
Chronic inorganic mercury poisoning treated with N-acetyl-D-penicillamine

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Gledhill, R. F., and Hopkins, A. P. (1972). *Brit. J. industr. Med.*, **29**, 225-228. **Chronic inorganic mercury poisoning treated with N-acetyl-D-penicillamine.** The case history is presented of a man intoxicated by mercury during his employment as a filler of thermometers. The mean daily urinary excretion of mercury was 661 μg for five estimations before treatment. The mean excretion was 875 μg for the first 10 days after beginning N-acetyl-D-penicillamine, 600 mg/day. This difference is not significant ($p < 0.1$). The literature of the treatment of mercury poisoning is briefly reviewed.

The use of penicillamine in the treatment of mercury poisoning was first suggested by Walshe (1956). Four patients treated in this way have been reported by Pagnotto, Brugsch, and Elkins (1960), Smith and Miller (1961), and Parameshvara (1967). The present case report demonstrates that a traditional occupational hazard still exists, and the circumstances provided a further opportunity to test the effect of N-acetyl-D-penicillamine in this disorder.

Case report

B.C. (NHQS A41264) aged 33, a 'white' South African, had lived in Great Britain for the last 16 years. During this time he had worked exclusively with metals, handling and processing brass, copper, and steel. For 18 months before admission to hospital his job entailed manufacturing mercury rotary thermometers.

Twelve months after starting this employment he began to feel tired and listless, particularly towards the end of the week. He felt much better at weekends. He then began to make minor mistakes at work, forgot where he put things, and became aware of an acid taste in the mouth, intense thirst, and excessive salivation.

His workmates remarked on his increasing pigmentation, and that his 'nerves had become bad'. Two months after the onset of these symptoms, tremor of the fingers began and insidiously spread to the arms, legs, and

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finally to the trunk and head. His speech became tremulous, his writing deteriorated, and his gait became unsteady. One month later (January 1968) he became increasingly nervous and timid of others, and was having so much difficulty doing his job that he left his employment. After a further month he was seen at the National Hospital for Nervous Diseases and was subsequently admitted.

On examination he was noted to be generally pigmented, nervous, timid, and excitable. His tongue was red and swollen, and there was a severe gingivitis with dark blue discoloration on the inside of the lips (Fig. 1). His speech was tremulous and he had a marked coarse, irregular tremor of the head, trunk, and limbs at a frequency of about 6 cycles per second. The tremor was worse on voluntary movement. His gait was ataxic and his writing severely affected (Fig. 2, top). There were no other abnormal findings on neurological, ophthalmological or general examination.

Investigations

The clinical diagnosis of inorganic mercury poisoning was supported by a blood mercury of 48.1 $\mu\text{g}/100\text{ ml}$ (normal 6-7 $\mu\text{g}/100\text{ ml}$). The first 24-hour urinary excretion of mercury was 1015 μg . Psychometry estimated the verbal and performance I.Q. at 85, levels considered to be in keeping with his previous attainments. The electroencephalogram showed a slight diffuse excess of fast activity. Tests of renal function and of copper metabolism were normal.

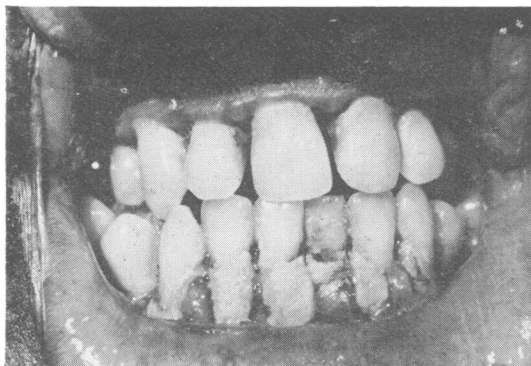


FIG. 1. Teeth and gums on admission to hospital.

MAY-22-68
 MR BERNARD Bovele
 19 MIDDLE Road

29 Oct 68 MR Bernard Bovele
 19 Middle Road

FIG. 2. Top: Writing on admission to hospital.
 Bottom: Writing five months later.

Treatment and progress

A marked decrease in both tremor and nervousness was noted during the first two weeks in the ward. A course of N-acetyl-D-penicillamine was then begun at a dose of 150 mg four times daily. The effect on the urinary excretion of mercury is illustrated in Figure 3. After three months of treatment the tremor had improved considerably. Shaving was easier and walking steadier. The improvement in his writing is shown in the lower

part of Figure 2. His nervousness and irritability persisted and were still present 16 months after withdrawal from exposure. At that time he remained unemployed, despite only a slight degree of tremor.

