Neurologic Effects of Manganese in Humans:

A Review

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Manganese, which enters the body primarily via inhalation, can damage the nervous system and respiratory tract, as well as have other adverse effects. Occupational exposures occur mainly in mining, alloy production, processing, ferro-manganese operations, welding, and work with agrochemicals. Among the neurologic effects is an irreversible parkinsonian-like syndrome. An estimated 500,000 to 1.5 million people in the United States have Parkinson's disease, and physicians need to consider manganese exposure in its differential diagnosis. Since 1837, there have been many reports of cases and case series describing manganese toxicity. More recently, there have been epidemiologic studies of its adverse effects on health. Occupational medicine physicians can play critical roles in preventing the adverse health effects of manganese. *Key words*: manganese; neurotoxicity; parkinsonism; occupational medicine.

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Manganese, a naturally occurring element, and its inorganic and organic compounds have a variety of adverse health effects in humans. We undertook this review because of the steadily increasing number of findings in the medical and scientific literature concerning manganese toxicity (few of which have been reported in occupational medicine journals) and the increasing likelihood of physicians' encountering patients with manganese-induced adverse health effects or at risk of these effects. This review, based on relevant publications that we identified through a Medline search and references listed in textbooks and government publications, focuses primarily on the adverse health effects of inorganic manganese on the nervous system.

Manganese is the 12th most common element and the fifth most common metal in the earth's crust. Its most important ore, manganese dioxide (MnO_2)—also known as pyrolusite, is found primarily in Ukraine, South Africa, Chile, Canada, Australia, China, and the United States. Pure manganese is produced by igniting an ore concentrate with aluminum powder (Thermit process) or by electric arc furnacing.[1] More than eight million tons of manganese are extracted each year. Manganese is the fourth most widely used metal in the world, after iron, aluminum, and copper. The primary industrial use of manganese is in the manufacture of steel, with approximately 95% used for this purpose.

Although manganese can enter the body by ingestion or inhalation, inhalation is the primary route of entry in most occupational settings and ingestion of manganese is generally thought to be minimal.[2] While the primary human health effect of inhaled manganese is neurologic damage, inhaled manganese can also adversely affect other organ systems. Manganese is a respiratory tract irritant and can cause an inflammatory response in the lungs. It has been associated with metal fume fever,[3] pneumonitis,[1,4,5] cough and bronchitis,[6] chronic obstructive lung disease,[3] and decrease in lung function.[6,7] When manganese is ingested, approximately 1–3% is absorbed. Iron deficiency, which appears to enhance absorption, may contribute to variations in individual susceptibility to the adverse health effects of ingested manganese.[1,4,6,8-10] Whether it is ingested or inhaled, manganese is rapidly cleared from the blood by the liver. Almost all absorbed manganese—approximately 98%—is excreted in the bile.

Occupational exposure to manganese appears to be greatest in manganese mining,[11] but also occurs in manganese alloy production (it is used to produce steel of high resistance against mechanical strain),[12] manganese processing, ferro-manganese operations (smelters and foundries), welding (particularly welding of soft steel), work with agrochemicals (particularly fungicides) containing organic manganese, and dry alkaline battery manufacturing.[13]

Manganese chloride has been used as a catalyst and an animal feed supplement, and in fertilizer production. Manganese dioxide has been used in the manufacture of fireworks, matches, porcelain, and glass-bonding materials. Other manganese compounds are found in pigments in paints, varnishes, and inks. Permanganate compounds are utilized as decoloring agents in the ceramics and glass industries.[1] An organic manganese compound (methylcyclopentadienyl man-

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ganese tricarbonyl, MMT) has been used as an additive to increase octane in gasoline. Some experts are concerned that use of MMT in gasoline may be creating a tragic situation analogous to the widespread neurological dysfunction that resulted from the presence of tetraethyl lead in gasoline.[14-17] Landrigan states that exposure of the U.S. population to MMT in gasoline may represent a "grave threat to our national security."[16] Others believe that more research studies are necessary in order to determine the possible adverse health effects from chronic, low-dose exposure to MMT and its combustion products.[18]

The recommended threshold limit value (TLV) for occupational exposure to elemental manganese and its inorganic compounds is 0.2 mg/m^3 as a time-weighted average (TWA). This TLV is intended to minimize adverse effects in the central nervous, respiratory, and male reproductive systems.[19] Although blood manganese (Mn_B) and urinary manganese (Mn_U) represent exposure indicators on a group basis, they are not considered as suitable biomarkers of exposure because of high variability of results.[20]

Environmental sources of manganese exposure include food (tea leaves, pecans and grape nuts, meats, poultry, grains, and green leafy vegetables),[3] water (median levels in two studies of U.S. water were 5 µg/L and 10 µg/L),[14] air, dyes, batteries, and ceramics.

Manganese is an essential trace element; although large amounts can be toxic, small amounts of manganese are normally present in the human body. Manganese is a component of some enzymes and activates others. Manganese deficiency has been observed in animals.

Manganese can cause an irreversible parkinsonian-like syndrome, characterized by fixed gaze, bradykinesia, postural difficulties, rigidity, tremor, dystonia, and decreased mental status. This neurologic condition, first described in two manganese ore-crushing mill workers by Couper in 1837,[21] has been referred to as manganism.

Within the basal ganglia of the brain, manganese deposits and exerts its adverse effects primarily in the cells of the striatum and globus pallidus. Manganese can reduce dopamine in the caudate nucleus, norepinephrine in the hypothalamus, and neuromelanin in the substantia nigra. It appears that manganese may increase dopamine oxidation with associated free radical formation.[22,23] Magnetic resonance imaging studies have shown that manganese accumulates primarily in the globus pallidus.[24,25] Manganese causes neuronal loss and gliosis in the striatum, subthalamic nucleus, and pallidum, but little change in the substantia nigra. Some research indicates that gene polymorphism might influence individual susceptibility to manganese-induced neurotoxicity.[26]

There appear to be three stages in the development of manganism.[21] The first stage is a prodrome of malaise, somnolence, apathy, emotional lability, sexual dysfunction, weakness, lethargy, anorexia, and headaches.[2,27,28] If there is continued exposure, progression to a second stage may occur, with psychological disturbances, including impaired memory and judgment, anxiety, and sometimes psychotic manifestations ("manganese madness"), such as hallucinations.[28] This second stage generally lasts from 30 to 90 days.[29-32] The third stage consists of progressive bradykinesia, dysarthria, axial and extremity dystonia (abnormal tonicity resulting in impairment of voluntary movement), paresis, gait disturbances (typically a slow and clumsy gait), cogwheel rigidity, intention tremor, impaired coordination, and a mask-like face. Many of those affected may be permanently and completely disabled.

Early manganism may be reversible upon removal from exposure, but signs of neurologic damage in the third stage have generally been reported to be permanent and progressive, even after removal from exposure.[21,32] For the occupational physician the concept of prevention of manganism is extremely important, as it appears that the early signs of manganism may be reversible while the later neurologic manifestations may be permanent, if not progressive, despite removal from exposure. Early evidence of subclinical neurologic abnormalities may include reduced performance on neuropsychologic testing, poor eye–hand coordination, unsteadiness of the hands, reduced reaction time, poor postural stability, and reduced cognitive flexibility.

