Manganese and Man

Barbara Aston, M.S.[1]

Abstract

The therapeutic use of manganese in schizophrenia began in 1927. Man's daily Mn requirements may range from 1.1 to 21 mg Mn/day. Absorption of Mn from the gastrointestinal tract is poor. That which is absorbed is almost completely removed from the circulation by the liver. Mn absorption depends upon body tissue levels of Mn, dietary calcium, zinc, phosphorus, iron, cobalt, choline and ethanol content in the diet. The excretory system for Mn is very efficient so the danger of causing Mn toxicity through the use of oral Mn supplements is minimal. Due to its poor absorption and rapid excretion, the differences in absorbability of various compounds of Mn need further study.

Postural and skeletal defects which occur in Mn deficiency seem to be related to connective tissue abnormalities involving the failure of cartilage and mucopolysaccharide formation. Mn is necessary for the activation of glycosyltransferase enzymes which play a major role in the synthesis of chondroitin sulfate, a major polysaccharide of cartilage. In dogs, Mn deficiency results in disc degeneration due to inadequate cartilage formation in the disc. In rats, Mn deficiency results in abnormal or no otoliths at all in the inner ear upsetting the balance mechanism of the body.

A Mn-superoxide dismutase occurring in the mitochondria may prevent damage to membranes and other biological materials. In Mn deficient mice all the Mn deficient tissues reveal alterations in the integrity of cell membranes. Therefore this enzyme is likely responsible for many of the defects occurring in Mn deficiency. Avimanganin, a manganoprotein, may be an inactive form of superoxide dismutase.

Manganese is important in the building and breakdown cycles of protein and nucleic acid. For RNA chain initiation, Mn was found to be a better effector than magnesium. Manganese stimulates adenylate cyclase activity in brain tissue. Because cyc-lic-AMP plays a regulatory role in the action of several brain neurotransmitters, Mn is important in brain function. Owing to the fact that zinc is well absorbed from the gut but Mn is poorly absorbed, all diagnostic categories may be harmed by large prolonged

■ Nutritionist, Brain Bio Center, Princeton, New Jersey 08540

This paper was presented at the Orthomolecular Medical Society Meeting in San Francisco, California, May 2-4,1980.

doses of zinc without Mn. In oral doses Mn has occasionally elevated blood pressure in patients over 40 years of age. Zinc alone can lower blood pressure in some hypertensive patients. Chronic hydralazine (a Mn chelator) in rats produced Mn deficiency which resulted'in convulsions. Low blood and serum Mn levels may play a role in epilepsy possibly by interfering with membrane stability.

Prolonged use of phenothiazines causes tardive dyskinesia. Phenothiazines might chelate Mn making it unavailable for some presumed function as an enzyme activator.

Introduction

The study of the micronutrients and their use in clinical medicine has been actively practiced by our group since 1967. Three micronutrients in particular, copper, zinc and manganese (Mn), have generated much research, especially concerning their roles in the schizophrenias. Heilmeyer et al. (1941) presented one of the earliest studies implicating excess copper in 32 of 37 schizophrenics. We continue to find similar blood serum copper elevations in our patients, particularly in the low histamine schizophrenic, depressives, epileptics, alcoholics, infectious diseases, and some cancer. The high copper level of many schizophrenics and other patients can be reduced by adequate dietary intake of zinc and Mn. Both Reiter of Denmark (1927) and English of Ontario (1929) found improvement in schizophrenic patients given manganese chloride. Manganese is similar to zinc in increasing urinary copper excretion. The combination of zinc and Mn is more effective than either alone.

One of our patients experienced skipped heart beats because of decreased conduction in the heart. The eating of tropical fruit high in Mn improved the heart rate. This effect, to regularize the heart, could be reproduced at will by an oral dose of five mg of Mn as the gluconate or by the ingestion of foods high in Mn.

Requirement

Williams (1967) was one of the first scientists to prove a wide disparity in requirement for nutrients, even among pure-bred strains of animals. Armadillos normally give birth to a set of monozygous quadruplets. These identical litter mates with similar genes, when analyzed, varied in the amount of adrenaline in their adrenal glands by as much as 32 fold. They also had a similar wide range in optimum requirements for ascorbic acid and other nutrients. If purebred strains of animals vary so greatly, it is certain that genetically heterogeneous animals, like man, will also have wide-ranging requirements. Thus, mean optimum daily values as recommended by nutritionists are a very rough guide for a given population and may be of limited value for any individual.

The minimum dietary requirements of Mn vary with the species and genetic strain of the animal, the chemical form in which the element is ingested, the composition of the rest of the diet and the criteria of adequacy employed (Underwood, 1977). At low or borderline levels of intake of Mn, the responses of individuals may vary greatly depending in part on their genetic background. The genetic constitution of mice affects their response to dietary deficiencies (Hurley and Bell, 1974). Therefore, we must be concerned with the amount of Mn which is needed for optimal health and all functional purposes in each individual and not be satisfied when employing the usual animal criteria of "adequate for growth and reproduction."

The literature states Mn requirements to vary between 0.02 to 0.03 and 0.2 to 0.3 mg per kg body weight and day (Schlage and Wortberg, 1972). This means the standard 70 kg man may require from 1.4 to 21 mg Mn per day. The standard 54 kg woman may require 1.1 to 16.5 mgMn per day.

Using data of other workers, Schlage calculated that intakes of 0.035 to 0.070 mg per kg body weight and day would result in balanced Mn intakes and excretions. Ranges of Mn intakes for some age groups are as follows:

9 kg infant	0.315 - 0.630 mg Mn/day;
28 kg child	0.980 -1.96 mg Mn/day;
54 kg female	1.89-3.78 mg Mn/day;
70 kg male	2.45 - 4.90 mg Mn/day.

However, these data completely ignore the individual whose genetic constitution makes him more susceptible to borderline levels of intake. While the Committee on Dietary Allowances, Food and Nutrition Board of the National Research Council has recommended an intake of 2.5 to 5.0 Mg/day of Mn, we know that some individuals may need much larger doses. For instance, an allergic patient with low blood Mn needed 300 mg of Mn per day in order to start the slow rise of blood Mn toward normal. With this large dose of Mn he gained 10 pounds in needed body weight and could tolerate an oral zinc supplement for the first time (Brain Bio Center, 1979).

