Chronic manganese poisoning

Clinical picture and manganese turnover

Ismael Mena, M.D., Oscar Marin, M.D., Sergio Fuenzalida, M.D., and George C. Cotzias, M.D.

SINCE COUPER'S FIRST DESCRIPTION,[1] human chronic manganese poisoning has been the subject of many reports and several reviews.[2–5] The aim of most publications seems to have been the definition of the clinical picture of this disease in relation to various environmental factors. The clinical picture has consisted of both psychiatric and neurological manifestations, the most crippling of which have been related to the extrapyramidal system.[6] The environmental factors investigated have included the physical characteristics of dusts inhaled by manganese miners as well as some chemical properties of ores which have induced the disease in high incidence.[7] Consequently, chelating agents have been introduced in the management of this disease.[8]

The present study was undertaken after consideration of some disease states in which abnormal metabolism of metals is correlated with chronic disturbances of the brain. Such correlations are particularly striking in lead encephalopathy and Wilson's disease. In both diseases the respective presence of high tissue concentrations of lead[9,10] and of copper[11] seems essential to the induction and, perhaps, to the progression of the symptomatology. It seemed reasonable to investigate chronic manganese poisoning with these precedents in mind.

The present publication is the initial report of studies on this problem. It develops arguments in favor of the thesis that chronic manganese poisoning may diverge significantly from the aforementioned diseases. If further substantiated by analytical evidence, these physiological findings must lead to fundamentally different therapy than that applied to lead poisoning and Wilson's disease. Hence, it is necessary to discuss the individuals under study in order to document the forms of manganese poisoning on which present and subsequent arguments rest.

The evidence obtained shows that the total body loss of the injected radioisotope ^{54}Mn is significantly faster among "healthy," working miners than among the victims of chronic manganese poisoning studied here. This finding is particularly striking because it was established following removal of these individuals from the mines and while they were in the hospital. It has been interpreted on the basis of previous observations on animals and man[2,12–14] as indicating that tissue burdens with manganese are significantly larger among "healthy" miners than either among patients with chronic manganese poisoning or normal individuals.

MATERIALS AND METHODS

1] *Patients.* A. The normal controls were 8 healthy medical personnel, equally divided by sex, with ages ranging between 20 and 30 years. They continued their work while under study.

From the Departments of Nuclear Medicine and Neurology, Catholic University, Santiago, Chile, and the Medical Research Center, Brookhaven National Laboratory, Upton, N.Y.

Dr. Cotzias' address is Medical Research Center, Brookhaven National Laboratory, Upton, New York.

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B. From a group of 114 "healthy," working, manganese miners, surveyed by physical and neurological examination, the rate of total body loss of manganese was determined in only 14. These were all males and their ages ranged between 23 and 60 (median, 37 years). They were transported from the Andacollo mine district in northern Chile to the Catholic University's Department of Neurology in Santiago, where they were studied as inpatients for twenty to thirty days.

C. Of the 13 hospitalized patients with chronic manganese poisoning, 12 had been pensioned off with the diagnosis of chronic manganese poisoning. The interval between termination of exposure and hospital admission varied between two and twenty-five years (median, five years), whereas their ages ranged between 18 and 56 years (median, 50 years). The thirteenth patient was studied immediately after termination of his work in the mines. This last patient, as well as 9 of the 12 pensioners, was subjected to measurements of total body loss of ^{54}Mn, while under study in the hospital as inpatients.

2] *Clinical procedure.* Each of the individuals admitted into the wards underwent the following examinations:

In obtaining a history and general physical examination, efforts were made to detect family histories of nervous disease and presence of intercurrent diseases such as syphilis, alcoholism, malnutrition, tuberculosis, and pneumoconiosis.

The neurological examination was supplemented by chemical and cytological examination of the spinal fluid in groups B and C and by electroencephalograms in group C. In 4 patients with the severest cases of chronic manganese poisoning, pneumoencephalograms were performed. In one (patient 1, Fig. 1), Wilson's disease was ruled out by means of serum ceruloplasmin and urinary copper determinations.