Manganism does appear to differ in significant ways from idiopathic Parkinson's disease. The tremor present in manganism is an intention tremor, while that present in idiopathic Parkinson's disease is a resting tremor.[6] Although there is some degree of dystonia in manganism,[28] it is generally not present in Parkinson's disease. Manganism generally does not respond well to levodopa therapy,[33,34] while idiopathic Parkinson's disease generally does. The areas of the brain most affected in manganism are the striatum and globus pallidus, with little effect on the substantia nigra; in contrast, the area of the brain affected by idiopathic Parkinson's disease is the substantia nigra, with the striatum and globus pallidus having only reduced dopamine concentration.[28] Other distinguishing features of manganism are the "cock walk" (a type of staggering gait), difficulty in walking backwards, a tendency to fall backward when pushed, and occasional psychiatric disturbances early in the course of the disease.[35]

It is estimated that there are between 500,000 and 1.5 million people with Parkinson's disease in the United States. According to studies conducted by the Mayo Clinic, the prevalence of Parkinson's disease in Olmstead County in Minnesota is approximately 200 cases per 100,000 people, and the estimated incidence of new cases each year is 20 per 100,000 people. An estimated 2% of Americans aged 65 and older develop Parkinson's disease. Given the many cases of Parkinson's disease and the many workers who have been exposed occupationally to manganese and manganese

compounds, it is likely that many of the cases diagnosed as Parkinson's disease in the United States and elsewhere are related to manganese exposure.

Physicians need to consider manganese exposure in the differential diagnosis of cases of suspected Parkinson's disease. Other diagnostic possibilities include drug-induced parkinsonism, essential tremor, multisystem atrophy, progressive supranuclear palsy, Huntington's disease, normal-pressure hydrocephalus, multiple lacunar strokes, pugilistic (post-traumatic) parkinsonism, and depression.[36]

REVIEW OF PUBLISHED REPORTS OF NEUROLOGIC EFFECTS OF MANGANESE

Case reports and case series describing manganese toxicity in humans date back to 1837 (Table 1). Edsall et al. (1919) summarized the characteristic findings of chronic manganese poisoning, in order of frequency: a history of work in manganese dust for at least three months; langour and sleepiness; stolid, mask-like facies; low monotonous tone and "economical speech"; muscular twitching; calf cramps and stiffness in leg muscles; slight increase in tendon reflexes; ankle and patellar clonus; retropulsion and propulsion; a peculiar slapping gait; and occasional uncontrollable laughter and, less frequently, uncontrollable crying.[37]

A number of epidemiologic studies have assessed and characterized adverse health effects, primarily among manganese-exposed workers. Illustrative studies and their findings are described below in chronological order of publication. (The findings of these studies are, in general, concordant with findings of animal studies concerning manganese,[38-48] although animal studies are not the focus of this paper.)

Schuler et al. (1957) studied 15 workers in a manganese-ore mine in Chile who were thought to have characteristic manganese poisoning.[2] This mine was chosen because the incidence rate of new cases increased sharply during a brief period due to dry pneumatic drilling. These workers were chosen from among all employees based upon two criteria: 1) long-term exposure and/or 2) the presence of symptoms or gross changes suggestive of manganism. Durations of exposure averaged eight years and two months (range: nine months to 16 years). Although all 15 workers had psychomotor disturbances, neurologic symptoms occurred with greater frequency and consistency. The authors attributed variability in duration of exposure for development of disease to 1) frequent changes in jobs and in the materials being mined, and 2) variations in natural ventilation that resulted in fluctuations in concentrations of airborne manganese dust. The authors believed that airborne manganese concentrations frequently exceeded occupational exposure limits. Cortical symptoms occurred most often among workers exposed to the highest manganese dust concentrations.

Abd El Naby and Hassanein (1965) described 45 cases of manganese poisoning in Egypt in an area where manganese miners lived.[49] Neuropsychiatric symptoms had developed between five months and 25 years after start of manganese exposure. Insidious onset with fatigue and langour was frequently reported, with these symptoms progressing to weakness, stiffness of gait, and balance disturbances. Marked emotional and neurovegetative disturbances were reported. The authors concluded that chronic manganese poisoning is a crippling disease with permanent disabilities, particularly related to use of the lower extremities. None of the cases showed any improvement after removal from the mines; in fact, all of them had neurologic disabilities that progressed after cessation of exposure.

Tanaka et al. (1969) studied manganese exposure in 75 Pennsylvania industrial plants and found that 12 plants had exposures in excess of the TLV for manganese.[4] Workers were examined in plants with high manganese exposures and also in several plants with low exposures. Of 117 workers from plants with excessive exposures, seven (6%) were found to have definite signs and symptoms of manganese poisoning. Two had been exposed in a manganese ore-crushing mill, one from arc-burning of 11%-manganese steel, and four in a large steel plant that casted and crushed ferro-manganese alloys. One case occurred in a general laborer for whom the diagnosis of manganese-caused neurologic problems was missed for many years because an adequate occupational history was never taken. Another worker presented with neurologic signs and was appropriately diagnosed with early manganism. An extensive industrial hygiene survey conducted at his plant revealed uncontrolled, high exposures to manganese. Despite removal from exposure, his health did not improve. The third case occurred in a burner of manganese steel who presented with signs of parkinsonism thought due to manganese after only one year of work in that environment. He improved symptomatically after chelation therapy.

Greenhouse (1971) described four laborers in a U.S. factory where manganese ore was crushed, processed into various-sized particles, and prepared for shipment.[50] These workers developed a progressive illness, with reduction in gross body movements and gait impairment. They also had difficulty in arising from the supine or sitting position, and invariably fell when walking backwards. They had relatively little face or limb hypokinesia, and no dystonia, rigidity, tremor, dysarthria, sialorrhea, other parkinsonian signs or symptoms, or psychiatric symptoms. Greenhouse concluded that these cases represented manganese intoxication since the laborers had been well before exposure and factory workers had handled no material except manganese. He observed that these workers had somewhat different neurologic deficits than had been previously described and suggested that there might be

TABLE 1. Illustrative Case Reports and Case Series of Manganese Exposure and Neurologic Disorders

