of Eaton agent and from several recent Dutch isolates of the organism from patients with atypical pneumonia (Marmion and Hers, 1963).

Summary

Sixteen sporadic cases in the general population and six cases in a small school outbreak of infections due to Eaton's primary atypical pneumonia agent are described with two characteristic clinical histories. The clinical features of these cases resemble those described in similar investigations in the United States. Thus patients had pneumonia, an acute febrile bronchitis or bronchiolitis, or fever of uncertain origin.

Diagnosis was made by serological methods, serum antibody being detected principally by immunofluorescent methods, using the indirect staining technique. The development of a complement-fixation test for the laboratory diagnosis of infections with Eaton's agent is described, the results of which appear to be in reasonable agreement with those obtained by immunofluorescent methods.

The antigenic similarity of agents causing similar illnesses in the United States, Holland, and England is shown, and evidence is presented that infection has been present in this country for at least twelve years.

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TREATMENT OF LEAD-POISONING WITH ORAL PENICILLAMINE

BY

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Lead-poisoning is still a disease of importance in industry and an occasional hazard in childhood. Sodium calciumedetate (calcium disodium ethylenediaminetetraacetic acid; $CaNa_2E.D.T.A.$) was first used 10 years ago for the treatment of lead-poisoning; when given intravenously it induces a marked urinary excretion of lead. There are obvious disadvantages in the use of a parenteral preparation, especially in children, and renal damage has been reported after excessive dosage (Dudley *et al.*, 1955; Foreman *et al.*, 1956). An effective oral non-toxic lead chelator would be of considerable value in the treatment and possibly in the prophylaxis (Seignette *et al.*, 1959) of lead-poisoning. The success of penicillamine ($\beta\beta$-dimethylcysteine) as a copper chelator in Wilson's disease (Walshe, 1956) suggested that this drug might be used in lead-poisoning.

Boulding and Baker (1957) reported an increased urinary excretion of lead in two patients with lead-poisoning after oral penicillamine. Ohlsson (1962) reported the intravenous use of penicillamine in five patients with lead-poisoning. Weight for weight penicillamine given intravenously appeared to effect an excretion of urinary lead similar to intravenous sodium calciumedetate. In three cases penicillamine, when given orally, caused a moderate increase in urinary lead excretion. The present studies were carried out on nine patients with chronic or subacute lead intoxication to determine the effect of oral D-penicillamine, in varying dosage, on the excretion of lead, urinary coproporphyrin, and δ-aminolaevulic acid, as well as on the clinical manifestations of the disease. The urinary excretion of coproporphyrin (Chisholm and Harrison, 1956) and of δ-aminolaevulic acid (Haeger-Aronsen, 1960) provides sensitive biochemical indices of "metabolically active" and presumably toxic lead in tissues.

A further study was carried out for periods of 9 to 16 weeks on four oxyacetylene metal-burners working

in a ship-breaking yard and one worker in an accumulator factory, each showing clinical and biochemical evidence of lead intoxication, to determine the effect of long-term oral penicillamine therapy.

Methods

Lead Determinations.—Lead was measured in urine, blood, and faeces by the dithizone method (Gonzales *et al.*, 1954). A wet digest was obtained from 30–100 ml. of urine, 30–40 g. of homogenized faeces, or 10–25 ml. of blood. The absorption maximum of lead dithizonate in chloroform was determined on the Hilger "Uvispek" absorptiometer at 516 mμ. The accuracy of the method of determination of blood lead was tested by the measurement of lead in six aliquots of a sample of blood from a single patient. The results were 63.4, 64.5, 63.9, 65.4, 63.0, and 64.7 μg./100 ml., mean 64.1 μg., standard deviation ±0.95; percentage coefficient of variance 1.48. On another occasion four aliquots of a sample of blood were tested for lead. The results were 72.0, 74.5, 73.3, and 74.1 μg./100 ml., mean 73.5 μg., standard deviation ±1.1; percentage coefficient of variance 1.50. These small deviations demonstrate the accuracy of the method.

Urinary Coproporphyrin.—This was determined by the method of Rimington (1961).