Absorption

Manganese is absorbed slowly and poorly from the small intestine (Cleason et al., 1969). Some studies suggest that Mn absorption is by an active process in the duodenum (Cikrt, 1970). However, Underwood (1977) states that Mn is equally well absorbed throughout the length of the small intestine.

Studies of Sansom et al. (1976) indicate that manganous ions traverse the mucosal cell and are absorbed into the portal circulation where they remain free or rapidly bind to *a* 2-macroglobulin before passing through the liver where they are almost completely removed. However, some of the manganous ions may pass into the systemic circulation, become oxidized to the manganic form and bound to transferrin or "trans-manganin".

Sansom et al. (1978) have extensively studied the absorption of dietary Mn by dairy cows. Manganese is absorbed from the diet in a proportion which is independent of dietary concentration. The cows apparently absorb 0.5 to 1.0 percent of dietary Mn whether the diet contains 50 or 1000 mg Mn/kg dry matter. The systemic Mn concentration varies little with changes in dietary Mn concentration. All of the Mn must presumably be excreted in the bile or stored in the liver. For the blood plasma Mn to rise, the liver's capacity to remove Mn from the circulation, store and excrete excess Mn would have to be exceeded.

Influences on Absorption

Apparent adequate dietary levels of Mn may not meet body needs due to the influence of other nutrients which affect Mn absorption. Manganese absorption depends upon body tissue levels of Mn, dietary calcium, zinc, phosphorus, iron, cobalt, choline and ethanol content in the diet. For example, Lassiter et al. (1974) have shown that ^{54}Mn retention in low Mn baby calves was nine times greater than in Mn supplemented calves. Also in calves, Howes and Dyer (1971) have shown increased absorption of Mn under conditions of low Mn intakes and decreased absorption at higher Mn intakes in a manner reminiscent of iron absorption in iron deficiency.

Manganese competes with cobalt and iron for common binding sites at the mucosal cell surfaces. Within the intestinal mucosa, Mn and iron compete for a common carrier which has less affinity for Mn than for iron. Cruden (1979) has shown that for Mn supplemented diets the duodenal transport and retention of Mn is greater on an iron deficient diet compared with a diet much higher in iron content. This provides further evidence that the absorption of iron and Mn is interrelated and that the duodenal transport and absorption of iron and Mn are competitive.

Dietary calcium and phosphorus modify Mn metabolism. In birds it has been found that excess dietary calcium phosphate can aggravate Mn deficiency (Wilgus and Patton, 1939) probably by absorption of the Mn to the calcium phosphate in the gut, thereby preventing absorption. Therefore, a greater Mn intake would probably provide a margin of safety and cope with variations in calcium and phosphorus intakes.

Lassiter et al. (1972) have shown liver stable Mn to be one-third higher in rats given low calcium diets (.1 percent). Dietary calcium, however, may not be the explanation. King et al. (1979) round a skim milk diet increased liver Mn and contained the higher calcium level than the alternate Mn-free purified casein-dextrose diet. The calcium-phosphorus ratios in the two diets were also similar. One important difference between the two diets was a higher amount of lactose in the corn-skim milk diet. Fournier and

Fournier (1972) suggest that lactose may in crease Mn absorption.

An association between choline and Mr metabolism has been recognized for som< years. In turkey poults, lack of choline ha been shown to produce perosis, a Mn de ficiency symptom (Jukes 1940, 1941). Cho line deficient rats show lower liver Mn level: (Keefer et al., 1973). Ethanol metabolism ir the gut causes an increase in hepatic Mr (Barak etal., 1971).

Excretion of Manganese

The excretory system for Mn is very ef ficient so the danger of causing Mn toxicity through the use of oral Mn supplements i: minimal. Most of the Mn ions which are ab sorbed into the portal circulation are almost completely removed by the liver and ex creted into the bile. Bile flow is ordinarily the main route of excretion. When bile flow
is blocked or the hepatic pathway is overloaded, excretion takes place via the pancreatic juice, the duodenum, the jejunum and, to a smaller extent, the terminal ileum. These routes represent alternate means of regulating tissue Mn levels.

Due to its poor absorption and rapid ex-cretion, the differences in absorbability of various compounds of Mn may be important. In animals, Mn appears more rapidly in the blood if fed in the form of chelates rather than in the form of inorganic salts (Cotzias, 1958). At present, at the Brain Bio Center, we are measuring the change in blood Mn levels of subjects fed different forms of Mn: sulfate, orotate, chelate, gluconate, as well as food sources such as tea, whole grains, nuts and tropical fruits.

Table 1
STUDIES OF MANGANESE INTAKES DURING THE PAST 10 YEARS

	Group Studied	Country	Intake mg/day
Kirkpatrick & Coffin (1977)	Total diet	Canada	2.93
Soman et al. (1969)	Total diet	India	5.8 - 12.4
Nakagawa (1968)	Adults	Japan	6.0 - 10.0
Gutherie & Robinson (1977)	Females age 19 - 50 yrs.	N.Z.	0.8 - 7.1
Zinkina & Baltabaev (1975)	School Children	USSR	5.2
Wenlock & Buss (1979)	Total diet	UK	4.6 (50% from tea)

Wenlock & Buss (1979)

Table 2
U.S.A. MANGANESE INTAKES

	Group Studied	Intake mg/day
Murthy et al. (1971)	Children 9 - 12 yrs. institutionalized diet	2.0
White & Gynne (1971)	Females 19 - 20 yrs	< 0.24 - 1.53
Price et al. (1970)	Girls 7 - 9 yrs.	2.3
Gormican (1970)	Hospital menus	< 0.36 - 1.78
White (1969)	Females 14 - 16 yrs.	< 0.24 - 1.53
	College women	< 0.38 - 1.38
Tipton et al. (1969)	Adult men	3.3 - 5.5

Wenlock & Buss (1979)

Manganese Intakes

By studying Tables 1 and 2 it is readily apparent that other countries have higher Mn intakes than does the U.S. It is plausible from the U.S.A. intakes that certain segments of the population are likely to suffer from Mn deficiency. Three striking facts from the U.S. data are apparent:

1) Females aged 19-20 years and college women are highly suspect of being deficient in Mn.
2) Adolescent females may be getting only minimal Mn from their diets, if indeed the estimates of daily requirements are accurate. We know the Mn requirementfoY growth is high.
3) Hospital menus are deficient in Mn. Consider the number of people who are in hospitals due to joint problems, diabetes, epilepsy and schizophrenia. All may be conditions in which Mn deficiency plays a major role.

