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A New Model of Cell Death in Neurodegenerative Disease

Researchers at the University of Toronto have discovered a common principle underlying the death of brain cells in a number of neurodegenerative disorders, including retinal degeneration, Parkinson's and Huntington's diseases. The scientists have shown that rather than gradually growing sicker and dying, neurons succumb to a single, rare catastrophic event that causes the cells to die randomly during the course of the disease.

The finding challenges commonly held assumptions about how and when nerve cells die as a result of neurodegenerative disorders. Many researchers had favored the "cumulative-damage hypothesis," which states that the death of specific types of neurons is caused by a buildup of damage sustained over time.

In an article in the July 13, 2000, issue of the journal *Nature*, HHMI international research scholar Roderick R. McInnes at the Hospital for Sick Children, working with colleagues at the University of Toronto and the University of British Columbia, reports evidence for a "one-hit" model of cell death in 15 different examples of neurodegenerative disease.

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According to the model, the mutant brain cells work well for years or decades even though they are at a constant risk of death. The researchers believe that the one-hit hypothesis can explain neuronal death in a wide variety of settings, including photoreceptor degeneration, excitotoxic cell death of hippocampal neurons, a mouse model of cerebellar degeneration, Parkinson's and Huntington's diseases.

The path to the discovery began when McInnes and his colleagues knocked out a mouse gene, *ROM-1*, that is essential for photoreceptor cells in the retina. As expected, the mouse photoreceptors died. (In humans, a similar

mutation causes retinitis pigmentosa, a form of retinal degeneration). The rate of cell death in the mouse photoreceptor population did not seem quite right, if cumulative damage was occurring. In most neurodegenerative diseases, scientists expect to see larger numbers of cells die as the disease progresses. This massive die-off of cells later in disease is one of the hallmark predictions of the cumulative damage hypothesis.

But the mouse cells in McInnes's lab defied the cumulative damage pattern. Instead, the proportion of photoreceptors that died remained constant at all times, indicating that their risk of death is constant. "It took us months and months to think about what a constant risk of cell death might mean," McInnes says.

Scanning the scientific literature, the team found similar cell death rates in data from 15 different neurodegenerative diseases -- hinting that a common biochemical principle drives these vastly different disorders. The scientists suggest that in each case, a disease-causing mutation or toxic insult upsets the biochemical balance in the affected brain cells. As long as the biochemical balance stays close to its normal range, the cell carries on perfectly well. But when the balance is randomly tipped in one direction, the mutant cell activates a genetic program that causes cell death.

"The new model shows that every once in a while, you can take a hard look at existing data and make a profound discovery," said Harvard University geneticist Thaddeus Dryja. "This finding has been staring science in the face for decades. The exponential declines in cell death in neurodegenerative disease are not a secret -- it's just that nobody has really stopped to think through what they mean for biology."

If the one-hit model is correct, McInnes says, it may mean that neurons affected by Parkinson's disease, for example, are not necessarily doomed. The right drug could reverse the critical chemical imbalance caused by a mutation, returning the cells to a normal state. "That's a lot less catastrophic than assuming a disease slowly causes the whole cell to fall apart," he says. The challenge, he adds, will be in identifying the precise chemical reactions -- and underlying mutations—that cause each neurodegenerative disease. "That's no easy task," McInnes admits. "But maybe we're one step closer now."