The Neuropathology of Manganese-Induced Parkinsonism

Daniel P. Perl, MD and C. Warren Olanow, MD

Abstract
Manganese is an essential trace metal that is widely used in industry, particularly in the manufacture of steel. Exposure to high levels of manganese can cause neurotoxicity with the development of a form of parkinsonism known as manganism. It has recently been hypothesized that manganese exposure might also cause or accelerate the development of Parkinson disease (PD). This article is a review of the pathologic studies that have been reported in patients with manganism and in primates experimentally intoxicated with manganese. They demonstrate a consistent pattern characterized by damage to the globus pallidus (particularly the internal segment) with sparing of the substantia nigra pars compacta and the absence of Lewy bodies. This finding contrasts with what is seen in PD, in which there is preferential degeneration of dopamine neurons in the substantia nigra pars compacta coupled with Lewy bodies and preservation of the pallidum. These pathologic findings do not support the notion that manganese causes PD but rather argues that manganese-induced parkinsonism and PD are distinct and separate disease entities.

Key Words: Etiology, Globus pallidus, Manganese, Parkinsonism, Parkinson disease.

INTRODUCTION
The capacity of high levels of manganese to damage the nervous system and to cause parkinsonism has been recognized since the initial report by Couper in 1837 (1). Over the ensuing 170 years, small numbers of cases of occupational manganism have been reported (2). With improvements in the workplace environment and reduced levels of exposure to manganese, cases of manganism are now rarely encountered. Recently, it has been proposed that chronic exposure to manganese in welding fumes may cause or accelerate the development of Parkinson disease (PD). This concept is based on anecdotal case reports of PD in welders (3, 4), reduced striatal fluorodopa uptake on positron emission tomography (PET) in a single parkinsonian patient thought to have manganism due to chronic liver failure (5), and a single epidemiologic study suggesting an increased frequency of PD in welders who were solicited by attorneys to participate in a medical-legal screening (6). This hypothesis has led to widespread litigation directed against the welding industry in the United States in an attempt to obtain compensatory damages for welders who suffer from PD, despite numerous epidemiologic studies that show no evidence of increased PD incidence or prevalence among welders (7–12).

A large body of evidence accumulated over more than a century has demonstrated that the pathology of PD is characterized by degeneration of dopamine neurons in the substantia nigra pars compacta (SNc) coupled with the presence of intracellular Lewy bodies (13–16). Neurodegeneration can also occur in other brain areas including the olfactory region, locus coeruleus, nucleus basalis of Meynert, dorsal motor nucleus of the vagus, pedunculopontine nucleus, and the cerebral cortex (17, 18). In contrast, quantitative studies have demonstrated that the globus pallidus pars interna and pars externa are intact in patients with PD (19, 20).

There have only been a small number of reports describing the neuropathologic findings in patients with manganese intoxication. However, they demonstrate a consistent pattern characterized by cell loss and gliosis in the globus pallidus (especially the pars interna) and to a lesser degree in the striatum, with sparing of the SNc and no Lewy bodies. This pattern of pathology has been precisely reproduced in nonhuman primates that have been experimentally intoxicated with manganese. In this article we will review all of the published pathologic findings associated with manganese intoxication in humans and experimental animals. These findings support the position that manganese-induced parkinsonism and PD have different pathologies and are distinct and separate conditions. These findings argue against the hypothesis that manganese intoxication causes or accelerates the development PD.