Manganese Deficiency Symptoms

With Mn deficiency likely in certain segments of the U.S. population, we must be aware of the possible consequences of Mn undernutrition. During growth, Mn deficiency would affect the development of bones and cartilage. Diabetes, hypoglycemia, arthritis, epilepsy and schizophrenia may be more serious consequences of low Mn intakes in later years.

Manganese has long been ignored because some believed magnesium could replace Mn in some biochemical systems. Also, a clear-cut case of Mn deficiency in humans had never been proven. Then, during an experiment in which Doisy (1973) was studying vitamin K deficiency, Mn was inadvertently left out of the diet mixture being fed to the patient. This patient underwent weight loss, transient dermatitis, nausea, and slow growth of hair and beard with changes in hair color. Biochemically, there was striking hypocholesterolemia. With recognition of the error, the stage was set for more intensive research into Mn and its biochemical roles.

Food Sources of Manganese — Why Deficiency is Likely

The richest food sources of Mn are nuts, whole grains, spices, legumes and tea leaves. Values for filberts, whole wheat, cardamon, dried split peas and Orange pekoe tea leaves are 4.2, 4.9, 24.0, 2.0, and 71.0 mg Mn/100 g respectively (Schlettwein-Csell and Mommsen-Straub, 1971).

Refined sugars, fresh and canned vegetables, fresh, dried, and canned fruits, meats, including organ meats, fish, eggs, milk products, and fats are relatively poor sources. In comparison to the above figures, molasses, green beans, apples, chicken, and cows milk contain only traces:0.04, 0.45, 0.035, 0,021, and. <0.01 mg Mn/100 g respectively.

Since Mn is involved in photosynthesis (Winget and Spector, 1980) Dr. Pfeiffer suggests that tropical fruits and nuts may be good sources of Mn. This appears so. Values for tea leaves, pineapple, macadamia nuts, dates, persimmon, and banana are 71.0, 2.76, 0.67, 0.53, 0.15, and 0.13 mg Mn/100 g respectively.

Foods rich in Mn derive it from the soil provided the soil has adequate Mn. Current farming methods, soil erosion, leaching and soil exhaustion result in less Mn in foods.

This depletion of the soil may be unsuspected since the foliage of the plants may be lush without Mn. This is typified by the growth of lettuce. If lime is applied to clay soils, the more alkaline soil will retain Mn and lettuce may grow abundantly but the leaves of the lettuce will have much less Mn because of the application of lime to the soil. This finding points out the real need for scientific farming wherein the fertilizer will contain all of the trace elements which are deficient in the soil (Pfeiffer, 1977).

Food processing strips the grains of Mn. The germ of the cereals is the richest source. For example, whole grain wheat contains 4.9, wheat germ, 13.74 and finely ground wheat flour, 0.46 mg Mn/100 g. Whole grain corn contains 0.284, corn germ, 10.0, and cornflakes, <0.04 mg Mn/100 g. Whole grain rice contains 1.7, polished rice, 1.5, and rice crispies, 0.99 mg Mn/100 g, one-half as much manganese!

The present trend of increased consumption of more refined foods leads to reduced Mn intakes. Increased consumption of

whole cereal grains and legumes is recommended. In cultures where corn and rice are the main dietary components or in which meat, milk, refined sugars and cereals are dietary staples, Mn supplementation should be considered. An excellent, detailed source of data on the Mn content of foods is Ubersicht Sprunelemente in Lebensmitteln, IV Mangan, by Daniela Schlettwein-Csell and Sibylle Mommsen-Straub, 1971, in German.

Effects of Manganese Deficiency in Experimental Animals

Some dramatic general effects of insufficient Mn in animals are impaired rate of growth, failure to reproduce, and shortened life span. These are not easily explained at the biochemical level. Explanations are more easily made for the postural and skeletal defects which occur. In the chicken the most striking effect is perosis or slipped tendon. In the rat there is failure of the otoliths to develop properly in the inner ear before birth with subsequent problems related to equilibrium. This failure in development of tendons and otoliths seems to be related to more extensive connective tissue abnormalities probably involving the failure of collagen and mucopolysaccharide formation. Other probable abnormalities in Mn deficiency include neurologic symptoms, impaired mitochondrial oxidation, impaired blood clotting and possible alterations in glucose metabolism (Utter, 1976).

Manganese and Those Sore Knees

The mechanism behind the skeletal abnormalities and joint deformities which occur in Mn deficiency is perhaps the best understood of all the Mn deficiency symptoms. In young children Mn deficiency may be called "growing pains" by the family physician. At the Brain Bio Center it is typified in the Sara syndrome (Pfeiffer et al., 1974). It is still occurring most frequently in athletes and today most notably in Bill Walton of the San Diego Clippers. In 1973, Walton was having problems with his knees. Dr. Bernard Rimland wrote him a letter suggesting that perhaps the widely prevalent zinc and Mn deficiency, so frequently diagnosed
at the Brain Bio Center, could be partly responsible for the problems he was experiencing. We never heard from Bill Walton nor of this matter again until January 25, 1980, when Dr. Rimland sent us a clipping of Neil Morgan's column from the San Diego Unida-Tribune, week of January 20, 1980. Mr. Morgan reported that biologist Paul Salt-man had suggested to Dr. Ernie Vandew-eghe, Walton's mentor, that perhaps Walton's diet lacked trace elements essential to bone healing. Blood tests at the UCSD Health Center confirmed shortages of iron, zinc, and Mn. A solution of calcium, magnesium and other trace elements has been added to Walton's diet along with more fish, milk, cheese and beans. Note that the beans are the only food with appreciable Mn. Too bad that they wasted those seven years!

Many of the overall effects of Mn deficiency can now be explained in terms of its specific effects on mucopolysaccharide synthesis. Mucopolysaccharides are constituents of cartilage and contain two types of alternating monosaccharide units attached to a protein. Chondroitin sulfate is a major polysaccharide of cartilage and is the mucopolysaccharide most severely affected by Mn deficiency.

