INDUSTRIAL MANGANESE POISONING

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I hereby recommend that the thesis prepared under my supervision by William F. Nardone, M.D.

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CHAPTER I

MANGANESE

History

Ancient writings concerning the use of manganese for coloring and decolorizing glass make it possible to trace the specific mineral from the first century to the present time. The Roman naturalist Pliny (23 - 79 A.D.), in his Naturalio Historia, refers to the magnes or lapis magnes:

> "Then as ingenuity was not content with the mixing of nitrum, they began the addition of lapis magnes, because of the belief that it attracts liquified glass as well as iron." Pliny XXXVI, 66.

A great deal of discussion has arisen over this passage concerning the actual composition of this lapis magnes. Pliny uses this term to describe the lodestone or magnetic oxide of iron but also says:

> "There, in Ethiopia also, is haematites magnes, a stone of blood color, which shows a red color if crushed, or of saffron. The haematites has not the same property of attracting iron as lapis magnes." Pliny XXXVI, 25.

Pliny described five different kinds of lapis magnes, and he classed them as male and female. The male varieties were said to be more red than black.

The early glass makers tried various minerals for coloring glass, and they must have found that one kind of

lapis magnes, according as it was used in greater or less quantity, imparted to glass many beautiful shades of color: violet, red and dark brown. They probably also found that when a very small proportion of lapis magnes was added, the glass became colorless. Investigators feel that some varieties of pyrolusite, on account of their external resemblance to the magnetic minerals, were classed with the lapis magnes, and that lodestone was not the substance meant by Pliny, but manganese. Pliny states that the term magnes comes from the name Magnes, the person first to discover the mineral. Magnes noticed, when he took his herds to pasture, that the nails of his shoes and the iron ferrule of his staff adhered to the ground. Later writers clearly differentiated the magnetic from the non-magnetic varieties of magnes.

Biringuccio, in his work Pirotechnica 1540, definitely mentioned manganese as a coloring agent in glass making. It was possibly the first specific mention of manganese under its own name.

> "Of a similar nature to Zaffer is also another mineral called manganese, which is found, besides in Germany, at the mountain of Viterbo in Tuscany---- It is the color of iron slag. In melting it one cannot obtain any metal--but it gives a very fine color to glass, so that the glass workers use it in their pigments to secure an azure color. It also has such a property that when put into melted glass it cleanses it and makes it white, even if it were green or yellow.

In a hot fire it goes off in a vapor like lead, and turns into ashes."

In 1826 W. Haidlinger called the different varieties of these ores pyrolusite, from the Greek words pyros - fire, and lovein - to wash. In 1774 Bergman, basing his findings on the investigations of Schule and Gahn, suggested the presence of a new element, manganese. It was first isolated by J. G. Gahn in 1774. Following its isolation, it was called Braunstein, Braunstein regulers, and Braunstein metal. The term manganese was advocated by P. K. Buttman in 1808, and it came quickly into general use. (1, 131, 172)

Occurrence and Sources

The metal manganese does not occur free in nature but is widely diffused, as it accompanies practically all iron ores. Manganese is about tenth (10th) on the list of the most abundant elements to be found in the earth's crust. The reported percentages of manganese in the earth's crust vary from 0.028 per cent to 0.125 per cent. F. W. Clarke estimates that the known terrestrial matter in the earth's lithosphere contains 0.09 per cent MnO. This percentage is the one most generally accepted. (131)

Over a thousand well-defined minerals have been recognized in the earth's crust. Of these about 150 contain

manganese as an essential constituent, and many more contain smaller proportions. Many minerals contain only traces of manganese, and these traces seem to influence the color of the mineral. In these instances manganese has been referred to as "nature's pigment". The oxides are usually different shades of black or grey. Other manganese minerals may be blue, pink, lilac, crimson, yellow, orange, green and brown.

Manganese also occurs in extra-terrestrial bodies. Reports of spectroscopic observations on the manganese lines in the solar and stellar spectra were made by numerous authors. Analyses on meteorites and lava rock show the manganese content to vary from 0.02 to 5.77 per cent.

Minute quantities of manganese occur in solution in the waters of oceans, seas, rivers, lakes and springs. Heavier concentrations are present in the mud, clay, concretions and other rock formations found in the sea and ocean floor.

Manganese is not found in the metallic state in nature but only in combination with other elements as oxides, manganates, sulphides, sulphates, chlorides, carbonates, silicates, tetanosilates, columbates, tantalates, phosphates, arsenates, antimonates, borates and tungstates. The chief minerals in which it is found are such oxides as pyrolusite (MnO_2); braunite ($3Mn_2O_3$, $MnSiO_3$); manganite ($Mn_2O_3H_2O$); hausmannite (Mn_3O_4); franklinite (Fe, Zn, Mn) O, $(Fe\ Mn)_2O_3$;

psilomelane (MnO_2 (H_2O, K_2O, or BaO); the sulphides as alabandite, manganese monosulphide (MnS), and hauserite, manganese disulphide (MnS_2); as the carbonate in rhodochrosite ($MnCO_3$); the silicates as tephroite (Mn_2SiO_4), knebelite $(Fe\ Mn)_2SiO_4$), helvite $(Be, Mn, Fe)_7Si_3O_{12}S$; as a phosphate in triplite, $R_3P_2O_8$, with R resembling iron and manganese; and bog manganese, an impure mixture of manganese oxides with oxides of iron, barium, aluminum, silicon, nickel and copper (131).

In 1949 the total world production of metallurgical-grade manganese ore containing over 30 per cent manganese amounted to approximately 5,000,000 long tons. It is estimated that the U. S. S. R. (Russia) produced 50 per cent of this amount. The other ore producing countries, in order of importance, are the Union of South Africa, India, the Gold Coast, French Morocco, Brazil, Egypt and the United States. It is further estimated that the United States produces one tenth of its required needs and utilizes about one third of the world's production. Montana is the principal ore producing state in the United States with Arizona, Arkansas, California, Minnesota, Nevada, New Mexico, Tennessee, Utah and Virginia producing token amounts of high grade ore (129).

International economic and political situations resulted in the removal by the Russians of their contribution from the world markets. The industrial and armament programs of the nations necessitated the overworking of remaining sources outside the "Iron Curtain" and the securing and refining of lower grade ores.

Properties

Physical and Chemical. Group VII of the periodic table comprises the sub-group b, containing the halogen elements, and sub-group a containing manganese and rhenium. Manganese remained the only known member of this sub-group until 1925 when Noddack, Tache and Berg announced the discovery of rhenium and masurium. (Masurium is considered a "uranide" element and is not accepted as a member of sub-group a.) There is a marked disparity in properties between members of sub-group a and sub-group b. The only way in which manganese resembles the halogens is in the formation of volatile acidic heptoxide Mn_2O_7, analogous to Cl_2O_7. Mn_2O_7 is explosive like Cl_2O_7. The perchlorates, $KClO_4$, and permanganates, $KMnO_4$, are isomorphous, and both silver perchlorate and permanganate are sparingly soluble in water.

In its remaining compounds manganese shows close analogies with chromium and iron. These metals are similar in

physical properties, and both manganese and chromium form basic sesquioxides, Mn_2O_3, dioxides, MnO_2, and acidic trioxides, MnO_3 (MnO_3 known only in its salts, manganates). Manganese resembles magnesium and zinc in forming a sparingly soluble $MnNH_4PO_4$, and it resembles iron in forming three oxides of the types MnO, Mn_2O_3, and Mn_3O_4, the first two basic, although the oxides Mn_2O_3 are also weakly acidic. The manganous salts are more stable than the ferrous salts; they do not oxidize in air, and the sulfate is more stable to heat. The ferric and chromic compounds, on the other hand, are more stable than the manganic; $MnCl_3$ very easily decomposes into $MnCl_2$ and chlorine, and manganic salts are powerful oxidizing agents.

Manganese occurs in its compounds with the valences of 1, 2, 3, 4, 6 and 7:

1. Univalent manganese is present in white $Na_5Mn(CN)_6$, deposited when the deep-yellow solution of alkaline $Na_5Mn(CN)_6$ reduced with aluminum is filtered into sodium cyanide solution saturated with sodium acetate.
2. Compounds of 2-valent manganese are the basic monoxide MnO and the common manganans salts, $MnCl_2$ and $MnSO_4$. Manganans salts will catalyze a variety of oxidations and are usually soluble in water.

3. Compounds of 3-valent manganese are the weakly acidic sesquioxide, Mn_2O_3, forming manganites, $M(MnO_2)$, and the manganic compounds, $MnCl_3$ and $Mn_2(SO_4)_3$. The trivalent manganese compounds can be made by the oxidation of manganous compounds or the reduction of those of higher valence.
4. Compounds of 4-valent manganese are the dioxide MnO_2, acidic and forming permanganites $M_2(MnO_3)$, and compounds such as $Mn(SO_4)_2$. Tetra-valent manganese compounds are nearly all insoluble substances.
6. Compounds of 6-valent manganese are the manganates, M_2MnO_4, isomorphous with sulfates.
7. Compounds of 7-valent manganese are permanganic acid, $HMnO_4$, its anhydrid, Mn_2O_7, and its salts forming permanganates, isomorphous with perchlorates.

Impure manganese is obtained by reducing the oxide Mn_3O_4 with carbon at a high temperature

$$Mn_3O_4 + 4C \rightarrow 3Mn + 4CO$$

A purer metal is obtained by reducing the oxide Mn_3O_4 with aluminum in the alumino-thermic process (Goldschmidt's method).

$$3Mn_3O_4 + 8Al \rightarrow 9Mn + Al_2O_3$$

The purest metal is obtained by electrolyzing concentrated manganous chloride solution with a mercury cathode and distilling off the mercury in a vacuum at 250° C.

Manganese is greyish-white or reddish-white in appearance, very much like iron, but is harder and much more brittle. It occurs in at least two forms, an α, stable from the ordinary temperature up to about 700° C., and a β, stable above this temperature.

Atomic number 25.
Atomic weight 54.93.
Melting point 1245° C. (2273° F.).
Boiling point 2150° C. (3900° F.).
Density at 20° C. (68° F.)
α 7.43 g. per cu. cm.
β 7.29 g. per cu. cm.

The crystalline structure is extremely complicated. In the α modification, the unit cell contains 58 atoms, whose positions and distances show that they are in at least four different states of valency or linkage, the inter-atomic distance varying from 2.25 - 2.95 A.U. The structure of β manganese with 20 atoms in the unit cell is imperfectly made out.