Urinary δ-Aminolaevulic Acid.—This was determined by the method of Mauzerall and Granick (1956). Blood and urine lead determinations were carried out in 18 and 20 normal subjects respectively (Table I). The urinary coproporphyrin and δ-aminolaevulic acid were also determined in 20 normal subjects (Table I). The "normal" subjects in these studies comprised medical and scientific staff, medical students, and patients in orthopaedic wards recovering from uninfected traumatic injuries. Haematological values were obtained by standard methods (Dacie, 1956). Haemoglobin was determined by the alkaline haematin method.

TABLE I.—*Normal Values of Blood Lead, and Urinary Lead, Coproporphyrin, and δ-Aminolaevulic Acid*

	No. of Subjects	Mean	S.D.	Range
Blood lead	18	22·9 μg./100 ml.	8·2	11·7–49·1
Urinary ,, ...	20	35·2 μg./day 23·3 μg./litre	19·9 12·5	5·4–84·8 7·0–65·2
Urinary coproporphyrin	20	148·3 μg./day 93·2 μg./litre	79·2 43·9	24·1–383·1 47·3–196·4
Urinary δ-aminolaevulic acid	20	2·99 mg./day 0·20 mg./100 ml.	0·44 0·08	0·38–5·38 0·02–0·35

Clinical Cases

Cases 1–7 are oxyacetylene metal-burners who have worked in a ship-breaking yard from 8 to 45 years. All of these subjects had been found to have increased coproporphyrin in their urine on routine testing.

Case 1.—Aged 42. Admitted to hospital two years previously with acute abdominal colic. He still had intermittent abdominal pain. Hb 14 g./100 ml., but punctate basophilia was present in the peripheral blood and bone-marrow.

Case 2.—Aged 55. Admitted to hospital in 1946, 1948, and 1957 for treatment of lead-poisoning. On the present admission he complained of intermittent abdominal pain. Hb 13 g./100 ml.

Case 3.—Aged 42. In the past year he had complained of weakness of both hands and wrists. Hb 12.5 g./100 ml.

Case 4.—Aged 52. Admitted to hospital in 1953, 1958, and 1960 for treatment of lead-poisoning. He had no symptoms on his present admission, but his haemoglobin level was 10 g./100 ml. and the reticulocyte count 4%.

Case 5.—Aged 60. No symptoms on admission. Hb 13 g./100 ml.

Case 6.—Aged 50. Admitted in 1948, 1952, 1953, and 1960 for treatment of lead-poisoning. On his present admission he complained of intermittent epigastric and lower abdominal pain. Hb 15 g./100 ml.

Case 7.—Aged 60. Admitted on two previous occasions (1948. 1954) for treatment of lead-poisoning. Hb 12 g./100 ml. He had no symptoms on admission.

Case 8.—A 48-year-old foreman of an accumulator factory had been at this employment for 15 years. One year previously he had been treated with sodium calciumedetate because of right wrist and finger drop. He was readmitted on January 24, 1962, because of a recurrence of this paralysis. He felt reasonably well, though his haemoglobin level was 10 g./100 ml. In 1952 he had a skin rash after a penicillin injection.

Case 9.—A man aged 38 had been making lead ingots for only six weeks. He presented with abdominal and lumbar pain, vomiting, and constipation. On examination he had a "blue line" at the gum-tooth margin. Hb 11 g./100 ml. Reticulocyte count 3%. Punctate basophilia was noted in bone-marrow smears but not in his peripheral blood.

Scheme of Therapeutic Investigation

Short-term Trial of Penicillamine

This was carried out in hospital in a metabolic ward. All patients had a pretreatment period of 7 to 12 days for the measurement of the daily output of urinary and/or faecal lead, urinary coproporphyrin, and δ-aminolaevulic acid as well as haematological and blood-lead estimations. Cases 1 and 2 had seven-day courses of penicillamine of 900 mg./day. Case 9 had two separate courses of penicillamine of 900 mg./day, each course lasting seven days. Cases 3 and 4 had 900 mg. of penicillamine daily for four days followed by 1,500 mg. daily for four days. Cases 5, 6, and 7 had 1,500 mg. daily for seven days (Table II). In view of the previous history of penicillin sensitivity in Case 8, penicillamine was given in gradually ascending dosage, from 150 to 1,200 mg./day (Fig. 1). The penicillamine was given in divided dosage thrice daily with a minimum single dose of 150 mg.