The formation of bone occurs in the cartilage at the epiphysis, and skeletal maturation is retarded if this process is inhibited in some manner. Research has focused on the organic matrix of the epiphyseal plate, an integrating part of the growth zone. The mucopolysaccharide and protein composition of the epiphyseal plate may be altered in Mn deficiency (Hidiroglou et al., 1979).

Chondroitin sulfate consists of a polypeptide backbone to which is attached a carbohydrate side chain composed of xylose and two molecules of galactose. To this is attached the main carbohydrate portion of the molecule, a repeating unit of glucuronate and N-acetyl-galactosamine. Leach (1971) has noted that Mn is a far more efficient divalent cation than magnesium in stimulating the incorporation of the various carbohydrates into this unit structure of cartilage. With xylose attached to the protein, the rest of the components are attached in a stepwise fashion.

Manganese is necessary for the activation of the glycosyltransferase enzymes (Leach et al., 1969) which synthesize chondroitin sulfate:

1) polymerase enzyme, is responsible for the polymerization of UDP-N-acetylgal-actosamine to UDP-glucuronic acid to form the polysaccharide and,
2) galactotransferase enzyme, incorporates galactose from UDP-galactose into the galactose-galactose-xylose trisac-charide which serves as the linkage between the polysaccharide and the protein associated with it.

With the postulated role for Mn in chondroitin sulfate synthesis it is possible to see why Mn deficiency may cause problems in connective tissue synthesis. What develops then are disease of osteochondrosis such as Osgood Slatter disease and Perthes disease. At the Brain Bio Center we have had good results in treating these patients with zinc, Mn and vitamin B6.

Manganese and Back Aches

One of the most common complaints we have in the U.S. is chronic and repeated back ache. Ashmead of Albron Laboratories, Inc. (Ashmead and Nipko, 1977) has applied the knowledge of manganese's role in cartilage formation to canine disc disease. This, in turn, may be applied to humans.

Many back problems are caused by degenerating and ruptured discs. The disc acts like a shock absorber or cushion between each vertebra. Often the disc hardens so it can no longer absorb the shock waves that occur when the back moves. When this happens the disc may rupture forcing some of the disc material against vital nerves. That pressure against the nerves in the spinal cord is what causes the acute back and leg pain and/or paralysis.

Generally the cause of the back problems centers around inadequate nutrition to the disc. There is 91 percent less Mn in the discs of dogs with degenerated discs. Manganese, as we know, is involved in the production of cartilage, the material which makes up the disc. The Mn content of the hair was significantly less in the afflicted dogs when compared to normal dogs.

In the Balance: Inner Ear Defect

A psychoanalyst who has made a study of skyjackers thinks Mn deficiency may be the key to some puzzling aspects of their behavior. The same key might even begin to unlock the mysteries of spontaneous abortion, stillbirth, crib death, autism, and childhood schizophrenia. This is the work of Dr David Hubbard of Dallas (Hubbard, 1974).

Hubbard's primary interest is in the tiny crystals, otoliths, within the vestibular apparatus of the inner ear. The crystals are the balance mechanism of the body. Hubbard's recognition of their importance originated with his observations of 53 skyjackers. The skyjackers reported an inordinate number of flying dreams, were often obsessed with space flights and described their thefts of airplanes as attempts to "stand on their own two feet".

A few investigators have long suspected vestibular involvement in some personality aberrations. Dr. Lawrence Erway's work with experimental animals lends some substance to Hubbard's ideas. Rats, mice and guinea pigs, which have been deprived of Mn during gestation or have inherited the mutant gene, are unable to land on their feet during a fall. They cannot distinguish between up and down while swimming and have abnormal or no otoliths at all in the inner ear.

Administration of Mn during pregnancy prevents these problems. Lucille Hurley and her colleagues have found that in both Mn deficiency and genetic cases there is a common impairment in mucopolysaccharide synthesis in the otolithic matrix (Erway et al., 1966). The vestibular system and the delicate otoliths are the balance mechanism of the body. Information about our relation to gravity and the perception of movement all determine perception of the body in space and of body motion. Therefore, the vestibular system plays an early and vital role in how we think and feel about our bodies.

It is assumed that the otoliths are perfect at birth but perhaps they are not. An infant with imperfect otoliths would not read gravity very well and might be three or four years old before standing. Such a child would not be good at sports and might be preoccupied with gravity and with antigravitational

ideas — space flights, flying dreams, odd body sensations.

Mice which possess the mutant gene resulting in malformation of the inner ear otoliths experience abortion, stillbirth, and sudden neonatal death which resembles crib death in human beings (Erway et al., 1966).

Glucose Metabolism

Everson and Shrader (1968), in their studies on guinea pigs, have found that Mn deficiency produces:

1) aplasia or marked hypoplasia of all the cellular components of the pancreas,
2) smaller numbers of islet cells containing fewer and less intensely granulated beta cells,
3) a diabetic-like glucose tolerance curve.

Rubenstein (1962) has shown tht Mn supplementation in deficient guinea pigs completely reverses the reduced utilization of glucose and, in some way, provides for normal glucose tolerance curves.

The mechanism of this effect and manganese's role in the mechanism is not well established. The most likely explanation is the participation of Mn in enzymatic reactions. The glycosyltransferase enzymes have been discussed previously in relationship to mucopolysaccharide synthesis and collagen formation. The role of two other enzymes, pyruvate carboxylase and superoxide dismu-tase, in Mn deficiency are also important.

Pyruvate Carboxylase

In liver, kidney and other gluconeogenic tissues, pyruvate carboxylase (PC) appears to catalyze the first step of carbohydrate synthesis from pyruvate. This pathway leads from pyruvate to oxalacetate to phospho-enol pyruvate and, after a series of steps, to glucose. PC, however, is not necessarily a manganoprotein for all species. In avian liver the metal ion is normally Mn (Scrutton et al., 1966). In other species the metal ion is a mixture of Mn and magnesium (Scrutton, 1973). In yeast the metal ion is zinc (Scrutton et al., 1970). PC is, therefore, a mangano-enzyme only in certain species. This is important for arguments concerned with the possible role of this enzyme in Mn deficiency.

The mechanism of the impairment of glucose utilization in Mn deficiency may be related to the connective tissue defect that occurs with defective carbohydrate metabolism. Decreased concentrations of stain-able mucopolysaccharides occur in the skin of young rats born to diabetic mothers (Zhuk, 1964).