MANGANESE NEUROTOXICITY
Manganese is a paramagnetic metal that is essential for cell survival. It is the 12th most abundant element in the earth’s crust and is widely distributed in the environment, being present in water, soil, and food (21). Manganese is the fourth most widely used metal in commercial products, with more than 8 million tons being extracted annually. More than 90% of manganese is used in the manufacture of steel in which it imparts hardness to the finished product. Manganese is also used in the manufacture of batteries, in bacteriocidal and fungicidal agents, for water purification, and as an antiknock additive in gasoline. Manganese is also a constituent of welding rods, and manganese-containing fumes are produced during the welding process.
Manganese is normally cleared by the liver and excreted in urine (22, 23). Manganese that exceeds the clearance capacity of the liver or that gains direct entry to the systemic circulation through respiration has the potential of gaining access to the brain (24). Radiotracer, magnetic resonance imaging (MRI), and pathologic studies demonstrate that manganese preferentially accumulates in the globus pallidus where it has the potential to cause neurotoxicity (25–27). Manganese neurotoxicity was first described in 5 workers who developed muscle weakness, limb tremor, and a whispering voice after exposure to manganese in an ore-crushing plant (1). Since that original report, a small number of similar clinical cases have been reported, almost exclusively among manganese miners, millers, and smelters and more rarely in workers involved in manufacturing dry cell batteries and fungicides (2, 28). Perhaps the best described cases are in a cohort from Taiwan (29–31) in which 6 of 13 individuals working in an iron foundry developed parkinsonism due to failure of the ventilatory system and consequent exposure to massively high levels of manganese. Manganese toxicity has also been described in patients with liver failure, presumably reflecting an inability of the liver to clear the normal dietary load of manganese, and in patients receiving long-term parenteral nutrition presumably due to the direct systemic administration of a high manganese-containing nutritional product (32–35). Manganese has also been described after ingestion and systemic administration of potassium permanganate (36).

Parkinsonism is the cardinal clinical feature of manganism and typically is manifested as an early onset of speech and gait disturbance with a tendency to fall backwards, symmetric bradykinesia, rigidity, micrographia, and masked facies (2, 28, 30). Tremor, when present, tends to be high frequency and postural or kinetic rather than resting as is classically seen in PD. Dystonic features are common and classically include facial grimacing and a distinctive gait abnormality characterized by marked plantar flexion of the feet known as “coq au pied” or “cock walk.” In contrast with PD, patients with manganese-induced parkinsonism have a poor or unsustained response to levodopa treatment (31, 37) and normal nigrostriatal function as illustrated by neuro-imaging of the dopamine system with PET or single photon emission computed tomography (38–41). Psychiatric manifestations have been described with acute manganese intoxication and include hallucinations, acute behavioral disturbances, and frank psychosis.

### TABLE 1. Neuropathologic Findings in Autopsied Cases of Manganese Induced Parkinsonism

<table>
<thead>
<tr>
<th>Case</th>
<th>Globus Pallidus</th>
<th>Substantia Nigra Pars Compacta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinsonism after Exposure to manganese-containing ore dust</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Casamajor, 1913 (42)</td>
<td>“Severe reduction in ganglion cells of pars interna and somewhat less severe in pars externa”</td>
<td>“Nerve cells not remarkably changed”</td>
</tr>
<tr>
<td>Ashizawa, 1927 (43)</td>
<td>“Marked failure of nerve cells in the putamen and pallidum”</td>
<td>Not reported</td>
</tr>
<tr>
<td>Trendtel, 1933 (45)</td>
<td>“There was a marked reduction in the number of nerve cells, so that whole fields of only glia occurred.”</td>
<td>Not reported</td>
</tr>
<tr>
<td>Canavan et al, 1934 (46)</td>
<td>“The pallidum shows a more diffuse failure of ganglia cells…failure of ganglia cells affects the inner part of the pallidum. Almost no ganglia cells remain.”</td>
<td>“Intact” (microscopic description)</td>
</tr>
<tr>
<td>Stadler, 1936 (47)</td>
<td>“The ganglia cells of the internal limb have mostly died and in their place the macroglia and microglia have increased.”</td>
<td>“Good pigmentation” (gross examination); “inconspicuous changes” (microscopic examination)</td>
</tr>
<tr>
<td>Parnitzke and Peiffer, 1954 (48)</td>
<td>“Atrophic and brown in color” (gross examination); “loss of nerve cells, which were marked in the medial segments and moderate in the lateral ones.” (microscopic examination)</td>
<td>“Melanic color normal” (gross examination); “the pigment cells of the substantia nigra were intact” (microscopic examination)</td>
</tr>
<tr>
<td>Parkinsonism after exposure to manganese-contaminated water</td>
<td>“Distinct changes …[nerve cells] were heavily injured and even necrosed.”</td>
<td>“No changes grossly visible”</td>
</tr>
<tr>
<td>Kawamura et al, 1941 (50)</td>
<td>“Remarkable atrophy, necrosis and decidualion of the nerve cells of the globus pallidus with reactive glia and microglia.”</td>
<td>Not reported</td>
</tr>
<tr>
<td>Parkinsonism associated with hepatic failure</td>
<td>“Vacuolar change, presence of macrophages, gliosis and neuronal loss in the pars interna of the globus pallidus and substantia nigra pars reticulata.”</td>
<td>Not reported</td>
</tr>
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in the globus pallidus, particularly the globus pallidus pars interna, with sparing of the SNc (when mentioned) and an absence of Lewy bodies. Different neuropathologic patterns were described in 3 cases, but in our opinion these cases corresponded both clinically and neuropathologically with alternative diagnoses.