3] *Laboratory investigations.* These may be subdivided into [1] those pertaining to general state of health and [2] those related to manganese overload. The first category included urinalysis, differential white cell counts, hemoglobin levels, red cell count, sedimentation rate, blood serology, and chest X-rays. The second category included plasma cholesterol level, fasting blood sugar level, prothrombin time determination, thymol turbidity, sulfobromophthalein (Bromsulphalein®, or BSP) retention. In one patient, a liver biopsy was performed.

Electrophoretic analyses of the plasma proteins on 3 "healthy" miners and 7 patients with chronic manganese poisoning were done in an Elphor-H machine, with naphthalene black 12B200 as the dye. The patterns were determined with a photoelectric scanner.

4] *Determination of total body loss of ^{54}Mn.* The isotope used was carrier-free $^{54}Mn^{++}$ (physical half-life (T ½) = three hundred fourteen days). (All manganese atoms were radioactive. Hence, detectable amounts of radiation could be delivered readily, without delivering detectable amounts of metal.) This was obtained from the Nuclear Science and Engineering Corporation in 20% hydrochloric acid (HCl) containing 0.5 mc. per milliliter. Standard-

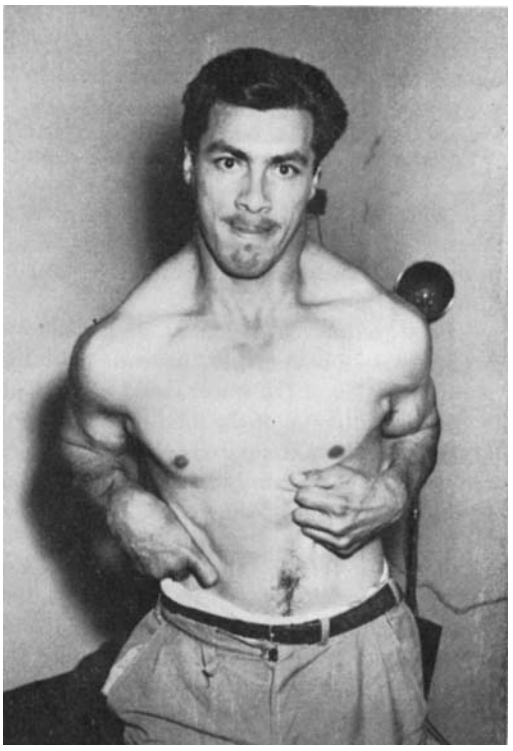

Fig. 1. Patient 1 showing elevation of upper lip, muscular contraction, and hypertrophy of the muscles over the neck. The position of the arms shown was assumed on standing up.

Fig. 2. Patient 10 after being pushed slightly from the back. Note flexing of the arms and knees accompanied by child-like smile.

ized dilutions in 1 ml. of a 0.9% sodium chloride (NaCl) solution containing 20 μc. of the tracer were injected into the patients intravenously.

Administration. Preliminary tests showed that partial subcutaneous instead of intravenous injection of the tracer could occur. This resulted in flattening of the total body retention curves of ^{54}Mn as compared to those obtained after intravenous administration. Short-beveled needles measuring 1.5 in. in length abolished this problem.

Radiation detection. The system consisted of a 4- × 2-in. thallium-activated sodium iodide (NaI) crystal, housed in a shielded collimator and centered at a distance of 6 ft. over the patient's xiphoid process. Both bed and radiation detector were in fixed positions, with the latter connected to a TMC 400-channel analyzer. Counting time was sufficient to accumulate at least 12,000 counts at the photopeak. Therefore, the ratio of photopeak counting to background counting was always higher than 20. Determinations of the isosensitivity area of this system were performed only by means of counting a standard at various points of the table[2] supporting the patients.[15] (Moving the standard from the table toward the detector must yield higher counting rates than those obtained at the table itself. Obviously, transport of tracer within the body in the same direction must also yield similar increases. See Figure 3.) These indicated that the isosensitivity area at that plane included the head and the knees. A standard was counted each time a measurement was made. The data were corrected for background and for occasional drifting of the photopeak. Corrections for coincidence and decay were not necessary.

