The overall effect of these kinds of environmental changes are generally favorable, and include an increase in productivity and the acceleration of nutrient recycling. "The disturbing effects of megaherbivores on vegetation can promote higher rates of production of more nutritious forage than occurs in their absence," says Owen-Smith, "and these habitat changes may benefit other mammalian herbivores with similar but more selective feeding habits."

The elimination of megaherbivores—by whatever agency—presumably would be followed by a reversal of these environmental impacts: specifically, open forest glades close up; shrubland becomes forested; grassland mosaics become uniform tall grassland; and so on. Transformations of this sort, which, says Owen-Smith, "seem to be just the kinds of changes in vegetation documented by the fossil pollen record," would severely restrict the habitat of smaller hebivores. "The restriction of associated herbivores to relatively isolated pockets would have made these herbivore species more susceptible to chance events, and may have blocked migratory routes they needed to follow shifting vegetation zones."

Such dramatic effects may be difficult to envisage, admits Owen-Smith. Nevertheless, he cites the example of Hluhluwe Game Reserve in Natal where, "following 100 years or so without elephants, three species of antelope have become locally extinct, while open country grazers such as wildebeest and waterbuck have been reduced to low numbers."

The keystone herbivore hypothesis links two events: the initial elimination of megaherbivores, probably by human hunting; and the consequent loss of medium-sized herbivores as a result of vegetational change. The hypothesis may be tested, notes Owen-Smith, by examining the nature of vegetational change during the late Pleistocene: is it the result of climatic change alone, or does the loss of megaherbivores contribute significantly? In addition, the timing of extinctions should provide a clue: if, for instance, the medium-sized herbivores became extinct before the larger species, then the hypothesis cannot be correct.

In any case, once the large herbivores became extinct, the removal of their environmental perturbation would surely have had an impact. This, urges Owen-Smith, "needs to be taken into account, in addition to climatic shifts, in explaining the vegetation transformation that occurred at the end of the Pleistocene." ■ **ROGER LEWIN**

ADDITIONAL READING

N. Owen-Smith, "Pleistocene extinctions: The pivotal role of megaherbivores," *Paleobiology* **13**, 351 (1987).

Animals Yield Clues to Huntington's Disease

Findings that quinolinic acid produces brain lesions in animals similar to those in Huntington's brains suggest a possible strategy for preventing the disease

THE excitation of certain receptors in the brain can, it seems, be a two-edged sword. Although the receptors are part of the normal machinery for receiving incoming nerve signals, overstimulation of the receptors may damage, or even kill, the neurons on which they are located. Such overstimulation may contribute to the nerve cell degeneration occurring in several brain diseases—of which Huntington's disease is a case in point.

Investigators have identified quinolinic acid, a chemical that occurs naturally in the brain, as an "excitotoxin" that may produce the brain degeneration of Huntington's disease by activating a receptor for the excitatory neurotransmitter glutamic acid. They have shown, for example, that treatment of experimental animals with the chemical produces brain lesions similar to those occurring in Huntington's patients.

If the proposal that quinolinic acid causes Huntington's disease is correct, then the way might be open to preventing the development of the condition by inhibiting the chemical's activity at the receptor. In fact, according to results presented at the recent meeting of the Society for Neuroscience,* a drug called MK-801 can reduce the brain damage caused in rats by quinolinic acid and is a possible candidate for human trials.

Although it is far from certain that the animal results are applicable to the human situation, a preventive treatment for Huntington's disease would be highly welcome. The condition is caused by a dominant gene, which means that a patient's children have a 50% chance of inheriting the gene and developing the disease themselves. The symptoms do not usually become apparent until the fourth or fifth decade of life, but, once the mental and physical decline that are characteristic of the disease begin, they progress inexorably, if slowly, until the patient dies.

Within the past few years, molecular biologists have devised a test for identifying those members of Huntington's families that carry the gene. In the current absence of a preventive treatment, however, an individual who learns that he is likely to develop the disease is put under a terrible burden as he anticipates the onset of symptoms.