Manganese forms numerous alloys. It gives a continuous series of solid solutions with each of the four elements next after it: iron, cobalt, nickel and copper. With aluminum and with antimony, especially in the presence of a small amount of copper, it forms the well-known Heusler alloys, which are highly ferromagnetic although they contain no

ferromagnetic element. The addition of a small quantity of silicon makes manganese as hard as steel.

Chemically manganese is a highly reactive metal. When pure it is not easily oxidized by air. The metal, unless very pure, decomposes water even at low temperatures with evolution of hydrogen and readily dissolves in dilute acids, forming manganous salts and evolving hydrogen.

$$Mn + H_2SO_4 \rightarrow MnSO_4 + H_2$$

It is converted by fluorine into the di- and tri-fluoride, and by chlorine into manganous chloride, $MnCl_2$; if it is heated in nitrogen above 1,200° C., it burns to form a nitride. (118, 143, 169)

Radioactive (Isotopes): There are five radioactive and one stable isotope of manganese known and reported (165). None of the radioactive isotopes are known to occur in nature but may be produced artificially in a cyclotron by bombarding various elements with different particles. An isotope chart with key is given:

Table 1

Manganese Isotopes

Z	Isotope	A	Class	Type of Radiation	Half Life	Energy of Radiation in Mev	
						Particles	Rays
25	Mn	51	A	B	46 min.	2.0	
	Mn	52m	A	B, γ	21 min.	2.2-2.66	1.46
	Mn	52	A	B, K	5.8-6.5 days	0.58-0.77	0.94-1.46
	Mn	54	A	K, γ	310 days		0.835-0.85
	Mn	55					
	Mn	56	A	B-, γ	2.59 hr.	0.75-2.86	0.82-2.13

Key:

Z	Atomic Number: number of protons in the nucleus of an atom
A	Mass number: the total number of protons and neutrons in the nucleus of an atom
Class A	Isotope certain (mass number and element certain)
m	Meta stable isomer of measured half-life of either a stable or unstable ground state
min.	Minutes
hr.	Hours
B	Positive beta-particles (positrons)
K	K-electron capture (orbital electron capture)
γ	Gamma rays
B-	Negative beta particles (negatrons)
IT	Isometric transition or double decay
p	Proton
n	Neutron
α	Alpha-particle
d	Deuteron
Mev	Million electron volts

Radioactive manganese is prepared in the cyclotron by bombarding chromium with deuterons, the reaction being:

$$Cr^{52} + d^2 \rightarrow Mn^{52} + {}^2n^1$$

The parent Cr^{52} is present in ordinary chromium in the amount of 83.78 per cent. There is also present in the amount of 2.30 per cent Cr^{54}, and under the same deuteron bombardment the additional reaction occurs

$$Cr^{54} + d^2 \rightarrow Mn^{54} + 2n^1$$

Radioactive isotope Mn^{54} has a half-life of 310 days. It has been estimated that it is present in activities of the order of 1 per cent of the total radioactive manganese produced in the above deuteron bombardment. Radioactive manganese decays to stable chromium, the decay process requiring that the atomic nucleus increase its negative charge by one unit. Approximately 50 per cent of the time this is achieved by the capture of an orbital electron, in which case very soft x-rays are emitted. The other 50 per cent of the time positrons are emitted by the nucleus with maximum energy of 0.582 million electron volts. Immediately after this process three gamma rays are emitted in cascade, their energies being 1.46, 0.940 and 0.734 million electron volts, respectively (145). It is suggested (80) that there are three useful radioactive isotopes of manganese:

(1) Mn^{52} (6.5 day half-life), made in the cyclotron by the reaction: $Cr^{52}(d, 2n) \rightarrow Mn^{52}$

(2) Mn^{54} (310 day half-life), made in the cyclotron by the reaction: $Fe^{56}(d, \alpha) \rightarrow Mn^{54}$ which is accompanied by the reaction: $Fe^{54}(d, \alpha) \rightarrow Mn^{52}$

(3) Mn^{56} (2.59 hr. half-life), made in the cyclotron by the reaction: $Mn^{55}(d, p) \rightarrow Mn^{56}$

Recent reports reveal the use of radioactive manganese in therapy (80, 168) and for biological tracer studies (44, 74). In 1940 Greenberg and Campbell (74) reported on the suitability of Mn^{54}, with a half-life of 310 days, for biological tracer studies. They also gave a complete procedure for assay of the radioactive isotope. Further consideration will be given these papers in the sections on absorption, metabolism, storage and excretion.

Hahn and Sheppard (80, 168) suggest five criteria for therapeutic use of radioactive isotopes and use these criteria to discuss the role of radioactive manganese in therapy and biological tracer studies. The criteria, method of preparation and administration of the radioactive solution and the determination of the amount of radioactive manganese in a dose are given.

Criteria:

(1) Determination and control of particle size; if the particle size is all important in determining the distribution of the particles, then the size must be controlled by the method of production.

(2) Element must be of well known chemical behavior.

(3) Knowledge of biological behavior.

(4) The "half-life" of the radioactive element must be considered in order that radiation be not prolonged beyond the desired time; yet be sufficiently long for its mission to be accomplished.

(5) The cost of production of the isotope in required amounts.

Preparation and administration of solution:

After purification (target separation), the manganese in the form of the chloride is autoclaved and 10 ml. of sterile 6 per cent gelatin solution are added. Potassium permanganate is added dropwise to oxidize the Mn to MnO_2 and the solution made slightly alkaline with strong NaOH. Sterile technique is followed throughout. A good dispersion is characterized by having a clear, deep, tawny, port wine color to transmitted light and a greenish grey cast under reflected light. The material may then be diluted with normal saline and administered with an ordinary infusion set. Extremely slow administration is not necessary.

Determination of radioactivity in a dose:

The amount of radioactive manganese in a dose may be determined by measuring the gamma ray intensity at a known distance from the sample, using a Geiger-Muller counter. The counter is first to be calibrated with a standard sample of radioactive manganese.

Uses

Throughout the world about 90 per cent of all manganese mined is used in alloy and steel manufacture. In the United States alone industrial needs increased from 640,842 tons in 1948 to 928,349 tons in 1949. Of the 1948 stock, 3 per cent was consumed in the manufacture of dry cells, 1 per cent went into chemicals, and 96 per cent was used in the metals industry (129).

The most important alloys of manganese are spiegeleisen and ferromanganese, which are made directly from the ores in blast or electric furnaces. The alloys silico-manganese and silico-spiegel follow next in importance. These are used extensively in the manufacture of steel to deoxidize and recarburize the molten metal. This process makes for cleaner and sounder ingots and gives strength and hardness to the finished product. Some manganese is used to form alloys with copper, zinc, aluminum and other metals. Manganese bronze (copper alloyed with small proportions of manganese, iron, aluminum, tin and lead) is used to produce a metal suitable for marine construction, mining machinery, and other equipment the use of which gives rise to a serious problem of corrosion. Manganin, an alloy composed of 83 per cent copper, 13 per cent manganese and 4 per cent nickel, is used in electrical resistance coils because of its very small

temperature coefficient of resistance. Manganese enters into the composition of certain non-ferrous alloys which possess desirable magnetic properties. These magnetic alloys of manganese with aluminum, tin, arsenic, antimony, bismuth and boron are called Heusler's alloys.

Manganese is used for the manufacture of manganese steel. The addition of small quantities of manganese to steel renders it brittle; but an alloy containing 12 per cent of manganese is very hard and tough, and remarkably resistant to shock. There is much need for this type of steel in the manufacture of rock crushers, railway points and crossings, couplings and other units exposed to heavy and hard wear.

The second largest use of manganese ore is in the manufacture of dry cell batteries, in which manganese dioxide is used to oxidize (depolarize) the hydrogen and prolong the life of the battery.

Comparatively small amounts are used in various chemical industries. These uses are widely diversified and are of increasing importance industrially. Materials used in making glass usually contain iron, and the ferrous silicate produced gives a green color to the glass. If pyrolusite (MnO_2) is added in small quantities, the ferrous silicate is oxidized to ferric silicate which has a pale yellow color,

neutralized by the purple tinge imparted by the manganese. Larger amounts are used to color glass violet, brown or black. The manganates and permanganates, in which manganese with a valence of 6 or 7 is in the anion, are oxidizing agents used in disinfecting and bleaching, in wood preservatives and in laboratory work. Manganese dioxide is also used in small quantities in the ceramic industry for coloring glazes. It is often referred to as "Glazier's soap". The hydrated peroxide of manganese is used in dyes and similar preparations. These manganese-containing dyes and colors are applied in the manufacture of enamel, linoleum, textile prints and marbled soap. Manganese dioxide is used as an oxidizer in the manufacture of matches and fireworks, in making products for burnishing gun barrels and in certain anti-rust coatings. Various manganese salts are added to paints and oils as driers because of their oxidizing action on the unsaturated fatty acids. Some salts are used as sterilizing agents, deodorizers, germicides, medicinal reagents, photographic reagents and leather fixing agents. Manganese sulphate is also used agriculturally as a fertilizer to enrich certain depleted soils. (63, 67, 144)

Exposure in Industry

The first cases of manganese poisoning, as reported in the literature by Couper in 1837, were contracted by workers employed as grinders of manganese dioxide for the manufacture of chlorine. He described the working environment as one heavily contaminated with a multitude of manganese dioxide dust particles and the bodies of the men as constantly covered with a thick layer of the oxide (45). Schlockow (160) in 1879 probably described the first cases of manganese intoxication which were caused by the inhalation of manganese fumes. He described the exposure of workers who were engaged for ten to twelve years in smelting zinc ores containing lead, arsenic, cadmium and large quantities of manganese. A more common exposure to the inhalation of metallic fume occurs in the process of electro-welding with the use of electrodes having a high manganese content. In 1932 Beintker (14) reported manganese poisoning in two electro-welders.

Davis and Huey (49) in 1921 described two cases due to fume inhalation in men engaged in handling manganese in the Bessemer process of making steel. In 1901 Von Jaksch (181) reported three cases of manganese intoxication in a chemical plant in which manganese dioxide was used in the manufacture of potassium permanganate. Neisser (141) reported a

questionable case in a man engaged as a color mixer in a mosaic factory. The first report of manganese intoxication in America was by Casamajor (36) who, in 1913, reported nine cases of intoxication of men separating iron from manganese with the use of an electro-magnet. In 1928 Zangger (198) reported a case of manganese poisoning in a varnish worker. In 1941 Kawamura (98) reported that 16 people had become intoxicated, 3 fatally, from drinking well water heavily contaminated with manganese and zinc from old dry batteries used as fill about the well.