The first count was obtained one hour after injection of the tracer, at which time more than 90% of the tracer is cleared from the bloodstream.[2,13,14] Subsequent counts were plotted as percents of the first count on semilogarthmic paper as a function of time. The slow components of the resultant curves were arbitrarily considered as single straight

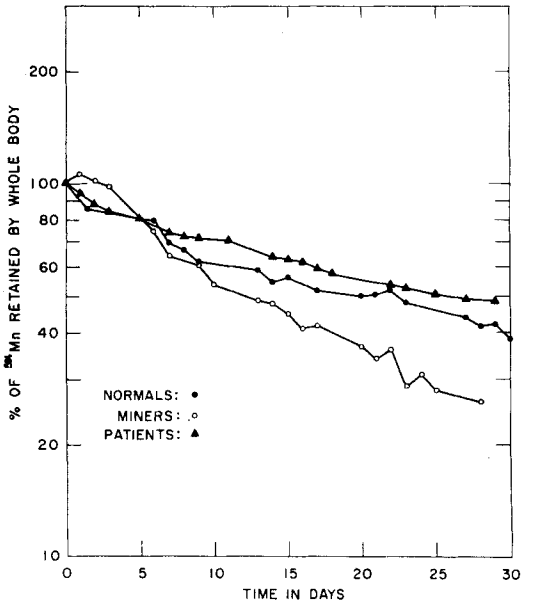

Fig. 3. Total body turnover of ^{54}Mn. Plotted semilogarithmically are the median curves from [1] the normal group, [2] the patients with chronic poisoning, and [3] the "healthy" miners. The statistical tests applied on the groups represented by the medians are listed in Table 2.

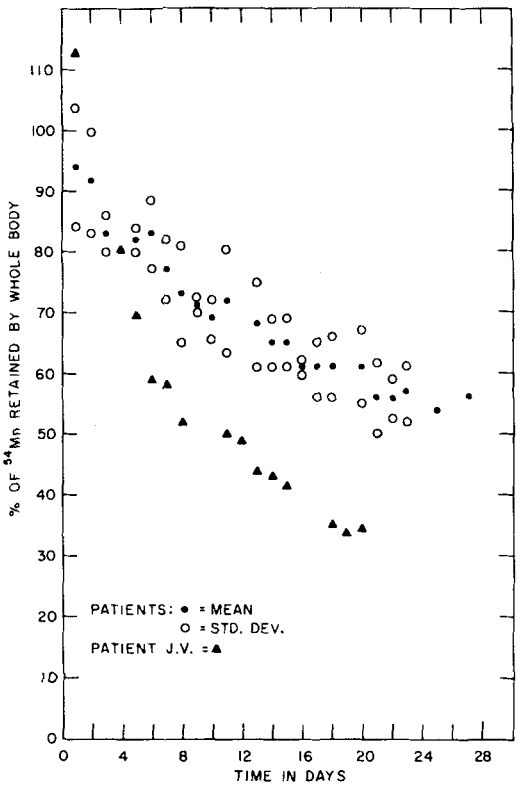

Fig. 4. A linear plot of the mean and standard deviation of the total body turnover data obtained from the patients with chronic poisoning. Note patient 7, who had just stopped working in the manganese mines.

lines and the best fit was determined visually for the curve representing each individual. Such lines are shown in Figure 3 as semilog plots and in Figure 4 as linear plots. Resolution of these curves into constituent exponential components was not practiced because the periods of observation were not deemed sufficiently long for good resolution.

RESULTS

1] *History and clinical findings.* The normal controls showed no significant physical or neurological findings. Among the total population of 114 "healthy" miners examined at the Andacollo Mine, 23 showed a positive cogwheel phenomenon without subjective or objective evidence of rigidity or tremor.[16] The 14 "healthy" miners discussed here were free from this phenomenon and displayed no abnormal physical or neurological signs.

By contrast, the patients classified as suffering from chronic manganese poisoning displayed many symptoms and signs. These are indicated in Table 1 as severe (++), moderate (+), or absent (−). Doubtful signs were classified as absent. Figures 1 and 2 are illustrative of two severe cases.

Constant in all cases was the occurrence of psychomotor disturbances early in the disease, which lasted for about one month whether the patients were immediately removed from the mines or not. There is a long acquaintance with this phenomenon in the mining villages of northern Chile where it is referred to as "locura manganica" or manganic madness. Although the duration of "locura manganica" in our patients seemed relatively fixed, its manifestations were variable in both intensity and kind. Nervousness and irritability occurred in all instances. Frequently, this resulted in arguments and friction among the miners, occasionally approaching violence. In most, there occurred compulsive acts. For example, one patient chased passing cars until exhausted, others ran during the night or could sleep only in the open air, and others displayed compulsive singing and dancing. All patients were conscious of their abnormal behavior but were unable to control it.