Researchers began to focus on excitotoxins as a possible cause of Huntington's disease about 10 years ago. The striatum is the area of the brain in which the principal neuronal losses of Huntington's disease occur. In 1976, Robert Schwarcz and Joseph Coyle of Johns Hopkins University School of Medicine noted that when kainic acid, an analog of glutamic acid, is injected into rat brains, it kills neurons originating in the striatum, but not those coming into the striatum from other parts of the brain. "That is what you see in Huntington's disease," explains M. Flint Beal of Harvard's Massachusetts General Hospital, "but Huntington's disease is more complicated."

Beal, Joseph Martin, also of Massachusetts General Hospital, and their colleagues have found that degeneration does not strike all types of striatal neurons equally in the brains of Huntington's patients. Nerve cells that make the neurotransmitters γ-aminobutyric acid (GABA) and substance P show the greatest losses. Neurons that make somatostatin and neuropeptide Y are relatively spared, as are cells that make the neurotransmitter acetylcholine.

Although the brain lesions caused by kainic acid bear some resemblance to those of Huntington's disease, the chemical does not occur naturally in brain and is therefore unlikely to cause the disease. Schwarcz, who is now at the Maryland Psychiatric Research Center in Baltimore, and his colleagues went on to show that quinolinic acid, which is present in brain and is another analog of glutamic acid, also kills striatal neurons.

Moreover, according to Beal, Martin, and their colleagues, nerve-cell killing by quinolinic acid is more specific than that by kainic acid and more similar to what is happening in Huntington's disease. Kainic acid kills all types of neurons, but Beal says, "To our surprise, we found that we did get a relative sparing of the cholinergic and somatostatin-producing neurons with quinolinic acid."

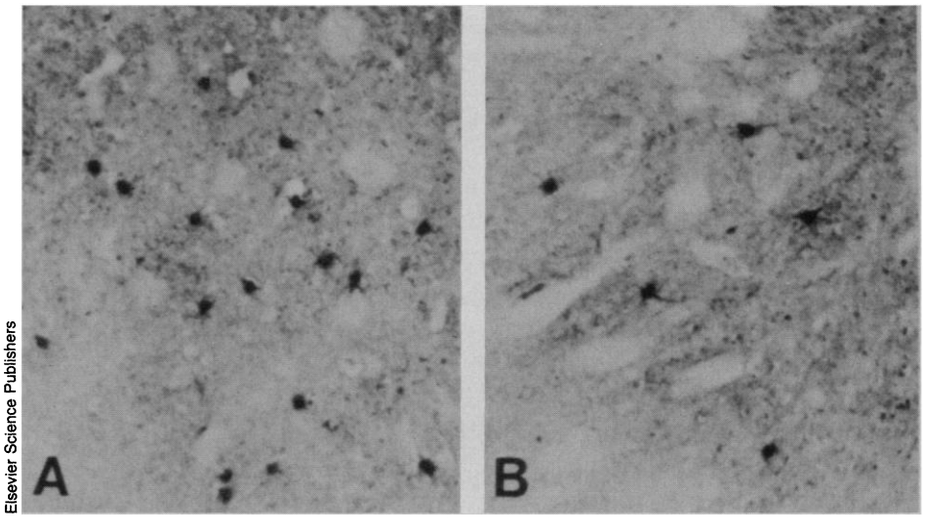
These results were challenged this sum-

*The 17th Annual Meeting of the Society for Neuroscience was held in New Orleans on 16 to 21 November.

mer, however, by Stephen Davies and Peter Roberts of the University of Southampton, England. They reported that somatostatin-producing neurons were not spared from death when quinolinic acid was injected into rat brains.

According to Beal and Martin, Davies and Roberts may have failed to see sparing of the neurons because they examined only the areas in the immediate vicinity of the injections where the quinolinic acid concentrations are high. "At the site of injection, everything dies," Beal concedes.

However, he and Martin find that in the region surrounding this area of total cell death is a transition zone in which the GABA-producing neurons are selectively killed while the other types are preserved. "Our assertion is that one has to look in the region adjacent to the injection site," Martin says. The concentration of the quinolinic acid will be lower there, perhaps more like that in the brain during the slow development of Huntington's disease.