TABLE II.—*Short-term Trial. Summary of Mean Urinary Lead, Coproporphyrin, and δ-Aminolaevulic Acid in Cases 1–9 Before and During Treatment*

Case	Penicillamine (mg. day)		Mean Lead (μg. day)		Mean Coproporphyrin (μg. day)		Mean δ-Aminolaevulic Acid (mg./day)	
	Dose	Duration	Before	During	Before	During	Before	During
1	900	7 days	398	939	975	377	40·0	10·8
2	900	7 ,,	218	855	588	211	25·5	17·1
3	900	4 ,,	192	796	1,269	983	31·5	25·8
	1,500	4 ,,		1,136		133		12·8
4	900	4 ,,	141	738	786	606	28·8	19·7
	1,500	4 ,,		946		198		12·2
5	1,500	7 ,,	202	1,033	722	224	22·6	11·9
6	1,500	7 ,,	149	521	612	159	23·2	5·1
7	1,500	7 ,,	200	746	499	158	12·9	6·0
8	150–1,200	23 ,,	242	756	878	276	43·8	11·7
9	900	7 ,,	—	—	1,502	851	64·9	36·4
	900	7 ,,	876	1,261	632	400	29·5	16·5

Long-term Trial of Penicillamine

A long-term trial of penicillamine lasting nine weeks was carried out on Cases 1, 2, 3, and 4 while they were at work in the ship-breaking yard. This long-term trial was begun three months after the end of the short-term

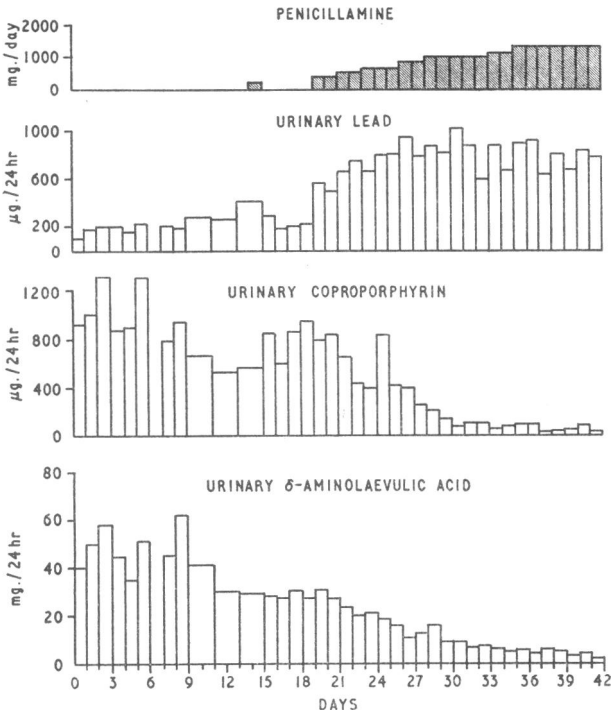

FIG. 1.—Short-term trial. Excretion of urinary lead, coproporphyrin, and δ-aminolaevulic acid in Case 8 before and after treatment with increasing doses of oral penicillamine.

trial in Cases 1 and 2 and 10 days after the end of the short-term trial in Cases 3 and 4. Before treatment was begun all of these men were anaemic, with haemoglobin levels of 11.4, 10.2, 10.8, and 8.9 g./100 ml. respectively. In addition all had an increased excretion of lead in the urine. Cases 1 and 2 had intermittent abdominal pain. Case 3 complained of weakness of his hands and wrists. Case 4 had no symptoms, although he was in fact the most anaemic of the group. Penicillamine was given in a dosage of 300 mg. daily for three weeks and then 600 mg. daily for the remaining six weeks. The capsules, each containing 150 mg. of penicillamine, were presented each morning to the men by a medical orderly and taken in divided dosage twice daily. On Friday sufficient capsules were given to suffice over the week-end.

