NEUROMUSCULAR MANIFESTATIONS OF EMETINE TOXICITY

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Amoebiasis occurs sporadically in this country either in the form of hepatic abscess, hepatitis or dysentery. Emetine was first used by Bardsley for diarrhoeas and dysenteries in 1829 and by Rogers in 1912 for amoebiasis. Since then it has become and is still one of the most useful and effective amoebicides used today. It is well known that emetine can cause a variety of toxic manifestations, but the exact incidence of toxicity varies with different investigators. Brown (1935) in a study of 554 patients treated with emetine for amoebiasis found that 23 (4·1%) developed symptomatic intoxication. Seven out of 259 cases who had at one time or other been receiving emetine were found by Manson-Bahr (1941) to have emetine intoxication. On the other hand Klatskin and Friedman (1948) revealed that 91% exhibited toxic symtoms out of 93 patients. In the study of 111 patients carried out by Sodeman (1952), 38 showed electrocardiographic changes while only 5 had symptomatic intoxication.

The toxic effects of emetine could be either mild or transient, disappearing after the drug has been discontinued or even inspite of continuation of therapy. They could either be local or systemic. The systemic intoxication affects the gastro-intestinal tract, the neuromuscular system or the heart, which can be so serious as to cause death. Of the systemic effects, the involvement of the neuromuscular system in the true form of muscular weakness and peripheral neuritis is relatively less well known. Manson-Bahr (1941) quotes a case resembling progressive muscular atrophy from the study of 259 cases. Of 5 cases of symptomatic intoxication reported by Sodeman (1952), 3 displayed muscular weakness and neuritis. Although one half of the series of Klatskin and Friedman (1948) were classified as having neuromuscular manifestations of emetine intoxication, only 14 subjects developed the syndrome commonly considered as emetine neuritis. We are reporting four cases of emetine toxicity affecting principally the neuromuscular system.

CASE 1

This Chinese patient was first seen in 1962 as a result of cerebral thrombosis with left hemiplegia. He was followed up as an outpatient for four months after which he was discharged when his recovery was almost complete. He was not seen again until April 1964, when he was readmitted for the second time with the complaint of fever not associated with chills or rigors, off and on for a period of five weeks. The fever was low grade and the urine was said to be darkly coloured. On examination he was found to be febrile and slightly icteric. The blood pressure was 140/80 and the liver was enlarged and tender. Investigations: haemoglobin 9 gm%; white blood count 10,000 with a normal differential count; blood film for malarial parasite negative; E.S.R. (Westergren) 106 mm./hour; Widal and Weil-Felix negative; urobilin trace and urobilinogen positive; S.G.O.T. 87 (Normal Value in this laboratory 25 - 125) S.G.P.T.—serum glutamic pyruvate transaminase 129 (Normal 30-110) and I.C.D.—isocitric dehydrogenase 372 (Normal 60 - 360).

He was diagnosed as a case of amoebic hepatitis and was treated with injection emetine hydrochloride grain one nocte. After receiving only one dose of emetine it was noticed that he was becoming mentally confused and that he was uttering a lot of nonsense. He even ran back to his house, but was brought to the hospital by his wife and children. As it was not certain whether this mental confusion was due to the disease process or the emetine, two further doses of emetine were given. Inspite of this his temperature kept on swinging and his mental confusion persisted. It was therefore decided to institute chloroquin instead of emetine. Four days after chloroquin was administered, he became less confused and was more cooperative, but the fever persisted. At this time it was found that he had a localised area of tenderness over the right lobe of his liver at the eighth intercostal space in the anterior axillary line. A liver aspiration was performed and typical amoebic pus was

obtained. Emetine was again reinstituted. The temperature began to subside after the aspiration.

After two doses of emetine had been given him, he again developed mental queerness and emetine had to be withdrawn, following which his mental state became normal again. As the liver still remained tender, a second liver aspiration was carried out, but unfortunately one hour after the practical procedure, he went into 'shock'. The blood pressure was not recordable; the patient was pale and perspired profusely. His extremities were cold and clammy. The abdomen was distended, guarded and tender, but there was neither rigidity nor shifting dullness. An E.C.G. was done in order to exclude failure from toxic myocarditis or myocardial infarction. Though the recording was not very good, there was no evidence of myocardial infarction. The T waves were slightly flattened in Leads II, III, AVL and AVF. 2 weeks later another E.C.G. was done. The flattened T waves in Leads II, III and AVF had returned (See Fig. 1). A surgical opinion was sought for and it was agreed that conservative therapy be carried out as there was no evidence of bleeding or peritonitis. As a result of the peripheral circulatory failure he developed prerenal uraemia. With intensive supportive measures his blood pressure was restored to normal and the blood urea fell to normal four days after this incident. It was at this time that he was noticed to have bilateral foot-drop with loss of reflexes in the knees and ankles. Though the muscles of the calves were tender, there was no loss of sensation to pin prick. Investigations were carried out to determine the cause of this peripheral neuritis, but they were negative. The temperature remained normal since the day after the first liver aspiration.

