

## "MANGANESE MADNESS" CLUES TO THE AETIOLOGY OF HUMAN BRAIN DISEASE EMERGES FROM A GEOLOGICAL ANOMALY

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A pleasant aspect of Captain Mathew Flinders circumnavigation of Australia in 1803 was that he was generally well received by the aboriginal inhabitants at dozens of scattered communities along the continent's enormous coastline. That changed dramatically, however, when he ventured into the Gulf of Carpentaria, in Australia's Northern Territories. As the ship approached one of the larger islands, one of a cluster of several located in the western end of the gulf, the ships company were entranced by the blue colour of the waters in one particular bay. They promptly named it Blue Mud Bay. Launching a small boat to make an inspection onshore, they were surprised at the aggressive behavior of the local inhabitants. The belligerent reception of the shore party caused alarm among the crew of HMS Investigator. Captain Flinders recorded in the ships log, "They come at us very strangely... sending off their children and women and approaching with spears held in a threatening fashion."

The brilliant hue from the waters of the pristine bay owed its origin to huge deposits of manganese nodules. Later, these were to provide a major economic benefit to the island when they were mined. The island, called Groote Eylandt, one of the largest islands in the Gulf of Carpentaria, possesses a Dutch name though likely discovered by the Portuguese. Its location is 138 degrees east longitude and 14 degrees south, some 50 km off the east mainland coast of Arnhem Land Aboriginal Reserve.

At the Universite' de Montreal in the late eighties I was engaged on a research project that attempted to unravel the intricacies of neurodegenerative disease, particularly Parkinson's disease (PD). Especially puzzling to our group was the severe deficiency of the neurotransmitter dopamine that occurred in the mid-brain of this disorder. The reason for the loss of dopamine producing cells in the corpus striatum region of brain was an enigma and we searched for clues that could aid in understanding this phenome-

non. I was intrigued to learn from neurologist Dr Andre' Barbeau, that in the manganese mines of northern Chile some miners came down with symptoms quite similar to PD.

Of particular importance was the finding revealed at autopsy of a loss of dopamine cells in the same brain region as PD. Known among the villagers as "locura manganica," or manganese madness, and sometimes as the voodoo metal, the intoxication expressed itself by compulsive, bizarre, and aggressive acts in the early stages. Later, neurological symptoms similar to PD appeared. The possibility that manganese could be involved in PD was exciting to me and became a major focus for investigation in our laboratory. However, numerous attempts to uncover a rationale for the highly-selective neurotoxic insult of the metal on brain tissue under experimental conditions proved fruitless. The ability of a metal ion like manganese to induce a disorder of the brain similar to that of PD itself could provide a useful probe with which to uncover the underlying intricacies of metal-neuron interaction thus aiding in understanding the degenerative process in the central nervous system (CNS). More importantly to assist also in developing a rational drug therapy for the disorder.

An especially baffling aspect of our attempts to produce an experimental model of manganese intoxication, was the lack of a suitable animal species. Also, the effect of systemically-injected manganese salts depended not only on the type of animal, but also its age and the oxidation state of the metal. Later, we came to appreciate that an important aspect of the pathogenesis of manganism relates to the unique ability of the metal to undergo changes in oxidation state. Divalent manganese salts were relatively benign, whereas in the trivalent state they possessed potent neurotoxicity. A weird kind of Jekyll and Hyde phenomena. Toxic effects were greatly influenced by the route of injection. Aerosol inhalation with manganese dioxide dust of a particle size less than 10 microns

was particularly effective. However, prolonged administration of the aerosol to monkeys required periods as long as 18 months to two years before lesions in the dopamine-rich corpus striatum were found. Primates are especially useful in manganese intoxication studies since unlike rodents they possess the brain pigment, neuromelanin, which undergoes degeneration in PD.

A strange twist to the manganese story occurred in 1986 when I was invited to present a paper on manganese neurointoxication at the University of New South Wales in Sydney, Australia. Following my presentation, Professor John Cawte, of the Department of Psychiatry discussed his research at Groote Eylandt in the Northern Territories. As a transcultural psychiatrist among the aboriginal population on the island he had been intrigued by the presence of a strange neurological disorder among the community. Known locally as "bird disease" because of the peculiar stance that afflicted individuals adopt, it has similar features to amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease). The clinical features include congenital malformations, psychiatric problems, and symptoms reminiscent of motor neurone disease. Professor Cawte terms the condition, "Groote Eylandt Syndromes."

