CHAPTER I

GENERAL INTRODUCTION
Manganese is an important metal widely distributed in the plants, animal tissues, soil and water. The deposits of manganese are found in the form of ores, the most important of which are pyrolusite ($\text{MnO}_2$), braunite ($2\text{Mn}_2\text{O}_3$, $3\text{Mn}_2\text{O}_3\cdot\text{MnSiO}_3$), hausmannite ($3\text{Mn}_3\text{O}_4$), rhodonite ($\text{MnSiO}_3$) and manganite ($\text{MnOOH}$). The chief ore producing countries are Russia, South America, India, South Africa, Ghana, Cuba and Morocco. In India extensive deposits of manganese ores are found in Bihar (Singhbhum), Gujarat (Baroda, Panch Mahal), Mysore, Orissa, Rajasthan and West Bengal. According to the latest estimates the total reserves of manganese ores are about 108 million tonnes (Times of India Directory and Year Book, Times of India Press, Bombay, 1972). The deposits in the main belt of Nagpur, Gondwana and Balaghat alone contain reserves of the order of 42 million tonnes. Out of the total output only a part of manganese ores is used in India and the rest is exported to U.S.A., U.K. and Japan. The foreign exchange earned by export of manganese ores comes to about rupees millions.

In India, the manganese industry according to the latest estimates employs over one lac workers which are faced with the toxicity hazards of manganese ores and its compounds.
Properties

<table>
<thead>
<tr>
<th>Chemical symbol</th>
<th>Mn</th>
</tr>
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<tbody>
<tr>
<td>Atomic number</td>
<td>25</td>
</tr>
<tr>
<td>Atomic weight</td>
<td>54.93</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>7.2</td>
</tr>
<tr>
<td>Oxidation states</td>
<td>${0, +1, +2, +3, +4}$</td>
</tr>
</tbody>
</table>

Industrial uses: Manganese ores are used for various industrial purposes such as:

(i) In the manufacture of alloys with iron, like ferromanganese and also with copper, zinc and aluminium.

(ii) In the manufacture of dry cell batteries.

(iii) In the manufacture of potassium permangenate which is a widely used disinfectant.

(iv) In ceramic industry - to decolourise glass.

(v) In the manufacture of various kinds of paints, varnishes, inks, and dyes including those used in Calico printing.

(vi) In the manufacture of matches and fireworks.

(vii) As fertilizer in agriculture to enrich manganese deficient soil.

(viii) Organic manganese compound methyl cyclopentadienyl-manganese tricarbonyl (MCT) is used as an additive in gasoline fuel and diesel for use in internal combustion engine and turbine engines.
Ore extraction and factory conditions: The extraction of ore involves many phases i.e. dry drilling, blasting, sorting and crushing etc. The exposure to ore dust in various phases of mining processes, besides exposure to manganese compounds used in other industries, are liable to produce chronic manganese poisoning in workers. The workers handling manganese ores are covered with ore dust while opportunities for washing are limited in their remote villages. According to Hodier (1935) drilling blast holes is the most hazardous phase in the mining processes.

Besides exposure to manganese ore dust, physico-chemical property and size of the dust particles are believed to be important factors in manganese poisoning as only atmospheric contamination by ore dust does not seem to be the only factor. According to Hodier (1935) fresh dusts obtained from drilling stone ores were more toxic than the old or dead particles, which undergo physicochemical modifications such as superficial oxidation, alteration of surface electric charges which might diminish its toxicity.

The clinical cases of manganese poisoning were reported for the first time by Couper in 1837 among the workers engaged in the grinding of manganese dioxide in a factory manufacturing bleaching powder in Scotland. In India the cases were detected by Miyogi (1938) among underground drillers in manganese mines.
in the district of Chhindwara (Madhya Pradesh). This lead to the appointment of an expert committee by the Government of India to investigate and report the causation, extent, diagnosis, treatment and preventive measures in regards to manganese poisoning amongst workers engaged in manganese mines, where the dust contents of the environment constituted the chief hazard. The enquiry committee in its report published in 1960 (Report₁) concluded that manganese intoxication amongst miners was only a problem due to improper measures of dust control.

In 1961 (Report₂) an environmental cum medical study was carried out at the insistence of Maharashtra Government in view of the persistent complaints of ill health from the employees of a plant manufacturing ferro-manganese alloys. The idea of this study was to find out the seriousness of poisoning when the manganese fumes constituted the chief hazard. The air sampling studies around the blast furnace, where the principal hazard was manganese fumes, and the other locations were carried out. It was found that the atmospheric concentrations of manganese were high at a few locations at the time of tapping.