Superoxide Dismutase

Superoxide dismutase (SOD) is the second known manganoenzyme. SOD ensures the complete reduction of tissue oxygen to water. Partial reduction yields extremely toxic products, the superoxide radical, 0~2 and hydrogen peroxide, H2O2 (free radicals). Both products are highly reactive and potentially destructive to certain types of functional groups present in biomolecules capable of producing irreversible damage. Fridovich (1974) has found several types of SOD. One form occurs in the cytosal and requires copper and zinc for activity and another form requires iron. Still another form occurs in the mitochondria and requires Mn for activity. Without Mn the mitochondrial SOD would be inactive and accumulation of 0~2 and H2O2 would lead to membrane damage and damage to a variety of biological materials. Mitochondrial damage and impaired function have been established as one of the effects of Mn deficiency.

The protective action of superoxide dismutase and catalase, which decomposes H2O2, is probably supported by ascorbic acid, glutathione (a tripeptide of glutamic acid, cysteine, and glycine), and vitamin E, which readily accept electrons and may serve a backup function by scavenging free radicals.

Avimanganin

While studying PC in chicken liver mitochondria, Scrutton (1971) isolated and purified a second Mn containing protein in the mitochondria and named it avimanganin. Due to the many strong similarities between SOD and avimanganin, it seemed reasonable to suggest that avimanganin was SOD. The only problem was that avimanganin had no enzymatic activity. Weisiger and

Fridovich (1973) provided a plausible explanation, They passed SOD over DEAE Sepha-dex to mimic the final purification step of avimanganin. SOD was about 90 percent inactivated. They concluded that avimanganin may represent an inactivated form of SOD. Scrutton (1971) carried out further experiments to see whether Mn deficiency led to abnormalities in pyruvate carboxylase and avimanganin. He fed chickens diets high and low in Mn. Chickens on the Mn-deficient diet developed Mn deficiency symptoms. The Mn in the enzymes from chickens fed Mn-poor diets was replaced by magnesium. The activity of PC was essentially the same whether or not it contained Mn or magnesium showing that Mn plays only a substitute role in this enzyme. However, there was a striking decrease in the avimanganin fraction (3.1 vs. 16.9 nanomoles/mg protein). Very low amounts of avimanganin were present suggesting that avimanganin is not present in manganese's absence. If avimanganin is not formed and avimanganin is SOD, we have an enzymatic factor linked to Mn deficiency.

What then are the biological consequences of this? Fridovich (1974) believes that superoxide radical, or a closely related molecule, may cause, widespread damage to a variety of biological tissues, including their membranes. Bell and Hurley (1973) have demonstrated in Mn-deficient mice that all the Mn-deficient tissues revealed alterations in the integrity of the cell membranes.

Manganese and Protein Synthesis

Manganese is important in the building and breakdown cycles of protein and nucleic acid. Hossenlopp et al. (1974) showed that a divalent cation was necessary for binding of calf thymus RNA polymerases to DNA and that Mn was a better effector of this reaction than magnesium. Nagamine et al. (1978) reported on the differences in the effects of Mn and magnesium on initiation and elongation in the RNA polymerase 1 reaction in RNA synthesis.

The process of RNA synthesis consists of three major steps: initiation, elongation and termination. For RNA chain initiation, Mn was found to be a better effector than magnesium. For RNA chain elongation, either Mn or magnesium acted as an effector, but a high concentration of Mn was inhibitory. It is likely that Mn regulated RNA polymerase 1 and that its concentration in the nucleoli is an important factor in repressing the production of ribosomal RNA in situ by inhibiting the elongation step of RNA synthesis. RNA synthesis may stop when the concentration of Mn around RNA polymerase 1 increases to above 3mM.

Manganese and Adenylate Cyclase

Manganese stimulates adenylate cyclase activity in brain tissue. This is of importance because cyclic-AMP plays a regulatory role in the action of several brain neurotransmitters. It acts as a second messenger within the cell to transmit the message of the hormone. Thus, Mn has an important role in brain function.

In 1973, Johnson and Sutherland noted that adenylate cyclase from rat brain was activated more by Mn than magnesium. Adenylate cyclase activities that require Mn specifically have been found in Neurospora crassa (Flawia and Torres, 1972) and in rat testis (Braun and Dods, 1975).

These studies, which appeared to demonstrate connections between Mn and adenylate cyclase prompted Baldessarini and Walton (1976) to study the effects of Mn on the activity of adenylate cyclase in the rat brain. Mn was found to be a potent stimulator of adenylate cyclase from different areas of the rat brain while lead, mercury, zinc and copper were powerful inhibitors of the enzyme. They found with 6mM magnesium present Mn stimulated adenylate cyclase formation in homogenates of six brain areas by as much as 16 fold. The site of interaction of Mn with adenylate cyclase is more likely to be the catalytic subunit of the cyclase than a receptive or regulatory subunit.

Schizophrenia and Manganese

Manganese chloride was first tested and found effective in treating schizophrenia by Reiter of Denmark (1927). This finding was confirmed by English of Brockville, Ontario

(1929). A later study, however, found Mn ineffective (Hoskins, 1934). Both Reiter and English used manganese chloride intravenously while Hoskins used suspended manganese dioxide intramuscularly. Since then, little attention has been paid to the possibility of its therapeutic effects.

When we discovered that zinc plus Mn was more effective in eliminating copper via the urinary pathway, we devised "ziman drops" which contained 10 percent zinc sulfate and 0.5 percent Mn chloride. The usual adult dose is six drops AM and PM. We further had multivitamin formulations prepared which contained zinc sulfate, USP 80 mg, and Mn chloride, 4 mg (Vicon-Plus or Ziman Fortified), **with no copper.** These preparations are popular but not perfect in that the Mn content is too low and many schizophrenic patients need less zinc and more Mn owing to the fact that zinc is well absorbed from the gut but Mn is poorly absorbed.