**Manganism After Occupational Exposure**

In 1913, Casamajor described a patient who died after working in an ore-separating plant that produced manganese-containing dust (42). The length of exposure and the clinical manifestations that were present in this patient were not clearly described. An autopsy was performed, and the brain and spinal cord were reported to have a normal appearance on gross examination. The report does not further describe the brain specimen.

In 1927, Ashizawa reported the autopsy findings of a man who had worked as a brownstone miller (43). He had a 3-year history of mask-like facies, slight muscular rigidity, impairment in performing fine motor tasks, trembling of the fingers, and micrographia. At autopsy no grossly visible abnormalities were noted in the brain, but the appearance of the corpus striatum and SNc were not specifically addressed. A detailed description of the microscopic appearance of a number of brain regions was provided. The report contains the following description of the pallidum: “The nerve cells in some areas of the pars externa are significantly decreased, and, particularly in the pars interna, are on the whole extraordinarily severely decreased, so that only a small number of them were visible close to the pars externa and sometimes they were not visible at all in an entire cross section.” In addition, the author described the appearance of the substantia nigra, indicating that the “nerve cells and myelin fibers are not remarkably changed....” The summary of the findings in this report states: “The changes in the pallidum were quite remarkable. They consisted of a severe reduction of the gangliocyes of the pars interna, and somewhat less severe in the pars externa....” It is stated that there were no significant changes in the cerebral cortex, thalamus, subthalamic nucleus, red nucleus, substantia nigra, corpora quadrigemina, dentate nucleus, inferior olive, and spinal cord. It is further specifically indicated that the findings observed in this case were very similar to what had been seen in the manganese-intoxicated monkeys described by Mella and that they are distinct from what is seen in PD (44).

In 1933, Trendtel described the findings in a dock worker who was exposed to manganese-containing dust while unloading brownstone ore from ships (45). The patient demonstrated masked facies, paucity of movement, shuffling gait, a tendency to fall backward, and weakness. A diagnosis of chronic manganese poisoning was made. The patient died, but his age at death and the circumstances leading to his death were not stated. At autopsy there was “…pathological sclerosis and scars in the striatum. In some parts there was extensive failure of nerve cells in putamen and pallidum.” A description of the SNc was not provided.

In 1934, Canavan et al reported the findings in a man diagnosed with manganese poisoning who died at age 69 years (46). The patient had been employed at several mills in which he was exposed to manganese dust. At autopsy, atrophy of the basal ganglia was specifically noted. In the “lenticular nucleus” [putamen and globus pallidus], they noted, “a marked reduction in the number of nerve cells, so that whole fields of only glia occurred.” There was no mention in this report of the appearance, either on gross or microscopic examination, of the SNc.