Author (Year)	Country	N	Exposure*	Disorders Described
Couper (1837)	Scotland	5	O: Grinding manganese	Paralysis of motor nerves, especially in lower extremities
Edsall (1919)	USA	3	O: Mill work	Various neurologic abnormalities
Canavan (1934)	USA	1	O: Mill where manganese fractions were separated from other ores	Manganese poisoning, with leg stiffness, abnormal gait, frequent falls, fatigability, and sleepiness. Autopsy performed after accidental death revealed brain atrophy over the vertex and lateral aspects, dilatation of the ventricles with marked shrinking of basal ganglia. Degeneration of nerve cells, satellitosis and gliosis were found in the basal ganglia and marked focal scars were seen in the caudate nucleus and the globus pallidus.
Kawamura (1941)	Japan	16	R: Well water	Extrapyramidal, motor symptoms
Rodier (1955)	Morocco	150	O: Manganese mining	Wide variety of symptoms and neurologic signs
Penalver (1957)	Cuba	1	O: Manganese mining	Severe neurologic disturbances
Schuler (1957)	Chile	15	O: Mining manganese ores	Chronic manganese poisoning and manganism
Whitlock (1966)	USA	2	O: Manganese steel work	Chronic neurologic disorders
Tanaka (1969)	USA	7	O: Various	Neurologic screening of 117 workers from plants with excessive manganese exposure revealed 7 cases found to have definite signs and symptoms of manganese poisoning. Clinical case descriptions of 3 cases.
Emara (1971)	Egypt	8	O: Dry battery industry	Chronic psychosis, Parkinson's disease, choreoathetosis
Greenhouse (1971)	USA	4	O: Manganese ore processing	Manganese intoxication and neurologic deficits, some resembling parkinsonism
Smyth (1973)	USA	5	O: Ferro-Mn alloy	Parkinsonism
Chandra (1974)	India	12	O: Manganese miners	Chronic manganese poisoning
Cook (1974)	USA	6	O: Mn ore	Chronic manganese intoxication
Kilburn (1987)	Australia	16	R: Possibly water	Unexplained neurologic dysfunction
Huang (1989)	Taiwan	6	O: Ferro-manganese alloy factory	Chronic manganese intoxication and parkinsonism
Wang (1989)	Taiwan	6	O: Ferro-manganese smelter	Parkinsonism
Goldsmith (1990)	Israel	13	R: Possibly maneb	Parkinson's disease
Huang (1993)	Taiwan	6	O: Ferro-manganese alloy factory	Chronic manganese intoxication and parkinsonism
Meco (1994)	Italy	1	O: Maneb	Parkinsonian symptoms developed 2 years after exposure ended
Ono (1995)	Japan	1	Total parenteral nutrition	Elevated blood manganese level associated with abnormal MRI
Huang (1998)	Taiwan	5	O: Ferro-manganese alloy factory	Chronic manganese intoxication and parkinsonian syndrome
Discalzi (2000)	Italy	1	O: Welding	Parkinsonism
Ono (2002)	Japan	1	O: Welding	Chronic manganese poisoning with myoclonic involuntary movement
Woolf (2002)	USA	1	R: Well water	Chronic manganese exposure with poor verbal and visual memory

*O = occupational exposure; R = residential exposure.

References for Reports Cited in Table 1

Couper J. On the effects of black oxide of manganese when inhaled into the lungs. Br Ann Med Pharmacol. 1837; 1: 41-2.

Edsall DL, Wilbur FP, Drinker CK. The occurrence, course and prevention of chronic manganese poisoning. J Ind Hyg. 1919; 1: 183- 93.

Canavan MM, Cobb S, Drinker CK. Chronic manganese poisoning: report of a case, with autopsy. Arch Neurol Psychiatr. 1934; 32: 501-12.

Kawamura R, Ikuta H, Fukuzumi S, et al. Intoxication by manganese in well water. Kitasato Arch Exp Med. 1941; 18: 145-71.

Rodier J. Manganese poisoning in Moroccan miners. Br J Ind Med. 1955; 12: 21-35.

Penalver R. Diagnosis and treatment of manganese intoxication. AMA Arch Ind Health. 1957; 16: 64-6.

Schuler P, Oyanguren H, Maturana V, et al. Manganese poisoning: environmental and medical study at a Chilean mine. Ind Med Surg. 1957; 26: 167-73.

Whitlock CM, Amuso SJ, Bittenbender JB. Chronic neurological disease in two manganese steel workers. Am Ind Hyg Assoc J. 1966; 27: 454-9.

Tanaka S, Lieben J. Manganese poisoning and exposure in Pennsylvania. Arch Environ Health. 1969; 19: 674-84.

References for Reports Cited in Table 1

Emara AM, El-Ghawabi SH, Madkour OI, et al. Chronic manganese poisoning in the dry battery industry. Br J Ind Med. 1971; 28: 78-82.
Greenhouse AH. Manganese intoxication in the United States. Trans Am Neurol Assoc. 1971; 96: 248-9.
Smyth LT, Ruth RC, Whitman NE, et al. Clinical manganism and exposure to manganese in the production and processing of ferromanganese alloy. J Occup Med. 1973; 15: 101-9.
Chandra SV, Seth PK, Mankeshwar JK. Manganese poisoning: clinical and biochemical observations. Environ Res. 1974; 7: 374-80.
Cook DG, Fahn S, Brait KA. Chronic manganese intoxication. Arch Neurol. 1974; 30: 59-64.
Kilburn CJ. Manganese, malformations and motor disorders: findings in a manganese-exposed population. Neurotoxicology 1987; 8: 421-30.
Huang C-C, Chu N-S, Lu C-S, et al. Chronic manganese intoxication. Arch Neurol. 1989; 46: 1104-6.
Wang J-D, Huang C-C, Hwang Y-H, et al. Manganese induced parkinsonism: an outbreak due to an unrepaired ventilation control system in a ferromanganese smelter. Br J Ind Med. 1989; 46: 856-9.
Goldsmith JR, Herishanu Y, Abarbanel JM, et al. Clustering of Parkinson's disease points to environmental etiology. Arch Environ Health. 1990; 45: 88-94.
Huang C-C, Lu C-S, Chu N-S, et al. Progression after chronic manganese exposure. Neurology. 1993; 43: 1479-83.
Meco G, Bonifati V, Vanacore N, et al. Parkinsonism after chronic exposure to the fungicide maneb (manganese ethylene-bis-dithiocarbamate). Scand J Work Environ Health. 1994; 20: 301-5.
Ono J, Harada K, Kodaka R, et al. Manganese disposition in the brain during long-term total parenteral nutrition. J Parenteral Enteral Nutr. 1995; 19: 310-2.
Huang C-C, Chu N-S, Lu C-S, et al. Long-term progression in chronic manganism: ten years of follow-up. Neurology. 1998; 50: 698-700.
Discalzi G, Pira E, Hernandez EH, et al. Occupational Mn parkinsonism: magnetic resonance imaging and clinical patterns following $CaNa_2$-EDTA chelation. Neurotoxicology. 2000; 21: 863-6.
Ono K, Komai K, Yamada M. Myoclonic involuntary movement associated with chronic manganese poisoning. J Neurol Sci. 2002; 199: 93-6.
Woolf A, Wright R, Amarasiriwardena C, et al. A child with chronic manganese exposure from drinking water. Environ Health Perspect. 2002; 110: 613-6.

a difference between the pathophysiologies of certain hypokinetic features of classical parkinsonism and those of manganese intoxication.

Chandra et al. (1974) studied 12 workers, all younger than 40, with suspected manganese poisoning among underground drillers in manganese mines in India.[51] They had been exposed to manganese for periods ranging from four to 16 years. A significant increase in serum calcium was described in the mild cases, and a significant increase in adenosine deaminase in the moderate cases. No relationship could be established between the period of exposure to manganese and the severity of poisoning. Normal or only slightly elevated serum manganese was observed. The authors concluded that estimation of serum manganese might have no significance in detecting manganese poisoning in its early stages, and that serum calcium could be very useful in early detection of manganese poisoning.