Case 8 remained anaemic after his initial treatment. He had developed paresis of his right hand on two occasions within one year and yet was determined to return to his work as a foreman in an accumulator factory. For these reasons he was given a course of penicillamine, 600 mg./day for a period of four months while he was at work.

In Cases 1, 2, 3, and 4, urine specimens were collected twice weekly and tested for lead, coproporphyrin, and δ-aminolaevulic acid. In Case 8 urine specimens were tested every four weeks. In all five cases haemoglobin levels and reticulocytes were assessed every four weeks.

Throughout these trials the subjects continued to use a protective mask in the same way as they had previously done.

Results

The levels of blood and urinary lead established in normal subjects (Table I) are in agreement with those quoted by Goodman and Gillman (1955). The levels of urinary coproporphyrin and δ-aminolaevulic acid in normal subjects (Table I) are also in agreement with those quoted by Rimington (1961) and Haeger-Aronsen (1960) respectively. In every patient, prior to treatment with penicillamine, the values of blood and urinary lead and urinary coproporphyrin and δ-aminolaevulic acid were greatly in excess of these normal levels. On the other hand, the faecal lead values in Cases 3, 4, 5, 6, and 7 prior to treatment fell within the normal range (Goodman and Gilman, 1955). This is explained by the facts that faecal lead excretion is not a satisfactory index of lead intoxication, where the exposure is mainly due to the vapours of lead, and that the faecal lead values approach normal within a few days after the termination of such exposure.

Short-term Trial

Clinical Course.—There was clinical improvement during treatment in each of the patients who had symptoms. In Cases 1, 2, and 6 there was an absence of abdominal pain. Case 3 claimed that there was a return of strength to his hands. In Case 8 there was improvement in muscle power after two weeks of treatment. Complete return of power occurred after a longer course of penicillamine. In Case 9 there was a rapid cessation of abdominal pain, vomiting, and constipation within three days of the beginning of penicillamine treatment.

TABLE III.—*Short-term Trial. Faecal Excretion of Lead in Cases 3, 4, 5, 6, and 7 Before and During Treatment with Penicillamine*

Case No.	Before Treatment		During Treatment	
	No. of Days Collected	Mean Output (µg./day)	No. of Days Collected	Mean Output (µg./day)
3	3	59·0	8	65·6
4	6	102·3	8	77·7
5	6	152·5	7	92·6
6	5	148·5	2	253·5
7	4	171·2	7	145·4

Urine.—The administration of penicillamine orally in as low a dose as 300 mg./day caused an immediate rise in the urinary lead excretion (Fig. 1). With increasing dosage more urinary lead was excreted. In Case 8 it appeared that a maximum level of excretion was reached at about 1,000 mg. of penicillamine a day. When 900 mg. of the drug was given daily as an initial dose there was a slight decline in urinary lead excretion several days after the early high output, but this increased when the dose was raised to 1,500 mg./day (Fig. 2). The urinary coproporphyrin and δ-aminolaevulic acid fell *pari passu*

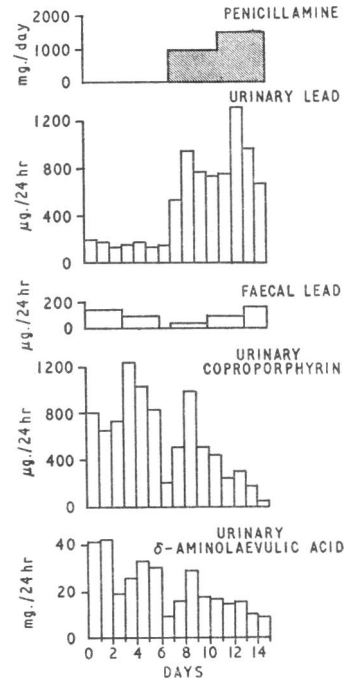

FIG. 2.—Short-term trial. Excretion of urinary lead, coproporphyrin, and δ-aminolaevulic acid in Case 4 before and during the treatment with oral penicillamine, 900 mg. daily for four days and 1,500 mg. daily for four days.

with the lead excretion, reaching normal or nearly normal levels after seven days of treatment. It is notable in Case 8 that excessive lead was excreted in the urine even when the levels of urinary coproporphyrin and δ-aminolaevulic acid had returned to normal.