A list of occupations offering opportunities for hazardous exposure to manganese has been compiled by Dublin and Vane (55) and reported in Department of Labor Bulletin No. 41. A list of the types of workers so exposed is given.

Alloy makers
Aluminum extractors
Battery (dry) makers
Bleaching-powder makers
Brick makers
Bronzers
Chlorine makers
Color makers
Concentrating-mill workers
Copper smelters
Dye makers
Dyers
Enamelers
Enamel makers
Fertilizer makers
Fireworks makers
Glass mixers
Glaze dippers (pottery)
Glaze mixers (pottery)
Linoleum makers
Longshoremen
Manganese-dioxide workers
Manganese grinders
Manganese-ore separators
Manganese-steel makers
Match-factory workers
Miners (manganese)
Open hearth-department workers
Painters
Paint makers
Pharmaceutical workers
Pottery workers
Puddlers (iron and steel)
Soap makers
Steel-alloy makers
Textile printers
Varnishers
Varnish makers
Welders
Zinc miners
Zinc smelters

Over 90 per cent of the world's production of manganese ore is utilized in the steel and allied industries; however, less than 2 per cent of the reported cases of poisoning can be related directly to these industries. Most cases reported are found in industries in which the atmosphere is heavily contaminated with manganese dioxide dust. Fairhall (63) mentions that in mining manganese ores the development of dusts is not severe, as the ores are moist (up to 40 per cent moisture); however, this exposure makes for the second largest group of intoxications reported (3, 47, 140). With the perfection of welding and cutting techniques and the use of high percentage manganese steel and alloys, we may expect an increased number of cases reported from these processes.

CHAPTER II

MANGANESE POISONING

Toxicology

In the industrial environment injurious and toxic substances may gain access to the body and cause damage by (22):

(1) Inhalation - breathing
(2) Skin contact - absorption through the skin; direct attack through direct contact with the skin
(3) Ingestion - swallowing (either directly or after collection in upper respiratory tract when breathing dust)

Industrial manganism has been shown to be due to exposure to high dust concentrations and is the result of manganese absorption from the lung tissue rather than from absorption in the digestive tract (56, 186). There are no reports of cases of industrial manganese intoxication resulting from absorption of the metal through the skin. In laboratory studies manganese in various forms was introduced into the body by numerous routes: inhalation (84, 109, 113, 114, 196), ingestion (74, 75, 83, 84, 109, 112, 152), subcutaneously (32, 65, 83), intraperitoneally (74, 75, 130), intravenously (32, 48, 54, 75, 116) and intramuscularly (109).

It has been shown by Sato (158) and Von Oettingen (185) that the toxicity of manganese varies with its salts, the bivalent or manganous salts being from 3 to 10 times more toxic than the trivalent or manganic salts. Hilpert (87)

maintains that because manganese intoxication does not occur in every factory in which manganese is used extensively, the specific toxic manganese compound is not known. Heine (84) offers the possibility that chronic manganese poisoning may be caused by metallic manganese as well as by its oxide. He found a 96 per cent mortality in a group of white mice after he exposed their shaved skin to a moist powder of manganese metal and an 11 per cent mortality in a similar group exposed to manganese oxide having a 6.7 per cent of metallic manganese.

Absorption. In 1884 Cahn (32) offered the following conclusions from his studies on the intravenous and subcutaneous administration of manganous oxide in rabbits:

"(1) If manganese be introduced into the blood stream it is not taken up by the blood cells. (2) The metal is taken up by the parenchymatous organs whence it is transported; the major part is eliminated through the gastro-intestinal tract and appears in the feces. (3) Manganese is not absorbed through the intact intestinal wall, at least not in significant amounts."

Contrary to the above, Harnack and Schreiber (83) in 1901 summarized their findings on feeding manganese salts to rabbits with the following remarks:

"Manganese is absorbed from the intestinal tract even if the mucosa be intact. However, it may not be possible through this route to produce general intoxication. If permanganate be injected subcutaneously, it becomes rapidly reduced into an insoluble manganese compound of which only a small fraction is reabsorbed and appears exclusively in the intestine and feces but it never appears in the urine."

Reiman and Minot (152) showed that manganese ores were soluble in gastric juice, and the possible risk of intoxication from

ingested manganese depended upon its solubility in the gastric juice, the gastric acidity and the duration of contact. They so concluded after the following experiments. One gram of representative manganese ores (franklinite, a mixed oxide of manganese, iron and zinc; rhodenite, manganese silicate; and manganese dioxide), ground to 200 mesh, was incubated for different lengths of time in 50 cc. of fasting stomach contents obtained from hospital patients. In one case 8 grams of franklinite was given with a test meal which was then removed and the stomach washed after 30 minutes. Some typical figures for solubilities found are as follows: 14.13 mg. of manganese dissolved after 96 hours at 37° C. in juice with total acidity of 74; 5.56 mg. of manganese dissolved after 22 hours at 37° C. in juice with total acidity of 40; and in the test meal case 1.10 mg. of manganese dissolved in contents with a total acidity of 21. The various ores showed practically the same solubility. These authors showed further, by means of blood studies on a group of employees exposed to manganese, that following the ingestion of a water suspension containing 8 grams of franklinite the maximum amount of manganese appeared in the blood in about one hour and then fell rapidly back to normal. At no time was this increase unusually high (Mn content per 100 gm. of blood before ingestion, 0.0105 mg.; after ingestion, first hour, 0.014 mg.; third hour, 0.012 mg.; sixth hour, 0.0105 mg.). McNally (128) felt that

these low levels could be explained by one or more of the following factors: the rate of solution of the ore by the gastric juice is very slow, or the rate of absorption into the blood stream is equally slow, or the rate of removal from the blood is too rapid to allow any considerable increase in the manganese content of the blood. Similar results, following the intravenous administration of manganese dioxide suspension to cats, were obtained by Drinker and Shaw (54) in 1921. In 9 out of 13 experiments the circulating blood contained no demonstrable manganese after 18 minutes. The remaining 4 cats showed a steady elimination which was incomplete at the end of one hour. Marzetti (122) held that the absorption of manganese from the gastro-intestinal tract was a slow process, occurring in the stomach and cecum, and that the nonassimilable manganese was absorbed into the circulation and then completely excreted. Von Jaksch (181, 184) and Hilpert (87, 88) asserted that the metal was absorbed directly by the pulmonary tissue, transformed into an albuminate and transported directly to the central nervous system via the blood stream. The manganese dusts which enter the oral cavity with respiration or by ingestion admix with food or saliva, enter the stomach where they are transformed into chlorides and are absorbed as such (35).

Metabolism. The exact biological role of manganese is not clearly defined; however, it is regarded as a biological

micronutrient necessary for all living systems and essential for the growth and reproduction of higher animals (80, 107, 173, 185). In 1941 Dastugue and Thonier (48) showed with experiments using tadpoles (Rana temporaria) that an optimum concentration of manganese was necessary for life. The following figures were submitted:

$MnCl_2$ solution of	1:300	the survival time averages	25.5 hrs.
	1:1000		50.0 hrs.
	1:2500		125.0 hrs.
	1:5000		272.0 hrs.

1:10,000 - 1:100,000 the tadpoles gain weight less than in pure water, but at 1:1,000,000 there is a stimulation of growth. Metamorphosis is also increased in solutions of 1:100,000 - 1:1,000,000 but is retarded in solutions of higher concentration.

Manganese is essential for prevention of perosis (a nutritional disease of young birds characterized by shortening and thickening of the bones and often accompanied by a deformity known as "slipped tendon" in chicks) (123).

Smith and Ellis (173) report that 0.3 mg. of manganese per rabbit per day is sufficient for normal bone development, but the minimum intake necessary for maximum growth appears to be somewhat higher. In rats skeletal development is not as sensitive to manganese deficiency as in rabbits and poultry. First generation rats on a low manganese diet show a decrease in bone length, density, breaking strength and phosphatase activity. Pigs on a diet containing 0.0011 to 0.0014 per cent manganese develop a lameness which is preventable by diets containing 50 to 60 parts per million of manganese.

Opinions (80, 173) are developing which support the view that manganese may be essential for normal development of bone in general.

Diets fed to rats, when supplemented with manganous sulfate in concentrations of 1:2000, 1:4000 and 1:10,000, had a marked catalytic action on their growth manifested by increased activity, sleeker and longer hair, and faster growing offspring. With a manganese-free diet the male rat showed degeneration of the testes and the female rat produced undersized offspring which she was not able to feed because of poor lactation (123).

Manganese within certain concentrations, when given intravenously to goats immunized against diphtheria toxin, stimulates the antitoxin formation. In the case of horses this same stimulation persists even if the antitoxin titer is already on the decline. Von Oettingen (185) feels that storage of manganese in the liver is somehow related to this increased antitoxin formation. Manganese, again within certain concentrations, aids tissue respiration by serving as an activator for certain enzymes including arginase, phosphoglucomutase, carboxylases and peptidases (185).

Manganese is a constant constituent of all plants. It is believed that the function of manganese in plants may be concerned with oxygen metabolism (73, 185).

Distribution and Storage. The recognized usefulness of manganese in plant and animal physiology might well presuppose its wide distribution in all biological tissues, fluids and excreta (173, 185). Manganese is widely distributed through the entire animal and plant kingdom, being a normal constituent of the tissues of plants, mammals, birds, amphibia, fish, insects, crustacea, mollusks, annelida and echinoderms (17, 18, 99, 131, 151, 152, 172). The animal kingdom as a whole is very poor in manganese as compared with the vegetable kingdom. Comparatively large amounts (approximately 4 mg. per day) are found in the normal human diet and substantially equal amounts are eliminated. The chief source of manganese in the diet is of vegetable origin, cereals being particularly rich in this metal (99). Manganese in concentrations varying from trace to 1.41 milligrams per liter is also found in drinking water (100). There is much agreement on the concentration of manganese in normal human tissue as determined by Kehoe (101) and Reiman and Minot (151). The regular occurrence of this metal in the tissues has also been demonstrated by Bertrand and Ciurea, Turnwald and Haurowitz, and Chevalier (99).