Saric et al. (1977) studied the relationship between manganese exposure and adverse health effects among 369 workers in the production of ferroalloys.[52] Sixty-two (16.8%) of the manganese alloy workers demonstrated neurologic impairment. The prevalence of neurologic signs appeared to be highest in the most exposed group, but the difference was not statistically significant. Tremor at rest was the neurologic abnormality most frequently detected.

Chandra et al. (1981) studied 60 welders (20 from each of three plants) and 20 control subjects for possible manganese poisoning.[53] The percentages of manganese in welding electrodes varied between 0.45 and 2.10 among plants. Durations of employment ranged from two years to more than 20 years. A total of 24 welders were diagnosed as having suspected early manganese poisoning. These diagnoses were based on increased urinary manganese levels, signs of early neurologic involvement (tremors and brisk deep-tendon reflexes), and increased serum calcium. However, the duration of exposure to welding fumes was not related to the presence of neurologic signs. The authors found that the urinary manganese levels in welders having signs of central nervous system involvement were much higher than those in controls. Serum manganese was felt to be too variable to be useful in diagnosis.

Barbeau et al. (1987) studied the distribution of Parkinson's disease in nine rural hydrographic regions of Quebec.[54] They found that Parkinson's disease prevalence was distributed unevenly among rural areas. The regions of high prevalence of Parkinson's disease were predominantly agricultural and areas of intensive market gardening, with high use of pesticides.

Roels et al. (1987) conducted a cross-sectional study among 141 men exposed to inorganic manganese in a manganese oxide and salt-producing plant (mean duration of exposure: 7.1 years; range: one to 19 years).[6] The results were compared with those of a matched control group of 104 subjects. The intensity of manganese exposure was moderate. Psychomotor testing was more sensitive than standardized neurologic examination for early detection of the central nervous system (CNS) effects of manganese. Significant alterations were found in simple reaction time (visual), audioverbal performance, short-term memory capacity, and hand tremor (eye–hand coordination and hand steadiness). There were no clear-cut dose–response relationships between urinary manganese (or duration of manganese exposure) and the prevalence

of abnormal CNS or biological findings. Prevalence of hand tremor and increased serum calcium were related to blood manganese. The response to the eye-hand coordination test suggested the existence of a blood manganese level threshold at about 1 μg of manganese per 100 mL of whole blood. The authors concluded that this study demonstrated that a worker exposed to airborne manganese dust at a concentration of about 1 mg/mg^3 for less than 20 years may present preclinical signs of manganese intoxication, and that psychomotor testing may be a sensitive tool to detect the CNS effects of manganese at an early stage.

The report of two young agricultural workers with a parkinsonian syndrome who had been exposed to maneb, a manganese-containing fungicide, led Ferraz et al. (1988) to study 50 male rural workers who had had maneb exposure and a comparison group of 19 rural workers without known maneb exposure.[55] They found in the maneb-exposed workers a statistically significant increase in the prevalence of plastic rigidity, with the cogwheel phenomenon as well as symptoms of headache, fatigue, nervousness, memory complaints, and sleepiness. These investigators also found that postural tremor, cerebellar signs, and bradykinesia were more prevalent in the maneb-exposed group, although this increase was not statistically significant.

Huang et al. (1989) described six cases of chronic manganese intoxication in workers at a ferromanganese alloy factory in Taiwan.[29] Diagnosis was confirmed by assessing increased manganese concentrations in the blood, scalp, and pubic hair, with values ranging from three to 300 times normal. Elevated manganese levels in the blood were thought to represent acute intoxication, while the elevated levels in the scalp and pubic hair were thought to represent chronic intoxication. In addition, high manganese levels in the work environment were discovered, with the highest being approximately 28 mg/m^3. The authors concluded that these six workers demonstrated a bradykinetic-rigid syndrome that was indistinguishable from Parkinson's disease and responded to levodopa treatment. (See 1993 and 1998 follow-up study results below.)

Kondakis et al. (1989) studied 188 people aged 50 years and older in three areas with different concentrations of manganese in their drinking water, although the three groups had similar social and dietary characteristics.[56] They found statistically significant differences in chronic manganese poisoning and hair manganese concentrations. They concluded that the concentration of manganese in drinking water was related to prevalence of the neurologic signs of chronic manganese poisoning.

Wang et al. (1989) described six cases of parkinsonism that developed among eight workers performing electrode fixation or welding in a ferromanganese smelter.[57] The ventilation system had broken down and had not been repaired for eight months. The studied workers were exposed for 30 minutes each day, seven days a week, to high airborne manganese concentrations greater than 28.8 mg/m^3. The authors found a consistent trend between manganese exposure and extrapyramidal signs, and concluded that manganese had played a causative role in the development of these cases. All six workers were below the usual age of onset of idiopathic Parkinson's disease: two were under age 47 and the other four under age 40. All six had worked in the same occupational setting, where the airborne manganese concentration usually exceeded 28.8 mg/m^3, and all but one (who had left work there six months before) had elevated blood manganese concentrations (>20 μg/L). Alternative causes of parkinsonism were considered and ruled out. After the ventilation system was repaired, the air concentration of manganese during electrode fixation and welding decreased to less than 4.4 mg/m^3 and no new case of parkinsonism was observed. The authors concluded that this outbreak of parkinsonism resulted from exposure to high concentrations of manganese fumes due to breakdown of the ventilation system.

Hertzman et al. (1990) performed a case–control study of 57 cases of Parkinson's disease and 122 controls in a mountainous, rural area of British Columbia.[58] They found a statistically significant increased risk of Parkinson's disease associated with work in orchards and a marginally significant increased risk associated with work in planer mills.

Sjögren et al. (1990) studied neuropsychiatric symptoms in 217 railroad track welders with the aid of the Q16 Questionnaire.[59,60] Semiquantitative data on exposure to metals, including aluminum, chromium, lead, manganese, and nickel, were recorded by questionnaire. Logistic regression was used to study the relation between exposure and the prevalence of symptoms. Welders exposed full-time to manganese for more than two years had a sixfold higher risk of three or more positive answers on the Q16 Questionnaire. The authors concluded that their results indicated that detailed psychometric studies should be performed on welders exposed long-term to specific metals, as such exposures might adversely affect the nervous system.

Hua and Huang (1991) performed comprehensive examinations of neurobehavioral function in two groups of workers with chronic exposures to industrial manganese and two control groups.[61] They found that there was no evidence of neurobehavioral impairment in the workers without parkinsonism, whereas impaired general intelligence, visuoperceptive impairment, defective manual dexterity, and decreased response speed were demonstrated in the workers with parkinsonism.