One of us (A.P.H.) visited the factory where this man worked. His occupation consisted of inserting the soft metal inlet of a rotary thermometer into a sleeve which was then tightened. Mercury at a pressure of 450-600 lb per square inch was then forced into the thermometer. If the sleeves were not adequately tightened, mercury

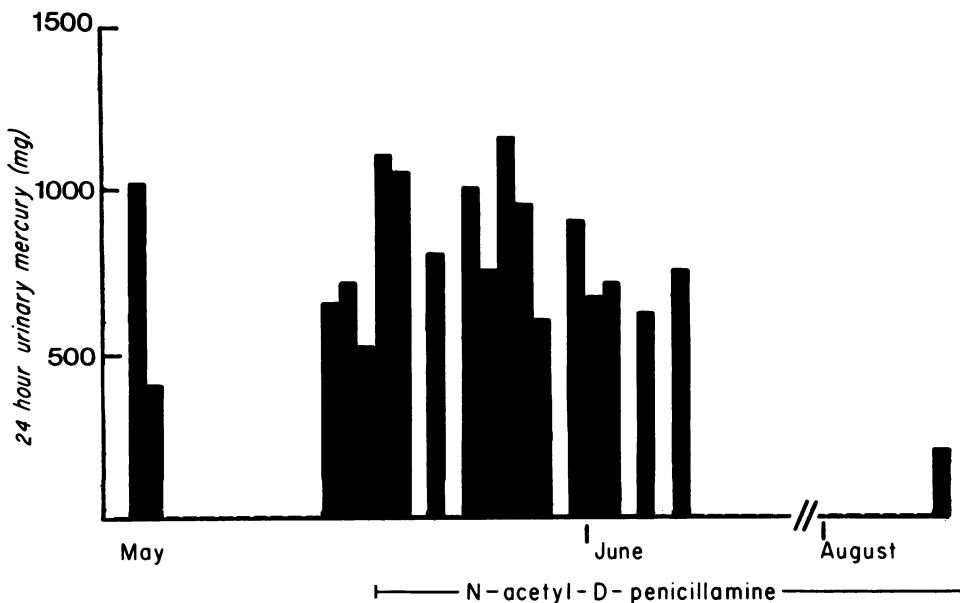


FIG. 3. Urinary excretion of mercury before and during treatment with N-acetyl-D-penicillamine, 600 mg per day.

could spray a considerable distance, and droplets of spilled mercury were found on and around his work bench, and in cracks in the floor nearly 20 feet distant.

The patient was naturally shy and became more so as intoxication progressed so that he preferred to eat his sandwiches at his workbench rather than in the canteen. The only other man doing a similar job had been there 17 years. When examined briefly he showed no signs or symptoms of intoxication apart from a slight tremor of the hands.

Diagnosis

It is generally accepted that urinary concentrations of mercury in excess of 100 μg per litre are abnormal, and toxic symptoms usually accompany levels in excess of 300 μg per litre (Noe, 1960).

In the presence of a constant exposure level, different levels of mercury can be excreted by the same person on different days (Battigelli, 1960); and Noe (1960) advises that at least six estimations should be performed. This point was substantiated in our patient, in whom urinary levels fluctuated almost threefold in the first five estimations (406 to 1 015 μg) but were all nevertheless in excess of 300 μg per litre. However, difficulties can arise from the fact that, for a given level of exposure, different people excrete different amounts of mercury (Battigelli, 1960; Parameshvara, 1967); and, furthermore, for a given vapour concentration women tend to excrete greater amounts than men (Noe, 1960).

Treatment

Prophylactic measures constitute the most important forms of treatment, which include an awareness of the potential hazards and symptoms of mercury poisoning and the provision of adequate protection at work (Cumings, 1959; Noe, 1960). Once a case of poisoning is diagnosed, the patient should immediately be removed from his environment. In many instances, and for reasons mentioned above, this will already have occurred (Cumings, 1959).

As far as specific measures are concerned, there appears to be little doubt of the efficacy of the chelating agent and -SH group inhibitor, dimercaprol, in the treatment of acute intoxication (Battigelli, 1960; Pagnotto *et al.*, 1960). The value of this drug and of sodium calcium edetate in improving the clinical state and increasing the urinary excretion of mercury, in chronic poisoning, is more doubtful (Woodcock, 1958; Battigelli, 1960; Pagnotto *et al.*, 1960; Kazantzis, 1965).

