Manganese: the Controversial Metal.
At What Levels Can Deleterious Effects Occur?

Manganese (Mn) is of particular importance to Canadians due to the inclusion, since 1977, of an organomanganese compound (MMT) as an antiknock agent and to enhance octane in unleaded gas in this country. In the United States, the Environmental Protection Agency (EPA) opposed approval of MMT on the grounds that critical information is lacking on exposure and dose and on low level, chronic toxicity of manganese to humans. However, this decision was brought before the courts and won by the manufacturers on grounds unrelated to the health issue. As of January, 1996, it is permitted for use in the United States. The Environmental Defense Fund, a Washington-based group representing 300,000 members, along with 36 other advocacy groups have called upon the gasoline refiners and marketers to adopt an “MMT Free” policy until unleaded gas in this country. In the United States, the pound (MMT) as an antiknock agent and to enhance octane in gasoline has not always been consistent, probably due to variations in species, type of manganese administered, means and time frame of administration. The bulk of neuropathology (neuronal loss and gliosis) seems to be located at the striatum, subthalamic nucleus and pallidum, with little change at the substantia nigra, but lesions are also found throughout the cerebrum, the brain stem and the cerebellum. Most investigations note reduced concentrations of dopamine in one or more of the basal ganglia structures and a recent study of manganese intoxicated monkeys shows alterations in dopaminergic post-synaptic structures, with a reduction of D1 receptors in the striatum without a concomitant loss of D2 receptors. Different hypotheses have been put forward to explain how manganese affects dopaminergic neurotransmission, including, the formation of free radicals through glutatione reduction, decreased glutathione peroxidase activity, the auto-oxidation of dopamine via the transformation of Mn2+ to Mn3+, inhibition of mitochondrial respiration, abnormal hydrocarbon metabolism and excitotoxic processes through NMDA receptors.

The possible role of manganese in basal ganglia disorders secondary to liver failure has recently been brought to light by a series of very elegant studies. In this issue of the Journal, Hauser and coworkers7 (see page 95) report their findings relating blood manganese and brain MRI changes in patients with...
biopsy-proven cirrhosis. Their results, coupled to a recent publication on the subject,\(^8\) suggest that manganese homeostasis, carefully regulated by hepatic enzymes, fails in certain forms of liver dysfunction leading to high levels of blood manganese. Taken up by the basal ganglia, particularly the globus pallidus and substantia nigra, the increased levels of manganese are monitored as MRI abnormalities. Indeed, chronic hepatic encephalopathy, characterized by signs and symptoms of pyramidal and extrapyramidal dysfunction, and neuropsychiatric disorders bears many similarities to manganism.

The notion of manganese overload, raised by the Hauser and colleagues,\(^7\) is probably one of the key issues in manganese intoxication. Since more than 98% of the absorbed manganese is excreted in bile, it is possible that liver failure precludes the regular excretion, thereby increasing blood manganese levels. But is there a threshold over which the control system ceases to function or is it a gradual process with possible compensatory mechanisms? Is there a cascade of control mechanisms? Where does manganese uptake in the brain fit into this scheme? The results presented by Hauser et al.\(^7\) are similar to those reported by others\(^8\) showing very strong correlations between MRI T1 scores and blood manganese concentration. These results are not only important to the understanding of chronic hepatic encephalopathy, but may be key to comprehending what takes place with environmental exposure below levels of extreme overload.

Although blood manganese levels were significantly higher among the exposed as compared to non-exposed reference populations in reports of early nervous system dysfunction among manganese exposed workers,\(^9\) the observed levels were considerably lower than those reported by Hauser et al.\(^7\) in the cirrhotic patients (although the reference levels are in the same range). A few studies indicate that even in the presence of low level environmental or workplace manganese exposure, blood manganese levels between subjects with higher and lower exposures do not differ, although signs of mild neurological and/or neuropsychological dysfunction are present among subjects that are more highly exposed. Although in these situations, homeostatic mechanisms appear to be able to keep blood manganese within certain limits, the neurological responses may reflect a certain degree of present or past manganese overload in the brain.

One of the public health concerns about manganese related disorders is that they appear to be progressive, even when exposure has ceased. Previous case reports of progression of signs and symptoms of manganism, following cessation of exposure, have been confirmed by the studies on the Taiwanese ferro-manganese workers.\(^3\) According to the authors,\(^3\) parkinsonian symp-mtoms showed a slow progression; review of video records confirmed worsening of parkinsonism, particularly in difficulty in turning and a highly significant increase in the mean disability scores over a four year period. A case report on the MRI of a welder with manganism, revealed that after a period of 6 months with no exposure, manganese was cleared from the basal ganglia although the neurological signs and symptoms remained.\(^10\)

Hauser and colleagues\(^7\) aptly point out links between Mn intoxication, encephalopathy, parkinsonism and chronic liver disease. Studies of neurological manifestations associated to manganese levels in persons with hepatic disorders may be of particular importance in determining dose-effect relations, however, the role of deficiency states of calcium and magnesium, which can also be present in liver failure, must be considered.

In September, 1984, an issue of the journal, Neurotoxicology,\(^11\) dedicated to the memory of George C. Cotzias, a pioneer in the area of manganese metabolism and its relation to extrapyramidal disorders, presented a series of papers based on presentations at the First Manganese Neurotoxicity Symposium. In his keynote address to this meeting, the late André Barbeau challenged the idea that manganism is an experimental model for Parkinson’s Disease and proposed that manganese may be one of many “triggering factors” acting at the dopamine synapse to increase dopamine turnover. With the current renewed interest in manganese neurotoxicity and the urgent need to determine at what levels long term exposure to manganese hinders brain functions, the time is ripe to hold a Second Manganese Neurotoxicity Symposium that would bring together the findings from current research in all areas of manganese neurotoxicity.

REFERENCES