With zinc alone and sometimes with Ziman Fortified AM and PM, the patient's whole blood Mn will decrease over a treatment period of four to 12 months. These low Mn levels can result in depression, intolerance to oral zinc, macrocytosis and possible increase in auto-immune reactions. The finding of a lowered Mn blood level with prolonged zinc supplementation has occurred in psychiatric, arthritic, senile and cardiac patients. Thus all diagnostic categories can be harmed by large prolonged doses of zinc without Mn. With this new concept we have treated problem patients with large oral doses of Mn. In one severely allergic male, age 45, whom we had treated for 14 years, we suggested 50 mg of Mn as the gluconate morning and night. He felt somewhat better with this dose, so he cautiously increased the dose to 100 mg, three times per day. Before starting this dose his blood Mn was six ppb (11/7/79). After three months of the big dose, his blood Mn was 11 ppb (4/22/80). On 5/20/80 the level was 8.5 ppb. Normal is 10 to 20 ppb. Physical examination, blood pressure, pulse and chem-screen showed no abnormalities. During the period of 300 mg Mn orally per day he gained 11 needed pounds in body weight and was able to tolerate foods that normally caused depressive reactions.

In summary then, the high copper level of schizophrenics, arthritics and patients with psoriasis can be reduced by dietary intake of zinc and Mn. Manganese is more effective than zinc in increasing urinary copper excretion; a combination of zinc and Mn is more effective than either alone.

Manganese Levels are Low in the Hair of Schizophrenics

Other than the therapeutic use of Mn in schizophrenics by Reiter and English, the first demonstration of a possible deficiency of Mn was reported in our survey (Pfeiffer, 1974). We found Mn to be low in the hair of schizophrenics, and in males (but not in females) Mn decreased with age. Barlow (1979) found Mn to be significantly lower in the hair of schizophrenics compared to a control population. Bowen (1972) found the Mn of Indonesian children to be normal but protein deficient Indonesian children had a level five times higher. The copper level of the hair in these same children was two times higher. Perhaps the continuous ingestion of tropical fruits (high in Mn) might account for the very high Mn level of the protein deficient Indonesian children.

Ryan et al. (1978) reported Mn levels of both male and female patients diagnosed as multiple sclerotic (MS) to be one-half that of a normal population. The hair zinc levels of the MS patients were not lower than the controls.

Manganese and Tardive Dyskinesia

Excesses of the polyvalent metal ions of Mn, mercury, copper, cadmium and lead all appear to cause malfunctions of the CNS in animals and man. Manganese is unusual among these ions since neurological abnormalities have been associated with both a deficiency and an excess of this metal.

Neuroleptic drugs are known to cause tardive dyskinesia in which the patient exhibits involuntary, rhythmic movements of the tongue, lips and facial muscles; sometimes he exhibits abnormal trunk movements or choreoathetoid movements of the extremities. This condition is reversible but in the long run may become irreversible in some

subjects.

In his earlier work with psychiatric patients who developed tardive dyskinesia on neuroleptic drugs, Kunin (1976) tried antiparkinson agents and Rauwolfia to no avail. He then recalled the work of Borg and Cotzias (1972) who reported that phenothiazines form free radicals with manganic (trivalent) ions in vitro. Manganese is found in high concentrations in the extrapyramidal system. He reasoned that phenothiazines might chelate Mn, thus binding it electrochemically, and that this might make Mn unavailable for some presumed function as an enzyme activator. It seemed plausible that by providing extra dietary Mn the deficiency would be corrected and the dyskinesia might thereby improve.

Kunin found in 15 cases of withdrawal and tardive dyskinesia treated with Mn, seven (46 percent) were cured outright; three (20 percent) cases were much improved; four (27 percent) were improved and only one *(7.7* percent) was unimproved. Good results followed Mn doses of at least 15 mg and up to 60 mg/day. Niacin, at doses of 100 to 500 mg, was of significant benefit in treating dyskinesia in three of the 15 cases.

Mean content of Mn in the hair of the psychiatric patient population averaged 0.8 ppm. The tardive dyskinesia patients averaged 0.46 ppm.

It is concluded that Mn appears to be of value in treating many cases of tardive dyskinesia and it may also be of value in preventing the occurrence of dyskinesias.

Manganese Can Elevate Blood Pressure

In oral doses Mn has not been found harmful, although in patients over 40 years of age it has occasionally elevated blood pressure. The elevated pressure returns to normal when Mn is discontinued and zinc alone is used. Zinc is effective in lowering the blood pressure of some hypertensive patients which is reminiscent of some of the early work of Schroeder and his co-workers. Comens (1960), working in Schroeder's laboratory, found that chronic hydralazine in rats (a Mn chelator) produced Mn deficiency which resulted in convulsions. These convulsions were antidoted by Mn but not by potassium, calcium, cobalt, zinc or nickel injections. Comens (1956) also postulated that Mn deficiency could be a factor in lupus erythematosus and other collagen diseases. Two of the side effects of hydralazine therapy, when used to lower blood pressure in man, are arthritis and lupus erythematosus. An acute rheumatic state occurred in as many as 10 percent of the hypertensive patients treated with hydralazine. From these findings we draw two conclusions:

1) zinc, by antagonizing Mn, may lower the blood pressure of some hypertensives and,
2) zinc, when used to treat arthritic patients, should be carefully balanced with adequate Mn to sustain any beneficial effect.

The determination of serum zinc and Mn will direct more beneficial nutrient therapy.

Epilepsy

Mn deficiency also affects cerebral function. Hurley et al. (1963) demonstrated a relationship between seizure activity and Mn deficiency in rats. The seizure threshold was found to be significantly lower in Mn deficient animals. Tanaka (1977) recently has presented a preliminary report on low blood Mn levels in epileptic patients.

Blood Mn levels in man may be a useful index for the determination of a deficiency or excess. Manganese is present in normal whole blood in a minute amount, usually between 10 and 20 ppb. Serum levels are between one and two ppb so the bulk (90 percent) of the Mn is found in the red cell. Sohler et al. (1979) compared blood Mn levels in a group of patients with seizure activity to a control group. Blood Mn levels from control subjects have a mean of 14.8 ppb while serum levels are 1.2 ppb. The Mn levels were significantly lower in the patients with seizure activity, 9.9±4.9 ppb ($p<.005$). The clinical significance of the low blood or serum Mn levels remain to be evaluated. In uncontrolled trials we find that Mn is helpful in controlling seizures of both the minor and major types.

Both Mn and choline deficiencies are believed to interfere with membrane stability and this could be responsible for facilitating

the propagation of seizure activity. We suggest these findings warrant the use of dietary supplements of Mn for the control of seizure activity.