A more recent therapeutic development has been the use of penicillamine following the suggestion by Walshe (1956) that this drug might be useful in mercury poisoning. Aposhian and Aposhian (1959) showed that N-acetyl-D,L-penicillamine could protect rats against the acute effects of mercuric chloride. Pagnotto *et al.* (1960) reported the clinical use of this drug in two patients with chronic mercury poisoning. In their first patient, the average urinary excretion of mercury increased from 1 200 μg to 2 120 μg per day when given 1g N-acetyl-D,L-penicillamine per day. These figures represent the mean of an unstated number of observations. The urinary excretion of their second patient, given 3g per day, increased from 610 μg to 800 μg per day averaged over three days. Single

patients treated with N-acetyl-D,L-penicillamine have also been reported by Smith and Miller (1961) and Parameshvara (1967). Smith and Miller noticed an increase in urinary mercury from 1 369 μg per day to 1 828 μg and 1 639 μg on the second and sixth days of treatment in a dose of 250 mg four times daily. In their case the treatment was continued for one month with both subjective and objective improvement in their patient's clinical status. It is not clear if these figures represent a significantly increased output of mercury, as the day to day variation before treatment is not reported. Parameshvara (1967) also does not report the daily figures for urinary excretion, but from his Fig. 2 it appears that N-acetyl-D,L-penicillamine in a dose of 250 mg four times daily approximately doubled the urinary output of mercury with accompanying improvement of his patient's tremor.

We thought we would use this further opportunity to observe the effects of N-acetyl-D-penicillamine at a dosage of 150 mg four times daily, realizing that there was no clear indication of either the optimal dosage or duration of treatment.

The mean daily urinary output of mercury in our patient was 661 μg for five estimations before beginning N-acetyl-D-penicillamine and was 875 μg for the first 10 days after beginning this drug. The difference is not significant ($p < 0.1$). In view of the little further clinical improvement, the falling levels of urinary mercury, and the known toxic effects of N-acetyl-D-penicillamine, it was discontinued after 80 days.

Discussion

It is clear that, on the basis of the limited number of patients so far reported, treatment with N-acetyl-D- or N-acetyl-D,L-penicillamine cannot be shown to alter significantly the naturally occurring variation in urinary excretion of mercury and, moreover, it is extremely difficult to evaluate any clinical benefits in view of the natural tendency to improvement on removal from exposure. Indeed this simple manoeuvre itself has been seen to result in some patients making a complete clinical recovery (Kazantzis, 1965). Dimercaprol has been shown experimentally to have little effect on elimination of intracellular mercury (Battigelli, 1960), and a similar situation might well prevail in the case of penicillamine. Indeed the value of this form of therapy may be as a means of combining with, inactivating, and assisting elimination of extracellular mercury. In view of the rarity of chronic mercury poisoning, and the ethics of withholding possible effective therapy, the real value of such agents will probably be resolved only on the basis of controlled animal experiments.

There is very little information regarding the long-term prognosis of both the tremor and erethism, though this would appear to vary with the severity at the time of diagnosis. From a series of 135 patients, Baldi, Vigliani, and Zurlo (1953) reported that only 15% of patients with marked symptoms of intoxication showed any improvement when

followed up from four to five years. In view of this fact, and the severe degree of intoxication seen in our patient, we feel that the ultimate prognosis should remain guarded.

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Postscript

Since the above paper was submitted for publication, one further case of mercury poisoning treated with N-acetyl-D,L-penicillamine has been reported (Kark, R. A. P., Poskanzer, D. C., Bullock, J. D., and Boylen, G. (1971). Mercury poisoning and its treatment with N-acetyl-D,L-penicillamine. *New Engl. J. Med.*, **285**, 10-16).

In this study, the patient was treated with 1 000 mg per day for three courses each of 10 days, followed by one course of 2 000 mg per day. Clinical improvement coincided with the administration of the first of these courses. Faecal mercury excretion was not significantly increased. The authors' Fig. 4 shows that the daily urinary excretion of mercury before the administration of the drug was about 1 430, 1 680, and 2 080 μ g. During the first 10-day course of penicillamine the urinary excretion exceeded 2 000 μ g on only two days and was less than 1 600 μ g on five days. The effect of the second course was equally modest. Their Fig. 4 also shows that the third and fourth courses had no effect on the urinary excretion of mercury.

These results do not suggest that the urinary excretion of mercury is increased over a long period of time by N-acetyl-D,L-penicillamine, though the drug may be of value in hastening the excretion of an easily mobilizable extracellular pool.

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