A table with comparative results is given:

Table 2

Concentration of Manganese in Normal Human Tissues

Manganese in Milligrams of Metal per 100 Gm. of Wet Tissue (17, 18, 53, 67, 101, 172)

Tissue	Kehoe et al.	Flinn et al.	Scattered Reported Results	
	Man	1 case*	Man	Animals
Liver	0.205	0.160	0.130-0.213	0.120-0.448
Pancreas			0.102-0.136	0.076-0.252
Kidney	0.060	0.080	0.068-0.083	0.061-0.277
Submaxillary Gland			0.091	0.105-0.114
Duodenum			0.092	0.084-0.333
Spleen	0.022		0.018	0.016-0.062
Colon			0.083	
Parotid Gland			0.050-0.086	
Lymph Node			0.021-0.063	
Lungs	0.022	Rt. 0.59 Lt. 0.85	0.040	Trace-0.055
Thyroid			0.049	0.036-0.054
Heart	0.032	0.050	0.021	0.020-0.069
Stomach	0.030	0.010	0.036	
Brain	0.030	0.020		0.033-0.035
Small Intestines	0.035	0.110		0.013-0.037
Muscle	0.050		0.017	0.015-0.024
Long Bone	0.300	0.080		0.047-0.200
Rib Bone	0.170			

*Flinn et al. (67) present the chemical analysis of the tissues of a 64 year old colored male with a 4-1/2 year exposure to manganese dust in an ore crushing mill. They attribute the heavy concentration in the lungs to the concentration of manganese in the man's environment (173 mg. per cubic meter of air). At the time of death the man had been removed from his exposure for 7 years.

Greenberg and Campbell (74), in their studies in mineral metabolism with the use of induced radioactive manganese, show that after oral administration 2.8 per cent of the retained manganese was found in the liver, bone, muscle and blood, the liver showing the largest uptake. They offer no explanation for the high values of radioactive manganese found in the bone and skin after intraperitoneal injection. Their tabulated results presenting the accumulation of labeled manganese in various tissues of the rat are given:

Table 3

Distribution of Labeled Manganese

(Dosage, 1 mg. Mn; sacrificed 75.5 hours after administration) (74)

Tissue	Oral Administration		Intraperitoneal Injection	
	% of dose in whole tissue	% of dose per gm. fresh wt.	% of dose in whole tissue	% of dose per gm. fresh wt.
Muscle	0.7	0.007	0.8	0.008
Bone	0.7	0.081	2.0	0.20
Skin	*	*	3.7	0.13
Whole Blood	0.5	0.097	*	*
Liver	0.9	0.14	1.2	0.14
Small Intestine	*	*	0.8	0.13
Stomach	*	*	0.8	0.22

*No significant radioactivity detectable in sample.

Other tissues measured but having no activity included heart, large intestine, spleen, kidney and lung.

In 1943 Mohamed and Greenberg (134), in their study with Mn^{56} on chicks with perosis produced by a synthetic manganese deficient diet, showed the partition of labeled and total manganese in manganese deficient and control chicks which were sacrificed 72 hours after the administration of the radioactive metal. They placed one group of newly hatched chicks on a synthetic ration containing 2.8 p.p.m. of manganese and another group on a control diet of 59.6 p.p.m. of manganese. In two weeks the deficient group showed definite signs of perosis. Both groups were then given 1 ml. of a solution containing 15.8 micrograms of labeled manganese (Mn^{56}) dissolved in a 0.9 per cent NaCl solution. Half of the group received the dosage orally and the other half subcutaneously. In both the deficient and control groups, the liver showed the greatest concentration of manganese. Their tabulated results are given:

Table 4

Partition of Labeled and Total Manganese in Manganese-Deficient and Control Chicks (134)

Group	Mode of Administration	Labeled Mn in Per Cent of Dose			
		Excreta	Liver	Kidney	Carcass
Deficient	Oral	96.3	1.0	0	2.4
Deficient	Injected	65.0	16.0	2.3	10.3
Control	Oral	99.0	0.3	0	0.7
Control	Injected	75.6	3.5	2.35	18.2
		Total Mn in mg. per 100 g. fresh tissue			
Deficient			0.053	0.05	0.023
Control			0.20	0.22	0.07

It is apparent from the studies reported in the literature that the liver shows the highest concentration of manganese and the kidney second.

Manganese is found regularly as a constituent of blood and urine in normal subjects (19, 99, 101, 151). Kehoe et al. (101) showed in their study of 60 normal adult males a mean concentration of 0.015 mg. of manganese in 100 gm. of whole blood, with a mean concentration of 0.004 mg. of manganese in the plasma, and the difference between the two results representing the mean concentration in the formed

elements. In contradiction to the observations of Reiman and Minot (151) that the level of concentration was constant for each individual, Kehoe (101) reports that there is a slight but definite variation in the manganese concentration of repeated samples from the same individual. The reported figures are as follows:

Table 5

The Concentration of Trace Metals in Successive Weekly Blood Samples of a Normal Adult American (101)

Milligrams per 100 Gm. of Whole Blood		Frequencies of Occurrence of the Quantities Indicated
0.005 - 0.0099		5
0.010 - 0.0149		4
0.015 - 0.0199		4
0.020 - 0.0249		4
0.035 - 0.0399		1
Mean	0.016	
Probable error of mean	0.001	
Standard Deviation	0.008	

Kehoe et al. (101) report a calculated mean of 0.010 mg. of manganese per liter of urine after the 24 hour urine specimens of 94 healthy experimental subjects were examined for 28 consecutive days. They attribute the failure of McCrackan and Passamaneck and Probst to find manganese in the urine of normal invividuals to technical difficulties (101). Perhaps this same reason may account for the failure of some investi-

gators to find traces of manganese in the urine of their cases, Seiffer (167), Casamajor (36), Davis and Huey (49), Gayle (72), Baader (10), Sourate (174) and McNally (127).

The presence and determination of manganese in human milk has been reported by Borovik and Kalinin (25) in 1944. Their results show a concentration varying from 0.01 to 0.050 per cent. Manganese was present in all samples analyzed.

Excretion. Manganese is excreted from the organism by various routes, by means of the feces, urine and sweat. The type of compound or the mode of administration has little if any effect on the excretory process. Investigators agree that the greatest percentage of manganese introduced into the organism is excreted in the feces. (10, 13, 15, 32, 74, 75, 78, 81, 83, 111, 122, 152, 158, 187)

The normal daily intake provided by the average diet in the average adult is about 4 mg. daily, and substantially equivalent amounts are eliminated daily (99). Approximately the entire daily intake is eliminated in the feces. Kehoe et al. (101) reported a mean of 3.69 mg. of manganese per 24 hour sample of feces and a mean of 0.01 mg. of manganese per 24 hour sample of urine. Mitchell et al. (134) in 1949 reported the presence of 0.006 - 0.02 mg. per cent of manganese in the sweat of each of six individuals on controlled

diets and exposed to environments of 39°, 73 per cent humidity and 27°, 43 per cent humidity.

Greenberg et al. (75), 1943, studied the distribution and excretion of manganese in normal and bile fistula rats with the aid of labeled manganese in stock and low manganese diets. They concluded from their tabulated results that the amount of intraperitoneally injected manganese appearing in the bile was from 1 to 3 times the quantity found in the gastro-intestinal tract and feces, indicating that 50 to 75 per cent of the injected manganese is probably carried by the bile and that urinary excretion was quite low regardless of the mode of administration. In 1940 Greenberg and Campbell (74) showed that on a normal diet the rat excreted over 90 per cent of radioactive manganese given either orally or intraperitoneally. This excretion was almost entirely in the feces.

Table 6

Partition of Labeled Manganese in the Rat in Per Cent of Administered Dose (74)

Diet	Type of Rat	Administration	Dose Mg.	Time Hrs.	Bile	Urine	Feces	G-I Tract	Liver
S	F.	I.P.	0.01	48	27.1	5.4	5.6	21.2	27.1
S	F.	I.P.	0.1	48	37.3	3.2	6.5	7.3	11.7
S	F.	0	0.1	48	1.1	1.2	39.1	42.7	
S	N.F.	I.V.	0.01	24		2.1	30.3	21.1	11.8
S	N.F.	I.V.	0.01	48		0.6	49.2	10.2	17.0
L.M.	N.F.	I.P.	0.01	24		0.9	16.0	39.0	26.6
L.M.	N.F.	0	0.01	24		0.7	44.0	42.0	1.4

Key: S = stock, L.M. = low manganese, F. = fistula, N.F. = no fistula, I.P. = intraperitoneally, 0 = orally, I.V. = intravenously

In their experiments on rats, Skinner and McHargue (170) found 2 per cent of the ingested manganese was excreted by way of the urine with a diet of 75 mg. of manganese per kg. On a ration containing 7.4 mg. of manganese per kg. the urinary manganese increased to 13.4 per cent of the total output. Following subcutaneous injection manganese was eliminated readily by way of the bowel. These findings are probably due to the relative increase of elimination in the

feces with large intake of manganese due to the poor absorption in the alimentary tract.

Sheppard and Hahn (168) reported on the retention and excretion of radioactive manganese dioxide dispersions administered intravenously to humans following the use of such preparations for the treatment of diseases in the lymphoid system. Urine determinations were made by taking aliquot samples from 24 hour specimens beginning immediately after the administration of the radioactive colloid material. The urine sample was then evaporated to dryness, and the radioactivity was determined by a bell-type Geiger-Muller counter. Aliquots from the 24 hour stool specimens were diluted with water and worked into a thin suspension. Primary aliquots were digested with sulphuric and perchloric acids, neutralized and diluted to 250 cc. Secondary aliquots were then evaporated to dryness and counted in the same manner as the urine samples. Their observations are in accord with the work of other investigators in the field of manganese metabolism. They report that the principal fraction of manganese released is excreted in the bile and appears in the stools. They suggest that the large amount of manganese (5 per cent of the initial dose) present in the first stool after administration of the radioactive colloidal suspension represents that proportion of the particles of manganese which approach

molecular size, and may be too small to be effectively phagocytosed. The remaining manganese is retained by the body and is excreted at a slower rate. They also noted an increased gamma ray intensity at the body surface over the liver area. Their reported results are tabulated and given (168):

Patient #1
Dosage: 5 millicuries (9-24)
Amounts excreted (millions of counts per minute)

Date	Urine	Stool	Estimated fraction of initial dose excreted
9-25	0.05	23	0.040
9-26	0.01	1	0.001
9-27	0.01	*	nil
9-28	0.05	0.7	0.001
9-29	0.01	0.1	nil
9-30	0.01	*	nil
10- 1	0.02	0.5	0.001
10- 2	0.004	5.0**	0.020
10- 3	lost	lost	lost
10- 4	0.03	2.0**	0.010

Patient #2
Dosage: 11 millicuries (10-3)

10- 3	0.03	*	*
10- 4	0.01	40	0.030
10- 5	0.01	0.7	0.001
10- 6	0.02	3	0.004
10- 7	0.01	2	0.003
10- 8	0.02	*	nil
10- 9	0.01	1	0.002
10-10	0.02	0.4	0.001
10-11	0.01	*	nil
10-12	0.01	0.6	0.002

* = no stools excreted this day
** = contamination suspected

Numerous authors (10, 78, 111, 187) report the presence of increased amounts of manganese in the stools in known

cases of manganese intoxication after the individuals involved were removed from their exposure. In some cases the increase persisted for 16 months (10). Flinn et al. (67) have demonstrated a high manganese content in the lungs of an ore crusher removed from his exposure for 7 years. Urinary manganese was demonstrable in this individual until 3 months prior to his death. They believe that urinary manganese reflects a present or past exposure to manganese rather than evidence of intoxication. In most instances of manganese intoxication reported in the literature, the urinary manganese determinations were reported as negative or trace (10, 36, 49, 72, 127, 167, 174), few reported determinations being as high as the levels in normal non-exposed subjects as determined by Kehoe et al. (101). Obviously the variability of the analytical data provided by various investigators relates to the variable sensitivity of the analytical method employed from time to time. Until more data have been obtained by methods of comparable or adequate accuracy under varying degrees of severity of exposure, the significance of the urinary excretion of manganese cannot be ascertained.

