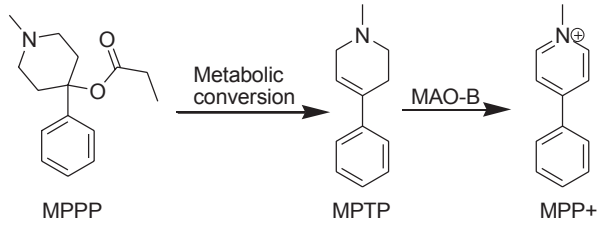

FIGURE 7.7 Desmethylprodine (1-methyl-4-phenyl-4-propionoxypiperidine (MPPP)), an opioid analgesic that was identified by scientists at Hoffmann-La Roche in the 1940s, is metabolically converted to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Metabolic processing of MPTP by monoamine oxidase-B (MAO-B) in the brain produces the cationic species 1-methyl-4-phenylpyridinium (MPP+), which enters the dopaminergic cells found in the substantia nigra region of the brain and kills them. Dopaminergic cells are the only cells in the brain that produce dopamine, a chemical required for movement. As these cells die, Parkinson's disease symptoms begin to emerge and become more pronounced as the dopaminergic cell population decreases.

and mice with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) (Figure 7.7). Although the exact cause of Parkinson's disease remains a mystery, it is clear that this chronic and progressive movement disorder results from the loss of dopamine producing cells in the substantia nigra region of the brain. The decline of these cells leads to the onset of uncontrollable tremors, rigidity of limbs, bradykinesia (slowness of movement), impaired balance, and diminished physical coordination. In the late 1980s, it was accidently discovered that MPTP causes rapid onset of Parkinson's disease symptoms, including death of dopamine-producing cells in humans (the details of this discovery will be discussed in Chapter 13), and as mentioned above, administering MPTP to primates[7] and mice[8] has the same effect. The dopamine-producing cells in the brains of both primates and mice die as a result of exposure to MPTP, creating a situation nearly identical to Parkinson's disease. Onset of symptoms occurs within 6–9 days of MPTP injection and in the absence of therapeutic intervention, symptoms persist just as they do in the human disease. The MPTP model of Parkinson's disease is often considered to have construct validity. The main criticism of this model has been the absence of Lewy bodies, an abnormal aggregation of proteins inside the neurons, which are a hallmark of Parkinson's disease.

The use of MPTP to induce a Parkinson's disease condition in an animal model provides an opportunity to study the associate neurodegeneration in a relatively short time frame and from two different perspectives. Compounds with the potential to prevent MPTP-induced neurodegeneration (neuroprotectants) can be assessed by dosing the animals with test compounds prior to administration of MPTP. Compounds that have efficacy