The island is also the site of the largest manganese mine in the Pacific. I was delighted to receive an invitation to visit the island since it is a closed aboriginal community reserve and therefore off limits to outsiders. During my stay I had the opportunity to visit the manganese mine site run by the Groote Eylandt Mining Company, a subsidiary of BHP. Although manganese levels among white miners are normal (150-200 nmol/l), likely because of occupational safety measures, among aboriginal inhabitants the levels are considerably higher, (400-700 nmol/l). Dr Mark Florence at CSIRO in Sydney has found that along with manganese dust from the mine being carried downwind to aboriginal community villages, additional sources of contamination are the soil and vegetables. Manganese concentration of soil ranged from 14,000 to over 100,000 ppm in contrast to a world average of 500 ppm. Fruits were also several

thousand fold higher. Aboriginals are earth dwellers and eat "bush tucker," consequently their exposure to manganese is considerable. Calcium levels in drinking water obtained from the Angurugu river were extremely low. Calcium levels regulate manganese uptake. Experimentally we have found an enormous increase in uptake of manganese during calcium deficiency in rats. Iron deficiency also results in a greatly enhanced intake of manganese. Epidemiological studies in the western Pacific region have revealed clusters of neurological disorders like Parkinsonism, Alzheimer's disease, and motor neurone disease in diverse geographic areas. Their location in Guam, Kii Peninsula, Japan, and Western New Guinea suggest an environmental agent(s) is a likely contributor to their etiology. The foci of neurological disorders on New Guinea, is only 600 km north of Groote Eylandt. These apparently disparate regions can be connected to Groote Eylandt by a line running through approximately 140 degrees of longitude. Local engineers indicate a geologic anomaly exists in this area of the Western Pacific. Anecdotal geological accounts suggest these regions could lie on top of the same rock basin. Studies by NIH researcher, Frank Garrutto, among the Chamorro tribe, have revealed a high incidence of motor-neurone disorders in the Western Pacific correlated with regions having low concentrations of calcium and magnesium in soil and water. Excessive amounts of metals such as manganese, or aluminum, and deficiencies of an essential mineral such as calcium or iron can greatly impede critical absorptive processes resulting in essential minerals becoming toxic. Due to its unique electronic configuration calcium acts like a goalkeeper in a hockey match. By deflecting potentially damaging metallotoxins it plays a pivotal role in maintaining mineral homeostasis.

Although data on the psychiatric manifestations of the Groote Eylandt Syndrome among aboriginal inhabitants is limited, violence is common. According to social service records arrests and incarcerations of the native population on the island are the highest in the country. Personal experience of this was obtained during my visit to the medical clinic. One individual, apparently frustrated by the long line-up, in

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a fit of rage threw a spear at the nursing sister. Fortunately she ducked in time as it thudded into the wall behind her!

It has been known for some time that there is a link between brain chemistry and aggression. Evidence that manganese maybe involved in the neurobiology of aggression is accumulating. Researchers at the University of California have found significantly higher levels of manganese in the hair of criminals convicted of murder, rape and other violent crimes. Dr Louis Gottschalk, professor of psychiatry at UCI, said that "manganese appears to be a marker for violence." Francis Crinella, professor of pediatrics at UCI in related studies reports that nutritional deficiencies such as calcium are common among criminals and exacerbate elevated manganese levels. Crinella also found high manganese in learning disabled children. This is particularly relevant since learning disabilities have been known for years to be a strong risk factor for criminality. Children have a reduced ability to excrete manganese and their brain

is selectively permeable to the metal ion making them particularly at risk. Serotonin, a key neurotransmitter, is reduced in violent individuals. The possibility that manganese could also be a physiological marker for detecting criminally aggressive individuals is exciting and supports a biological basis for violence. A pilot study is presently underway at California prisons to determine the effect of dietary intervention on violent prisoners. Preliminary data indicate that recidivism in younger inmates declined significantly following nutritional intervention using various neurotransmitter co-factors. In this regard, use of the manganese containing additive, MMT in North American gasolines has caused alarm among environmentalists who suggest chronic low level exposure of manganese from tailpipe emissions may constitute a serious public health risk. Whatever the eventual outcome of manganese role in the neurobiology of aggression, there is little doubt that unraveling its role in the geochemical environment and its relation to health will prove a stimulating challenge for the emerging field of medical geology.