Industrial Manganese Poisoning

The manifold uses of manganese as enumerated earlier make one free to speculate on the number of individuals who are exposed to the hazard of manganese intoxication. The literature

offers little data on the subject. According to Public Health Bulletin No. 259 (24), the estimated number of workers in the United States potentially exposed to manganese and its compounds in 1939 was 23,340. In 1940 and 1943 India was regarded as a secondary supplier of manganese ore; however, in a report published in 1946 (150) it was revealed that 35,000 people were employed in the manganese mines of British India in 1940, and 24,000 persons were similarly employed in 1943. These groups were reported as being equally divided with regard to sex, 50 per cent being males and 50 per cent females.

Considering the comparatively small number of cases reported (see Table 7), and making allowances for cases which have been missed or wrongly diagnosed, it would appear that industrial manganese poisoning is relatively a rarity in spite of the large groups exposed to the varied applications of manganese compounds (9, 104, 107, 172, 196). Investigators and clinicians have suggested one or more of the following explanations: (1) the chronic condition can only arise where manganese or its compounds are inhaled or swallowed in dust or fume for a sufficiently long time and in sufficient amount; (2) cases of manganese poisoning may go unrecognized, or cases that have developed may fail to be reported; (3) not all compounds of manganese produce chronic poisoning (the toxicity of manganese varies with its salts, the bivalent or manganous salts are 3 - 10 times more toxic than the trivalent or manganic salts) (158, 185).

Table 7

Cases of Manganese Poisoning Reported to Date

Date	Name	Reference Number	Number of Cases
1837	Couper	45	5
1879	Schlockow	160	42
1901	Von Jaksch	181	3
1903	Friedel	69	1
1904	Seiffer	167	1*
1904	Wagener	190	1*
1904	Von Jaksch	182	1
1907	Von Jaksch	183	1
1913	Casamajor	36	9
1913	Seelert	166	1*
1913	Chop	41	4
1919	Edsall, Wilbur and Drinker	56	38
1920	Sato	157	1
1921	Davis and Huey	49	2
1922	Charles	40	3
1922	Embden	59	1
1922	Wilson	195	1
1924	Kober	103	1
1925	Gayle	72	6
1926	Beyer and Gerbis	20	1
1927	Charles	39	7
1927	Embden	58	1
1927	Ashizawa	3	1
1928	Zangger	198	1
1928	Cohen	43	10
1929	Hilpert	89	1
1930	Hilpert	88	13
1930	Meyer	133	1
1930	Embden	60	1
1930	Flintzer	68	12
1930	Schwarz	162	1
1930	Schopper	161	2
1932	Beintker	14	2
1932	Wilbur	192	32
1932	Baader	10	2
1932	Schwarz	163	3
1932	Mosheim, D.	136	1

*Identical with other cases reported in this table.

Table 7 (Page 2)

Date	Name	Reference Number	Number of Cases
1932	Mosheim, F.	137	1
1933	Bickert	21	42
1933	Salmon and Planque	156	2
1934	Owen and Cohen	142	4
1934	Surat, W.	177	4
1934	Canavan, Cobb and Drinker	34	1
1934	Lyon-Caen and Jude	117	1
1934	Sourate, V.	174	3
1934	Dantin-Gallego	47	2
1934	Dhers	50	2*
1934	McNally	127, 128	2
1935	Labeylies and Planque	106	3
1934	Stadler	175	1
1935	Trendtel	179	1
1936	Loebe	115	2*
1936	Crouzon and Desoille	46	1*
1936	Schwarz	164	1
1936	Nazif	140	26
1936	Scander and Sallam	159	26*
1936	Cochard, Jacquier, Balgaires	42	1
1936	Bryan	27	1
1936	Manganese Poisoning	120	1
1937	Muller and Christiaens	138	4
1937	McCormick	125	1
1937	Riedl	155	1
1937	Vigliani	180	1
1937	Baader	12	1
1937	Buttner and Lenz	31	11
1937	Dragonetti	52	1
1938	De Lisi	51	1
1939	Grewel and Sassen	78	1
1939	Baader	8	3
1939	Muller and Christiaens	139	1
1939	Baader	7	5
1939	Voss	187	1
1939	Voss	188	1
1939	Flinn, Neal and others	67	11
1940	Slezinger	171	1
1940	Wilkinson	193	2
1941	Grewel and Blok	77	1
1942	Manganese Poisoning	121	1
1942	Kaffman and Donoso	95	1

*Identical with other cases reported in this table.

Table 7 (Page 3)

Date	Name	Reference Number	Number of Cases
1942	Kaffman et al.	96	2
1942	Hermosilla and Roa	86	1
1943	Heine	84	5
1943	Castro Diabuno	37	1
1946	Kanevskaja and Abramson	97	8
1946	Ansola Jimenez et al.	2	29
1948	Wallgren	191	2
1949	ReyArdid and Serrate Torrente	153	1
	Total		407

Acute Manganese Poisoning. No case of acute industrial intoxication has ever been reported in the medical literature. Couper (45), in the first cases ever reported, referred to one of his 5 cases as being acute. In the instance mentioned, the patient ingested an ounce of manganese with only a purgative effect. Zanetti (196, 197) in 1940 reported that acute manganese poisoning is caused by potassium permanganate, manganese sulfate and manganese alum, while chronic intoxication is caused by the manganous components. His animal experiments showed that a paralysis of the central nervous system established itself in acute intoxication only in the case where the poisoning was abrupt and where there was a marked concentration of manganese in the blood. Many investigators (38, 53, 54, 81, 130, 152, 158,

185, 186) have dealt with the acute toxicity of manganese compounds when administered subcutaneously, intraperitoneally or intravenously. Sato (158) reported, when comparing the toxicity of bivalent and trivalent manganese, that when given intravenously the bivalent ion was 2 to 3 times more toxic as far as the lethal dose was concerned. In general, the lethal dose of most soluble manganese salts by the intravenous route lies between 18 and 50 mg. per kilogram, the precise figures varying with the salt chosen on the species to which it is administered (144).

The literature abounds with cases of vaginal hemorrhage following the use of potassium permanganate as an abortifacient. There are scattered reports of death and acute intoxication with the use of potassium permanganate in suicide and attempted suicide.

Chronic Manganese Poisoning. Chronic manganese intoxication has been known for 125 years, and some 407 cases (using only 29 of the 64 reported by Ansola et al. (2) and excluding the 16 reported by Kawamura et al. (98)) of manganism have been reported since 1837. Although some 41 occupations offering an exposure to industrial manganese poisoning (55) have been listed on Page 19, a search of the literature reveals that most cases of intoxication occurred in workers employed as grinders and packers of manganese ore

(11, 46, 51, 72, 117, 137, 142, 164, 174), in workers exposed to the metallic fume (14, 49, 97, 133), in workers employed as miners and loaders of manganese ore (28, 95, 96), and in workers sorting and separating the ore (36, 56).

With industries spreading to all points of the globe and with the increasing use of manganese, cases of industrial manganese intoxication have been reported from England (39, 142), France (42, 46, 105, 138, 139, 156), Germany (10, 11, 43, 81, 88), Japan (3, 157), China (193), Chile (2, 95), Italy (51), Egypt (140), Holland (78), Czechoslovakia (155), Poland (149, 172), Russia (168, 177, 178) and the United States (27, 34, 49, 67, 72).

Manganese Pneumonia. The syndrome of chronic manganese intoxication as characterized by Edsall et al. (56) has been accepted as the extent of the toxicological potentialities of manganese; however, since 1921 the question of "Manganese Pneumonia" as a disease entity has been offered for consideration and study. Brezina was the first to draw attention to the relationship of manganese to pneumonia. In a report cited by Fairhall and Neal (63), he states that workers in manganese mines and mills are particularly prone to pulmonary disease, pleuritis and severe fatal pneumonia. Statistical evidence (12, 84, 102, 113, 114), supported by some animal experimentation and observations (114), shows a high incidence of a fatal form of pneumonia among workers exposed to

manganese dioxide dust. Baader (12), in reporting a case of "Manganese Pneumonia" in 1937, cites much of the early literature on the subject of "Manganese Pneumonia". Some salient facts and figures are offered from this publication:

1. Brezina reported that 5 out of 10 men working in a pyrolusite mill had died of pneumonia in a period of two years.

2. Bakradse, S., 1923, demonstrated that during a ten year period of observation lobar pneumonia was one of the most frequent and severe illnesses among the Caucasian manganese mine workers. The average mortality rate among these workers for seven years due to reasons other than pneumonia was 8.24 per cent and for pneumonia an average of 31.23 per cent.

3. Schopper (161) reported that there is a high frequency of fatally ending cases of pneumonia in pyrolusite miners.

4. In 1931 a study published by the Ukranian Sanitary Inspector of Odessa, A. S. Bubarev, shows a 53 per cent incidence of pneumonia among 70 men employed as loaders of manganese ore.