In Summary and Reflection

Apparently the essential trace element Mn is a basic, direct legacy from vegetable life to animal life. Plants cannot convert the sun's energy without Mn (photosynthesis) and man cannot live without Mn since at least six important enzymes require Mn for normal function. Compared to zinc, Mn is poorly absorbed and both Mn and zinc are rapidly excreted. The absorption of Mn and copper are equally slow but copper is sequestered in the absence of zinc and Mn and may cause harmful effects. Because of the slow absorption of Mn the beneficial effects of Mn in man may not be evident for weeks and months. Except for the occasional elevation of blood pressure, oral Mn is harmless so the use of Mn food supplements and foods high in Mn can be tried in some of the diseases which still baffle the medical profession. Patience may provide good rewards with manganese.

Acknowledgements

This research was sponsored by The Marian and Tom Peters Foundation.

The author wishes to thank the scientists and staff of the Brain Bio Center, particularly, Carl C. Pfeiffer, M.D., Arthur Sohler, Ph.D., and Rhoda Papaioannou, M.S. for their advice and original research contributions.

References

ASHMEAD, D. and NIPKO, R.: Canine Disc Disease; Cause, Prevention and a New Approach to Treatment. Vet. Med./Sm. Anim. Clin., 1337-1342, Aug., 1977.

BALDESSARINI, R.J. and WALTON, K.G.: Effects of Mn 2' and Other Divalent Cations on Adenylate Cyclase Activity in Rat Brain. J. of Neurochem., 27,557-564,1976.

BARAK, A.J., KEEFER, R.C., and TUMA, D.J.: Nutr. Rep. Int., 3, 243, 1971.

BARLOW, P.: Hair Metal Analysis and Its Significance to Certain Diseases, presented at the 2nd Annual Trace Minerals in Health Seminar, Boston, MA., Sept. 8-9,1979.

BELL, L.T. and HURLEY, L.S.: Lab. Invest. 29,723,1973.

BORG, D.C. and COTZIAS, G.C., quoted in Davies, I.J.T.: The Clinical Significance of the Essential Biological Metals, p. 74. C.C. Thomas, 1972.

BOWEN, H.J.M.: Determination of Trace Elements in Hair Samples from Normal and Protein Deficient Children by Activation Analysis. Sci. Total Environ. 1,75-78,1972.

BRAIN BIO CENTER: Unpublished communications, 1977.

BRAUN, T. and DODS, R.F.: Proc. Natn. Acad. Sci., U.S.A., 72, 1097-1101,1975.

CIKRT, M.: The Uptake of Hg203, Cu64, Mn52, and Pb212 by the Intestinal Wall of the Duodenal and Ileal Segment in Vitro. Int. Z. Klin. Pharm-akol. Ther. Toxikol. 3,351-357,1970.

COMENS, P.: Chronic Intoxication from Hydralazine Resembling Disseminated Lupus Erythematosus and Its Apparent Reversal by Manganese. In: Metal Binding in Medicine (Ed. by Seven, M.J. and Johnson, LA.I Lippincott, Philadelphia, 1960.

COMENS, P.: Manganese Depletion as an Etiological Factor in Hydralazine Disease. Am. J. Med. 20,944,1956.

COTZIAS, G.C.: Manganese in Health and Disease. Physiol. Rev. 38, 503-532,1958.

DOISY, E.A.: In: Proceedings of the University of Missouri's 6th Annual Conference on Trace Substances in Environmental Health, p. 193, (D.D. Hemphill, ed.l, Columbia, Mo., University of Missouri Press, 1973.

ENGLISH, W.M.: Report of the Treatment with Manganese Chloride of 181 Cases of Schizophrenia, 33 of Manic Depression, and 16 Other Defects of Psychoses at the Ontario Hospital, Brockville, Ontario. Am. J. Psychiat. 9,569-580,1929.

ERWAY, L, HURLEY, L.S., and FRASER, A.: Neurological Defect: Manganese in Phenocopy and Prevention of a Genetic Abnormality of Inner Ear. Sci. 152,1766-1767,1966.

EVERSON, G.J. and SHRADER, R.E.: J. Nutr. 94, 89,1968; Shrader, R.E. and Everson, G.J., ibid. p. 269.

FLAWIA, M.M. and TORRES, H.N.: J. Biol. Chem., 247,6873-6879.1972.

FOURNIER, P. and FOURNIER, A.: The Influence of Lactose Ingestion on the Absorption and Retention of Manganese. C.R. Seances Soc. Biol. Fil. 166,29,1972.

FRIDOVICH, I.: Superoxide Dismutases. Adv. Enzymol: 41, 35-97,1974.

GLEASON. N.M., GOSSELIN, R.E., HODGE, H.C. and SMITH, R.P.: Manganese Salts. Section II, page 89 In: Clinical toxicology of commercial products, acute poisoning. 3rd ed. Williams & Wilkins Co., Baltimore, Md.,1969.

GRUDEN, N.: Dietary Variations and Manganese Transduodenal Transport in Rats. Periodicum Biologorum 81,567-670,1979.

HEILMEYER, L, KEIDERLING, W., and STRUVE, C: Kupfer und Eisen als Korpereigene Wirkstoffe und ihre Bedeutung beim Krankheitsgesche-hen. Fischer, Jena, Germany, 1941.

HIDIROGLOU, M., WILLIAMS, C.J., SIDDIQUI, I.R., and KHAN, S.U.: Effects of Manganese Deficit Feeding to Ewes on Certain Amino Acids and Sugars in Cartilage of Their Newborn Lambs. Am. J. Vet. Res. 40, 1375-1377,1979.

HOSKINS, R.G.: The Manganese Treatment of Schizophrenic Disorders. J. Nerv. and Ment. Disease 79, 59,1934.

HOSSENLOPP, P., OUDET, P., and CHAMBON, P.: Eur. J. Biochem. 41, 397-411; 1974.

HOWES, A.D. and DYER, I.A.: J. Anim. Sci. 32,141,1971.

HUBBARD, D.: In the Balance: Inner Ear Defect. Column by Eleanor Brown In: The Milwaukee Journal, July 23,1974.

HURLEY, L.S. and BELL, L.T.: J. Nutr. 104,133,1974.

HURLEY, L.S., WOOLEY, D.E., and TIMIRAS, PS.: Threshold and Pattern of Electroshock Seizure in Ataxic Manganese Deficient Rats. Proc. Soc. Exp. Biol. Med. 106,343-346,1963.

