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16. Abstract (Limit: 200 words)

Study is reported of chronic manganese poisoning in miners and factory workers. Topics include: symptoms of neurologic and psychiatric disorders; treatment; similarily to parkinsonism and distinction between the two disorders; response of patients to levodopa; and relationship between metabolism of catecholamines and of manganese.

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MANGANESE POISONING: Its Therapy, and the Relationship Between Metabolism of Manganese and That of Biogenic Amines

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Chronic manganese poisoning is an environmental disease of manganese miners and of workers in manganese mills. It occurs more frequently in the manganese mining villages of Russia, India, North Africa, Yugoslavia, Cuba, Chile, etc. (1). Its estimated incidence is as high as 25% of the exposed population in some areas and as low as 2 to 4% in Chile. It occurs after variable periods of exposure to ore dust by inhalation.

Symptoms. Chronic manganese poisoning has both psychiatric and neurological manifestations, the most crippling of which have been related to the extrapyramidal system of the brain. The psychiatric symptoms are transient, but the neurological damage may be irreversible although some patients experience partial regression of their symptomatology after early removal from exposure (1).

Consistently appearing in all cases in Chile but notably absent in reports from steel foundries and ore crushing plants in the U.S. (2,3) has been the occur-

rence of a psychotic period at the onset of the disease, defined by the villagers as "manganic madness." It is characterized by hallucinations, delusions, and compulsions; in most cases the patients are aware of the abnormal nature of these phenomena. The psychosis lasts from 1 to 3 months whether or not the patients are immediately removed from the mines (1). Towards the end of the psychotic period or immediately after it, neurological symptoms characteristic of extrapyramidal involvement emerge. In the Chilean patients these included loss of facial expression, rigidity, slowness of movements, diminution of postural reflexes, and impairment of speech. A few patients developed a dystonia similar to the spontaneously occurring dystonia musculorum deformans. In one study of U.S. workers in a crushing plant, rigidity was notably absent, while the slowness (hypokinesia) and impairment of balance were predominant (2,3).

Background for treatment. The successful treatment of Wilson's disease with metal-binding agents seemed to provide a precedent for treating chronic manganese poisoning since copper and manganese have chemical similarities and the two diseases present some clinical similarities. This notion was weakened when excesses of manganese were found only in the tissues of healthy, exposed manganese miners, whereas crippled ex-miners who were no longer exposed had cleared these loads. Their brain damage seemed to

have been caused by flooding with manganese, but their symptoms persisted after such flooding had been terminated. Even if some parts of their brains still contained an excess of metal, this must have been in a tightly sequestered state; it thus appeared that the brain had suffered a structural injury due to manganese. Neff et al. (4) injected monkeys with MnO_2 and produced rigidity, changes of posture, and tremor. The concentration of the neurotransmitters dopamine and serotonin in the caudate nuclei of the extrapyramidal system were reduced, but no anatomical changes were observed.

Similarity to parkinsonism. Manganese poisoning has many features in common with Parkinson's disease, in which the structural damage to the brain consists of depigmentation of the substantia nigra and the metabolic changes consist of diminished melanin in the substantia nigra and diminished catecholamines and serotonin in the corpus striatum (5). The function of melanins is still unknown, but the biogenic amines are neurotransmitters. Upon systemic administration, these amines are bound or inactivated in the periphery and are prevented from entering the brain; therefore, inactive precursors must be administered from which they can be synthesized by the brain (Fig. 1). A common precursor of both melanin and catecholamines is the amino acid 3,4-dihydroxyphenylalanine (dopa). The administration of L-dopa to parkinsonian patients

was found to improve them significantly, regardless of the cause of the disease; this suggests that the metabolic sequelae were related to the localization (not to the nature) of the brain damage.

Although the pathology of chronic manganese poisoning has not yet been sufficiently studied, it was speculated that at least some of the symptoms common to the two diseases might be due to similar metabolic sequelae within surviving neurons. In Parkinson's disease, slowly increasing doses of levodopa have produced marked improvement of rigidity and hypokinesia, and high doses have decreased or stopped tremor. During treatment some previously hypokinetic patients have developed involuntary movements; other side-effects have been the emergence of mental aberrations and intermittent loss of the therapeutic action of levodopa (5).