In 1936, Stadler reported the autopsy findings of a patient who had been exposed to manganese while working in a brownstone mill between the years 1910 and 1915 and 1918 and 1921 (47). He developed a variety of parkinsonian signs and symptoms including micrographia, rigid facial features, bent body posture, stiff movements, trembling, and gait dysfunction with an inclination to fall forward. He died at age 56 years. At autopsy, nothing unusual was noted on gross examination. However, microscopically both focal and widespread neuronal loss was observed in the globus pallidus and striatum. The neuronal damage was described as most extensive in the medial portion of the globus pallidus. The report points out that almost no neurons remained in the internal aspect of the globus pallidus and that there was almost complete replacement of nerve cells with glial cells. The striatum was also affected. The author specifically comments in the microscopic notes that the “substantia nigra” was intact. He further comments: “the pallidum seems to be affected by manganese poisoning with a regularity that is elsewhere in human pathology only found in carbon monoxide poisoning.”

Parnitzke and Peiffer reported the autopsy findings of a 43-year-old man who had occupational exposure to manganese-containing dust while working as a brownstone miller (48). The patient first noted trembling of the right leg at age 19, 1 year after he had begun to work in the mill. Over the following 1 or 2 years he developed generalized muscular rigidity. Five years into his illness he had difficulty speaking, mask-like facies, and a propulsive gait. When he was 38 years of age he was described as having an almost complete lack of mobility and being unable to sit unassisted or to feed himself. On gross examination of the brain, no specific abnormalities were noted and the substantia nigra was described as showing “good pigmentation.” On microscopic examination, it was noted that “…in the pallidum: the ganglia cells in the internal limb have mostly died” and “the cell failure [in the globus pallidus pars externa] in no way approaches the failure level of the internal pallidum.” In summarizing, the authors note: “In our case, the ganglion cell damage occurring in the pallidum and particularly that located in its internal limb fits with the presentation that neuropathologists have become familiar with.”

In 1986, Yamada et al published the last available and most complete brain examination of a case of manganese-induced parkinsonism due to occupational exposure (49). The report describes a 52-year-old man who had been employed in a manganese ore-crushing facility. Clinically, he experienced gait disturbance with difficulty walking backwards and cock walk, masked facies, monotonous speech, and neuropsychiatric features including loss of libido, euphoria, and emotional incontinence. There was no improvement with levodopa.
Manganese levels were increased in the urine (10.4 μg/100 mL; normal, <2.0 μg/100 mL), and blood (3.4 μg/100 mL; normal, 0.4–2.0 μg/100 mL). Intravenous infusion of a chelating agent (20 mg/kg EDTA) was associated with a marked increase in the urinary excretion of manganese (56.4 mg/100 mL), but no clinical benefit. He died 4 years after his initial evaluation. At autopsy the brain was of normal weight. The globus pallidus was noted to be atrophic and brown in color and “the melanic color of the substantia nigra appeared normal.” Microscopic examination revealed marked loss of nerve cells in the medial segment of the globus pallidus and moderate loss in the lateral portion. There was moderate astrocytosis and mild gliosis noted in the globus pallidus. The pigmented neurons of the substantia nigra were described as being intact. In summary, the brunt of the damage described was localized to the globus pallidus, especially its medial portion, and the SNc was specifically noted to be of normal appearance on both gross inspection and microscopic examination. The authors note that “preferential affection of the basal ganglia, especially of the pallidum, seems to be related to the extrapyramidal and other characteristic manifestations of CMP [chronic manganese poisoning]” and that “chronic manganese poisoning appears to be different from PD neuropathologically.”

**Manganism After Exposure to Manganese-Contaminated Water**

Kawamura et al reported an outbreak of manganese poisoning related to exposure to contaminated well water (50). The report describes 16 individuals who developed a parkinsonian syndrome after drinking well water that had become contaminated with manganese due to the decay of storage batteries buried in nearby soil. Clinical features included lethargy, masked facies, increased muscle tone, and an action tremor. Histologic examination in 1 autopsy case (a 46-year-old man) revealed “distinct changes” in the globus pallidus: “nerve cells...were heavily injured and even necrosed.” No changes were visible in the thalamus, the caudate nucleus, or the substantia nigra. The authors conclude: “In this case, as to the changes in the central nervous system, degeneration and destruction of nerve cells in the globus pallidus were considered most important.”