With physiotherapy his peripheral neuritis improved. At the time of his discharge from the hospital, he was able to walk with support though the reflexes of the lower limbs were still absent. Three months after the discharge he could walk without any aid and his reflexes had returned.

CASE 2

A Chinese lady aged 30 was admitted to Middleton Hospital for Infectious Disease because of abdominal pain and diarrhoea for three weeks, vomiting for two weeks, fever for two days. Despite exhaustive investigations, no definite cause could be found. As her conditions were getting worse, it was decided to give her emetine. After 5¼ grain of emetine, she complained of extreme weakness and paraesthesia of both her lower limbs. It was because of this neurological complication she was transferred to our hospital. By this time her diarrhoea had cleared up. On physical examination she looked ill and anaemic but was afebrile. The blood pressure was 140/100 and the pulse was 100/minute and regular. The abdomen was distended and tympanitic and the liver was just palpable. The spleen was not palpable. In the central nervous system, the cranial nerves were intact, the motor power in the lower limbs was poor and the reflexes were absent. There was diminished sensation to pin prick from below the knee. E.C.G. (Fig. 2) showed toxic myocarditis as evidenced by low voltage and inverted T waves in Leads II, III, AVF and all the chest leads.

Nine days after admission she was able to move her lower limbs and by 11th day her knee jerks and ankle jerks returned. Within a fortnight the motor power of the lower limbs had improved considerably and by one and a half month she was able to walk again without any support. About this time her E.C.G. returned to normal (Fig. 2).

CASE 3

A Muslim Indian aged 54 was admitted in August, 1963 with the complaint of pain in the right hypochondrium and epigastrium, associated with fever, nausea and vomiting for three days. On physical examination, he was found to have a temperature of 101° F and was jaundiced. The blood pressure was 114/70 and the heart was normal. In the abdomen the liver was enlarged and tender. No other abnormality was found in the other systems. Invesitigations revealed a leucocytosis of 10,400 with a differential count of polymorphs 86%, lymphocytes 10%, monocytes 3% and eosinophils 1%. Of the liver function tests done serum bilirubin was 1·8 mg.% while the others were normal. No amoeba was ever found in the stool. He improved after 10 grs. of parenteral emetine hydrochloride and oral chloroquin had been given. He was then sent home with a further course of emetine bismuth iodide of 3 grains for 10 days.

18 days after leaving the hospital, he was readmitted for the second time with the history that 4 days prior to admission he lost his appetite for food and at the same time he also experienced aching pain in both thighs, associated with tiredness and weakness of both lower limbs. The weakness was worse in the afternoon.

