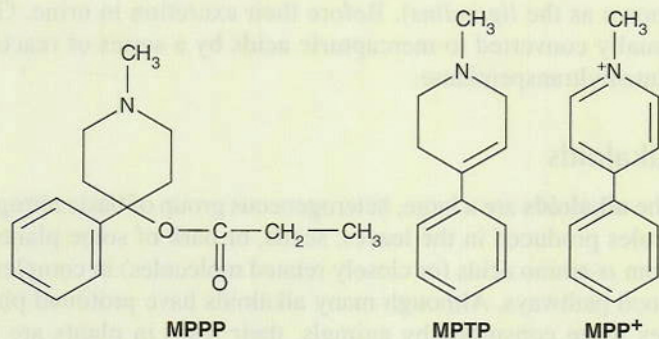


## SPECIAL INTEREST BOX 14.3 Parkinson's Disease and Dopamine

Parkinson's disease, formerly known as *paralysis agitans*, is a movement disorder caused by damage to brain structures called the basal ganglia and substantia nigra. Symptoms of Parkinson's disease, most commonly observed in adults past 40 years of age, include tremor, skeletal muscle rigidity, and difficulty in initiating movement. The inability of certain neurons within the substantia nigra to produce and release dopamine is believed to be the primary cause of Parkinson's disease. (Dopamine produced within the substantia nigra normally acts to inhibit neural activities within the basal ganglia.) As stated, because dopamine does not cross the protective blood-brain barrier, the precursor molecule L-DOPA (also known as levodopa) is used to treat Parkinson's patients.

In the late 1970s a substantial clue to the cause of the nerve cell destruction in Parkinson's disease was provided by young drug addicts using the synthetic heroin substitute MPPP (1-methyl-4-phenyl-4-propionoxypiperidine) (Figure 14B). Several unfortunate individuals, later found to have consumed MPPP, were diagnosed with Parkinson's disease despite their youth and lack of a family history of the disease. Considerable research revealed that under certain reaction conditions the synthesis of MPPP produces a toxic by-product called MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Once it has been consumed, MPTP is converted to MPP<sup>+</sup> (1-methyl-4-phenylpyridinium) in the brain by the enzyme monoamine oxidase. After its synthesis, MPP<sup>+</sup> is transported by a

dopamine-specific transport mechanism into certain neurons. Although the mechanism by which nerve cells are destroyed by MPP<sup>+</sup> is not completely understood, it appears that one of its effects is to inhibit NADH dehydrogenase, a component of the mitochondrial electron transport complex.



**FIGURE 14B** Formation of MPP<sup>+</sup>, a Neurotoxin.

MPPP, also referred to as meperidine, is a synthetic analgesic with morphinelike properties. If the chemical reaction used to synthesize MPPP is not carefully regulated, a toxic by-product is also produced. When this latter molecule, MPTP, is inadvertently consumed, it is converted in the brain to MPP<sup>+</sup>, a neurotoxic agent, in an oxidation reaction catalyzed by monoamine oxidase (see p. 517).