5. Freise in 1932 showed that in a group (442 persons) of manganese ore loaders examined periodically over a period of four years 61 per cent had had lobar pneumonia as compared with a 3.85 per cent incidence for all industries in the same area over a sixteen year period.

6. Vigliani, in a personal communication, reported a case of a fatally ending pneumonia in a 30 year old male with a ten day exposure in an environment heavily contaminated with manganese ore dust. The patient died on the sixth day of his illness.

7. Buttner, 1936, in a paper read at a meeting of the German Scientists and Physicians in Dresden, reported that of 40 manganese miners who died in the past ten years (1926 - 1936) 23 or 57.5 per

> cent died of pneumonia. In comparison, the fatalities from pneumonia in iron ore miners for the same ten year period was 19.7 per cent.

Baader (12) concluded on the strength of the statistical value of the above reported figures that pneumonia must be considered as a typical occupational illness of manganese workers. He referred to this type of pneumonia as "Manganese Pneumonia". In 1939, Elstad (57) reported a tenfold increase in fatal pneumonia in the population of Sauda, Norway, after the opening of a manganese alloy smelting works. Lloyd Davies (113) in 1948 published observations on a group of male workers exposed to manganese dioxide dusts. Over a period of eight years this exposed population varied in number from 47 to 124 and exhibited a pneumonia rate of 26 per thousand as compared with a pneumonia rate of 0.73 per thousand in a population of non-exposed adults. The pneumonia which occurred in the manganese workers was not different clinically from that which may develop in any individual. He suggested, however, that manganese affected the whole respiratory tract, from the nose to the alveoli, and that the fever and general condition of the patient suffering with "Manganese Pneumonia" responded more slowly than usual to therapy. Cases of pneumonia in manganese workers have been reported and described by Baader (4, 5, 8, 12), Bubarev (28), Buttner (29, 30), Elstad (57), Kenneth (102), Lloyd Davies (113), Vigliani (180) and Schopper (161).

Lloyd Davies and Harding (114), in an excellent paper on "Manganese Pneumonitis" in experimental animals, reported the following conclusions:

> "The intratracheal injection of suspensions of manganese dioxide in normal NaCl and solutions of manganese chloride in normal NaCl into the lungs of rats cause characteristic histologic changes. Within 15 minutes of contact with Mn dioxide the epithelial cells of the bronchi discharge their mucus and the epithelium becomes ragged and may be loosened from the basal membrane. An intense mononuclear-celled infiltration of the alveolar walls and alveoli develops after about 24 hours, and shortly after this large hydropic cells appear, often in large numbers. Late and inconstant changes are granulomatous reaction and giant-cell formation. After about a year these changes have disappeared and the lung appears normal. The injection of Mn chloride causes intense congestion of the lung; many animals die from pulmonary edema. The bronchial epithelium is disorganized and often detached but compared with the effect of Mn dioxide the histiocytic (mononuclear) infiltration of the alveoli is less intense."

Lloyd Davies (113) reported that pulmonary effects rather than systemic poisoning are more likely to occur with a fine dust. He found that although the particle counts varied from 5,000 to 20,000 per cc. of air, the particle size was fine, for 90 per cent of the particles were less than 1 μ in diameter and 80 per cent of these were less than 0.2 μ in diameter. He maintained that the workers he observed did not absorb a sufficient quantity of manganese to cause systemic poisoning, but the fine particle size

made for such intimate contact with the pulmonary epithelium that pulmonary symptoms resulted.

In view of the above reported observations and findings this author feels that "Manganese Pneumonia" is to be regarded as a secondary, but important, consequence of manganese exposure in industry.

Chronic Industrial Manganese Poisoning

Chronic industrial manganese poisoning occurs among workers exposed to atmospheres laden with fine dust of manganese compounds and ores and manganese fumes. The earliest reference to industrial intoxication from manganese is that of Couper (45). In 1837 he reported four cases of chronic poisoning, and one case of "acute poisoning" in a man who had ingested an ounce of manganese with only a purgative effect. In view of the number of people exposed to manganese intoxication because of such extensive and varied applications of manganese compounds in industry, manganese poisoning is regarded as a relative rarity, for in the past 125 years, some 400 cases have been reported in the literature. Edsall, Wilbur and Drinker (56), in an excellent review published in 1919, suggest a "Manganese Poisoning Syndrome" characterized by the following:

1. A history of work in manganese dust for at least three months.

2. Languor and sleepiness.

3. Stolid, mask-like facies.

4. Low monotonous voice, economical speech.

5. Muscular twitching, varying in degree from a fine tremor of the hands to gross rhythmical movements of the arms, legs, trunk and head.

6. Cramps in the calves and a complaint of stiffness in the muscles of the legs, the cramps usually coming on at night and becoming worse after a day of exertion.

7. Slight increase in tendon reflexes.

8. Ankle and patellar clonus. Frequently by stretching any of the muscles of the body it is possible to elicit rhythmical contractions. Romberg sign is inconstant; there is no incoordination.

9. Retropulsion and propulsion.

10. A peculiar slapping gait. The patient keeps as broad a base as possible, endeavoring involuntarily to avoid propulsion.

11. Occasionally, uncontrollable laughter; less frequently, crying.

12. Uniformly absent are any disturbances of deep or superficial sensation, eye changes, rectal, genito-urinary or gastro-intestinal disturbances, reactions of degeneration, blood, urine and spinal fluid alterations.

Occupational History. The most important single element in the diagnosis of manganese intoxication is a history of industrial exposure, for no case of manganism has ever been reported without a history of an industrial exposure. It is

apparent from a review of the literature that the individual predisposition to manganism seems to influence the exposure period necessary for the manifestation of early symptoms. Baader (6) reported a case of a miner operating a mechanical drill who developed mental disorders after working for 3 weeks. Numerous cases have been reported with a more complete symptom complex after a 3 to 5 month exposure to manganese dust and fumes. The usual history of exposure may vary from 5 months to 20 years, but the typical syndrome manifests itself in the first 2 years (9).

Medical History. The past medical history offers no aid in the early diagnosis of industrial manganese intoxication. In the cases of manganism reported in the literature there was no incidence or reference of any disease or disorder which predisposed the exposed individuals to their intoxication. The medical history serves no other purpose than to reflect the individual's habits of living, such as diet and excessive use of tobacco, drugs and alcohol; former occupational hazards, age and hereditary background; and general physical, mental and emotional status. Flinn et al. (67), in their report of 11 cases of industrial manganism in an exposed group of 34, mentioned an increased incidence of genito-urinary and kidney disturbance and pleurisy in the affected and exposed group as compared with a control group.

The genito-urinary and kidney complaints were explained on the basis of increased age, a previous history of a similar complaint and the result of prostatic hypertrophy. The pleurisy, as may be expected, was explained as a result of a heavy exposure to dust. With the knowledge of the distribution and storage of manganese in the body, it might be well to consider individuals with histories of liver or kidney disease for selective employment or complete deferral in industries with a known exposure to manganese intoxication.

Especial attention should be given to the present medical history, for it serves as an important measure in the diagnosis, prevention and treatment of early manganese intoxication. In view of the incurability of the disease, it is most important to be familiar with its onset to prevent a further development of the condition. A recent history of lassitude, drowsiness, tremors of body or extremities, muscular weakness, muscular cramps, speech disturbances, anorexia, muscular pains, increased perspiration, increased salivation, impulsive laughter and impulsive weeping should direct all investigators towards a diagnosis of manganese intoxication, especially among persons who work in an environment involving exposure to manganese. In brief, individuals in a manganese environment who present such symptoms should be removed from such exposure and considered as suffering with manganese poisoning until proved otherwise.

Symptoms and Signs. The basic symptoms of chronic industrial manganese intoxication were first described by Couper in 1837 (45). Following an exposure to manganese dusts and fumes varying from 3 months to 3 years, the following symptoms and signs may manifest themselves. All reported signs and symptoms will never be found in any single case, but most of them are always present. An insidious onset usually occurs with languor, fatigue, general weakness and sleepiness. The patient cannot resist the temptation to sleep; Flinn et al. (66) reported that one patient slept during the short waiting periods in the examination process.

Gait disturbances are one of the most constant and persistent signs of industrial manganism. Following the development of weakness in the lower extremities, there is an instability with a resulting disturbance in equilibrium. The gait is spastic in character with marked incoordination in movement. Occasionally a peculiar gait, characterized by walking on the metatarsophalangeal joint, is observed. This was first reported by Von Jaksch (181) and was described by him as a "cock-walk". There may be flexion and swinging of the arms to help maintain equilibrium. There may be difficulty in beginning to walk, the steps at first being very short and spastic but eventually lengthening with increasing speed and resulting in the characteristic propulsion. Both

propulsion and retropulsion can easily be initiated with a mild shove. Once initiated, the propulsion or retropulsion continues for a short while until the victim reaches some support or falls. There is great risk in descending stairs or walking down inclines. Turning around may be accomplished with difficulty. Walking up hill is especially difficult due to the inability to raise the toes off the ground and muscular weakness both of the legs and body.

A stolid mask-like facies is one of the early developments of manganism. This condition may vary from a stony stare to a fixed wide grin with lips parted and may at times be accompanied by drooling. While talking the fixed facies persists but may sometimes be interrupted by impulsive movements. Spasmodic laughs and cries may occur without any apparent reason or at the slightest provocation.

Speech difficulties are prominent and persistent findings in manganese poisoning. These have been described as monotonous economical speech. The speech is especially affected when the patient does not talk on his own initiative but only in response to questions. There may be great difficulty in formulating sentences. Enunciation may be so poor that monosyllables can be understood only with considerable difficulty and uncertainty. There is a tendency to speak in a low muffled monotonous voice without modulation

and without moving lips, tongue, or teeth. At times there may be stuttering, drawling or a rapid running together of words. These speech difficulties may be further complicated by profuse salivation.

Micrographia is also regarded as a typical finding. In writing, the letters become progressively smaller and soon become illegible. To overcome the disturbances of coordination, the patient frequently starts with a large letter, but after the third or fourth letter the writing becomes illegible. With mercury poisoning, on the other hand, the patient begins with small letters and continues as such. There may be muscular twitchings in the legs followed by cramps and stiffness. Coarse and fine tremors of the fingers, hands and arms have been reported. These may be intermittent in character or may persist even during sleep. The tremors of the upper extremities may become exaggerated with purposeful movements such as eating or dressing. Stretching of any muscle may elicit rhythmical contractions of the part. There is no muscle atrophy or real paralysis. The pill rolling movements of paralysis agitans have been seen, but there is no intention tremor or ataxia.