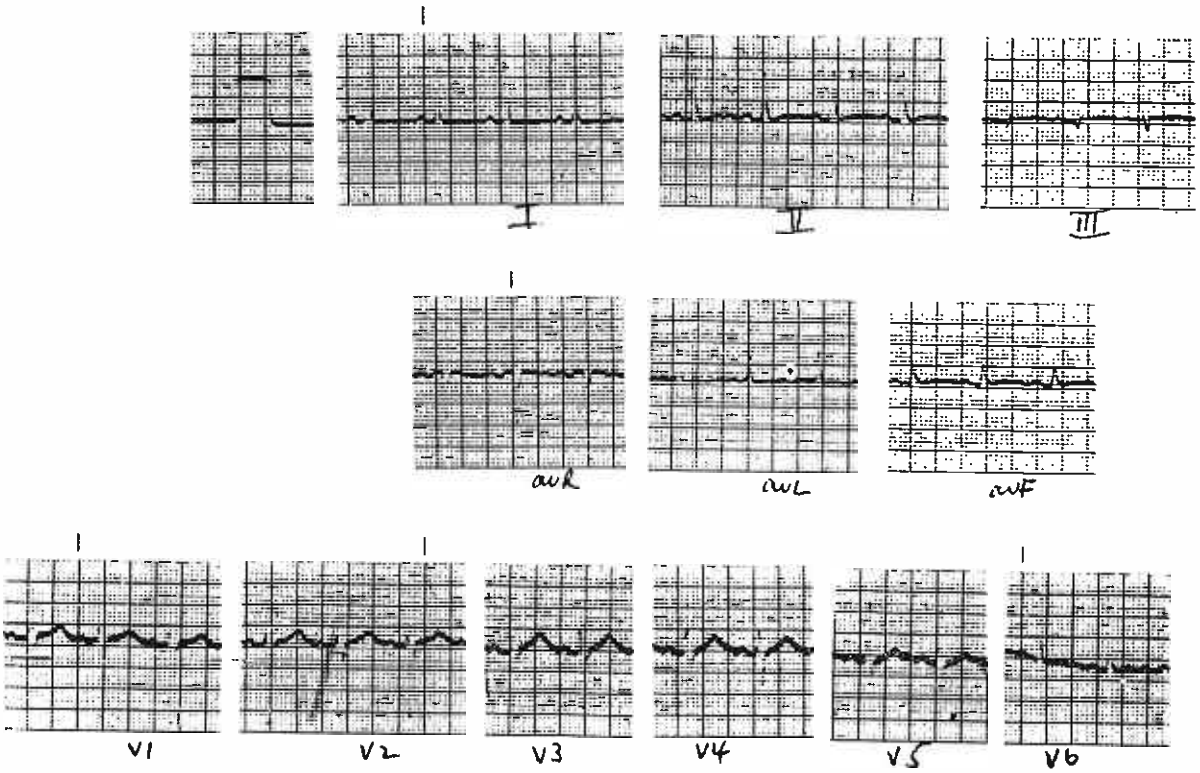

Fig. 1a. Slightly flattened T in Leads I, II, III, AVL and AVF.

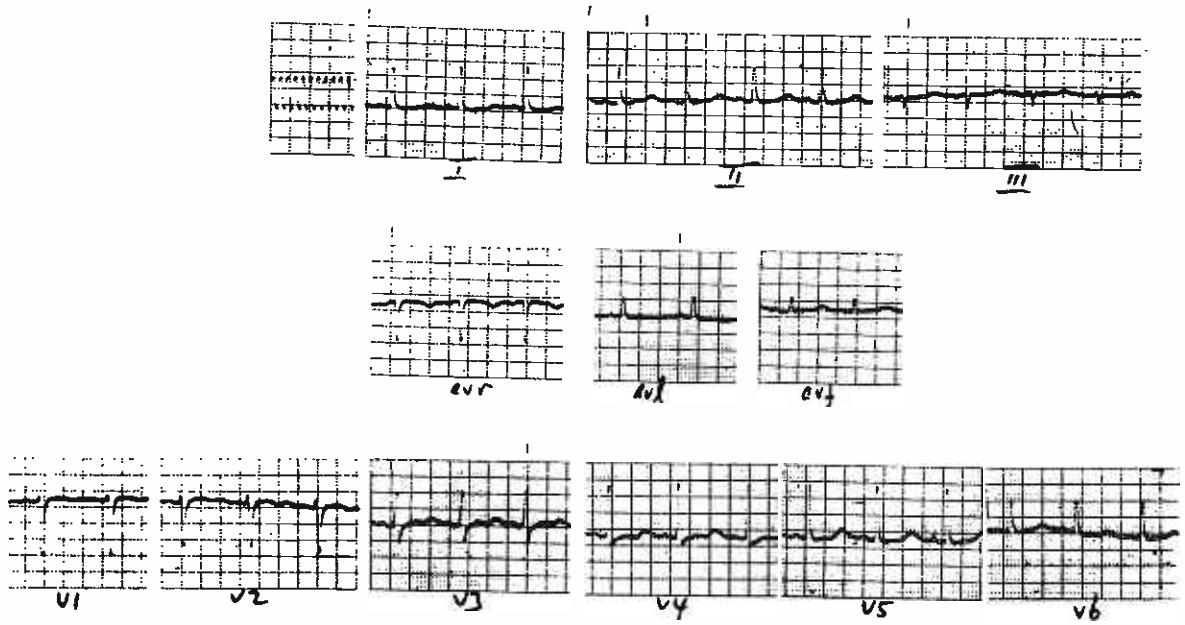

Fig. 1b. Taken two weeks later. T waves still flattened in Leads 1 and AVL.