Four patients had emotional instability: easy laughter or ready crying occurred without apparent reason. Four of the patients heard hallucinatory voices calling them by their names or experienced visions in which their tools appeared to them either gigantic or microscopic. These same patients had clear visions of their favored foods. All knew that they were experiencing hallucinations.

While the "locura manganica" was still in evidence, neurological symptoms and signs started to emerge. One of the first complaints was generalized muscular weakness. Difficulty in walking, impaired speech, and headache developed sooner or later in all patients.

Muscular weakness became initially evident during the heavy work at the mine and resulted in inability to perform familiar tasks. This, in turn, led to severe anxiety. Climbing up or down hills or mine shafts became cumbersome. All patients described their difficulty as "stiffness," "heaviness," or "weakness" of the legs, but only a few reported falls.

TABLE 1

LIST OF SYMPTOMS AND NEUROLOGICAL SIGNS ENCOUNTERED AMONG 13 PATIENTS WITH CHRONIC MANGANESE POISONING DISCUSSED

Patient no.	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*
Age of onset	18	35	40	38	46	44	56	44	40	39	39	32	55
Period of exposure to manganese dust	8 mo.	7 yr.	1 yr.	7 mo.	6 yr.		20 yr.	2 yr.	14 yr.	21 yr	3 yr.	1.5 yr.	16 yr.
History of alcoholism	—	—	+	+	+	—	—	—	+	+	++	+	—
History of syphilis infection	—	—	+	+	—	—	—	—	—	—	—	—	—
Symptoms													
Difficulty in walking	++	++	++	+	+	++	++	+	+	++	++	++	++
Asthenia	++	++	++	+	+	+	++	++	+	++	+	++	+
Speech disturbance	++	++	++	+	+	+	++	+	+	++	++	++	+
Sialorrea	++	++	++	+	+	+	+	+	—	—	—	—	+
Profuse sweating	+	+	—	—	+	—	—	+	+	+	—	—	+
Clumsiness in movements	++	++	+	+	+	—	+	—	—	+	+	+	+
Tremors	—	+	+	—	+	—	+	—	+	+	—	+	+
Impotence	—	++	+	—	+	+	—	+	+	—	+	++	—
Insomnia	—	—	—	+	+	—	+	+	+	+	—	—	—
Memory impaired	—	—	—	+	+	—	++	+	—	—	—	—	—
Lumbar pain	—	+	—	+	+	—	—	—	+	—	—	—	+
Mental irritability	++	++	++	+	+	—	—	++	+	+	++	—	—
Compulsive actions	++	++	++	—	++	—	+	++	—	—	++	—	—
Hallucinations	—	—	—	++	—	+	—	++	+	—	++	—	—
Terrifying dreams	—	—	—	++	—	+	—	++	++	—	—	—	—
Weeping	++	++	—	—	+	—	—	—	+	—	—	+	—
Muscle cramps	+	+	—	+	—	+	—	—	+	—	+	+	+
Signs													
Abnormal gait	++	++	++	+	+	++	++	+	+	++	+	++	+
Retropulsion	++	++	++	—	—	+	++	+	—	++	+	++	—
Propulsion	++	++	++	—	—	+	+	+	—	++	—	++	—
Beam sign	++	++	++	—	—	—	++	+	—	++	—	++	—
Speech defect	++	++	+	—	—	—	+	+	—	++	+	++	—
Increased tone in upper extremity	++	—	—	—	—	+	+	—	—	—	—	—	—
Increased tone in lower extremity	++	—	+	+	+	+	+	—	—	—	+	+	+(R)
Cogwheel	—	—	—	—	—	—	+	—	—	+	—	—	+
Expressionless facies	—	++	+	+	—	—	+	+	—	++	+	++	—
Laughter	+	—	+	—	—	+	+	+	—	+	—	—	—
Depression	—	++	+	—	+	—	+	—	—	+	—	++	—
Diminished power in upper extremity	—	—	+	—	—	—	+	—	—	+	—	++	—
Diminished power in lower extremity	—	+	+	—	+	—	+	—	—	+	—	++	+(R)
Tremors	—	+	+	—	—	—	+	+	—	—	—	+	—
Deep tendon reflexes, upper extremity	—	++	—	—	—	—	—	+	—	++	+	—	—
Deep tendon reflexes, lower extremity	—	++	+(R)	—	—	—	—	—	—	++	+	+	++(R)
Weeping	+	+	—	—	+	—	—	—	—	+	—	—	—
Salivation	—	++	—	—	—	—	+	—	—	—	—	—	—
Micrographia	—	—	—	—	—	—	—	—	—	++	—	—	—
Babinsky	—	—	—	—	—	—	—	—	—	—	—	—	+(R)