Response to levodopa. In manganic patients the response to levodopa has been a function of the neurological pattern of symptoms. Rigid, hypokinetic patients with loss of postural reflexes and impairment of gait have responded to doses greater than 3 grams per day with marked to total reduction of rigidity, improvement of postural reflexes and gait, and correction of hypokinesia, but no improvement of speech. The therapeutic effects lasted while levodopa was given (for periods of up to 4 years), but the symptoms reemerged after 7 to 10 days on placebo therapy.

Notably absent in these patients have been side-effects such as involuntary movements, mental aberrations, or intermittent loss of therapeutic effect. Several of these patients returned to minor menial jobs.

A second type, dystonic manganic patients, on doses of 4 to 5 grams of levodopa per day showed improvement of dystonia and diminution of passive muscular tonus. However, physical strain and emotional stress can trigger the appearance of dystonic crisis. After periods of 3 to 4 months, levodopa has lost its effectiveness, and dystonia has reemerged with greater intensity than the pretreatment level. Placebo administration for 10 to 30 days caused this abnormality to regress, and levodopa therapy was reinstituted with the same therapeutic effects as before.

A third type was represented by one patient without rigidity but rather with muscular hypotonus, tremor, slowness, and impaired postural reflexes. Treatment with 1.2 grams of levodopa per day caused a marked aggravation of hypotonia, impairment of postural reflexes, and further impairment of gait; 3 grams per day also caused worsening of tremor. Placebo administration restored pretreatment levels after 48 hours.

In the United States Rosenstock (2) has reported that in a patient working in a steel foundry levodopa improved mask-like face (Fig. 2), markedly improved rigidity, slightly improved slowness, and did not improve dystonia. Greenhouse (3) has reported in four

patients from a manganese ore crushing plant a clinical pattern of impairment of postural reflexes and slowness of movements without major extrapyramidal symptoms such as rigidity, tremor, etc.; these patients did not respond to doses of 5 grams of levodopa per day. These investigators have not reported major side-effects with levodopa treatment.

In summary, rigid, hypokinetic Chilean miners have responded in a sustained way to treatment with levodopa; an American industrial worker with rigidity responded less well; and American industrial workers with impairment of stability as the major finding did not respond at all.

Further Relationship between metabolism of catecholamines and of manganese. Cotzias has demonstrated in the pallid strain of mutant mice a link between the transportation of manganese and that of levodopa into the brain (6). This mutant exhibits congenital ataxia that can be prevented in offspring by feeding large amounts of manganese to mothers during pregnancy; furthermore, it is insensitive to the cerebral effects of levodopa. These findings are in contrast to those with black C57Bl/6J mice, different by one gene which show neither large requirements for manganese nor abnormal cerebral responses to levodopa.

Although brain concentrations of manganese are diminished in purina fed pallid mice, intraperitoneal injection of levodopa and of L-tryptophan, produces

smaller brain increases of levodopa, dopamine, and serotonin in pallid mice than in black mice. Thus a single gene appears to influence transport into the brain of manganese and of two amino acids in the same direction – if pallid and black mice indeed differ by only a single gene.

Finally, a large body of in vitro work shows manganese to be an antagonist of Ca^{++} in functions pertaining to release of acetylcholine and norepinephrine from motor, splenic, or vascular terminals. Ca^{++} increases the release of these neurotransmitters while manganese blocks it (7).