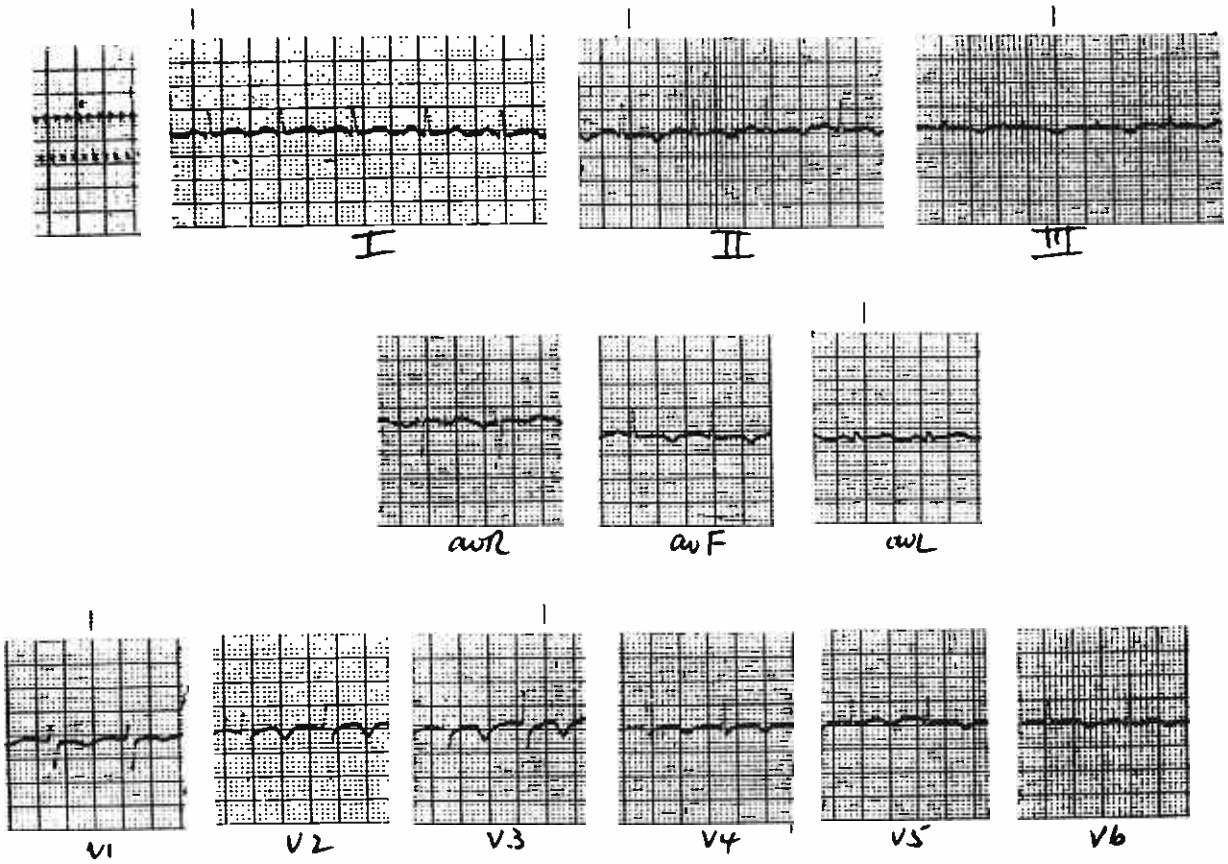

Fig. 2a. E.C.G. taken on day of admission showing low voltage and inverted T waves in Leads II, III, AVF and all chest leads.