**Manganism Associated With Hepatic Failure and Total Parenteral Nutrition**

There are significant amounts of manganese in the normal diet (daily intake is about 5 mg/kg). Normally, about 98% of dietary manganese is eliminated by the liver through biliary excretion (22, 23). In cases of hepatic failure, however, impaired liver clearance can lead to elevated serum manganese levels, high signal changes in the pallidum bilaterally on T1-weighted MRI characteristic of manganese accumulation, and parkinsonism with symmetric rigidity and bradykinesia with a poor or unsustained response to levodopa (21). The neuropathologic features of 4 cases of parkinsonism occurring in the setting of hepatic failure have been reported.

Maeda et al described the autopsy findings of 3 patients with hepatic failure who demonstrated extrapyramidal features on clinical examination and increased signal in the pallidum bilaterally on T1-weighted MRI characteristic of manganese accumulation (51). At autopsy, the authors described “remarkable atrophy, necrosis and decidualization of the nerve cells of the globus pallidus with reactive glia and microglia. Similar changes of moderate severity were seen in the putamen.” They specifically noted the marked severity of the nerve cell loss in the medial segment of the globus pallidus in each case. The SNc was not described in this report.

In 2004, McKinney et al described the autopsy findings of a patient with hepatic failure who was also receiving total parenteral nutrition, known to contain high levels of manganese (52–54). MRI showed symmetrical hyperintensities in the globus pallidi on T1-weighted imaging, consistent with manganese accumulation. The patient subsequently died of systemic aspergillosis. At autopsy there was “vacuolar change, presence of macrophages, gliosis, and neuronal loss in the pars interna of the globus pallidus” as well as similar changes in the substantia nigra pars reticularis. It should be kept in mind that the substantia nigra pars reticularis does not contribute to the dopaminergic nigrostriatal system and is anatomically and functionally related to the globus pallidus. No findings were described in the SNc. This pattern of findings was considered by the authors to be “very specific for manganese poisoning.”

**Autopsied Cases of Patients Who Were Exposed to Manganese but Do Not Fit the Pattern of Neuropathologic Damage Described Above**

There are 3 autopsy reports of patients who were reported to have been exposed to manganese but with a different pattern of neuropathology than described above. In each case, we believe this represents an example of a different neurologic disease entity that developed coincidentally in an individual who also happened to be exposed to manganese. In each of the 3 cases we do not believe there is sufficient evidence to conclude that the damage suffered by the nervous system was related to the manganese exposure.

In 1939, Voss described a patient who had worked for 15 years in a battery factory and also had occupational exposure to brownstone dust (55). At age 37 years he developed difficulty swallowing, dysarthria, weakness with atrophy of the extremities, atrophy of the tongue (with “fibrillary twitching”), increased deep tendon reflexes, and sustained clonus. Eye movements and sensory examination were intact, and cognitive function was normal. Electromyographic examination showed evidence of “degeneration” in the tongue and hand muscles. The patient’s weakness progressed over 2 years to the point at which he could not walk, and he died of aspiration pneumonia. At autopsy, there was pallor of the lateral and ventral corticospinal tracts in the spinal cord, particularly in the cervical region. In addition, there was diffuse anterior horn cell loss with atrophy of the anterior spinal roots and preservation of dorsal horn neurons. Neuronal loss was also seen in the hypoglossal nucleus. Both the substantia nigra and globus pallidus were described as being intact. The final diagnosis was amyotrophic lateral sclerosis with no pathologic...
evidence of manganism. We believe that the author is correct and that there is no reason to think this is anything but a case of amyotrophic lateral sclerosis in an individual with incidental manganese exposure. We further note that no similar pathologic picture has been described in association with manganese intoxication in either the clinical or experimental literature.