Wennberg et al. (1991) investigated 30 men (aged 20 to 64) at two steel smelter works who had had low-level exposure to manganese and 60 unexposed referents.[62] They found an increase in early subclinical signs of disturbances of the same type as Parkinson's disease. They

concluded that hygiene limits for manganese exposure (2.5 mg/m^3 in Sweden and 5.0 mg/m^3 in most other countries) were insufficient to protect workers from the adverse CNS effects of manganese.

Roels et al. (1992) studied the prevalence of neuropsychological and respiratory symptoms, lung ventilatory parameters, neurofunctional performance, and several biologic parameters in a group of workers exposed to manganese oxide dust in a dry alkaline battery factory and a matched control group.[63] The manganese workers performed several neurofunctional tests (visual reaction time, eye–hand coordination, and hand steadiness) less satisfactorily than did the control workers. For these tests, the prevalences of abnormal results were associated with lifetime integrated exposures to both total manganese dust and respirable manganese dust. These authors also found, on the basis of a logistic regression analysis, that an increased risk of peripheral tremor exists when the lifetime integrated exposure to manganese dust exceeds 3,575 µg or 730 µg of manganese per cubic meter per year for total or respirable dust, respectively.

Huang et al. (1993) conducted a follow-up study on the six workers with chronic manganese-induced parkinsonism upon whom they had earlier reported following cessation of manganese exposure.[35] Compared with the findings reported in their 1989 study, the parkinsonian symptoms of these patients demonstrated a slow progression, particularly in gait disturbances, such as freezing during turning and walking backward with retropulsion. The authors concluded that 1) patients with manganese-induced parkinsonism may develop increasing neurologic dysfunction long after cessation of exposure, and 2) their responses to levodopa are different from those of patients with Parkinson's disease. (See 1998 follow-up study results below.)

Mergler et al. (1994) studied nervous system dysfunction among 115 workers employed in manganese alloy production.[22] A matched-pair design was used; actively working men, with no history of workplace exposure to neurotoxins, were recruited from the region as referents. Stationary environmental sampling indicated that manganese levels varied widely. The alloy workers had significantly higher levels of whole blood manganese, although median values for both groups were within the normal range. No difference was observed for urinary manganese levels. Univariate and multivariate analyses of variance revealed that the pairs differed on symptom reporting, emotional state, motor functions, cognitive flexibility, and olfactory perception threshold; however, their verbal fluency, basic mathematics, reading capability, and attentional capacity were similar. The authors suggested that manganism probably progresses infraclinically on a continuum and that initial manifestations can be observed in well-designed population studies by using sensitive test methods.

Lucchini et al. (1995) investigated 58 workers at a ferroalloy plant who had had exposure to low air concentrations of manganese.[64] There were statistically significant relationships between blood manganese and urinary manganese, and between these biologic parameters and cumulative exposure index. In addition, all of these parameters correlated with abnormalities in several neurobehavioral tests.

Ono et al. (1995) described the case of a Japanese pediatric patient who had received two years of total parenteral nutrition (TPN) for chronic medical problems.[65] Manganese, among other trace elements, was added to the TPN solution. The patient's whole-blood manganese level during TPN was 135 µg/L (normal range 14.6 ± 4.7 µg/L). T1-weighted magnetic resonance images revealed high-intensity areas in the globus pallidus during TPN. Two months after the first magnetic resonance examination, manganese was removed from the patient's TPN solution. After a manganese-free period of five months, the whole-blood manganese level decreased to 20.0 µg/L. Abnormal high-intensity lesions in the globus pallidus on T1-weighted images contemporaneously disappeared. There were no neurologic manifestations that were related to the elevated manganese level. The authors concluded that it was probable that the high manganese level was due to the manganese supplementation in TPN and was associated with abnormal high-intensity lesions on T1-weighted magnetic resonance images. They suggested that magnetic resonance imaging may be a useful noninvasive test to detect the degree and extent of deposition of manganese during TPN administration. (A recent article reviewed manganese intoxication and parenteral nutrition.[66])

Hochberg et al. (1996) studied 27 miners over the age of 50 years who had had heavy exposures to manganese for more than five years, ending more than five years before the investigation.[67] They found increased occurrences of resting tremor, action tremor, and repetitive hand movements among these miners. Hochberg and colleagues concluded that chronic asymptomatic exposure to manganese results in movement abnormalities late in life.

Sjögren et al. (1996) studied neurologic effects of welders who were exposed to both aluminum and manganese, using symptom questionnaires, psychological and neurophysiological tests, and determination of blood and urine concentrations of these metals as well as lead.[68] The 12 welders exposed to manganese had decreased motor function in five tests as well as an increased latency of event-related auditory evoked potential. Their median exposure to manganese was 270 hours to fumes that had approximately 22% manganese; none had had more than 1,700 hours of exposure. They did not have higher concentrations of manganese in their blood than the controls. The authors stated that it was remarkable that poor performance on tests was present

with such low exposure to manganese for such a short period of time in a well-ventilated outdoor atmosphere.

Gorell et al. (1997 and 1999) conducted a case–control study in the Detroit area to assess occupational exposures to manganese and four other metals as risk factors for Parkinson's disease.[69,70] They found that more than 20 years of exposure to manganese (OR = 10.61, 95% CI = 1.06–105.83) or copper (OR = 2.49, 95% CI = 1.06–5.89) was associated with Parkinson's disease. They also found occupational exposure for more than 20 years to combinations of lead–copper, lead–iron, and iron–copper were statistically significantly associated with Parkinson's disease. No association between occupational exposure to iron, mercury, or zinc and Parkinson's disease was found.

Huang et al. (1998) performed another follow-up study to assess the long-term clinical course of five surviving patients with chronic manganese intoxication.[32] (One of the original six patients had died in 1990.) These remaining five had been followed using the King's College Hospital Rating Scale for Parkinson's disease. Concentrations of manganese in blood, urine, scalp hair, and pubic hair were also followed. The mean scores in the Parkinson's disease rating scale over time increased from 15.0 ± 4.2 in 1987 to 28.3 ± 6.70 in 1991, and then to 38.1 ± 12.9 in 1995. Deterioration was most prominent in gait, rigidity, and speed of foot-tapping and writing. Tissue concentrations of manganese returned to normal over time from the very high levels that had been measured initially. The authors concluded that clinical progression in patients with manganese parkinsonism continues, even ten years after cessation of exposure.

Hudnell (1999) attempted to combine existing literature on non-occupational manganese exposures with results from a study in Quebec on environmental manganese exposure within the framework of a biologically-based dose–response model.[71] He concluded that his study, a study from Greece, and some clinical studies all suggested that the risk of a Parkinson-like syndrome diagnosis may increase with continued manganese exposure and aging.