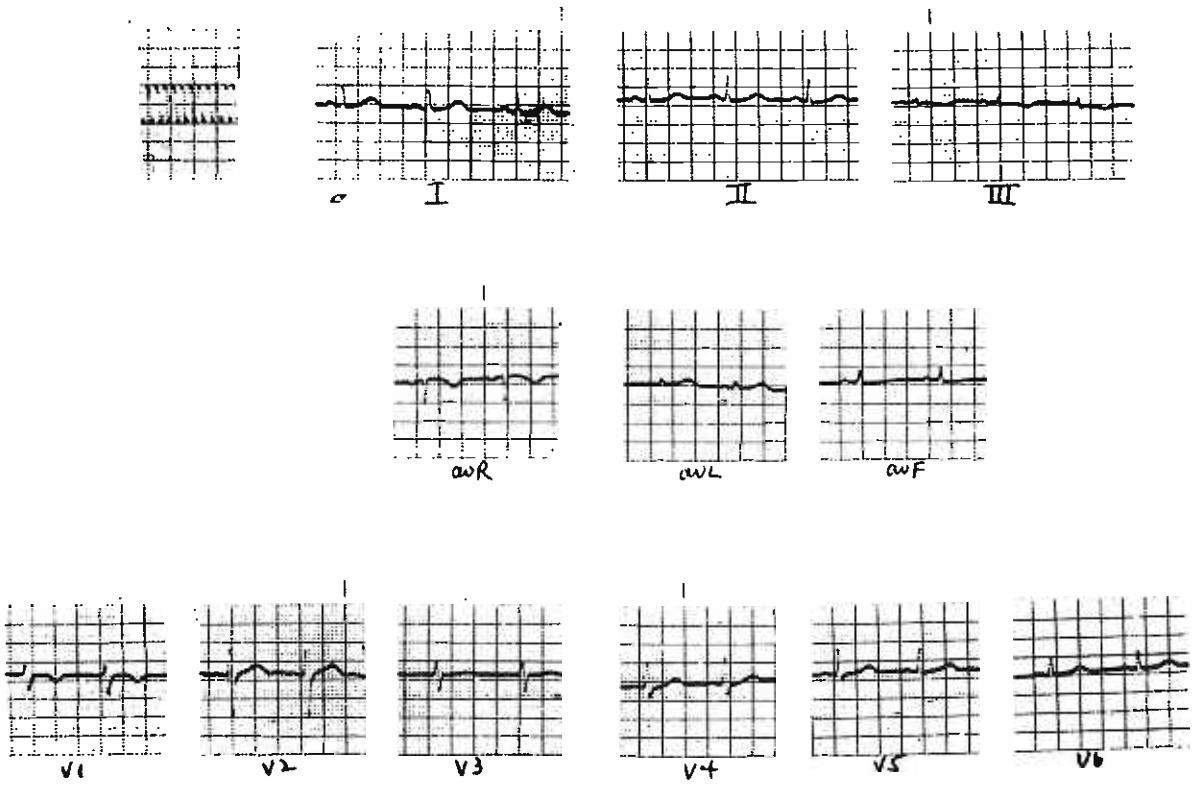

Fig. 2b. E.C.G. Taken about one month later — a return to normal.

At the same time he also found that he was unable to open his mouth wide and had difficulty with swallowing. He had to live on fluids. Two days later (2 days prior to admission) the weakness became worse until he could hardly support himself. His legs began to tremble and the following day his hands became affected.

Physical examination on the day of his second admission revealed that his blood pressure was 90/60 and the pulse was 80/minute and regular. The heart and the abdomen were normal and the main findings were in the central nervous system. His mental functions were good and the cranial nerves were intact. The sternomastoid and other muscles of the neck were very weak. In the upper limbs there was generalised wasting but without any fasciculation. The tone was flaccid and he was hardly able to lift up his arms. There were coarse tremors of the limbs on attempted voluntary movements. The weakness was most marked in the proximal group of muscles and the trunk muscles were also weak. There was generalised wasting of the muscles of the lower limbs. The tone of the muscles was also poor. All the reflexes were present and equal.

Investigations: haemoglobin 14 gm.%; white blood count 8,900 with the differential count of polymorphs 61%, lymphocytes 25%, monocytes 5% and eosinophils 9%. E.S.R. (Westergren) 23; blood for Kahn test negative; blood pyruvic acid 0·8 mg.; serum electrolytes: K. 4·2 mEq/L, Na. 141 mEq/L, Cl. 111 mEq/L; urine creatine 17 mg./day; urine creatinine 824 mg./day; E.C.G. low voltage and flattening or marked inversion of T waves in all the leads (vide Fig. 5). A lumbar puncture was done and the cerebrospinal fluid was not under tension. The fluid was normal and the Kahn test was also negative. A piece of muscle was taken from the left deltoid for histological examination. The report read as follows:- There is degeneration of muscle fibres with loss of striation and hyalinization. There is a marked proliferation of sarcolemmal cells. Focal lymphocytic aggregates are also present. Features are suggestive of a primary myopathy (Fig. 3).

One week after hospitalisation he improved and was able to lift up his head. The motor power on all the four limbs became stronger and the tremors of the hands disappeared. Within one and a half months he made an almost complete recovery. By this time he was able to walk, lift up his arms. He was able to eat well without having any difficult in swallowing. The blood

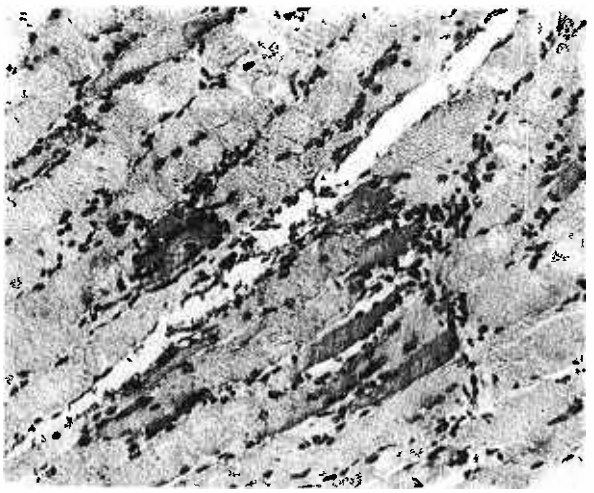

Fig. 3a.

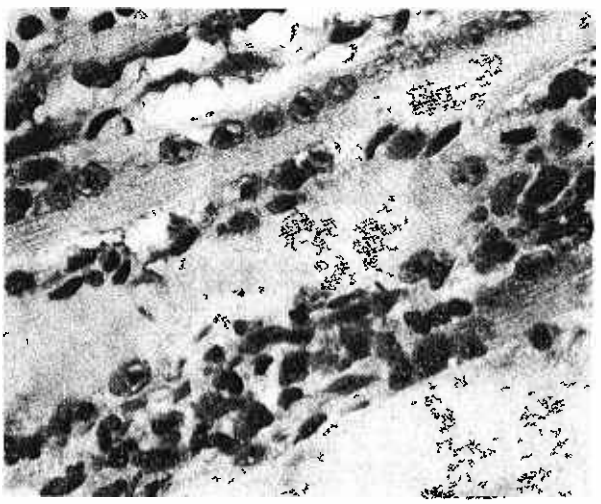

Fig. 3b.