In 1953, Scholten described a 49-year-old man who was exposed to manganese ore, but the duration and nature of that exposure were not provided (56). The patient presented with gait dysfunction (feet described as being “stuck to the ground”), postural instability, prominent dysarthria with hypophonia, cerebellar signs, increased deep tendon reflexes, stooped posture, thoracic kyphosis, ante-rocollis (head hung forward), and dementia. His condition gradually worsened, and he developed marked dementia and died at age 60 years. He was diagnosed clinically as having manganese encephalopathy. At autopsy, the striatum, thalamus, and globus pallidus were described as well preserved. In contrast, cell loss was described in the substantia nigra, locus coeruleus, and cerebellum (Purkinje cells). In addition, there was degeneration of the ventral medulla with prominent loss of neurons of the inferior olives. The author of this report concluded that he could not be certain which, if any, of the pathologic changes were due to manganese. We believe that the clinical features and neuropathologic changes in this case were most consistent with a diagnosis of multiple system atrophy. In contrast to manganese, there was degeneration of the ventral medulla with prominent loss of neurons of the inferior olives. The author of this report concluded that he could not be certain which, if any, of the pathologic changes were due to manganese. We believe that the clinical features and neuropathologic changes in this case were most consistent with a diagnosis of multiple system atrophy with cerebellar predominance, a condition that was not well defined until several years after the time of this report (57). Multiple system atrophy has never been linked to manganese exposure, either clinically or in experimental animals. We believe manganese exposure in this case was probably coincidental and not etiologic in nature.

Finally, in 1973, Bernheimer et al wrote a lengthy paper on the clinical, neuropathologic, and neurochemical aspects of various forms of basal ganglia disorders. Included in the study are 39 cases of PD, 12 cases of postencephalitic parkinsonism, 7 cases of “arteriosclerotic-senile” parkinsonism, and 10 cases referred to as unclassified and atypical cases with parkinsonian symptomatology (58). Within this latter group a single patient (case 69) was described by the authors as suffering from “chronic manganese encephalopathy.” This was a 67-year-old woman who, in her mid-30s, had been exposed to manganese dioxide while working in a battery factory. Twenty-three years before her death, and approximately 10 years after manganese exposure had ceased, she developed a tremor and progressed to develop rigidity and akinesia. Morphologic examination of this patient’s brain revealed a mild degree of pallidal atrophy with astrocytosis in the putamen, globus pallidus, and red nucleus. In addition, the SNc was reported to show spotty degeneration with occasional Lewy bodies in the remaining nigral neurons. In this case, the development of progressive tremor, rigidity, and bradykinesia beginning approximately 10 years after cessation of exposure to manganese and pathologic findings of cell loss and Lewy bodies in the SNc strongly suggest that the patient had PD. Although the patient’s exposure to manganese while working in a battery factory and modest changes in the pallidum suggest the possibility that she may also have had a mild form of manganism, it is hard to imagine that all of the pathologic features were directly related to manganese intoxication. There is no precedent for patients developing manganism 10 years after exposure to the metal had ceased. This case represents the one and only autopsy of an individual exposed to manganese who showed evidence of SNc cell damage accompanied by the appearance of Lewy bodies. It is noteworthy that PD is a common disorder with a lifetime risk for an individual of approximately 1% to 2%, and there is no reason to think that exposure to manganese would diminish the risk of an individual developing PD. We believe that in this case the patient probably had 2 different conditions, PD and mild manganism, but we cannot conclude that both conditions were directly related to manganese toxicity.

Manganese-Induced Parkinsonism in Rhesus Monkeys

Animal models have provided additional information on the pathology associated with manganese-induced neurotoxicity. In 1924, Mella chronically exposed monkeys to intravenous manganese chloride for 18 months. At necropsy, the animals showed localized degeneration in the globus pallidus and striatum (44). Pentschew et al exposed rhesus monkeys to multiple intramuscular injections of MnO₂ (suspended in olive oil) (59). After 9 months the animals began to show motor symptoms with gait and balance disturbances and generalized clumsiness. One animal was killed, and the brain was described in detail. The findings included severe damage to the medial portion of the globus pallidus with dramatic loss of neurons and gliosis with “immature” glia having the appearance of Alzheimer type 2 astrocytes. Similar changes were seen in the substantia nigra pars reticularis and the subthalamic nucleus. The SNc was intact. The authors reviewed the human pathology literature and concluded: “the neuropathologic findings in the manganese monkey showed such striking similarities to those in human cases of manganese encephalopathy that they could be said to be identical.”