The critical faculties, including intelligence and memory, are usually not affected. A diminution of sexual impulse, incomplete erection and a profuse perspiration

after sexual intercourse have been reported. The following have also been reported: increased tendon reflexes, irritability, lack of sociability, indifference, causeless suspicion, paresthesias, graying of the hair, exaggerated reflexes, positive Romberg, tremors of tongue, disturbances in swallowing, cough, euphoria, anorexia, dizziness, mental dullness, headache, ankle clonus, insomnia, fainting, numbness of fingers and toes, impaired memory, laziness, violent temper and loss of hair.

The diagnosis of chronic manganese poisoning would be a comparatively simple procedure if investigators would keep in mind the picture of the intoxication as characterized by Edsall et al. (56) and reported earlier in this chapter.

Pathology. The availability of human autopsy material for the study of the pathologic changes in chronic manganese intoxication has been very limited, and consequently the majority of observations of organ changes in such cases have been the result of animal experimentation. In both animals and humans the characteristic lesion is destruction of the ganglion cells of the basal ganglia with scarring and shrinking. The most important pathological changes in man are those which occur in the central nervous system. There are no characteristic changes evident in the spinal cord or peripheral nerves.

Autopsy findings on patients with a history of manganese poisoning have been reported by Casamajor (36), Ashizawa (3), Canavan et al. (34), Stadler (175), Trendtel (179), Voss (188), and Flinn et al. (67). Casamajor (36) reported a bilateral interstitial nephritis and extensive biliary cirrhosis of the liver. There was some degeneration of the longitudinal fibers of the pons in the brain, and the perivascular spaces of the lenticular nuclei and the outer part of the optic thalami were larger than usual. Ashizawa (3) reported alterations in the putamen and caudate nucleus with more pronounced degeneration in the larger ganglion cells as compared with the smaller ganglion cells. Canavan et al. (34) found an atrophy of the frontal cortex, more marked on the right, and some indistinctness in the basal ganglia. One slice of brain, including both striate bodies and optic thalami, also showed atrophy. There was a decrease in size of the basal ganglia which were between 3 and 10 mm. smaller than those in control sections. Microscopic examination showed cells of choroid plexus on outside of tufts, mostly low and single but occasionally heaped up. Some tufts showed enlarged vessels. In the basal ganglia degeneration of nerve cells, satellitosis, and gliosis were found. Stadler (175) found perivascular degenerative areas in the striatum and pallidum and to a lesser extent in the frontal and

parietal cortices. Trendtel (179) found wasted areas and scar formations in the corpus striatum in addition to a decreased number of nerve cells in the putamen and pallidum. The findings of Flinn et al. (67) may well be discounted because of the marked post mortem changes. Basically the clinical and anatomical findings of manganese poisoning point to lesions in the basal ganglia, caudate and lenticular nuclei, corpus striatum, globus pallidus, pons, internal capsule, peduncle and putamen, with occasional changes in the frontal and parietal cortices and more rarely in other portions of the central nervous system.

With animal autopsy material similar changes have been found, and in most instances these brain, liver and kidney lesions can be produced experimentally. Hepatic lesions vary from hyperemia, hemorrhages, degenerative cell changes in the periphery of the acini, with occasional formation of connective tissue similar to an early cirrhosis, to only small hemorrhages with stasis. Acute hepatitis with necrosis has also been described (65, 130). Kidney changes have been shown to consist of venous enlargement, epithelial degenerative alterations, occasional fatty degeneration and lymphocytic cellular collections in the lower cortex (65, 79). Animal brain changes are very similar to those reported in human cases (65, 79, 130). These changes consist of

degenerative phenomena in the basal nuclei. Perivascular round cell collections have been noted in these areas as well as gliosis and neuronophagia. Areas of gliosis have been seen in white and grey matter. Less marked changes may occur in varying degrees in the cortex, optic thalamus and cerebellum. Lung findings have been discussed in the section on manganese pneumonia. The findings in the remaining body organs do not contribute to the picture of industrial manganese poisoning.

Laboratory Findings. Laboratory examinations and findings have not been shown to be of aid in the diagnosis of chronic industrial manganese poisoning.

Urine. Kehoe et al. (101) in 1940 suggested a normal urine manganese level in non-exposed healthy adult individuals. This level varies from trace to 0.02 mg. per liter of urine, and the mean normal level was reported as 0.01 mg. per liter of urine. Flinn et al. (67), in a study of 11 cases of manganism in a group of 34 exposed adults, reported the following: 9 of the 11 affected workers and 16 of the 23 exposed but non-affected workers showed urinary levels varying from 0.004 to 0.048 mg. of manganese per liter of urine. The average determination for the affected group was 0.010 mg. of Mn per liter and 0.014 mg. of Mn per liter for the non-affected group. Six of the 7 exposed adults with no

urinary manganese had short intermittent exposures. If the 7 cases with no urinary manganese were removed from the group, the average value for the remaining workers would rise to 0.020 mg. per liter, which is double that of the affected group. They reported that the urinary content of manganese decreases roughly with the increasing length of time the man has been removed from the exposure.

"This accounts for the increased average in the non-affected group as compared with the affected group, for several of the affected group were removed from the exposure, one for 7 years, one for 9 years and one for 19 years. Larger amounts were found in 3 of the affected group who were still working."

They further reported that because the urinary manganese content was higher on the average in the exposed but non-affected workers than in those suffering with manganese poisoning, who, however, in many instances had discontinued their exposure some time prior to the time at which analyses were made, the urinary manganese is a reflection of exposure to manganese, with absorption, rather than evidence of manganese poisoning. In many reported cases of industrial manganism no urinary manganese was found (10, 36, 49, 72, 128, 164, 174). These data, in the main, are without meaning for purposes of diagnosis or physiologic interpretation, either because of the inadequacies of the analytical methods, or because of the time interval between the last date of exposure and the analyses, or for both reasons combined.

Blood. As in the urine, Kehoe et al. (101) suggested a normal blood manganese level in normal non-exposed adults. This level varies from 0.005 to 0.0249 mg. per 100 grams of blood, and the mean normal level was reported as 0.015 mg. per 100 grams. Because of the rapidity with which intravenous manganese preparations are removed almost quantitatively from the blood stream, it seems likely that blood manganese determinations can offer little or no aid in the diagnosis and prognosis of manganese intoxication. However, systematic observations have not been made on an adequate scale and by means of analytical procedures of high precision to establish the facts with reference to existence or non-existence of a relationship between the concentration of manganese in the blood and the current level of exposure to and absorption of manganese. Most investigators report negative to trace amounts of manganese in the blood in their cases of true manganism, because, no doubt, of their use of inadequate procedures of sampling and analysis. There have been scattered and suggestive reports concerning the cellular elements of the blood in chronic manganism; however, the reports serve only to strengthen the fact that hematologic findings do not aid in the diagnosis of manganese intoxication. Davis and Huey (49) showed a high erythrocyte count in their 2 cases, but they attributed this to an accompanying carbon monoxide exposure. Schwarz (163)

also reported a high erythrocyte count. Surat et al. (178) reported that an increase in the hemoglobin and the enlargement of the lymph glands were among the early symptoms of manganese poisoning. Flinn et al. (67) suggested that a low white cell count with a decreased percentage of neutrophils is associated with manganese poisoning. Baader (10) mentioned anemia. To repeat, blood studies offer little in the diagnosis of manganese poisoning.

Cerebrospinal Fluid. Flinn et al. (67) reported a slight but definite change in the middle zone of Lange's test in 6 out of 9 of his group of 11 exposed and affected cases. They suggested this as an aid in diagnosis. McCormick (163) also reported a lowering of the middle zone in his one case. Not having any laboratory aid in the early diagnosis of manganese poisoning, one may look with some favor on such consistent findings; however, much remains to be determined as to its usefulness in early diagnosis. The cases reported were true cases with histories of removal from the exposure varying from 1 to 19 years. We have no information concerning what might be found by laboratory examination after short exposures and prior to the stage where the diagnosis is obvious.

Feces. Kehoe et al. (101) found that the mean daily output of manganese in the feces of a normal group of persons who were not and had never been subjected to unusual exposure

to manganese, was 3.69 mg. Comparable amounts of manganese were found in the food and drink consumed daily by these persons. As reported in the chapter on excretion, most investigators are in agreement that the greatest percentage of manganese absorbed into the organism is excreted in the feces apparently by way of the biliary apparatus. Several authors have reported that an increased amount of manganese appears in the stools of individuals suffering with manganese intoxication (10, 78, 111, 187), but it is not always clear from the examination of the data that those quantities were derived from past occupational exposure to manganese or from their current dietary intake of manganese. In some cases the increase persisted for 16 months (10). Baader (11) reported amounts varying from 2.2 to 7.5 mg. per 100 grams of feces. Davis and Huey (49) and McNally (128) failed to find manganese in the feces of their patients. There are no reports in the literature which give any significance to the amounts of manganese found in the stool. Here, again, the laboratory procedure offers little in the early diagnosis of industrial manganese intoxication. An abnormal amount of manganese in the stools may serve to confirm a history of recent or past exposure, but considering the variability of the amounts which may be taken in with the food, such results, unless

controlled by determination of the current intake of manganese must be interpreted with caution.

Special. There are no special laboratory procedures which can be utilized as aids in the early diagnosis of industrial manganism or utilized as confirmatory tests in cases of true manganese intoxication. Flinn et al. (67) reported normal findings in their series of 11 affected and 23 exposed but not affected cases in blood platelet counts, coagulation times, bleeding times, blood sugar determinations, serum chloride determinations, serum phosphorus (inorganic) determinations and total non-protein nitrogen determinations. The serum calcium determinations in the manganese-affected group were lower (average 8.8 mg. per 100 cc. of serum) as compared to the manganese exposed but not affected group (8.8 - 11.2) and normal non-exposed individuals (9.8 mg. per 100 cc.). They concluded that manganese poisoning may result in a reduced serum calcium content. Zanetti (196) reported normal serum calcium levels in his exposed but not affected cases. McNally (128), in his one case, reported normal liver function as determined by the rose bengal liver function test. Flinn et al. (67) reported 2 abnormal results out of 12 determinations of liver function as determined by the galactose tolerance test of Bauer. Both abnormal results

were found in the affected group. They further commented that whatever liver damage was present was not sufficient to result in an appreciably decreased tolerance to galactose. They also reported normal findings in x-ray films of jaw, hands and forearms. In "Manganese Pneumonia" Lloyd Davies (113) reported a typical consolidation of the affected area on x-ray examination of the chest. Baader (12) submitted x-ray evidence of a "dust-lung" six months prior to the development of "Manganese Pneumonia".