Faeces.—There was no significant increase in faecal lead after the administration of penicillamine in Cases 3, 4, 5, 6, and 7 (Table III ; Fig. 2).

Blood.—There was a fall in the blood lead of Cases 5, 6, 7, and 8, comparing the levels before and during penicillamine treatment (Table IV).

TABLE IV.—*Short-term Trial. Mean Blood Lead in Cases 5, 6, 7, and 8 Before and During Treatment with Penicillamine*

Case No.	Before Treatment		During Treatment	
	No. of Samples	Mean Blood Lead (μg./100 ml.)	No. of Samples	Mean Blood Lead (μg./100 ml.)
5	2	82·7	5	77·0
6	5	67·6	8	57·7
7	5	83·4	8	76·0
8	3	146·3	3	89·9

Long-term Trial

In Cases 1, 2, 3, and 4 there was no significant response to 300 mg. of penicillamine daily. It must be repeated that this trial was carried out while the subjects were at work and exposed to further lead intoxication. After three weeks the dose was raised to 600 mg./day, and this was continued for six weeks. There was a marked rise in urinary lead excretion and a gradual fall to normal levels of the urinary coproporphyrin and δ-aminolaevulic acid. Within four weeks of discontinuation of penicillamine there was a gradual rise in the urinary excretion of coproporphyrin and δ-aminolaevulic acid (Fig. 3). After treatment with the penicillamine the haemoglobin levels in Cases 1, 2, 3, and 4 rose to 14.5, 13.3, 13.2, and 11.8 g./100 ml. as compared with 11.4, 10.2, 10.8, and 8.9 g./100 ml. respectively before treatment (Fig. 4). Cases 1 and 2

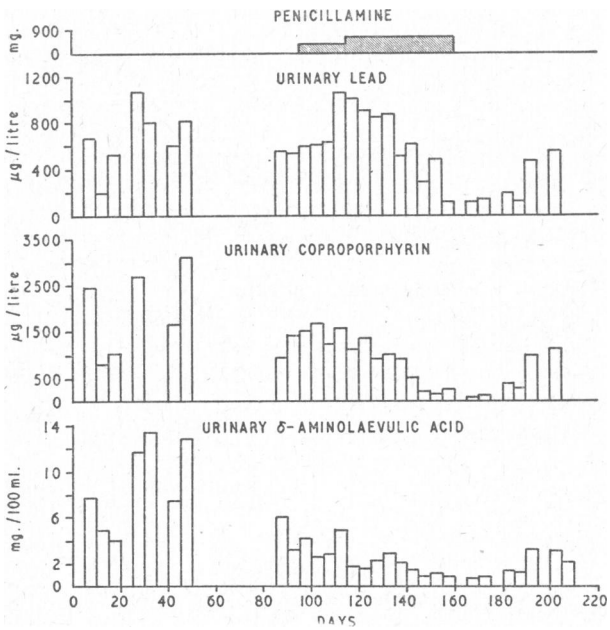

FIG. 3.—Long-term trial. Excretion of urinary lead, coproporphyrin, and δ-aminolaevulic acid in Case 1 before, during, and after treatment with oral penicillamine 300 mg. daily for three weeks and 600 mg. daily for six weeks.

claimed that their abdominal pain had ceased, and Case 3 stated that his wrists and hands had regained their former strength. Throughout these months of treatment with penicillamine none of these four subjects had any untoward effect of drug therapy ; in particular, the urine was free of protein at the end of the treatment period.