Figs. 3a & 3b. Case III. First muscle biopsy: Loss of muscle striation and hyalinization and marked proliferation of sarcolemmal cells. Focal lymphocytic aggregates also present. (Top: H & E × 150 and Bottom × 500).

pressure was 120/80 and the electrocardiographic tracing had returned to normal. Another muscle biopsy was done from the left deltoid and it was reported that there were increased sarcolemmal cells in only a few places. The florid changes seen in the previous biopsy were not present (Fig. 4).

CASE 4

This patient, a Chinese girl of 18, who 6 months prior to admission developed intermittent colicky pain in the right iliac fossa and a month after that it became worse. She was then seen by a private practitioner who examined her abdomen and found that she had thickened caecum. She was thus treated as a case of amoebiasis with chloroquin, terramycin and emetine. She had altogether 12 grains of emetine. After six doses she felt weak and lost her appetite.

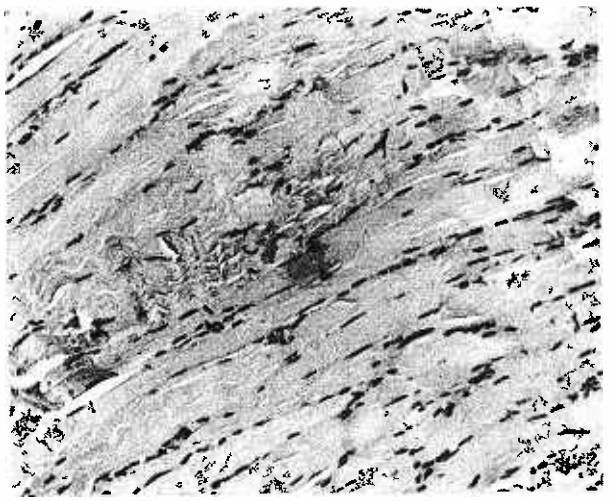

Fig. 4a.

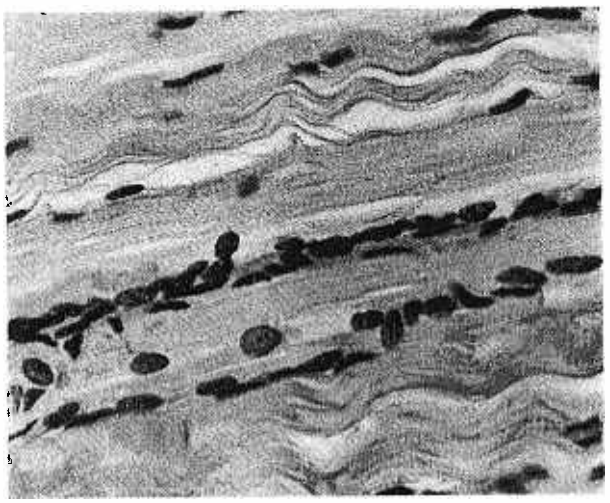

Fig. 4b.

Figs. 4a & 4b. Second muscle biopsy at the time of recovery showing only increased sarcolemmal cells in a few places. The muscle structure normal. (Top: H & E × 150; Bottom: H & E × 500)

Inspite of this, another six doses were given and one week after the twelfth and last dose was given, she became very weak indeed. She was unable to take solids but managed to take fluids. Even then sometimes the fluid regurgitated through her nostrils. It was also noticed that her voice had changed and she was unable to hold up her head, which would flop forwards when she tried to sit up. It was because of these complaints she was admitted to this hospital.

On examination, she was found to be afebrile, the blood pressure was 120/80 and the pulse was 80/min. and regular. The main findings were in the C.N.S. Her voice was nasal in character. She was unable to walk or stand up. There was weakness of facial muscles and the sternomastoids. The palate was paralysed. In the limbs there was weakness in the limb-girdle group of muscles, while the distal muscles were fairly strong. All the reflexes were present and there was no sensory disturbance. Throat swabs sent for culture for Corynebacterium diphtheriae were negative and repeated therapeutic tests with prostigmine gave no response. A lumbar puncture was done and the cerebro-spinal fluid was normal. E.C.G. showed inverted T waves from VI-3.

No specific treatment was given her and within a fortnight she was able to eat normally again and able to walk, though she got easily tired after a short distance. Two months later the weakness of all the muscles disappeared and she was completely well thereafter.