At the present time, and with present techniques, it is apparent that the laboratory offers little direct aid in the early diagnosis of chronic manganese intoxication.

Differential Diagnosis. The important considerations in the differential diagnosis of chronic industrial manganese poisoning are: multiple sclerosis, paralysis agitans (Parkinson's disease), progressive lenticular degeneration (Wilson's disease) and amyotrophic lateral sclerosis.

Multiple sclerosis. This degenerative disease of the central nervous system occurs in young adults (20 - 30 years of age, rarely over 35). Latins, Negroes and Hebrews are rarely affected. It is characterized by spasticity, well marked nystagmus, loss of abdominal reflexes, intention

tremor, ataxia, abnormal and hyperactive reflexes, and speech disturbances (scanning speech). There is a paretic gold curve in 20 - 25 per cent of the cases. The classical course is characterized by periods of remissions and exacerbations with a tendency toward a progressive downward course, with death due to intercurrent infection or to infections dependent upon bladder paralysis, such as cystitis or nephritis.

Paralysis agitans. This condition usually occurs in older sclerotics when the arteriosclerotic process affects the basal ganglia and the extra-pyramidal system. It is characterized by rigidity (the patient appears to be cast "en-block" and walks with very short spastic steps), mask-like facies, tremors which are slow and coarse, lessened during sleep and voluntary movement and increased during emotional upsets, constant nodding of the head and a rhythmic pill-rolling tremor of the hands. Weakness develops, and the course is progressive and downhill.

Progressive lenticular degeneration. This is a rare, severe and progressive disease, with a high familial incidence, beginning about the period of adolescence and terminating fatally in 3 or 4 years. It is characterized by a gradually increasing hypertonia which develops into a true spasticity and rigidity, mental changes which may lead to complete dementia, and cirrhosis of the liver.

Amyotrophic lateral sclerosis. This disease is characterized by the gradual development of muscular fibrillations, muscular atrophy, spastic phenomena and hyperactive and abnormal reflexes. It is a disease of the motor portions of the central nervous system. When lower motor neuron involvement occurs, the condition is referred to as progressive bulbar paralysis with a resulting atrophy of the muscles of the face, jaws and tongue, and difficulty in speech and swallowing. The disease follows a rapid downward course, patients rarely surviving for longer than a few years. In the presence of bulbar paralysis death may occur in 6 to 8 months.

In the event of any serious difficulties in the differential diagnosis of industrial manganism, it is apparent that time will eventually prove the diagnosis for there is no specific therapy for the aforementioned diseases, manganism included, but manganese intoxication enjoys the most favorable prognosis when the patient is removed from the exposure. Too much emphasis cannot be placed on the fact that removal of affected persons from the manganese exposure will halt, if not entirely cure, the disease process (66, 67, 107, 128, 172, 197).

Prognosis. There have been no deaths reported as a direct result of manganese intoxication due to an industrial

exposure. In industrial manganese intoxication the prognosis as regards life is relatively good, but there is no cure. It must be remembered that the sooner an affected individual is removed from the exposure, the more favorable is his prognosis. Many symptoms will disappear or regress if the worker is removed shortly after the onset of his symptoms. The lesions in well advanced manganese poisoning are persistent and progressive and may result in a crippling disease with permanent disability, particularly with regard to the use of the legs (49, 63, 66, 67, 128, 172, 197). It is encouraging to note that Couper (45) in 1837 reported that one of his cases recovered after 6 years following his removal from the toxic exposure.

Treatment.

(a) Prophylaxis. At the present time the treatment of chronic industrial manganese intoxication lies in its prevention. This role of prevention is the responsibility of the industrial hygienist and engineer as well as the industrial physician. On pre-employment physical examination, it is the duty of the examining physician to defer or selectively place (no exposure to manganese) all employees who show evidences of arteriosclerosis, pulmonary pathology, hepatic disease and diseases with chronic nerve changes. The physician should be sufficiently informed on the subject of manganese

poisoning to recognize readily the early symptoms of this condition. Because of the individual predisposition to manganese intoxication and because of the favorable prognosis with early diagnosis, periodic physical examinations should be made on all workers in an atmosphere of manganese dust. Any worker showing signs of early intoxication, such as drowsiness, languor, fatigue, muscular cramps, twitching or tremors, should be transferred immediately to a manganese free environment until such time as he is completely free from such complaints. These findings may also serve to detect possible defects in the dust control measures in use and to point out operations that need further control measures. Workers with signs and symptoms of severe intoxication, such as gait and speech disturbances and muscle stiffness and incoordination, are to be removed immediately from their jobs and never placed in a manganese exposure again. The physician is also responsible for the education of supervision and labor in the matter of the hazards of their work and the means of controlling such hazards by both environmental and personal hygiene. Hygienic control measures which the physician should recommend and enforce include a daily change of work clothes, clean and well ventilated locker rooms for storage of street clothes, suitable shower facilities so arranged with reference to the locker room that the workers can remove

their work clothes prior to entering the locker room, washing facilities to enable workers to wash and gargle before meals and, finally, dining room facilities. When exposure to dust is unavoidable dust masks should be employed under supervision in order to minimize the inhalation of excessive amounts of dust. The physician is also responsible for the initiation and maintenance of complete, detailed records of all medical findings on each worker. It is the duty of the industrial engineer to create and maintain a work environment well within the limits recommended by the American Standards Association (60 mg. of manganese per 10 cubic meters of air) and to provide a safe, well ventilated environment with a minimum of daily exposure. Such small "miracles" have been accomplished by the following means: enclosure of the harmful process, isolation of the harmful process from the remainder of the plant with special protection for workers necessarily included in the area isolated, local exhaust ventilation, general ventilation, the use of wet methods, modification or elimination of a hazard-producing process and, finally, the use of appropriate personal protective devices, particularly for respiratory protection (22). The factors that determine whether or not injury or disease will probably result from any given exposure can be stated quite simply, but the making of an analysis adequate to determine

the degree of atmospheric contamination and to guide proper corrective action usually requires the services of an experienced industrial hygienist. It is the duty of the industrial hygienist to appraise the environment and check on the efficacy and efficiency of the existing processes, operations and methods of ventilation (22).

(b) Specific and Symptomatic. The course of chronic manganese poisoning is progressive, and there seems to be no effective treatment other than removal from the exposure (63, 185). Not a single case of manganese poisoning has ever been reported as cured (172). Charles (39) in 1927 reported that while his patients were subjected to liver therapy there was an amelioration of symptoms; however, there were no cures. The suggested methods of treatment have included electro-therapy (181), hydrotherapy and massage (172), potassium iodide (41), sodium thiosulphate (58, 76), atropine (8, 87), scopolamine (87), adequate rest and nutritious diet (76) and treatment of any foci of infection (172). There seems to be little hope for recovery in severe cases of manganism, no matter what treatment is used.

CHAPTER III

METHODS OF DETERMINATION

The colorimetric estimation of manganese by oxidation of manganous compounds with strong oxidizing agents, such as sodium periodate and ammonium persulfate, to permanganates in acid solution is regarded as one of the most specific and sensitive methods for the determination of manganese in dusts. It is also accepted by the American Public Health Association and the American Water Works Association as the standard method in water analysis (176). Willard and Greathouse (194) in 1917 were the first to propose the use of periodate for the oxidation of manganous salts to permanganate in the colorimetric determination of manganese. The dust samples are best collected with the electrostatic precipitator (sampling rate 85 liters/minute) or the impinger flask with distilled water as the collecting medium (sampling rate 28.3 liters/minute) (26).

Several methods are offered for the determination of manganese in biological materials. Gates and Ellis (71) developed a microcolorimetric method with results comparable to the periodate method. A spectrographic method reported by Kehoe, Cholak and Story (101) is also suitable. Detailed

methods of procedure may be found in many different reports (26, 71, 101, 176, 194).

CHAPTER IV

MAXIMUM ALLOWABLE CONCENTRATION

The maximum allowable concentration of manganese has not been determined. In the survey conducted by Flinn et al. (67) no cases of typical manganism developed among men exposed to concentrations of less than 38 mg. of manganese per cubic meter, but one man exhibited symptoms after ten months of exposure to that concentration and another after an exposure of less than one year to a concentration of 50 mg. per cubic meter. Two men who were exposed to concentrations between 30 and 59 mg. of manganese per cubic meter, and eight men exposed to concentrations of more than 90 mg. per cubic meter, were victims of chronic manganese intoxication. The proposal of 60 mg. of manganese per 10 cubic meters, arrived at in this survey, was adopted as a war standard of maximum allowable concentration by the American Standards Association on July 16, 1942 (144). The maximum permissible concentration is 60 mg. per 10 cubic meters of air (144).

CHAPTER V

OCCUPATIONAL AND PUBLIC HEALTH PROBLEM

Chronic industrial manganese intoxication was first recognized in 1837 (45), and although 125 years have passed some 400 cases have been reported. This accepted sparse incidence, coupled with the fact of individual predisposition, may well serve to diminish the necessary efforts for early diagnosis of manganese intoxication. Industry can prevent manganese intoxication by preventing or minimizing exposure to manganese. The required procedures to achieve these goals may be fairly expensive; however, an award of $25,000 (120) for one case of intoxication also appears expensive. Manganese intoxication is included in the Workmen's Compensation Acts of Chile, Germany, Great Britain, Switzerland and the United States. There is no known treatment for manganese intoxication, and if the condition is allowed to progress, the affected worker may eventually become a permanent cripple. Such an individual is a burden to himself as well as to society. Prognosis with regard to life is good, and manganese poisoning usually occurs in young adults, 25 to 35 years of age. Therefore, such cripples will sharply focus attention on industrial negligence for long periods. A secondary result may be the

precipitation of a "manganophobia" among other employees, as reported by Von Jaksch (183).

The public health problem of manganese has little if any significance because no cases of manganism have been reported in the absence of industrial exposure to manganese dust and fume. Elstad (57) reported a tenfold increase in pneumonia among the inhabitants of Sauda, Norway, after the opening of a plant in which manganese alloys were smelted. These findings were utilized in the literature to strengthen the case for "Manganese Pneumonia". Perhaps the reports of Elstad (57) and Baader (12) will serve to stimulate further study on the public health problem of manganese.

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