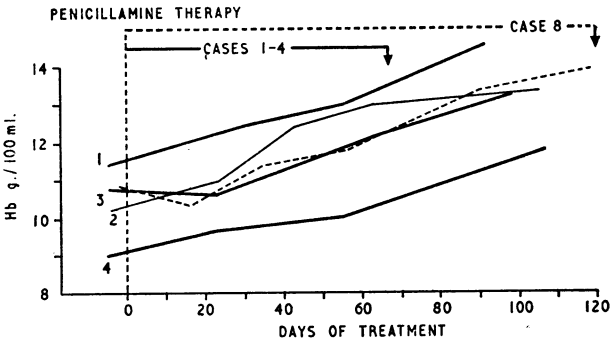

FIG. 4.—Haemoglobin levels in Cases 1, 2, 3, 4, and 8 before, during, and after long-term trials of penicillamine.

Case 8, after the initial short-term treatment, had only slight residual weakness of his right hand, but he was still anaemic (Hb 10.4 g./100 ml.). After four months of treatment with 600 mg. of penicillamine a day he had normal power in his hand and his haemoglobin level had risen to 13.8 g./100 ml. Throughout this period a persistently high excretion of lead was maintained (mean 387 μg./litre), although the levels of urinary coproporphyrin and δ-aminolaevulic acid had again increased slightly, with a mean excretion of 369 μg./l. and 1.3 mg./100 ml. respectively. At the end of the four months' treatment this patient, though without symptoms, was found to have protein in his urine, 0.4 g./100 ml. ; his blood urea was 73 mg./100 ml. ; serum cholesterol 450 mg./100 ml. ; serum albumin 3.5 g./100 ml. ; serum globulin 2.5 g./100 ml. ; maximum specific gravity of urine 1018. After a few days his urinary protein excretion fell to 0.1 g./100 ml. and within two weeks his blood urea had fallen to 53 mg./100 ml. and the serum cholesterol to 390 mg./100 ml. He continued to excrete about 0.1% protein in his urine two months after the cessation of penicillamine. He has maintained the power of his right hand, and his haemoglobin level has remained normal. His exposure to lead has been discontinued.

Discussion

These studies have shown that penicillamine, given orally, causes a prompt and marked excretion of urinary lead in patients with lead intoxication. A dose of 300 mg./day is sufficient to effect a significant lead excretion, provided the patient is no longer exposed to further lead intoxication, but marked excretion was induced by daily doses of 900 to 1,500 mg. The increased lead excretion was not effected through the faecal route. There was a significant fall in the blood-lead levels with treatment and also a marked fall in the urinary levels of coproporphyrin and of δ-aminolaevulic acid. The urinary excretions of these substances are thought to be sensitive indices of metabolically active lead (Haeger-Aronsen, 1960). For this reason it is of considerable interest that the continued administration of penicillamine in Case 8 yielded a marked excretion of lead at a time when the urinary levels of coproporphyrin and

δ-aminolaevulic acid were normal. This suggests that penicillamine can mobilize stored lead for excretion.

There was a substantial elevation of the haemoglobin levels in Cases 1, 2, 3, 4, and 8 after long-term treatment from two to four months, even though these patients were still engaged in a lead-exposed occupation. The anaemia of lead-poisoning is due to two main factors. Firstly, an inhibition of haem synthesis, at several stages in the formation of haem and especially in the final phase of iron incorporation into the haem or haemoglobin molecules (Goldberg *et al.*, 1956). There is in addition a haemolytic factor (Wintrobe, 1961); a significant reduction in the erythrocyte life-span has been demonstrated, returning to normal after treatment (Goldberg, 1960). Both of these effects are probably caused by a direct effect of lead on the biosynthesis of haemoglobin in the marrow and on the erythrocyte membrane respectively, and it is therefore not surprising that the simple removal of body lead should prompt an increase in the haemoglobin level. It is notable, however, that the relief of the anaemia was a gradual process over a period of two to four months. There was, in addition, a complete return of motor power to the right hand of Case 8 after a prolonged course of treatment, as well as a rapid cessation of abdominal pain, vomiting, and constipation in Case 9.