Eriksson et al described the effects of chronic subcutaneous injections of manganese oxide in rhesus monkeys (60). The animals developed an unsteady, hypocaotic gait with an action tremor and clumsiness of the limbs. At necropsy, there was severe nerve cell loss and astrogliosis in the globus pallidus with preservation of the caudate and putamen. While striatal dopamine levels were said to be low, there was no loss of pigmented neurons in the SNc or locus coeruleus and a ¹¹C-L-dopa PET study was normal (61).

In 1980 Gupta et al reported the appearance of monkeys who had oral exposure to manganese chloride, and these authors claim to have seen evidence of damage to the pigmented neurons of the substantia nigra in the exposed monkeys (62). However, the data they provided do not permit confirmation of this finding. The article contains no quantitative assessment of damage to the SNc, and the only evidence provided for this finding is photomicrographs of an exposed and unexposed monkey. Specifically, Figures 3a

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and 3b in the Gupta et al publication (62) are said to represent a single pigmented neuron of the substantia nigra stained with silver diamine in a control and manganese-treated monkey. However, the diameter of the neuronal soma in the control monkey depicted in this figure is at least twice that of the neurons in a control monkey pictured in Figure 1 (same reported magnification) and is well beyond the known dimensions of such cells. Furthermore, the figures do not provide sufficient cytologic detail (i.e. the appearance of the nucleus or outer cell membrane of the neuron) to permit the reader to confirm the purported finding of cellular damage to these pigmented neurons.

Finally, Olanow et al exposed 3 adult rhesus monkeys to weekly manganese chloride injections administered intravenously (38, 63). Two of the exposed animals developed a severe parkinsonian syndrome characterized by gait disturbance, bradykinesia, rigidity, and facial grimacing (but not tremor), which did not respond to levodopa treatment. MRI revealed bilateral high signal abnormalities in the striatum and globus pallidus on T1-weighted scans, indicative of manganese deposition. Striatal fluorodopa uptake on the PET scan was normal in each of the animals, as were postmortem dopamine levels, indicating preservation of the nigrostriatal dopaminergic system. In contrast, striatal raclopride binding on PET was reduced, suggestive of damage to striatal neurons. At necropsy, prominent gliosis and Alzheimer type II astrocytes were seen in the globus pallidus, especially its medial portion, and there was no evidence of damage to neurons of the SNc.

**DISCUSSION**

It is clear that manganese can act as a neurotoxin and produce a parkinsonian syndrome. As reviewed here, most of the reported morphologic studies (11 of 14) show a consistent and characteristic pattern of damage primarily involving the globus pallidus (especially its medial portion) and to a lesser extent the striatum with sparing of the SNc and no Lewy bodies (Table 1). The 3 other autopsied cases reported to have manganese exposure are consistent with alternate diagnoses. The case reported by Voss did not indicate damage to the pallidum or the SNc and is almost certainly an instance of amyotrophic lateral sclerosis in a person who had incidental exposure to manganese (55). The cases reports by Scholten and by Bernheimer et al did note changes in the SNc, but the clinical picture and pathologic findings are consistent with different conditions and do not follow the pattern of damage described in any other clinical or experimental case of manganism (56, 58). The patient described by Scholten probably represents a case of multiple system atrophy with a completely different pattern of clinical findings and pathologic lesions than those described in patients with manganism (56). The patient reported by Bernheimer et al with SNc damage and Lewy body formation probably represents an example of PD that occurred in a woman with coincidental manganese exposure many years before the onset of parkinsonian features (58).

All other cases described in the human literature show a specific and reproducible pattern of damage to the globus pallidus with sparing of the SNcs (explicitly stated in some cases and not reported in others, which we assume implies that none were found). The animal literature precisely confirms these findings, demonstrating a pattern of damage after manganese intoxication that primarily affects the globus pallidus (particularly the inner segment) and to a lesser extent the striatum with sparing of the dopaminergic nigrostriatal pathway. The sole exception is the brief report of Gupta et al for which insufficient information is available to confirm the reported findings (62).