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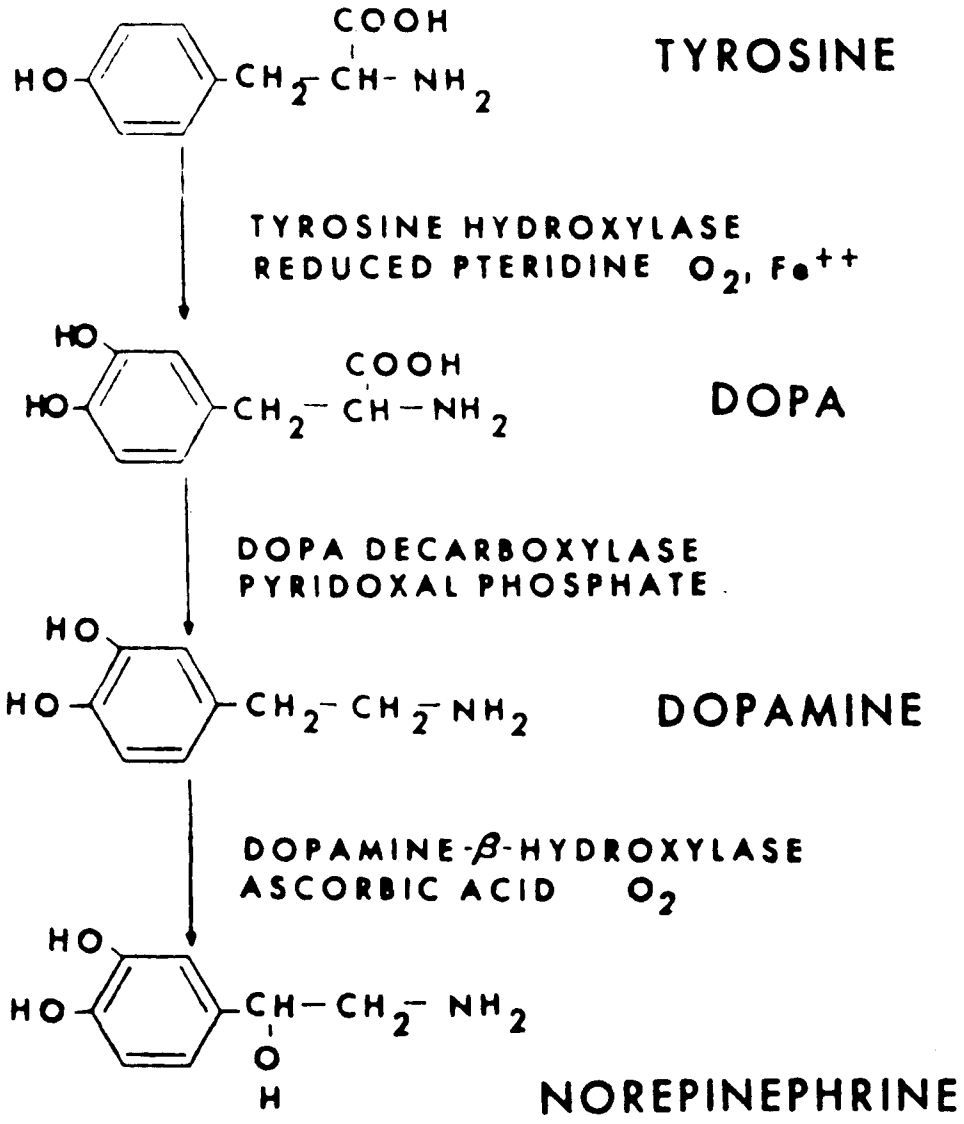
Figure 1. Figure 1 of Metabolic Modification of of Parkinson's Disease and of Chronic Manganese Poisoning. Cotzias, G.C. et al. Ann. Rev. of Med. 22: 307, 1971

Legend: "Known metabolic pathways of L-dopa ..."

Figure 2. Composite of Figure 1 and 2. Chronic Manganism. H. A. Rosenstock, JAMA 217: 1355, 1971.


COOH
HO
CH2 CH NH2
TYROSINE
TYROSINE HYDROXYLASE
REDUCED PTERIDINE O2, Fe++
HO
HO
COOH
CH2 CH NH2
DOPA
DOPA DECARBOXYLASE
PYRIDOXAL PHOSPHATE
HO
HO
CH2 CH2 NH2
DOPAMINE
DOPAMINE-β-HYDROXYLASE
ASCORBIC ACID O2
HO
HO
CH CH2 NH2
O
H
NOREPINEPHRINE