Among other factory conditions i.e. in welding operations the fumes arising in metal arc welding may contain manganese compounds which originate from the electrode coating, the electrode metal and the base
material. The manganese fumes enter as its oxides. The concentration of manganese in the welder's breathing zone are low in open shops whereas in confined spaces the concentration are many times over toxic limits (Tolonen, 1972).

The industrial threshold limit values (TLV) for 8 hours for manganese in some countries (Tolonen, 1972) have been shown in Table 1.

**Manganese and Environmental Pollution**

A few reports regarding health hazards due to the air pollution with manganese near ferromanganese plants have caused a great concern recently. In USSR residents living within 500 m of a plant have complained unfavourable effects of manganese dust in the atmosphere. Children in that area had ear, nose and throat problems (Sullivan, 1969). Likewise in Italy increased frequency of pneumonia near a metallurgical plant emitting manganese dust has been reported (Pancheri, 1955). However, these reports and their possible relationship to the air borne manganese is not certain.

**Metabolism of manganese:**

Manganese is an essential element for both plants and animals. In plants it is mainly concentrated in the reproductive parts. Seeds are specially rich
<table>
<thead>
<tr>
<th>Country</th>
<th>TLV (8 hours)</th>
<th>mg/m³</th>
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</thead>
<tbody>
<tr>
<td>Yugoslav</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>FGR</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>CSSH</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>USSR</td>
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<td></td>
</tr>
<tr>
<td>Poland</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td>0.3</td>
<td></td>
</tr>
</tbody>
</table>
In manganese contents. Among foods nuts have the highest contents (22.7 ppm) of manganese (Browning, 1969).

In animals within certain concentration manganese stimulates respiration of tissues (von Oettingen, 1935). Deficiency of manganese in animals is known to produce defective growth, bone abnormalities and reproductive and nervous disorders (Browning, 1969).

In birds manganese deficiency produces porosis, characterized by deformity of the bone and dislocation of the achilles tendon (Wilgus et al., 1936; Wilgus and Patton, 1939).

In mammals ovarian dysfunction, testicular degeneration and high incidence of abortion are frequent in cases of manganese deficiency (Bentley and Phillips, 1951) Plumlee et al., 1956). The disorders of the central nervous system in mammals include lameness and loss of equilibrium.

The man's daily requirement of manganese is estimated to be at 1.2 mg which is easily obtainable from the freely chosen diets and therefore, the deficiency of manganese is unlikely to occur.
Manganese in the body is stored in the organs rich in mitochondria such as liver, kidney and pancreas. In a recent study (Wong and Fritze, 1969) pineal gland has been found to be the richest in manganese contents among 11 different parts of the brain.

(a) **Modes of absorption:** Absorption of inhaled manganese is through alveolar mucosa by the scavenger activity of alveolar phagocytes. Dusts of less than 5 microns reaching the alveoli come in contact with the phagocytes, which after ingesting them, enter the general circulation through lymphatic channels (Modier, 1955). The inhaled manganese is also transferred to the intestine (Mena et al., 1969). Absorption of manganese through gastrointestinal tract is slow and incomplete in normal conditions, chiefly because of low solubility of manganese in the gastric juice. Sufficient absorption can only be achieved with large doses which however, produce gastrointestinal injury (von Oettingen, 1935; Chandra and Imam, 1973). The absorption of manganese through the intestinal wall appears to be an active process and is almost similar to the absorption of iron (Mena et al., 1969). Alterations in the iron absorption and excretion are reported to influence parallel changes in the manganese metabolism (Diez Kwald et al., 1969). The absorption of most Mn$^{2+}$ is through duodenum where it is oxidised to Mn$^{3+}$ in the mucosa (Sandstead et al., 1970).
The absorption of inorganic manganese through skin is negligible (Rodier, 1955), but the organic compounds of manganese (i.e., MnCl) are absorbed through intact skin (Sullivan, 1969).

(b) Circulation: The absorbed manganese Mn$^{3+}$ is bound to specific plasma $\beta$-l-glubulin transport protein, the transmagnin (Cotzias, 1964; Cotzias and Papavasiliou, 1962) or transferrin (Keefer et al., 1970). In the red blood cells the manganese combines with the porphyrin molecule (Borg and Cotzias, 1958). The serum level of manganese remains relatively constant in an individual and the massive administration does not increase manganese level to a great extent (Mahoney et al., 1969). Injected manganese (Mn$^{54}$) rapidly disappears from the blood and is concentrated in organs rich in mitochondria (Borg and Cotzias, 1958). Manganese both intracellular and extracellular constitute the labile pool which is freely exchangeable (Schroeder et al., 1966) and is maintained in dynamic equilibrium by an unknown mechanism (Sandstead et al., 1970).

