Short Notes and Clinical Cases.

THREE CASES OF MANGANESE POISONING.

By J. R. CHARLES, Bristol.

Physiologically manganese occurs in small amounts in the human body, traces of it having been found in milk, bone, and hair, and from 0·5 to 2·5 mgrm. of MnO per litre in the blood.[1]

Reiman and Minot[2] found that ores containing oxides and silicates were soluble in the gastric juice, and might be absorbed into the blood, causing a slight temporary rise in manganese concentration, which, however, was followed by a speedy return to normal. In no case was the manganese content of the blood increased by the ingestion of manganese to more than the normal level, and in some cases no increase at all was noted.

Large amounts of manganese ores given to dogs over a prolonged period failed to produce any definite changes in the manganese content of the blood or tissues, or to produce any pathological effects.

Manganese ores, therefore, appear to be non-toxic as a rule, and, in order to produce symptoms of poisoning, must be ingested by persons who have a personal idiosyncrasy; this may account for the rarity of pathological signs and symptoms which can be attributed to this cause in clinical practice.

There is, however, a definite grouping of symptoms attributed to manganese intoxication. Emotional disturbances may be manifest, with uncontrollable laughter, or weeping, more particularly at the beginning of the illness.

Sometimes mental languor and lack of energy are prominent symptoms at the onset. This feeling of fatigue is probably due to excessive exertion produced by the hypertonic condition of antagonistic muscles, involving excessive muscular work.

Later on the face wears a mask-like expression. Quite early in the disease there is a tendency to retropulsion, or in some cases to propulsion. The gait then becomes spastic, with a peculiar tendency for the patient to step forward on the metatarsophalangeal joints, a feature so marked in one of the cases described below that the patient had, of his own accord, the heels of his boots raised for ease in walking some time before he was examined.

The voice becomes monotonous, and increased salivation has been noted. There may be general paresis of the muscles of the limbs, but without atrophy or reaction of degeneration.

Tremors of the head and limbs are common, and are increased on intentional movement, and after exertion. These tremors vary from a fine twitching of the hands to gross rhythmical movements of the limbs, trunk, or head. The deep reflexes are increased. Paræsthesias and pains occur in the limbs. There may be complaints of cramps in the calf muscles, generally worse after exertion. Œdema of the legs is said to occur. Romberg's sign is not constant. There are no disturbances of deep or superficial sensation, no eye changes, no sphincter trouble, and no changes in the blood or urine. There are said to be no alterations in the cerebrospinal fluid, but in each of the following cases an excess of globulin was found.

Manganese produces no life-shortening degenerations. Slight cases in the early stages may recover from their symptoms, but advanced cases become life-long cripples, some non-vital part of the nervous system being irrevocably destroyed.

Manganese is used commercially in making chlorine gas, and in the manufacture of paints, varnish, enamel, and linoleum. It is also used in marbling soap and in making steel. Cases of manganese poisoning have been found among French workers who make bleaching powder, among Germans who grind manganese dioxide, and in Americans who work in a dust containing the oxide and silicate. Some fifteen cases have been described in Europe. Probably, however, the disease is not infrequently unrecognized.

The three cases described below had all been in hospital previously.

Case 1, J. B., was under my care a year ago, when his condition was regarded as one of functional aphonia, which was confirmed by the throat specialist, and functional paresis of legs.

Case 2, F. J., was also under my care, in May, 1919. His case was diagnosed as one of syphilitic myelitis. At that time he had a positive Wassermann reaction in his blood, spastic paresis of his legs, increased knee-jerks, and an extensor plantar response on the right side. He was given antisyphilitic treatment, including six injections of novarsenobillon, and was discharged with a much-improved gait, though his blood still gave a strongly positive Wassermann reaction. On readmission both blood and cerebrospinal fluid gave negative Wassermann reactions. He showed, however, throughout, signs of degeneration of the pyramidal, as well as the extrapyramidal, motor systems.

Case 3, S. W., had been in another hospital, under another physician, and was diagnosed as functional.

