phosphorylates DARPP-32. Greengard suggests that the protein mediates certain responses to dopamine acting through the D_1 receptor. Whereas synapsin I appears to participate in releasing neurotransmitter signals from all neurons, DARPP-32 may be involved in receiving them in a limited group of neurons.

Similarities between DARPP-32 and a protein that inhibits the activity of protein phosphatase-1, one of the enzymes that removes phosphate groups from proteins, gave a clue to how DARPP-32 might work. The cyclic AMP–dependent kinase phosphorylates several proteins in addition to DARPP-32 in response to dopamine. DARPP-32 in its phosphorylated state, but not when unphosphorylated, proved to be a very efficient inhibitor of protein phosphatase-1 when this was tested directly. Phosphorylated DARPP-32 may thus potentiate dopamine's effects by preventing phosphate removal from other dopamine-regulated phosphoproteins.

DARPP-32 may also provide a means of integrating dopamine's effects with those of other neutrotransmitters. For example, the medium-sized spiny neurons of the caudatoputamen are innervated both by dopamine-releasing and glutamate-releasing neurons. Glutamate, acting through calcium ions as a second messenger, probably stimulates a calcium-dependent kinase. Phosphorylated DARPP-32 may inhibit the removal of phosphate from these kinase substrates, too. If that is the case, then DARPP-32 may account for the ability of dopamine to potentiate the effects of glutamate.

These possible interactions are still speculative, Greengard notes, and require further confirmation. Nevertheless, he maintains, "Even if some details of these interactions are wrong, I still think that phosphatase inhibition will prove to be an important component of the molecular mechanisms underlying interactions between neurotransmitters."

—JEAN L. MARX

Catastrophism Not Yet Dead

The recently announced demise of the notion that major extinction events punctuate the history of life at some 26-million-year intervals is, as Mark Twain put it, greatly exaggerated.

In his paper in *Nature* (*1*), Antoni Hoffman of the Lamont-Doherty Geological Laboratory, New York, outlined some of the frustrating uncertainties inherent in dealing with the fossil record in any large-scale quantitative analysis. He went on to conclude that the 26-million-year cycle of extinction reported in February 1984 by David Raup and John Sepkoski of the University of Chicago is the inevitable outcome of the nature of the data and the analytical manipulation employed upon them. An editorial in the same issue (*2*) emphasizes Hoffman's message and declares that "Last year's fashion for explaining a supposed 26-million-year periodicity in mass extinctions of species has been made to seem a little spurious."

Hoffman's criticisms rest on three main points: that the database used by Raup and Sepkoski is culled, which distorts comparison of the record through the 250 million years ago to the present; that uncertainties in the geological time scale, and of the stages within it, introduce large potential errors; and that the artificial nature of the measuring unit used—the paleontological stage— makes periodicity inevitably fall out of any statistical analysis.

Raup and Sepkoski's original analysis was based on a subset of 567 families of marine organisms that was extracted from a total of some 3500 available in a recent compilation. The data set was culled so as to remove all families of uncertain taxonomic or stratigraphic provenance. In addition, all extant families were removed so as to avoid the damping effect of "the pull of the recent." Hoffman notes that one effect of this culling is to allow the disappearance of five families in recent times to be classified as a possible mass extinction compared with many times that number earlier in the record. One counter to this criticism is that there has in fact been a substantial reduction in overall extinction rates in the marine record through time. A more direct response comes from the demonstration that even when the data set is maintained intact the 26-million-year signal still emerges, though less sharply.

Uncertainties in the timing of the geological time scale and its components are of course a constant frustration to those who use it. Raup and Sepkoski argue, however, that it is more reasonable to note that the 26-million-year signal comes through in spite of these uncertainties, not because of them, and to be impressed by that fact.

Hoffman's third point—on the question of paleontological stages—is clearly attractive. Each stage is defined by the special features of the fossil assemblage within it, and, by definition, each must differ from the next. Stages range from just a couple of million years in duration to more than 15 million, though many are in the region of 6 to 7 million. Given the restriction that adjacent stages must differ, Hoffman argues, there is a 1 in 4 probability that any single stage will stand out as a major extinction, given a random distribution; and with stages averaging 6.2 million years long, a 26-million-year signal (4×6.2) is statisically inevitable. In fact, although some kind of nonrandom pattern would emerge from a random distribution of extinctions between stages, a clear 26-million-year cycle is unlikely. But, again, the most telling counter to this challenge is that Raup and Sepkoski's analysis included a comparison of the real data against a random distribution of the data between stages: a random distribution was the null hypothesis, which was statistically rejected.

The *Nature* editorial, in supporting Hoffman's challenge to periodicity notes that " . . . human nature being what it is, it seems unlikely that the enthusiasts for catastrophism will now abandon their quest." The new catastrophism may well have to be abandoned, but not yet.—ROGER LEWIN

References

1. A. Hoffman, *Nature* (*London*) **315**, 659 (1985).
2. J. Maddox, *ibid.*, p. 627.