Kim et al. (1999) performed an epidemiologic study on asymptomatic manganese-exposed workers in order to clarify the clinical significance of increased signal intensities on T1-weighted magnetic resonance imaging. They found that the proportion of workers with increased signal intensities was 46.1% among the exposed manual workers, 18.8% among the non-exposed manual workers, and 0% among the non-exposed clerical workers. They also found that among welders 73.5% demonstrated increased signal intensities. In no subject, however, did they observe clinical signs of manganism. They concluded that increased signal intensities on T1-weighted images reflect recent manganese exposure, but not necessarily manganism, and that it remains to be determined at what increase of signal intensity the progression of manganism from manganese exposure occurs.[71a]

Lucchini et al. (1999) administered a battery of neuropsychological tests to 61 ferroalloy workers and 87 controls. A cumulative exposure index was calculated for each alloy worker, and blood and urinary manganese concentrations were determined. A positive correlation was observed between blood manganese and airborne manganese concentrations in total dust. Dose–effect relationships were observed between some of the neuropsychological test results and cumulative exposure index. The authors concluded that their findings were consistent with a cumulative mechanism of action of manganese.[71b]

Luse et al. (2000) studied workers in the welding and metal-processing industries.[72] They found significantly higher levels of manganese in blood and hair than among control subjects, and observed that welders had a decline in memory, concentration difficulties, and problems with understanding text that they had read, as compared with control subjects.

Deschamps et al. (2001) examined 138 manganese-exposed workers and 137 control subjects.[73] The workers were employed in production of enamels, during which they had been exposed to airborne manganese for a mean duration of almost 20 years (at approximately 200 $\mu g/m^3$). The manganese-exposed workers had more subjective complaints than did the control subjects, although there was no effect of manganese exposure indicated in neuropsychological testing. The manganese-exposed workers did not have higher blood concentrations of manganese than the controls.

Racette et al. (2001) performed a case–control study of 15 career welders and two groups of control subjects with idiopathic Parkinson's disease.[74] They found that the welders developed parkinsonism at a younger age (on average, 46 years) than sequentially ascertained controls (63 years; $p < 0.0001$). They found no difference between the frequencies of welders and subjects in the two control groups in the following parameters: tremor, bradykinesia, rigidity, asymmetric onset, postural instability, family history, clinical depression, dementia, drug-induced psychosis, motor fluctuations, and dyskinesias. Positron emission tomography (PET) scans of two welders showed abnormalities typical of idiopathic Parkinson's disease. The authors concluded that parkinsonism in welders cannot be distinguished from idiopathic Parkinson's disease, except by early age of onset. (Discussion of their findings can be found in an accompanying editorial[75] and subsequent letters to the editor.[76-78])

Santos-Burgoa et al. (2001) conducted a cross-sectional study of a sample of long-term adult residents in a manganese mining district.[79] Environmental air manganese concentrations were two to three times higher than in other urban areas. Blood manganese levels ranged from 7.5 µg/L to 88 µg/L, with a median of 15 µg/L. On the basis of a multivariate logistic regression,

the authors determined that increased blood manganese levels increased the risk of deficient cognitive performance 12-fold. They also found reduction in plasma lipid peroxidation activity and poor motor function among those with elevated blood manganese levels.

Sinczuk-Walczak et al. (2001) assessed the effects of manganese on the nervous systems of workers who had been exposed in the ship and electrical industries (62 welders and 13 battery-production workers).[80] Increased emotional irritability, memory impairment, concentration difficulties, sleepiness, and limb paresthesias were found in the manganese-exposed workers. The authors concluded that manganese exposure up to 2.67 mg/m^3 (arithmetic mean, 0.4 mg/m^3; geometric mean, 0.15 mg/m^3) induces subclinical nervous-system effects.

Sassine et al. (2002) performed a population-based investigation of early neurotoxic effects of environmental manganese exposure to study the relationship among blood manganese levels, consumption of alcohol, and risk of alcohol use disorders and mental health.[81] They found that psychological distress increased along with risk for alcohol use disorders and consumption of alcohol. Prevalence odds ratios for cases of psychological distress with risk for alcohol use disorders were 1.34 among those with lower blood manganese levels and 4.22 among those with higher blood manganese levels. The authors stated that their findings suggested that high blood manganese levels increase the neuropsychiatric symptoms associated with risk for alcohol-use disorders.

In addition to the published reports described above, there have been a number of review publications, dating back to at least 1935, that have provided summaries and analyses of the adverse health effects of manganese.[8,12,82-93] None of these review publications, however, has been in the literature specific to occupational medicine.

ROLES FOR OCCUPATIONAL MEDICINE

Occupational medicine physicians can play critical roles in the prevention of the adverse health effects due to manganese. With regard to primary prevention, they can help identify workplace situations in which workers are being exposed, or may be exposed, to manganese, and to recommend effective primary prevention measures, such as using safe substitutes for manganese and manganese compounds and engineering measures to reduce worker exposure. Occupational medicine physicians can also develop and implement surveillance and medical monitoring programs for groups of workers at risk of manganism, such as miners and welders.

In addition, occupational medicine physicians can help identify workers who are in the early stages of chronic manganism and help remove them from further manganese exposure and provide appropriate treatment for them.

Occupational medicine physicians can help to develop and facilitate additional epidemiologic and toxicologic research projects on the adverse health effects of manganese and manganese compounds to address emerging research needs.[94]

Finally, occupational medicine physicians can play important roles in addressing public policy issues concerning manganese exposure, including the establishment of improved occupational and environmental regulations for manganese.[95,96]

References

1. Baxter PJ, Adams PH, Aw T-C, et al. Hunter's Diseases of Occupations. 9th ed. London, U.K.: Arnold, 2000: 107.
2. Schuler P, Oyanguren H, Maturana V, et al. Manganese poisoning: environmental and medical study at a Chilean mine. Ind Med Surg. 1957;26:167-73.
3. Hayes AW. Principles and Methods of Toxicology. 4th ed. Philadelphia, PA: Taylor and Francis, 2001: 659-60.
4. Tanaka S, Lieben J. Manganese poisoning and exposure in Pennsylvania. Arch Environ Health. 1969:19:674-84.
5. Davis JM. Manganese and Rhenium. In: Bingham E, Cohrssen B, Powell CH (eds). Patty's Toxicology. 5th ed. Vol 3. New York: John Wiley & Sons, 2001.
6. Roels H, Lauwerys R, Buchet J-P, et al. Epidemiological survey among workers exposed to manganese: effects on lung, central nervous system, and some biological indices. Am J Ind Med. 1987;11:307-27.
7. Boojar MMA, Goodarzi F. A longitudinal follow-up of pulmonary function and respiratory symptoms in workers exposed to manganese. J Occup Environ Med. 2002;44:282-90.
8. Penalver R. Manganese poisoning: The 1954 Ramazzini oration. Ind Med Surg. 1955;24:1-7.
9. von Oettingen WF. Manganese: Its distribution, pharmacology and health hazards. Physiol Rev. 1935;15:175-201.
10. Mena I, Horiuchi K, Burke K, et al. Chronic manganese poisoning. Individual susceptibility and absorption of iron. Neurology. 1969; 19: 1000-6.
11. Pal PK, Samii A, Calne DB. Manganese neurotoxicity: a review of clinical features, imaging and pathology. Neurotoxicology. 1999;20:227-38.
12. Wennberg A, Hagman M, Johansson L. Preclinical neurophysiological signs of parkinsonism in occupational manganese exposure. Neurotoxicology. 1992;13:271-4.
13. Mergler D, Baldwin M. Early manifestations of manganese neurotoxicity in humans: an update. Environ Res. 1997;73:92-100.
14. Frumkin H, Solomon G. Manganese in the U.S. gasoline supply. Am J Ind Med. 1997;31:107-15.
15. Solomon GM, Huddle AM, Silbergeld E, et al. Manganese in gasoline: are we repeating history? New Solutions. 1997;17-25.
16. Landrigan PJ. MMT, déjà vu and national security [editorial]. Am J Ind Med. 2001;39:434-5.
17. Zayed J. Use of MMT in Canadian gasoline: health and environment issues. Am J Ind Med. 2001;39:426-33.
18. Lyznicki JM, Karlan MS, Khan MK. Manganese in gasoline. J Occup Environ Med. 1999;41:140-3.
19. Documentation of the TLV's and BEI's. 7th ed. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 2001.
20. Apostoli P, Lucchini R, Alessio L. Are current biomarkers suitable for the assessment of manganese exposure in individual workers? Am J Ind Med. 2000;37:283-90.
21. Couper J. On the effects of black oxide of manganese when inhaled into the lungs. Br Ann Med Pharmacol. 1837;1:41-2.
22. Mergler D, Huel G, Bowler R, et al. Nervous system dysfunction among workers with long-term exposure to manganese. Environ Res. 1994;64:151-80.
23. Donaldson J, LaBella FS, Gesser D. Enhanced autoxidation of dopamine as a possible basis of manganese neurotoxicity. Neurotoxicology. 1980;2:53-64.
24. Lucchini R, Albini E, Placidi D, et al. Brain magnetic resonance imaging and manganese exposure. Neurotoxicology. 2000; 21: 769-76.