As the disease became established, impairment of speech occurred with a wide range of intensity. At one extreme, there was only defective modulation (one patient), whereas at the other extreme 4 patients were barely understandable and another seemed mute. In the individuals who were least handicapped, speech improved to almost normal one year after removal from the mine. The other 8 had marked difficulty with speech as of the present writing.

The headache, which occurred in all cases early in the disease and lasted no more than a week, was, as a rule, generalized and of mild to moderate intensity, but in 4 patients, it was severe and accompanied by vomiting.

Other symptoms reported by the patients were sialorrhea, clumsiness of movements, tremor, and sexual impotence. Finally, a few patients complained of insomnia, sleepiness during the day, muscle cramps with lumbar pain, and loss of memory for recent events. The last-named symptom produced mix-ups in the use of explosives and tools.

The neurological signs are listed in Table 1. By history, these abnormalities had become permanently established one or two years after the onset of the disease. Chief among them were disorders of gait, speech, and postural reflexes; in addition, increased muscle tonus and an expressionless facies were prominent.

The abnormality in walking varied from loss of associated movements or mild rigidity to a gait that was slow and shuffling, with the legs apart. In the latter instance, the arms hung sluggishly, without any associated movements, giving the impression of hypotonia. The trunk was flexed anteriorly. Indicative of impairment in postural reflexes were retropulsion and propulsion (8 patients) and a positive "beam" sign (7 patients). (A positive "beam" sign was considered to be present when the patient fell backward like a rigid beam on being given a push against the chest—the opposite of the state shown in Figure 2.) Increased muscular tone was present in 9 patients and the cogwheel phenomenon (involving all four extremities) in 3. In all patients the Romberg test was negative.

The one patient (patient 1, Fig. 1), in whom Wilson's disease was specifically excluded, showed a different set of signs from those of the others. In this instance, there was prominent rigidity and significant dystonia of the muscles, both of which became exacerbated by emotional stress. The neck muscles were hypertrophic. His gait was spastic, the feet were high arched, and the steps very large. In spite of a marked tendency to fall forward, he fell backward if given a slight push (positive "beam" sign).

The facies was expressionless at rest in all patients, but it was rigidly mask-like in only 3. Another 4 displayed intermittent childish smiles, inappropriate laughter, and hypersecretion of tears.

Tremor was present early in the disease in 7 patients. This was generally fine, intermittent, of small amplitude, and particularly evident upon hyperextension of the arms or hands. In 1 patient, the tremor was of the pill-rolling type. Diminished muscular strength was present in the limbs of 5 patients. The Babinski sign was elicited in only 1. Additional findings are listed in Table 1.

2] *Laboratory data.* With one exception, tabulation of these findings as means ± one standard deviation showed no significant differences among these groups. The exception was an elevated eosinophil count in the group of healthy miners, due to a 13% eosinophilia in a single patient.

The urinalyses, fasting blood sugar, blood urea nitrogen, and plasma cholesterol level were within normal limits, but the latter were determined thus far in only 3 of the "healthy" miners and in only 3 of the patients with chronic manganese poisoning.