COMMENTS

Although Sodeman et al (1952) pointed out that female patients and those with anaemia or general debility are more prone to toxic reaction of the drug, there is still a great variability in patient's reaction to the drug as is shown by the above four patients who developed toxicity with differing dosages of emetine. The first case developed toxic complications after two grains, the second five and a quarter grains, the third ten grains of emetine hydrochloride and thirty of emetine bismuth iodide and the fourth twelve grains. In Case one, the symptoms of toxicity which developed after one grain of emetine suggest that this was most probably due to hypersensitivity. In order to emphasise the individual tolerance to the drug, Brown (1935) recorded three patients of having high doses of emetine—first, 125 grains (8·3 gm.); second, 134 grains (8·7 gm.) and the third 180 grains (11·6 gm.)—administered to them within a period of 8 to 12 months without toxic complications.

In the series of Klatskin and Friedman (1948) 14 patients developed neuritis, but none of these exhibited loss of reflexes, whereas the above first two cases had loss of reflexes. Whether the loss of reflexes was due to definite inflammation and degeneration of the nerves is difficult to say because no biopsy of the affected nerve was done at that time. Klatskin and Friedman (1948) considered that true degeneration and inflammation of the nerves does occur, but it is quite rare. Since the studies of Young and Tudhope (1926) on emetine poisoned rabbits, most people tend to consider that emetine neuritis is probably a primary disorder of the muscle or myositis. In this group falls the last two cases, which presented clinically like that of a primary muscle disease and the muscle biopsy in Case 3 was even