25. Dietz MC, Ihrig A, Wrazidlo W, et al. Results of magnetic resonance imaging in long-term manganese dioxide-exposed workers. Environ Res. 2001;85:37-40.
26. Zheng YX, Chan P, Pan ZF, et al. Polymorphism of metabolic genes and susceptibility to occupational chronic manganism. Biomarkers. 2002;7:337-46.
27. Rodier J. Manganese poisoning in Moroccan miners. Br J Ind Med. 1955;12:21-35.
28. Barbeau A, Inoué N, Cloutier T. Role of manganese in dystonia. In Eldridge R, Fahn S (eds). Advances in Neurology. New York: Raven Press, 1976: 339-52.
29. Huang C-C, Chu N-S, Lu C-S, et al. Chronic manganese intoxication. Arch Neurol. 1989;46:1104-6.
30. Mena I, Marin O, Fuenzalida S, et al. Chronic manganese poisoning. Clinical picture and manganese turnover. Neurology. 1967;17:128-36.
31. Greenhouse AH. Heavy metals and the nervous system. Clin Neuropharmacol. 1982;5:45-92.
32. Huang C-C, Chu N-S, Lu C-S, et al. Long-term progression in chronic manganism: ten years of follow-up. Neurology. 1998;50: 698-700.
33. Shinotoh H, Snow BJ, Chu N-S, et al. Presynaptic and postsynaptic striatal dopaminergic function in patients with manganese intoxication: a positron emission tomography study. Neurology. 1997;48:1053-6.
34. Lu C-S, Huang C-C, Chu N-S, et al. Levodopa failure in chronic manganism. Neurology. 1994;44:1600-2.
35. Huang C-C, Lu C-S, Chu N-S, et al. Progression after chronic manganese exposure. Neurology. 1993;43:1479-83.
36. Young R. Update on Parkinson's disease. Am Fam Physician. 1999;59:2155-67, 2169-70.
37. Edsall DL, Wilbur FP, Drinker CK. The occurrence, course and prevention of chronic manganese poisoning. J Ind Hyg. 1919; 1:183-93.
38. Pentschew A, Kovatch RM. Experimental manganese encephalopathy in workers. J Neuropathol Exp Neurol. 1963; 22:488-99.
39. Neff NH, Barrett RE, Costa E. Selective depletion of caudate nucleus dopamine and serotonin during chronic manganese dioxide administration to squirrel monkeys. Experientia. 1969; 25:1140-1.
40. Dastur DK, Manghani DK, Raghavendran KV. Distribution and fate of ^{54}Mn in the monkey: studies of different parts of the central nervous system and other organs. J Clin Invest. 1971;50:9-20.
41. Shukla GS, Chandra SV, Seth PK. Effect of manganese on the levels of DNA, RNA, DNase and RNase in cerebrum, cerebellum and rest of brain regions of rat. Acta Pharmacol Toxicol. 1976; 39:562-9.
42. Chandra SV, Shukla GS. Manganese encephalopathy in growing rats. Environ Res. 1978;15:28-37.
43. Bird ED, Anton AH, Bullock B. The effect of manganese inhalation on basal ganglia dopamine concentrations in rhesus monkey. Neurotoxicology 1984;5:59-66.
44. Morganti JB, Lown BA, Stineman CH, et al. Uptake, distribution and behavioral effects of inhalation exposure to managanese (MnO_2) in the adult mouse. Neurotoxicology. 1985;6:1-16.
45. Brouillet EP, Shinobu L, McGarvey U, et al. Manganese injection into the rat striatum produces excitotoxic lesions by impairing energy metabolism. Exp Neurol. 1993;120:89-94.
46. Olanow CW, Good PF, Shinotoh H, et al. Manganese intoxication in the rhesus monkey: a clinical, imaging, pathologic, and biochemical study. Neurology. 1996;46:492-8.
47. Witholt R, Gwiazda RH, Smith DR. The neurobehavioral effects of subchronic manganese exposure in the presence and absence of pre-parkinsonism. Neurotoxicol Teratol. 2000;22: 851-61.
48. Shukakidze A, Khetsuriani R, Darbaidze M, et al. The behavioral disorders in rats exposed to acute and chronic manganese intoxication. Ann Biomed Res Educ. 2001;1:4-13.
49. Abd El Naby S, Hassanein M. Neuropsychiatric manifestations of chronic manganese poisoning. J Neurol Neurosurg Psychiatry. 1965;28:282-8.
50. Greenhouse AH. Manganese intoxication in the United States. Transactions of the American Neurological Association, 1971; 96: 248-9.
51. Chandra SV, Seth PK, Mankeshwar JK. Manganese poisoning: clinical and biochemical observations. Environ Res. 1974;7: 374-80.
52. Saric M, Markicevic A, Hrustic O. Occupational exposure to manganese. Br J Ind Med. 1977;34:114-8.
53. Chandra SV, Shukla GS, Srivastava RS. An exploratory study of manganese exposure to welders. Clin Toxicol. 1981;18:407-16.
54. Barbeau A, Roy M, Bernier G, et al. Ecogenetics of Parkinson's disease: prevalence and environmental aspects in rural areas. Can J Neurol Sci. 1987;14:36-41.
55. Ferraz HB, Bertolucci PHF, Pereira JS, et al. Chronic exposure to the fungicide maneb may produce symptoms and signs of CNS manganese intoxication. Neurology. 1988; 38: 550-3.
56. Kondakis XG, Makris N, Leotsinidis M, et al. Possible health effects of high manganese concentration in drinking water. Arch Environ Health. 1989;44:175-78.
57. Wang J-D, Huang C-C, Hwang Y-H, et al. Manganese induced parkinsonism: an outbreak due to an unrepaired ventilation control system in a ferromanganese smelter. Br J Ind Med. 1989; 46:856-9.
58. Hertzman C, Wiens M, Bowering D, et al. Parkinson's disease: a case-control study of occupational and environmental risk factors. Am J Ind Med. 1990;17:349-55.
59. Sjögren B, Gustavsson P, Hogstedt C. Neuropsychiatric symptoms among welders exposed to neurotoxic metals. Br J Ind Med. 1990;47:704-7.
60. Hogsted C, Andersson K, Hane M. A questionnaire approach to the monitoring of early disturbances in central nervous system functions. In: Aitio A. Ruhimake V, Vainio H (eds). Biological Monitoring and Surveillance of Workers Exposed to Chemicals. Washington, DC: Hemisphere Publishing Corporation, 1984: 275-87.
61. Hua M-S, Huang C-C. Chronic occupational exposure to manganese and neurobehavioral function. J Clin Exp Neuropsychol. 1991;13:495-507.
62. Wennberg A, Iregren A, Struwe G, et al. Manganese exposure in steel smelters a health hazard to the nervous system. Scand J Work Environ Health. 1991;17:255-62.
63. Roels HA, Ghyselen P, Buchet JP, et al. Assessment of the permissible exposure level to manganese in workers exposed to manganese dioxide dust. Br J Ind Med. 1992;49:25-34.
64. Lucchini R, Selis L, Folli D, et al. Neurobehavioral effects of manganese in workers from a ferroally plant after temporary cessation of exposure. Scand J Work Environ Health. 1995;21: 143-9.
65. Ono J, Harada K, Kodaka R, et al. Manganese deposition in the brain during long-term total parenteral nutrition. J Parenteral Enteral Nutr. 1995;19:310-12.
66. Dickerson RN. Manganese intoxication and parenteral nutrition. Nutrition. 2001;17:689-93.
67. Hochberg F, Miller G, Valenzuela R, et al. Late motor deficits of Chilean manganese miners: a blinded control study. Neurology. 1996;47:788-95.
68. Sjögren B, Iregren A, Frech W, et al. Effects on the nervous system among welders exposed to aluminium and manganese. Occup Environ Med. 1996;53:32-40.
69. Gorell JM, Johnson CC, Rybicki BA, et al. Occupational exposures to metals as risk factors for Parkinson's disease. Neurology. 1997;48:650-8.
70. Gorell JM, Johnson CC, Rybicki BA, et al. Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson's disease. Neurotoxicology. 1999;20:239-48.
71. Hudnell HK. Effects from environmental Mn exposures: a review of the evidence from non-occupational exposure studies. Neurotoxicology. 1999;20:379-98.
71a. Kim Y, Kim KS, Yang JS, et al. Increase in signal intensities on T1-weighted magnetic resonance images in asymptomatic manganese-exposed workers. Neurotoxicology. 1999; 20: 901-8.
71b. Lucchini R, Apostoli P, Perrone C, et al. Long term exposure to "low levels" of manganese oxides and neurofunctional changes in ferroalloy workers. Neurotoxicology. 1999; 20: 287-98.
72. Luse I, Bake MA, Bergmanis G, et al. Risk assessment of manganese. Central European J Public Health. 2000; 8 suppl: 51.
73. Deschamps FJ, Guillaumot M, Raux S. Neurological effects in workers exposed to manganese. J Occup Environ Med. 2001;43: 127-32.
74. Racette BA, McGee-Minnich L, Moerlein SM, et al. Welding-related parkinsonism: clinical features, treatment, and pathophysiology. Neurology. 2001;56:8-13.