The three cases were sent to me again early in February, 1922,

by Dr. Coode, of Stroud, who pointed out that all three had been working in the same factory in manganese dust. The shortest time since any of them had been working in manganese was two years, and no manganese was found in the urine of any of them; nor was any found in their skin. They were given injections of pilocarpine, and their sweat was examined spectroscopically with negative results. The clinical picture of their signs and symptoms corresponded so closely with the recognized symptoms of recorded cases of manganese poisoning, as to leave no doubt with regard to the diagnosis in these patients. Their trouble probably represented irrevocable damage done to the nervous system, rather than any active and progressive lesion.

The following is a description of the cases :—

Case 1.—J. B. was admitted to the Bristol Royal Infirmary in October, 1921. He complained of inability to walk, except on his toes, and loss of voice.

Previous History.—Has had childish affections, but nothing else. Passed out of the army quite strong and healthy. (Class B 2, owing to loss of thumb in circular saw at the age of 19.) Went into manganese works at Stroud when he came out of the army. He worked at the electric elevator, into which he shovelled the mineral manganese from Japan, China, or Russia. The elevators take the manganese up to sieves, and the dust in the elevator department he described as terrible. He has never had anything to do with paint or lead. No history of rheumatism, gout, cancer, syphilis. Blood tests stated to be negative.

Present Illness.—He went to the manganese works quite fit and well. He gradually got weaker while there, till he could not swing a sledge, and could hardly walk; at the same time he gradually lost his voice. Two or three days after he left the works he found he had to walk on his toes uphill. He shuffled along fairly well on the level, ran uphill on his toes, and when going downhill he got faster and faster until he ran into everything or fell over. He had to go upstairs on his hands and knees. In the beginning he had a tendency to fall backwards, but now he cannot walk backwards. He left the manganese works two years ago, after being there seven months, and went to an iron foundry. Since that time he has got no worse, but his voice has got a little better, if anything.

On Admission.—Pulse 70, regular, artery slightly thickened. No enlargement or abnormality of heart. Lungs, abdominal organs, and urine all normal.

Central Nervous System.—He can only whisper, and speaks in a monotonous way, but articulation good in spite of weakness of voice. Immobility of face muscles, cannot whistle, defective response to emotional stimuli. Other cranial nerves normal, except for tremor of his tongue.

Motor System.—Power in arms and legs not very strong either in flexion or extension. No spasticity in arms, but definite spasticity in all the leg muscles. Co-ordination good, gait dragging, spastic in type, walks on a wide base, and treads on his metatarsophalangeal joints, instead of on the soles of his feet. He has a marked tendency to fall backwards, and, when he does so, falls like a rigid pillar, due apparently to spasticity of trunk

and leg muscles. He walks with his arms rigid, and an absence of the normal automatic swing of arms.

Reflexes.—Knee-jerks present, equal on both sides, brisk; Achillis-jerks present on both sides; plantar reflex flexor, no ankle-clonus; no knee-clonus; wrist-, biceps-, and triceps-jerks all present on both sides.

Sweats a good deal at night, mostly from his back.

Nov. 4, 1921.—Pathological report of cerebrospinal fluid: Globulin increased; cell count 10 per c.mm; colloidal gold one degree of change in tubes 1 and 2, not characteristic; Wassermann negative.

Nov. 11, 1921.—Report on voice affection: Nasopharynx normal; nose septum irregular, some deflection to right, but fair airway; larynx normal, except slight weakness of apposition in anterior portion of glottis; tremors of cords; no redness of cords or any signs of laryngitis.

Dec. 5, 1921.—Patient has much improved as regards walking. His voice is not much improved; it is variable in strength from day to day. Blood-pressure, 118.

Case 2.—F. J. Complained of paralysis of legs, Nov., 1921.

Previous History.—Nothing of importance in family history. He had influenza three or four years ago. Twenty-three years ago he was in hospital with 'diseased hip', and was cured. Patient was employed shovelling manganese into machine sieve for three years. He left off three years ago, and has done nothing since.

Present Illness.—Three years ago (May, 1919) patient noticed that he stumbled when walking; he lost power gradually, till at length, a year later, he could stand only with difficulty. He suffered from acute cramp-like pain down the front of both legs and the backs of his thighs. He has remained in this condition ever since, but recently has noticed weakness of his arms.