(c) Excretion: The main route of excretion is gastrointestinal tract. Besides, kidneys, hair also assume as minor organs in the elimination of manganese.

(i) Feces: Almost 95 to 98% of manganese is excreted in the gastrointestinal tract. Manganese in liver combines with bile salts which is excreted in the intestine.
Some of it is again reabsorbed and utilized (Maynard and Fink, 1956; Papavasiliou et al., 1966). The pancreas also eliminates some of the manganese through pancreatic juice in the intestine. If the passage of manganese through liver is blocked the pancreas concentrates manganese and maintains its homeostasis (Tolonen, 1972). Intravenously injected manganese ($^{54}\text{Mn}$) is excreted at the rate of 5% during the first day and even less thereafter (Mena et al., 1969). However, excreted manganese in feces reflects both the amounts not absorbed and the amounts absorbed and excreted.

(ii) Urine: Normally very little manganese is excreted in the urine (Kehoe et al., 1940). However, in excessive manganese exposure the urinary excretion is much higher (Tanaka and Lieben, 1969; Tolonen, 1972).

(iii) Hair: Hodier (1955) considers hair as the second important route for the elimination of manganese. Simons and Meyer (1971) have reported that the chest hair have manganese concentration three times more than the concentration in the scalp hair.

Retention of manganese is not common. However, some manganese may be retained in the body in the melanin granules in the central nervous system and pineal body (Cotzias, 1964; Cotzias et al., 1964; Wong and Fritze, 1969).
**Toxicology of manganese poisoning:** In acute toxicity manganese produces metal fume fever caused by inhalation of manganese (Browning, 1969). In chronic poisoning manganese is primarily a nerve toxin and it produces psychic and neurological disorders. Manganese poisoning is generally chronic which is slow and progressive. It usually takes few months to years to develop neurological syndrome after manganese exposure. However, in some cases symptoms may develop after one or more months of work or may even appear suddenly within a week accompanied by severe lumbar pain (Rodier, 1955).

The clinical cases of manganese poisoning have been classified into three phases by Rodier (1955).

(i) **The prodromal period:** The first disorders are subjective which are nonspecific such as heavy tiredness, muscular pain and weakness, headache, mental excitability and muscle spasms etc. The signs may, however, vary from patient to patient.

(ii) **The intermediate phase:** In this phase certain objective symptoms may develop. The earliest symptoms are disturbances of speech such as monotonous voice, lacking pitch and modulation. Words are slow, irregular and badly articulated. The laughter is spasmodic. Loss of coordinated movements begin. Climbing or descending ladder becomes difficult. Backward walking becomes more difficult and in some cases is accompanied by retropulsion and loss of balance.
(iii) The established phase: After the intermediate phase within a few months the disease manifests itself by an increase in both subjective and objective symptoms. At this stage muscular hypertonia in extension is the essential symptom dominating the clinical picture. Hypertonia is expressed as muscular rigidity seen as a slow spasmodic, staggering and sometimes high stepping or swinging gait. Slowness of speech, loss of memory, impotence etc. are other features of established phase.

The neurological symptoms are difficult to observe in experimental animals, intoxicated with manganese. Efforts have been made by various workers to reproduce human manganism in animals. Mella (1924) produced Parkinsonian syndrome in monkeys by intraperitoneal administration of manganese chloride. A more successful attempt to reproduce human manganism was that of van Bogaert and Dallemagne (1945) who used manganese in the form of aerosol. The animals showed initial acute symptoms i.e. alternating sudden movement and torpor, nervousness and severe tremor, yawing, cyanosis etc. later after five months the animals developed severe nervous syndrome such as uncertain gait and paresis. Chandra (1972) produced experimental model of manganese toxicity by intratracheal administration of manganese dioxide in rabbits. The rabbits after 12 to 16 months became increasingly lethargic and inactive. At the interval of 18 to 24 months hind limb paralysis occurred in rabbits (Fig. 1).
Fig. 1: (a) A clinical case of advance manganese poisoning showing typical pattern of gait "cock walk".

(b) A rabbit showing paralysis of the hind limb after 19 months of intratracheal inoculation with manganese dioxide.