75. Rajput AH. Environmental toxins accelerate Parkinson's disease onset [editorial]. Neurology. 2001;56:4-5.
76. Pezzoli G, Canesi M, Antonini A, et al. Hydrocarbon exposure and Parkinson's disease [letter to the editor]. Neurology. 2000; 55:667-73.
77. Sadak AH, Schulz PE. Welding-related parkinsonism: clinical features, treatment, and pathophysiology [letter to the editor]. Neurology. 2001;57:1738-9.
78. Racette BA, Perlmutter JS. Welding-related parkinsonism: clinical features, treatment, and pathophysiology [letter to the editor]. Neurology. 2001;57:1739.
79. Santos-Burgoa C, Rios C, Mercado LA, et al. Exposure to manganese: health effects on the general population, a pilot study in Central Mexico. Environ Res. 2001;85:90-104.
80. Sinczuk-Walczak H, Jakubowski M, Matczak W. Neurological and neurophysiological examinations of workers occupationally exposed to manganese. Int J Occup Med Environ Health. 2001; 14:329-37.
81. Sassine M-P, Mergler D, Bowler R, et al. Manganese accentuates adverse mental health effects associated with alcohol use disorders. Biological Psychiatry. 2002;51:909-21.
82. Cotzias GC. Manganese in health and disease. Physiol Rev. 1958; 38:503-32.
83. Utter MF. The biochemistry of manganese. Med Clin North Am. 1976;60:713-27.
84. Barbeau A. Manganese and extrapyramidal disorders. Neurotoxicology. 1984;5:13-36.
85. Donaldson J, Barbeau A. Manganese neurotoxicity: possible clues to the etiology of human brain disorders. In: Gabay S, Harris J, Ho BT (eds). Metal Ions in Neurology and Psychiatry. New York: Alan R. Liss, 1985: 259-85.
86. Donaldson J. The physiopathologic significance of manganese in brain: its relation to schizophrenia and neurodegenerative disorders. Neurotoxicology. 1987;8:451-62.
87. Bleecker ML. Parkinsonism: a clinical marker of exposure to neurotoxins. Neurotoxicol Teratol. 1988;10:475-8.
88. Calne DB, Chu N-S, Huang C-C, et al. Manganism and idiopathic parkinsonism: similarities and differences. Neurology. 1994;44:1583-6.
89. Barceloux DG. Manganese. Clin Toxicol. 1999;37:293-307.
90. Mergler D. Neurotoxic effects of low level exposure to manganese in human populations. Environ Res. 1999;80:99-102.
91. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Manganese. Atlanta, GA: ATSDR, 2000.
92. Albin RL. Basal ganglia neurotoxins. Clin Neurobehav Toxicol. 2000;18:665-80.
93. Lee J-W. Manganese intoxication. Arch Neurol. 2000;57:597-9.
94. Aschner M. Manganese: brain transport and emerging research needs. Environ Health Perspect. 2000; 108 (suppl 3): 429-32.
95. Mergler D. Manganese: the controversial metal. At what levels can deleterious effects occur? Can J Neurol Sci. 1996;23:93-4.
96. Hermanus MA. Manganese—a public health concern: Its relevance for occupational health and safety policy and regulation in South Africa. Int J Occup Environ Health. 2000;6:151-69.