decrease in somatostatin, neuropeptide Y, or NADPH-diaphorase (*3*). These observations do not appear to be consistent with a sparing of peptidergic neurons within a peripheral transition zone. In recent studies (*1*, *2*, *5*) it has been shown that low doses of excitotoxins will selectively spare striatal cholinergic neurons. Indeed, in striata showing a 26% reduction in cholinergic neurons there is an accompanying 82% reduction in NADPH-diaphorase–containing cells (*5*) [see also Boegman *et al.* (*2*), where a 32% decrease in acetylcholinesterase-containing cells was accompanied by a 61% decrease in cells containing neuropeptide Y].

Thus, while Beal *et al.* reported a relative sparing of neurons containing somatostatin, a finding which has not been substantiated by subsequent studies, they did not detect the sparing of cholinergic neurons, which seem to be a prominent feature of excitotoxin-induced degeneration of the striatum.

We therefore wish to caution against either adopting the animal lesioned with quinolinic acid as an appropriate model of Huntington's disease or, perhaps more important, the use of this model to predict a possible strategy for preventing the disease; despite suggestions to the contrary, major differences between these two examples of striatal nerve cell degeneration appear to remain.

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4. This represents the mean reduction from figures 1 and 2 in (*3*).
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Response: Davies and Roberts disagree with our observations on effects of quinolinic acid lesions in striatum. Their objections are inconsistent with their own reported data on several points. Moreover, they base their criticism on morphologic studies and have not reported confirmatory biochemical data. They contend first that we did not detect a sparing of cholinergic neurons after the striatal excitotoxin lesions were made, which they now seem to have found. This is at variance with their initial report (*1*), in which they stated, "The intrastriatal injection of 120 nmol of quinolinic acid completely eliminated both AChE- and diaphorase-containing perikarya throughout the . . . lesion area as seen with nissl staining." They also presented a graph in figure 2 and stated "There was no significant difference between the cell losses for both cell types at any position within the striatum." It is therefore surprising to learn that they now report sparing of cholinergic neurons in the context of challenging our results.

Indeed we have already presented data showing a preservation of acetylcholinesterase neurons at the lesion core and have confirmed this with choline acetyltransferase staining (*2*, *3*). At the lesion core these neurons are preserved out of proportion to NADPH (nicotinamide adenine dinucleotide phosphate, reduced)-diaphorase neurons. This relative sparing occurs with excitotoxins acting at all three subtypes of glutamate receptors (*3*). This provides a further parallel with Huntington's disease, in which we have also demonstrated preserved cholinergic neurons (*4*).

We do not agree with Davies and Roberts that "quinolinic acid demonstrates a spectrum of neurotoxicity similar to that of other excitotoxins, there being no preferential sparing of neurons containing somatostatin, neuropeptide Y, or NADPH . . . diaphorase." We have reexamined this question with both biochemical measures and novel histochemical procedures (*3*). We have performed full dose-response curves using quinolinic acid, *N*-methyl-D, L-asparate, L-homocysteic acid, kainic acid, quisqualic acid, and AMPA (D,L-α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid). At doses that resulted in equivalent 50% reductions in GABA (γ-aminobutryic acid), only NMDA (*N*-methyl-D-aspartic acid) agonists (quinolinic acid, *N*-methyl-D, L-aspartate, L-homocysteate) showed sparing of somatostatin–neuropeptide Y concentrations, while kainic acid, quisqualic acid, and AMPA resulted in significant depletions of both somatostatin and neuropeptide Y. At high doses, NMDA agonists caused significant depletions of somatostatin and neuropeptide Y, which indicates a relative but not absolute sparing of these neurons. Although we initially did not find sparing with NMDA, only a single high dose was examined. We have recently developed techniques for double staining for enkephalin and NADPH-diaphorase. Using this technique we have counted directly the number (ratio) of NADPH-diaphorase neurons to enkephalin neurons in a single section at the transition zone (the border between the lesion core and normal striatum) where we consistently find selective neuronal sparing. We have demonstrated that there is relative sparing of NADPH-diaphorase neurons with several NMDA agonists, whereas preferential loss of this cell class is seen with agonists acting at the kainate and quisqualate receptors (*3*).

We have recently extended our studies to 1-year quinolinic acid lesions (*5*). These experiments provide even more convincing evidence of sparing of somatostatin–neuropeptide Y neurons. One year after the acute lesions were made, the striatum had shrunk to about 50% of its normal volume. At that time the number of NADPH-diaphorase neurons on the lesion side had increased more than twofold per unit area in a region in which there was a 64% depletion of enkephalin neurons. Neurochemical measurements confirm this finding, showing significant increases in both somatostatin and neuropeptide Y concentrations.

Our studies therefore demonstrate (i) a selective sparing of cholinergic neurons with excitotoxins acting at all three subtypes of glutamate receptors and (ii) a relative but not absolute sparing of NADPH-diaphorase neurons, with excitotoxins acting at the NMDA receptor subtype but not with those acting at quisqualate or kainate receptors. Our results have been confirmed by Choi and his colleagues in both cortical and striatal cell cultures (*6*).

We maintain that Davies and Roberts have only provided histochemical studies of quinolinic acid lesions at the lesion core. We believe our detailed studies comparing the effects of a variety of excitotoxins with the use of both neurochemical and histologic parameters provide compelling data which show that quinolinic acid and other NMDA agonists result in a pattern of neuronal sparing that closely mimics that of Huntington's disease. We believe this model may prove useful in evaluating potential treatments of Huntington's disease (*7*).

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