He lies still in bed. His face lacks expression, and is very definitely mask-like in character. He speaks slowly and quietly, in low monotone. He cannot move his face muscles well. No response to emotion. Tongue shows slight tremor.

Motor System.—All the muscles of the right arm are fairly strong, with the exception of flexion of the wrist, which is definitely weak. The muscles of the left arm are all somewhat weaker than those of the right. The power in all the muscles of both legs is impaired. No spasticity in arms, but this is marked in his legs. Gait spastic, with feet wide apart, and putting toes down first. His heels barely touch the ground. He cannot turn round without holding on to some support. His arms are rigid and fixed to his sides when walking, without any swinging movement. Tremor in the muscles after exertion was not a marked feature in this case. Romberg's sign negative.

He sometimes gets aching pains in his knee.

Reflexes.—Arm-jerks normal; both knee-jerks exaggerated; patellar clonus on left side; plantar reflex extensor on right, flexor on left; ankle-clonus on left.

Nothing abnormal found in heart, lungs, abdominal organs, or urine.

Cerebrospinal Fluid.—Globulin increased; cell count no increase; colloidal gold slight change in tubes 1 and 2, nothing characteristic; Wassermann negative. (Blood Wassermann reaction also negative.)

Case 3.—S. W. Admitted Oct. 10, 1921. Complained of inability to work.

Previous History.—Has not had measles, chicken-pox, scarlet fever, or rheumatism. Very moderate with alcohol and tobacco. No venereal disease. Previous health had always been good; worked as a walking-stick maker. Family history showed nothing of importance.

Present Illness.—In January, 1915 (nearly seven years ago), patient got a job in a factory where manganese ore was handled. His work was to grind the ore and throw the dust when ground into an electric shoot. He took due precautions about washing his hands before meals, etc., whether at the factory or at home. He did not find that the dust irritated his throat, but he noticed soon after he commenced to work that his voice began to get indistinct. After about six months he found he was liable to have rheumatic pains along the course of the bones of the thigh and legs, which were made worse in damp weather. He noticed, too, that he was liable to fits of depression and suffered from a dull heavy headache at the vertex. When he had been at work nine months in the factory he noticed a tendency to stagger backwards when throwing the ore on to a heap. At the same time there was a change in his gait: he scuffled because he could not lift his feet properly clear off the ground. He could walk uphill fairly easily with the aid of a stick, but on coming downhill he had a tendency to fall, as one leg particularly failed to support him. The patient had high heels fitted to his boots in order to make walking easier, as he could not lift his toes off the ground properly. The legs trembled, especially after exertion. He also had trouble with micturition: hesitancy about the act, but no pain. After a rest the patient returned to a different part of the factory, but had to give up after six months. Since that time he has not been at work (nearly five years). Since May, 1916, patient has been at home, completely crippled. He usually gets up in the morning, and sometimes walks a few yards with the aid of a stick.

On Admission.—Sits up in bed. He has a remarkably sallow face, at first glance suggestive of pernicious anæmia. Expression varies very little, with a typical Parkinsonian mask. Speaks in a monotone.

Central Nervous System.—Articulation: expressionless, monotonous voice of low tone. Pupils react to light and accommodation sluggishly. He has a fine tremor in the tongue on protrusion.

Motor System.—No loss of power in arms. All movements extremely weak in both legs. This weakness appears to be largely due to spasticity of his muscles. He walks with the greatest difficulty, and only with support. Exertion of the leg muscles is followed by coarse tremor. He puts his feet forward on his metatarsophalangeal joints, and walks on a broad base, with knees bent, and has to be supported each side. He has a great tendency to fall, especially backwards, and when he does so, falls in a rigid pillar, due apparently to spasticity of trunk and leg muscles. He has great difficulty in turning. His writing is very tremulous. No hypertrophy or atrophy. He complains of cramp-like pains in his knees, especially at night.