The pathogenesis of the neurological and abdominal symptoms in lead-poisoning is unknown. It is possible that the mechanism of production of these symptoms has a common biochemical pathway with that of acute intermittent porphyria (Goldberg *et al.*, 1962). In both diseases there is a marked increase in the excretion of δ-aminolaevulic acid. In lead-poisoning these symptoms are relieved by the removal of lead from the body by chelators of lead, such as sodium calciumedetate or penicillamine. Peters *et al.* (1957) have suggested that in their experience the symptoms of acute intermittent porphyria may also be relieved by chelating agents. There is, however, insufficient confirmatory evidence on this point.

The studies on the long-term administration of penicillamine are of practical importance to the prophylaxis of lead-poisoning. The best prophylaxis is, of course, prevention of entrance of the metal into the body by the established methods of industrial hygiene. Nevertheless, it must be accepted that some lead-workers find it impossible to wear a mask constantly; nor is the general standard of industrial hygienic equipment of such efficiency as to allow us to ignore the drug prophylaxis of lead intoxication. Penicillamine has now been used in the long-term treatment of Wilson's disease for six years; Walshe (1962), whose experience in this field is extensive, has found this drug to be particularly non-toxic. There was no evidence, in his experience, of renal damage with the D isomer of penicillamine, which is that used in this country. I. H. Scheinberg (personal communication, 1962), who has also had considerable experience in the treatment of Wilson's disease with penicillamine, has not found proteinuria in any of his patients which could be attributed to the drug. Fellers and Shahidi (1959) noted the onset of frank nephrotic syndrome in a male patient of 16 years who had been given 2 g. of penicillamine a day for nine months. The clinical manifestations, including the proteinuria, disappeared after the withdrawal of the drug. Our experience of Case 8 has shown that, in lead-poisoning, penicillamine given over a period of four months can be nephrotoxic.

In the present studies it has been shown that 600 mg. of penicillamine a day orally is an effective dose. When given over a period of two to four months to lead-workers it has induced a marked lead excretion, a return to normal levels of urinary coproporphyrin and δ-aminolaevulic acid, and a rise of the haemoglobin level. Case 8 had a history of skin reaction following a penicillin injection 10 years previously. With a gradually increasing dosage of penicillamine, no skin reaction occurred, but at the end of this period he developed protein in his urine, with other evidence of renal damage. This evidence must, at present, contraindicate the possible use of penicillamine on a long-term basis in lead-poisoning; nevertheless, penicillamine is a useful drug in short-term courses of not more than four weeks. Subjects showing early clinical evidence of lead intoxication—for example, with mild anaemia or occasional gastro-intestinal symptoms—might receive oral penicillamine while at home or after being transferred to work not involving the risk of exposure to lead. The urine should be tested for protein at least once weekly. Any worker with a more severe degree of lead-poisoning should be treated in hospital. It should again be emphasized that the established protective measures form the best prophylaxis. In addition to these industrial indications for penicillamine the drug has obvious advantages over a parenteral lead chelator in the treatment of lead intoxication in children.

Summary

D-Penicillamine, given orally in doses of 600 to 1,500 mg./day, induced a marked excretion of urinary lead in nine patients with subacute or chronic lead intoxication. There was a concurrent fall in the urinary coproporphyrin and δ-aminolaevulic acid levels and in the level of lead in the blood. The route of excretion was entirely by way of the urine.

Five lead-exposed subjects, while working in a ship-breaking yard or in an accumulator factory, were given oral penicillamine for periods of from two to four months. There was a persistent excretion of urinary lead, a fall in the urinary coproporphyrin and δ-aminolaevulic acid to normal levels, a rise in the haemoglobin levels, and a relief of neurological or abdominal symptoms. The effective dose of penicillamine for this trial was 600 mg./day. One patient developed proteinuria after four months of penicillamine treatment. For this reason routine testing for proteinuria should be carried out in patients during treatment; the duration of a single course of penicillamine should not exceed four weeks; patients during treatment should be removed from a lead-exposed environment.

It is suggested that, with these stipulations, oral penicillamine is a useful drug in the treatment of lead-poisoning and may be of value in the treatment of lead-poisoning in children.