The total plasma proteins ranged in both groups between 6.8 and 7.9 gm. per 100 ml., and the albumin concentration ranged between

TABLE 2

TOTAL BODY TURNOVER OF ^{54}MN IN THE THREE GROUPS DISCUSSED IN THE TEXT

Group	*Mean (in days)*	*Standard deviation (in days)*
A=normals	35.5	±8.40
B="healthy" miners	12.5	±2.3
C=patients	26.5	±4.78

Listed the half-lives and their standard deviations in days. The p values and T tests are shown among these groups. A vs. B:T=7.5, $p<0.01$. B vs. C:T=6.7, $p<0.01$. A vs. C:T=2.5, $0.02<p<0.5$.

only 38 and 52% of the total protein:albumin globulin ratio (A/G) from 0.6 to 1.2. The electrophoretic studies did not show significant differences among proteins other than albumin. Results of additional liver function tests were as follows: the prothrombin times, flocculation tests, plasma bilirubin levels, and alkaline phosphatase activities were all normal. The BSP retention at forty-five minutes was below 5% in 10 patients, while 1 patient with chronic manganese poisoning had a 20% retention and another a 12% retention. The latter showed normal liver tissue on histological examination following biopsy. The chest films showed definite mineral deposits in only 1 patient with chronic poisoning, whereas in all other instances the findings were noncontributory.

The spinal fluid showed a total protein content between 15 and 50 mg. per 100 ml. among the "healthy" miners and between 25 and 55 mg. per 100 ml. among the patients. Whereas the former group showed 2 instances of a positive Pandy reaction, the latter group showed 6 positive tests out of the 12 patients so studied. The cell counts showed occasionally rare lymphocytes.

The electroencephalogram was within normal limits in all patients and the pneumoencephalograms showed no visible cortical atrophy or enlargement of the ventricles.

3] *Total body loss of ^{54}Mn.* Review of each plot of the total body radioactivity against time showed that the half-lives of the radioactivity (time necessary for the radioactivity to reach one-half of its initial value) amounted to several days in each individual. Dissimilarities among groups of curves became evident when the curves were grouped in the same manner as the individuals under study. There was one meaningful exception, namely, the curve representing the one patient with chronic manganese poisoning (patient 7) discovered by our team while he was still at work in the mines (see below). The remaining 28 curves showed the following differences from group to group. Only in group B ("healthy" miners) was there observed a significant rise of the counting rate between the measurements performed ten minutes after injecting the tracer as compared with those recorded twenty-four hours later. Indeed, this phenomenon occurred in 8 out of 10 records, including patient 7. Expression of these data in terms of the half-life of the total body loss of ^{54}Mn seemed to separate these cases into 3 different groups. The median curve from each group is shown in Figure 3, as contrasted to the mean half-lives and their standard deviations, which are summarized in Table 3. The same table shows the tests of statistical significance applied and the results therefrom. Figure 4 shows the data representing the group of patients with chronic manganese poisoning, as contrasted to patient 7, who, following removal from the mines, had joined the group of patients.

DISCUSSION

The clinical findings, the laboratory data, and the rate of loss of injected ^{54}Mn from the whole body are touched upon in that order.

The histories and findings leave little doubt that the clinical picture of chronic manganese poisoning encountered in Chile shows striking similarities to that reported from other parts of the world, including the United States.[2-5] At the same time, these cases illustrate the gravity of the disease, which affects not only the patients themselves but the industries concerned as well. Indeed, both miners and management have become discouraged—a fact that has contributed to the closing down of many Chilean mines. In our cases, the disease has consisted of an apparently self-limited but severe psychiatric disorder (locura manganica) which has been followed by a permanently crippling, neurological picture. The former did not abolish the patients' insight, but the ensuing compulsive acts rendered the afflicted workers potentially dangerous.

Whereas the patients with chronic manganese poisoning resembled those previously reported in the literature, the "healthy" working population of miners from which our subjects were drawn showed the presence of the "cogwheel" phenomenon as a single finding in significant proportion.[16] Whether this finding was related to manganese exposure or not is still under investigation.