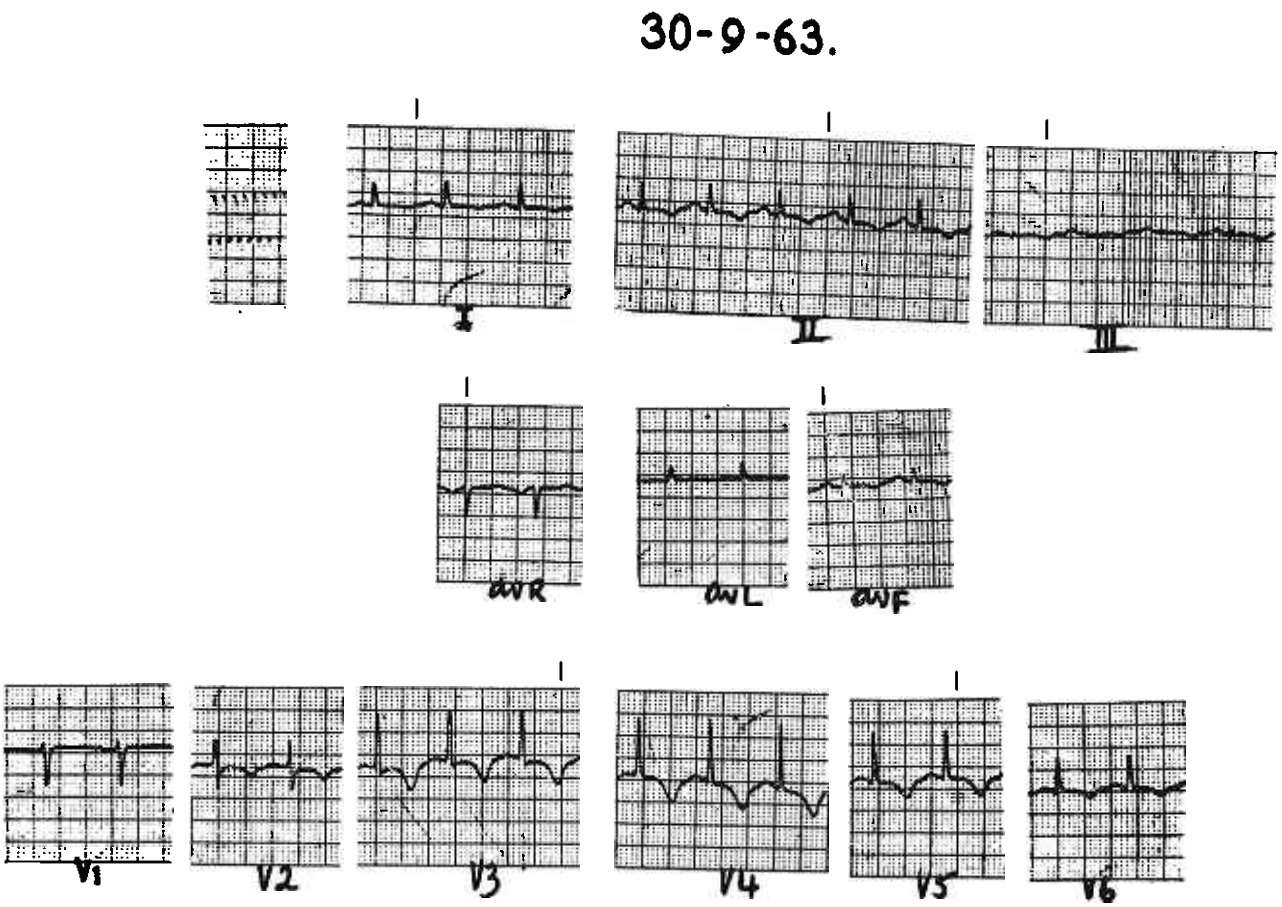

Fig. 5a. Case III. Low voltage with flattened and marked inverted T waves in all the leads. This E.C.G. was taken at the time of admission.

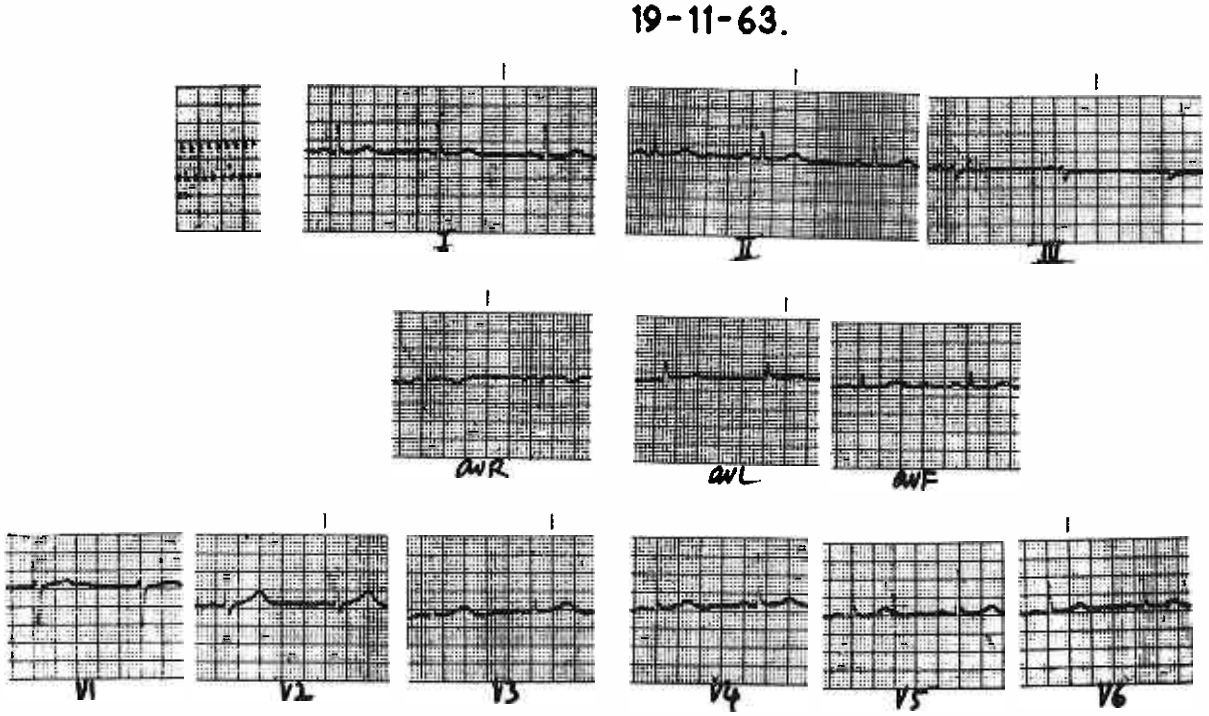

Fig. 5b Case III. Second E.C.G. Showing a return to normal when the patient was recovering.

suggestive of primary muscle disorder. The important feature about this myopathy is that recovery takes place after 1½ to 2 months.

Mental confusion and disorientation can occur in patients who are seriously ill, but in Case 1 the complication was probably due to emetine and not the toxic process of the disease, because on withdrawal of the drug his mental function was restored to normal, but only to recur on readministration of emetine. Furthermore, according to Manson-Bahr (1941) emetine intoxication can give rise to asthenia and mental depression and a case was reported by Ratnesan and Pobee (1962) in which there was mental dullness, disorientation, nystagmus, loss of tendon reflexes, a rise in cerebrospinal fluid protein and all other features of emetine toxicity. The shock that occurred following liver aspiration in Case 1 was in our opinion due to what we would like to call 'peritoneal shock', not unsimilar to 'pleural shock' that may occur following pleural aspiration. This type of reaction has been known to occur following liver biopsies (Shiff-1962). Another possibility is that the shock might be due to toxic myocarditis, though there was not much electrocardiographic evidence to support this conclusion.

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