Neuronal sparing in Huntington's disease. *The cholinergic neurons (dark-stained cells) of the brain striatum are relatively spared from the degeneration of Huntington's disease. Consequently, they become denser in tissue from Huntington's brains (A) than in that from normal brain (B).* [*Reprinted with permission from R. J. Ferrante* et al., Brain Res. ***411***, *162 (1987)*]

The resemblance between the neuronal degeneration caused in rat brains by quinolinic acid and that occurring in the brains of Huntington's patients is not the only reason for thinking that the chemical might play a role in the etiology of the disease. At the neuroscience meeting, Schwarcz reported that he, William Whetsell of Vanderbilt University School of Medicine in Nashville, and Edward Bird of Massachusetts General Hospital found that the activity of the enzyme that synthesizes quinolinic acid is higher in the brains of persons who died of Huntington's disease than in control brains.

The difference is especially marked in the striatum, Schwarcz says. Meanwhile, the activity of the enzyme that degrades the chemical is essentially the same in control brains and those from Huntington's patients.

The findings mean, Schwarcz says, that "the Huntington's disease brain has a much larger than normal capacity to make quinolinic acid." He emphasizes that there is a caveat, however.

The synthetic enzyme is made primarily in nonneuronal glial cells. The striata of Huntington's brains, which lose nerve cells, have higher concentrations of glial cells than do normal striata. "The increase in enzyme activity might be secondary to the neuronal losses," Schwarcz says. However, the increases could also be detected in those areas of Huntington's brains in which appreciable amounts of neurons are not lost.

More work will be needed to confirm the role proposed for quinolinic acid in Huntington's disease. Investigators want to know, for example, whether the concentration of the chemical is increased in the brain tissue or spinal fluid of patients. It may nevertheless be difficult to demonstrate such an increase. "If you could measure a large increase, the disease wouldn't take 20 years to develop," Schwarcz points out.

Meanwhile, researchers are beginning to look for drugs that block quinolinic acid's neurotoxicity as potential preventives of Huntington's disease. In particular, they are focusing on drugs that block the receptor through which the chemical works.

This is the NMDA receptor, which has been implicated in the pathology of several brain diseases and is generally a very hot topic these days in neuroscience circles. The NMDA receptor was so named because it is activated by *N*-methyl-D-aspartic acid (NMDA), a synthetic analog of the natural neurotransmitters glutamic and aspartic acids. The effects of kainic acid may be different from those of quinolinic acid, because it acts through another glutamic acid receptor.

Activation of the NMDA receptor apparently has the potential to kill because it leads to the opening of a channel for letting calcium ions into the cell. "It's the calcium that damages the cell," Martin explains. "It activates intercellular proteases that lead to cell destruction." Calcium ions might also activate other enzymes and damage the mitochondria, which produce most of the cell's energy.

Normally, neurotransmitters are released in brief bursts, and the excitation is not harmful. The trouble arises when the receptor excitation is excessive or prolonged.

Beal, Martin, and their colleagues have now tested several agents to see whether they block the toxicity of quinolinic acid in rats. The only one found to work is MK-801, a drug that apparently binds to the NMDA receptor and inhibits its activity. "MK-801 will completely block quinolinic acid toxicity when it is given systemically," Beal said at the neuroscience meeting. The researchers injected the drugs into the test animals either intraperitoneally or intravenously.

Systemic administration, preferably by mouth, is a must for any drug intended for use by people. Although the Harvard group tried two additional inhibitors of the NMDA receptor, the agents were not effective, presumably because they are highly charged and cannot pass from the bloodstream into the brain. MK-801, which is very lipid-soluble, is capable of crossing the blood-brain barrier and can be taken by mouth.

Whether the drug is suitable for human consumption, especially for long periods of time, remains to be established. It appears to act at the same receptor site as PCP—"angel dust"—a widely used illicit drug that causes hallucinations and other psychotic effects. When given to animals in high concentrations, MK-801 also has strong sedative effects.

As mentioned previously, the slow development of Huntington's disease suggests that if quinolinic acid is at fault, the elevations in the concentration of the agent may be slight. In that event, Beal suggests, only very low doses of MK-801 may be required to counteract quinolinic acid's toxicity and untoward psychoactive effects may not occur. Alternatively, it may be possible to devise drugs that inhibit quinolinic acid synthesis or block its effects without mimicking PCP's effects. ■ JEAN L. MARX