If it were granted that the clinical picture discussed here represents chronic manganese poisoning, some of the laboratory data as well as the measurements of total body loss of $^{54}Mn^{++}$ must be pertinent to other populations. The laboratory data were characterized generally

by normal results, including electroencephalography and pneumoencephalography. Specifically, the changes in hematopoesis encountered by others[17,18] were not evident here. Furthermore, clear-cut demonstration of cirrhosis was not achieved. Yet, it might be worth noting that the A/G ratios of "healthy" miners and chronic patients were low and that two of the latter showed elevated BSP retention. These changes might possibly characterize the population from which both groups originated rather than the metabolic processes under investigation. By the same token, one cannot ascribe significance to either the positive Pandy tests or to the mildly elevated levels of spinal fluid protein. The metabolism of cholesterol might be worthy of more detailed study, since Curran[19] has demonstrated the stimulation of cholesterol synthesis by manganese, while others have corroborated his findings.[2]

The rate of loss of ^{54}Mn merits detailed discussion in view of the significant differences between groups alluded to above. The following must be conceded at the outset: the tracer was divalent and was administered via an arbitrarily selected route. The valence states of tissue manganese have not been as yet precisely quantified. The metal enters the body normally by mouth or, in these miners, also by inhalation. Finally, judged by the incidence of chronic poisoning, the most neurotoxic ores seem to contain manganese of a valence higher than two.[7] The foregoing suggest that the data reported here may primarily represent the fate of the divalent metal in tissues. Still, this reservation does not affect the validity of comparisons among the groups studied here.

Comparison of data from these groups has shown that the curves representing the "healthy" miners (group B) differed significantly from those of the other two groups. Some of their curves showed an initial rise before the decline in radioactivity. This indicates that following the initial clearance of the tracer from the blood the "healthy" miners tended to concentrate the radioactivity at a level nearer to the radiation detector than did the others, strongly suggesting a larger early accumulation of the tracer in the liver. Subject to confirmation now in progress, this finding is compatible with more rapid excretion of ^{54}Mn by the "healthy" miners than by the other groups: this metal is normally excreted by the liver and by the uppermost gastrointestinal tract.[12,13]

This interpretation is strengthened by the fact that the rate of total body loss of this metal was higher in the group of "healthy" miners than in either of the other two groups. This is shown by the estimated half-life of this tracer in the whole body: whereas the curves representing the patients with chronic poisoning did differ somewhat from the normal controls, the curves representing the "healthy" miners showed significant increases in the rates of total body loss of this isotope.

On the basis of previous work on experimental animals and man,[2,12–14,20] it is most probable that this increase in the rate of loss of ^{54}Mn indicates the existence of an elevated tissue burden with metal. Burdening of the body with manganese must have been taking place during work at the mine as illustrated by one patient, whose turnover data conformed to those in the "healthy" miners with whom he was working and not to those in the patients with chronic manganese poisoning, whom he joined in the hospital. Both the "healthy" miners and the patients with chronic manganese poisoning consumed the same diets in the hospital. Therefore, although their manganese intake was not quantified, the increased manganese turnover cannot be ascribed to dietary differences existing while these observations were in progress.

Whereas the presence of actively exchanging, large stores of manganese is a safe postulate for the "healthy" miners, the localization, magnitude, and chemical nature of these stores must await further work. Some of this is now in progress: various tissue samples are being analyzed for manganese by means of neutron activation.[21] By the same token, it is reasonable to assume that the patients with chronic manganese poisoning originally had body stores similar to those of the "healthy" miners and that these were largely eliminated after their leaving the mines. Therefore, no compelling reason existed for treating these patients with metal-binding agents.

SUMMARY

Clinical, laboratory, and isotopic studies are reported on groups of individuals representing

a normal population, a population of "healthy" manganese miners, and patients suffering from chronic manganese poisoning. The "healthy" miners were selected among workers who had previously shown a significant incidence of the cogwheel phenomenon as an isolated finding. With this exception, there were no apparent psychiatric or neurological abnormalities among the two control groups. The patients with chronic manganese poisoning, on the other hand, displayed transitory psychiatric symptoms, followed by permanent neurological changes, including disorders of the extrapyramidal system. With the exception of low plasma protein concentrations encountered in both "healthy" miners and patients, the laboratory data showed no striking abnormalities among these subjects. Specifically, no hematological or significant hepatic disorder became evident. By contrast, determinations of the rate of loss of the radioisotope ^{54}Mn from the whole body following intravenous injection showed faster losses in the case of the "healthy" miners than in either the normal controls or the patients with chronic metal poisoning. This is interpreted as indicating the presence of large, actively exchanging stores of tissue manganese in the case of the healthy miners as contrasted to the patients suffering from chronic manganese poisoning. Consequently, chelation therapy was not practiced.

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Ismael Mena, Oscar Marin, Sergio Fuenzalida, et al.

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