Reflexes.—Arm-jerks normal. Knee-jerks exaggerated on both sides. Ankle-clonus on both sides. Plantar reflex flexor in type on each side.

No sign of disease in heart, arteries, lungs, abdomen, or urine. No manganese found in urine.

Cerebrospinal Fluid.—Clear; globulin increased; cell count 10 per c.mm.; colloidal gold reaction shows slight change, one degree in tubes 1, 2, and 3, not characteristic.

Blood-films.—No poikilocytosis; no anisocytosis; no basophil stippling; no normoblasts; no leucocytosis; Hb 75 per cent.

Dec. 12, 1921.—His gait has much improved on education. Still has difficulty in turning round; has a good deal of difficulty in starting to walk, but once in motion can walk better than he could, with the aid of a stick, or behind a wheel-chair.

In all these cases memory and intelligence were unimpaired, and no abnormalities were found in the special senses, fundi, or any of the cranial nerves, apart from those mentioned. There was no muscular atrophy. No objective sensory changes were found with regard to touch, pain, temperature, stereognosis, or sense of position. The sphincters were uninvolved.

It is very unfortunate that virtually nothing is known about the pathology of the disease. Casamajor had an autopsy in 1916, in which the following was found.

" Patient died from pneumonia.

" *Kidneys.*—Moderate chronic interstitial nephritis.

" *Liver.*—Considerable biliary cirrhosis, and the liver-cells contained much pigment, the majority of the granules being iron-containing.

" *Brain.*—There was some degeneration of more or less regular character in the longitudinal fibres of the pons which run with those of the pyramidal tracts. While these degenerations are regular enough to be assembled into clearly defined tracts, nevertheless it was impossible to determine either the upper or lower level of the tracts in question. The degenerated portion does not appear to go above the upper level of the pons, nor does the lower portion extend to any appreciable extent into the medulla. The pyramidal-tract elements are clearly defined, and those of the frontopontine and temporopontine tracts are fairly so."

He was unable to reproduce this condition in animals (rabbits and dogs). From analogy, however, one cannot refrain from surmising that the disease may prove to be one involving the basal ganglia, i.e., the lenticular nucleus, or its connections, and possibly also the optic thalamus, since subjective sensations such as pains and cramps are prominent features in some cases. The striothalamic fibres may be involved. These run to the outer part of the thalamus, which is the part more definitely connected with the sensory system. One wonders if the cerebello-rubro thalamic system may also share in the trouble. From the nature of the symptoms it appears certain that manganese has a definite selective affinity for some definite nervous structures, that these structures are mainly motor in function, and that they are extrapyramidal.

Many of the clinical features of this complaint are similar to those described by Kinnier Wilson[3] in ' progressive lenticular degeneration ', though there are also many differences. The prognosis, too, is

different, for the latter disease is invariably progressive and fatal. Kinnier Wilson, in his monograph on progressive lenticular degeneration, points out that he does not consider this disease to be produced by congenital causes, by microbic agency, or by syphilis. Perhaps it may be shown that some metallic poison similar to manganese is the etiological factor, some poison to which most people are insusceptible (as in the case of manganese), but to which there may be a family susceptibility, and this may account for the familial incidence of his cases.

Lastly, the possibility of manganese as an etiological factor should be borne in mind, and excluded, before making a diagnosis of functional disease or of disseminated sclerosis.

BIBLIOGRAPHY.

[1] OPPENHEIMER, *Handbuch der Biochemie*, i, 83.
[2] REIMAN, C. K., and MINOT, A. S., *Jour. of Biol. Chem.*, 1920, Dec.
[3] WILSON, S. A. KINNIER, *Brain*, 1912, xxxiv, 295.
SEEBERT, *Monats. f. Psychiat. u. Neurol.*, 1913, xxxiv, 82.
EDSELL, WILBUR, and DINKER, *Jour. of Industrial Hygiene*, 1919, 183.
VON JAKSCH, R., *Wien. klin. Runds.*, 1901, 729.
CASAMAJOR, L., *Jour. Amer. Med. Assoc.*, 1913, 60.
DAVIS and HUEY, *Jour. of Industrial Hygiene*, 1921, Dec.