JOHNSON, R.A. and SUTHERLAND, E.W.: J. Biol. Chem. 248, 5114-5121,1973.

JUKES, T.H.: Effect of Choline and Other Supplements on Perosis. J. Nutr. 20,445-458,1941.

JUKES, T.H.: Prevention of Perosis by Choline. J. Biol. Chem. 134, 789-790,1940.

KEEPER, R.C., TUMA, D.J., and BARAK, A.J.: Am. J. Clin. Nutr. 26, 409, 1973.

KING, B.D., LASSITER, J.W., NEATHERY, M.W., MILLER, W.J., and GENTRY, R.P.: Manganese Retention in Rats Fed Different Diets and Chemical Forms of Manganese. J. Anim. Sci. 49,1235-1241,1979.

KUNIN, R.A.: Manganese and Niacin in the Treatment of Drug-induced Dyskinesias. J. Ortho. Psych. 5,4,4-27,1976.

LASSITER, J.W., MILLER, W.J., PATE, F.M., and GENTRY, R.P.: Effects of Dietary Calcium and Phosphorus on 54Mn Metabolism Following Single Tracer Intraperitoneal and Oral Dose in Rats. Proc. Soc. Exp. Biol. Med. 139,345,1972.

LASSITER, J.W., MILLER, W.J., NEATHERY, M.W., GENTRY, R.P., ABRAMS, E., CARTER. J.C. (JR.), and STAKE, P.E.: In: Trace Element Metabolism in Animals. (W.G. Hoekstra et al., eds.). Vol. 2, p. 557. Univ. Park Press, Baltimore, MD., 1974.

LEACH, R.M., JR.: Role of Manganese in Mucopolysaccharide Metabolism. Fed. Proc. 30, 991-994,1971.

LEACH, R.M., JR., MUENSTER, A.M., and WIEN, E.M.; Arch. Btochem. Biophys. 133,22,1969.

NAGAMINE. Y., MIZUNO, D., and NATORI, S.: Differences in the Effects of Manganese and Magnesium on Initiation and Elongation in the RNA Polymerase 1 Reaction. Biochemica et Biophysica Acta, 519, 440-446, 1978.

PFEIFFER, C.C.: Observations on Trace and Toxic Elements in Hair and Serum. J. Ortho. Psych. 3,4,259-264,1974.

PFEIFFER, C.C., SOHLER, A., JENNEY, E.H., and ILIEV, V.: Treatment of Pyroiuric Schizophrenia (Malvarial With Large Doses of Pyridoxine and a Dietary Supplement of Zinc. J. Orth. Psych. 4,292-300,1974.

PFEIFFER, C.C.: Unpublished communications, 1977.

REITER, P.J.: Behandlung von Dementia Praecox mit Metallsalzen a.m. Walbrim I. Mangan. Z. Neur. 108.464-480,1927.

RUBENSTEIN, A.H.. LEVIN, N.W., and ELLIOTT, G.A.: Hypoglycemia Induced by Manganese. Nature, (London) 194,188-189,1962.

RYAN, D.E., HOLZBECHER, J., and STUART, D.C.: Trace Elements in Scalp-Hair of Persons With Multiple Sclerosis and of Normal Individuals. Clin. Chem., 1996.2000,1978.

SANSOM, B.F., GIBBONS. R.A., DIXON, S.N., RUSSELL, A.M., and SYMONDS, H.W.: In: Nuclear Techniques in Animal Production and Health. IAEA. Vienna, 1976.

SANSOM, B.F., SYMONDS, H.W., and VAGG, M.J.: The Absorption of Dietary Manganese by Dairy Cows. Res. in Vet. Sci. 24,366-369,1978.

SCHLAGE, C. and WORTBERG. B.: Manganese in the Diet of Healthy Preschool and School Children. Acta Paediat. Scand. 61,648-652.1972.

SCHLETTWEIN-GSELL, D. and MOMMSEN-STRAUB, S.: Ubersicht Spurenelemente in Lebensmitteln IV. Mangan. Internat. Z. Vit. -Era Forschung 41,268-285,1971.

SCRUTTON, M.C.: Purification and Some Properties of a Protein Containing Bound Manganese (Avimanganin). Biochem. 21,3897-3905,1971.

SCRUTTON, M.C., GRIMINGER, D., and WALLACE, J.C: Pyruvate Carboxylase. Bound Metal Content of the Vertebrate Liver Enzyme as a Function of Diet and Species. J. Biol. Chem. 247.3305-3313,1973.

SCRUTTON, M.C., REED, G.H., and MILDVAN. A.S.: Pyruvate Carboxylase VI. The Presence of Tightly Bound Manganese. J. Biol. Chem. 241, 3480-3487,1966.

SCRUTTON, M.C., YOUNG, M.R., and UTTER, M.F.: Pyruvate Carboxylase from Baker's Yeast: The Presence of Bound Zinc. J. Biol. Chem. 245,6220-6227.1970.

SOHLER. A. and PFEIFFER, C: A Direct Method for the Determination of Manganese in Whole Blood: Patients with Seizure Activity Have Low Blood Levels. J. Orth. Psych. 8,4,275-280,1979.

TANAKA, Y.: Low Manganese Level May Trigger Epilepsy, JAMA, 238, 1805.1977.

UNDERWOOD, E.J.: Manganese Section IV, p. 185 in: Trace Elements in Human and Animal Nutrition, 4th ed.. Academic Press, New York, New York, 1977.

UNDERWOOD: ibid, Section II, p. 175.1977.

UTTER, M.F.: The Biochemistry of Manganese. Med. Clin. N. Am. 60, 713-727,1976.

WEISIGER, R.A. and FRIDOVICH, I.: Superoxide Dismutase: Organelle Specificity. J. Biol. Chem. 248,3582-3592,1973.

WENLOCK, R.W. and BUSS, D.H.: Trace Nutrients. 2. Manganese in British Food. Br. J. Nutr. 41,253-261,1979.

WILGUS, H.R., JR. and PATTON, A.R.: J. Nutr. 18,35,1939.

WILLIAMS, R.J.: You Are Extraordinary. New York, Random House. 1967.

WINGET, D. and SPECTOR, M.: A Protein Linked to Photosynthesis. Science, 227,38-39,1980.

ZHUK, V.P.: Bull. Exp. Biol. Med. (Engl, transl.) 54,1271.1964.