(By courtesy: Dr. Satya V. Chandra)
Pathogenesis of manganese toxicity is not very well understood. Rodier (1953) carried out many investigations on sick, suspect and healthy subjects. Laboratory investigations revealed increase in white cell count and in the basal metabolism of the body. The rate of excretion of 17-ketosteroids was found to be decreased. Anaemia preceded by hyperglobulia have also been described (Leclerq, 1934; Lyon-Caen and Jude, 1934).

The selective action of manganese on the central nervous system is known since 1837 but the underlying mechanism is not well understood. The early biochemical and histological changes in the human brain due to manganese toxicity are not known. Very few autopsy reports are available in the literature, which have dealt with the brain pathology in chronic manganese toxicity.

Canavan et al. (1934) observed atrophy of the frontal lobes with marked gliosis in the cells of optic-thalamus, globus pallidus and caudate nucleus. Van Hogaert and Innes (1962) described degeneration of the cortical layers, dentate nuclei and the olives, with total cellular disappearance in cerebellum. Pentschew et al. (1963) have described in monkeys holotropistic alterations involving the subthalamic nuclei and the pallidum with proliferation of bizzare glial cells.
called immature glia all over the cerebrum and the cerebellum.

The characteristic pathological lesions in all these studies is the destruction of the cells of basal ganglia. However, the development of brain lesions and the mechanism responsible for their production is not known.

However, efforts have been made by various workers to explain the mechanism of action of manganese on the CNS. Saxena (1967) after injecting manganese chloride directly into the subarchnoid space of rats found localized changes in the cortex, in the form of pyknotic nuclei, vacuolated cytoplasm with focal neuronal loss. The paucity of marked histological changes in the basal ganglia and their presence in the cortex is highly suggestive of cortical involution in the initial stages of manganese toxicity.

Chandra and Srivastava (1970) similarly produced lesions in the cerebral and cerebellar cortex of rats by injecting manganese chloride intraperitoneally and demonstrated direct relationship of brain lesions to the amount of manganese present in the brain tissue. They found maximum number of degenerated neurons present when the amount of manganese in the brain was at its maximum thus indicating that the extent of damage was directly related to the manganese present in the brain.
Chandra (1972) produced manganese encephalopathy in rabbits after intratracheal administration of manganese chloride. She found widespread neuronal loss and neuronal degeneration in the cerebral cortex, caudate nucleus, putamen, substantia nigra and cerebellar cortex associated with astrocytic proliferation. The histochemical changes found were inhibitory effects on the acid phosphatase and adenosine triphosphatase in the affected neurons in chronic toxicity. She concluded from her studies that manganese in the brain was particularly localized in the neurons and not in the other structures of the brain.

The biochemical studies on the protein pattern of serum in manganese toxicity have been studied by Hassanein et al. (1966) and Mustafa and Chandra (1972). Hassanein et al. (1966) in seven cases of chronic manganism in humans found a decrease in total serum protein, where albumin: globulin ratio was lowered due to reduction in albumin and increase in globulin fractions. Mustafa and Chandra (1972) though found increase in total proteins there was similarity between increase in globulins both in human manganism and in manganese treated animals. The later workers have suggested that the increase in globulins in manganese toxicity may be due to the formation of manganese globulin complex. In CSF obtained from the manganese treated rabbits, there was marked reduction in the total protein due to low
concentration of albumin and globulins. On the contrary Mena et al. (1967) in a few human cases of manganese toxicity have reported an increase in total CSF proteins. Mustafa and Chandra (1972) have also reported marked elevation in adenosine deaminase in CSF of experimental animals suggesting that this test may be used as a clinical diagnostic index in patients with chronic manganese poisoning.

Mustafa and Chandra (1971) have also shown that the concentrations of dopamine and norepinephrine are considerably lowered whereas no change in 5-HT level occurs in rabbits intoxicated with manganese. Similarly, a large number of reports by various other workers have shown biochemical alterations and histopathological changes in other body organs i.e. liver, testis, gastrointestinal tract, kidneys and adrenals (Flin et al., 1940; Hurst and Hurst, 1929; Chandra, 1971; Chandra and Imam, 1973; Jonek et al., 1965; Imam and Chandra, 1974; Chandra and Imam, 1974).

Treatment of manganese poisoning

In the treatment of manganese poisoning L-dopa has been found to be the most effective drug (Editorial, Lancet, 1970; Mena et al., 1970; Rosenstock et al., 1971). However, metal binding agents like EDTA have also been tried. These agents increased the excretion of manganese in the urine (Barborik and Sehnalova, 1967; Folprechtova et al., 1970; and Penalver, 1957).