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Medical Memoranda

Two Cases of Chloroquine Psychosis

Chloroquine and allied substances have been used extensively in a variety of diseases on account of their efficacy and their relative freedom from serious side-effects. Glickman *et al.* (1959), in their review of antimalarial agents, stated that chloroquine, hydroxychloroquine, and amodiaquine had about the same toxicity. Except for the occurrence of nausea, vomiting, diarrhoea, anorexia, weakness, and occasional cycloplegia, they noted little else in the way of toxic reactions. Recent publications mention certain dangerous complications of chloroquine, such as corneal opacities and retinopathy (Hobbs *et al.*, 1961; Ormrod, 1962), and fatal pancytopenia (Glick, 1957).

The purpose of this communication is to draw attention to the occurrence of toxic psychosis due to this drug in two patients, a complication not previously encountered.

Case Reports

Case 1.—A Pakistani Muslim aged 34 was seen by his family physician for fever and right hypochondrial pain associated with an enlarged and tender liver. He had no jaundice, and a routine blood count showed a polymorphonuclear leucocytosis. He had suffered on and off from amoebic dysentery, but otherwise had enjoyed excellent mental and physical health. He was diagnosed as suffering from amoebic hepatitis and given chloroquine sulphate, 250 mg. q.i.d., to which he responded, with amelioration of fever and pain. On the sixth day, however, he complained of lightheadedness, and on the seventh day was completely confused and disorientated and suffered from ideas of persecution. When seen by me the same day he was confused, irrational, and agitated, and there were occasional outbursts of violence. His irrational acts included assaulting his wife and father and walking nude in the streets. He subsequently became withdrawn and mentally inaccessible. A diagnosis of toxic psychosis was made and chloroquine was stopped. He was treated with chlorpromazine and intravenous fluids, and within two days he became lucid and rational. It will be observed that this patient developed toxic psychosis after having taken 6 g. of chloroquine sulphate containing 4.8 g. of the base, and also that there was a dramatic recovery after the drug was withdrawn.

Case 2.—A 24-year-old male Pakistani was seen for amoebic hepatitis and given chloroquine sulphate, 250 mg. q.i.d. He had previously been in excellent mental and physical health. All the liver-function tests were within normal limits. On the sixth day of treatment he was observed to be moody and agitated, and reacted violently to minor emotional experiences. He had complained of severe headache, insomnia, and restlessness since the previous evening. By the following day he had developed frank psychosis. He was confused and disorientated, and had delusions of persecution with an occasional exhibition of aggressive behaviour. The drug was stopped at once and he was treated with chlorpromazine. Within three days his mental status had reverted to normal. After recovery he apologized to persons around him for his behaviour and blamed the drug for whatever had happened.

Comment

These two patients developed toxic psychosis during chloroquine therapy and responded dramatically when the drug was withdrawn. The absence of any past history of mental ailment in both patients and also the lack of any clinical features of hepatocellular failure make any other possibility very unlikely. Although textbooks mention slight mental confusion as a rare complication of chloroquine therapy (Dunlop *et al.*, 1961), a frank psychosis has not been described. The doses in our cases were small compared with the much larger doses employed in dermatology and rheumatic disorders. Even Scull (1962) in his recent paper does not mention psychosis as a complication during 24 months' treatment of 160 patients. The only experience is that of J. Schneider (personal communication, 1962), who has written about a patient who developed maniacal symptoms after accidental administration of 6 g. of chloroquine base which cleared up on stopping the drug. This is in agreement with my experience.

The occurrence of toxic psychosis after such small amounts of the drug can perhaps be explained on the basis of an initial sensitization in an indigenous population taking chloroquine from time to time for various ailments.

I have no views on the mechanism of its action on the central nervous system—one can only draw an analogy with mepacrine. The latter is known to have caused psychosis (Dunlop *et al.*, 1961). Chloroquine is an aminoquinoline, while mepacrine is an acridine, but they have a common side-chain. Both are antimalarials and have practically the same therapeutic indications in various parasitic, dermatological, and rheumatic disorders. There the similarity ends, and the mode of action on the brain remains a matter of speculation.

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