The clinical picture, lack of response to levodopa, MRI changes, and neuroimaging studies that have been reported in patients and animals with manganese intoxication (2) are consistent with the pathologic pattern of damage to the pallidum and sparing of the SNcs seen in this condition and are distinctly different from what is found in PD (Table 2). PD is characterized by neurodegeneration involving SNc neurons, Lewy bodies, and reduction in striatal dopamine. PD can also affect other regions of the nervous system, including the dorsal motor nucleus of the vagus, nucleus basalis of Meynert, locus coeruleus, olfactory regions, and peripheral autonomic neurons (15, 18), but this is a very different pattern from what is found in manganism. None of these changes have been described in either a patient or animal model with manganese neurotoxicity. Further, the

<table>
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<th>Pathology</th>
<th>Degeneration of SNc neurons</th>
<th>Degeneration of pallidal neurons (especially internal segment), striatum</th>
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<tbody>
<tr>
<td>Clinical</td>
<td>Parkinsonism (bradykinesia, rigidity)</td>
<td>Parkinsonism (bradykinesia, rigidity)</td>
</tr>
<tr>
<td>MRI</td>
<td>Good response in virtually all patients</td>
<td>Minimal or no response</td>
</tr>
<tr>
<td>Fluorodopa-PET</td>
<td>Reduced striatal fluorodopa uptake</td>
<td>Normal</td>
</tr>
</tbody>
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SNC, substantia nigra pars compacta; MRI, magnetic resonance imaging; PET, positron emission tomography.

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pallidum, which is characteristically affected in manganese neurotoxicity, is specifically spared in PD. Indeed, careful stereologically based quantitative studies demonstrated no loss of neurons in either the external or internal portions of the globus pallidus, even in cases of advanced PD (19, 20). Rare cases of PD have been described without Lewy bodies (64), but these have primarily been seen in genetic cases for which there is debate as to whether they truly represent PD, and none has shown pallidal damage, as is seen with manganese intoxication.

With the exception of a small number of families displaying specific gene mutations, the cause of PD remains unknown (65). On the basis of epidemiologic data, it has been assumed for many years that environmental factors play a major role in the etiology of sporadic cases of PD. Nevertheless, no specific environmental etiologic factor that causes PD has been identified. Specifically, several recent epidemiologic studies involving many thousands of subjects have shown no increase in the frequency of PD in welders compared with control populations (8, 9, 11, 12). For example, in a large cohort study involving 12,595 employees of Caterpillar, there was no increase in reporting of PD or parkinsonism among welders compared with control subjects, and welding did not accelerate the age of onset of PD (50). Similarly, a case-control study from the Mayo Clinic that examined all incident cases of PD in Olmstead County over the previous 20 years found no increased risk of PD in welders or metal workers in comparison with age- and sex-matched control populations.

The absence of evidence of degeneration in neurons of the SNc or of Lewy body formation in manganese-induced parkinsonism cases or of damage to the globus pallidus interna in PD, makes it most unlikely that exposure to manganese represents an etiologic factor for the development of PD. Although manganese can gain access to the CNS and has the potential to be neurotoxic, it preferentially accumulates in and damages the striatum and pallidum, regions that are not affected in PD, and does not affect the SNc or other areas that are characteristically affected in PD. These pathologic findings suggest that manganese is a separate and distinct entity from PD with a recognizable pattern of neuropathologic damage that does not overlap with PD (Table 2). Indeed, the concept that manganese causes or accelerates the development of PD would presuppose the possibility that manganese promotes damage to the SNc (which it does not affect in classic human or experimental cases) and spares the globus pallidus (which is the primary site of damage in known cases of manganese). The body of pathologic evidence discussed here thus supports the position that manganese and PD are 2 specific and distinct disease entities and speaks strongly against the concept that environmental exposure to manganese plays a role in the etiology of PD.

ACKNOWLEDGMENTS

The authors indicate that they have provided legal testimony and expert consultation to the defendants in the welding litigation. English quotations that are included in the text are derived from publications originally published in foreign languages and are based on certified translations.

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