Letters

Excitotoxic Disorders

Marcia Barinaga's article about the potential of exogenous excitatory amino acids to induce neurodegenerative diseases (Research News, 5 Jan., p. 20) needs clarification. The best studied excitotoxic disorder is lathyrism, a form of irreversible spastic paraparesis caused by excessive continuous intake of the seed of *Lathyrus sativus* (LS, known as chickling or grass pea) or other neurotoxic *Lathyrus* species (*1*). Lathyrism has affected certain European, Asian, and African populations throughout human history and is endemic today in parts of Bangladesh, Ethiopia, and India. Risk factors other than the amount of grass pea intake appear to include malnutrition, physical exhaustion, and being male. Primate studies have confirmed the likely etiological role of beta-*N*-oxalylamino-L-alanine (BOAA), a quisqualate receptor agonist present in LS seed in concentrations approximating 1% (*2*), but well-nourished macaques continuously fed either LS seed or BOAA develop only reversible clinical signs consistent with the earliest phase of the human disorder. The motor performance of subjects with long-standing lathyrism may deteriorate slowly with advancing age, but there is little evidence to suggest a progressive neuronal disorder akin to the more familiar neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS). Thus, lathyrism is a largely self-limiting disease comparable to many other human neurotoxic disorders that stabilize after the culpable agent is withdrawn. Similarly, Canadians with memory and motor dysfunction following oral exposure to the kainate receptor agonist domoic acid are not likely to develop an ongoing fatal neurodegenerative disorder in forthcoming years.

By contrast, the Western Pacific ALS Parkinsonism-dementia (PD) complex is a progressive, terminal neurodegenerative disease that shows, in its various clinical and neuropathological forms, remarkable similarities to ALS, PD, and Alzheimer's disease found elsewhere. There is widespread agreement that ALS-PD is triggered by disappearing environmental factors peculiar to the life-style of the affected populations of the Marianas Islands of Guam, the Kii Peninsula of Honshu Island, Japan, and southeastern Irian Jaya, Indonesia; the weight of evidence indicates that ALS-P-D is related to use of the seed of the neurotoxic cycad plant (*Cycas* spp.) for medicine or food. Cycad seed contains about 2% cycasin, the glycone of the potent nucleic acid alkylating agent methylazoxymethanol (MAM), which has carcinogenic, teratogenic, and neurotoxic properties. MAM also methylates free amino acids to produce unknown excitotoxic agents. Beta-*N*-methylamino-L-alanine (BMAA) is a low-potency excitotoxin present (0.02%) in cycad seed. Huge subconvulsive doses of BMAA produce in macaques a constellation of clinical, electrophysiological, and neuropathological changes that shows some similarities to ALS-PD, but the changes fall short of a model of the human disease (*3*). Because BMAA is only one of several potential neurotoxins present in or generated by cycad seed, it is premature to assign a causal role to any single agent. Current research is focused on the identification of cycad chemicals that behave as "slow toxins," hypothetical substances that initiate an irreversible sequence of cellular events leading to progressive neuronal degeneration and the clinical appearance of ALS-PD years or decades later. Given that lathyrism is a largely nonprogressive disorder, exogenous slow toxins are most unlikely to act as typical excitotoxic amino acids; rather the search in cycad seed is focused on compounds that employ cell surface receptors to gain access to selected neurons, enter the cell's nucleus, and therein alter genomic expression. Because oral doses of cycasin induce muscle weakness and wasting in grazing animals, it is conceivable that human long-latency neurotoxins are masquerading as carcinogens that alkylate DNA, RNA, and proteins. The action on nondividing nerve cells of agents that induce uncontrolled division of nonneural cells is largely unexplored.

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REFERENCES

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2. S. M. Ross *et al.*, *J. Neurochem.* **53**, 710 (1989).
3. P. Spencer *et al.*, *Science* **237**, 517 (1987).

Ads in Scientific Journals

As an editor, I took a special interest in the recent letters (2 Feb., p. 515) about *Discover's* advertisements. Both Paul Hoffman, editor of *Discover*, and Martin Gardner seem to suggest that if a journal accepts ads for questionable products, the reasons must be financial. Although financial considerations are important to any journal, I believe