

STUDIES IN LEAD POISONING

Comparison between different Laboratory Tests

BY

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The urinary output of δ -aminolaevulic acid (ALA), coproporphyrins, and lead in 15 lead-intoxicated workers was determined and correlated with the degree of intoxication. Raised levels of ALA in the urine show the best agreement with clinical evidence of intoxication.

In addition these values were correlated with the amount of lead excreted after treatment with a total dosage of 9 g. penicillamine. Weak correlations were found between therapeutically excreted lead and initial values for lead and coproporphyrin in urine. In contrast the initial values for ALA correlate very closely ($P < 0.001$). It is concluded that determinations of the output of ALA are to be preferred in the evaluation of lead intoxication and that they point directly to the amount of metabolically active lead in the organism.

Several reports from 1957 onwards (Haeger, 1957, 1958; Griggs and Harris, 1958; Haeger-Aronsen, 1960; de Kretser and Waldron, 1963; Goldberg, Smith, and Lochhead, 1963) have shown that an increased urinary output of δ -aminolaevulic acid (ALA) appears to be closely correlated with lead intoxication. As a rule the ALA output has been correlated with the concentration of lead in the urine or in whole blood, though neither of these appears to be definitely correlated with the degree of lead intoxication. Thus, Holmqvist (1960), in an investigation of 140 workers, found a correlation between lead in the blood and the exposure to lead, but raised levels of lead in the blood did not always mean lead intoxication. de Kretser and Waldron (1963) found only a poor correlation between ALA and the urinary lead output in an investigation of 100 lead workers, whereas Haeger-Aronsen (1960) found a good correlation.

The aim of the present investigation was to study the correlation between initial values for the urinary output of ALA, lead, and coproporphyrins and also their correlation with the degree of lead intoxication as judged by clinical manifestations. Further, we have correlated the results of the laboratory tests with the amount of lead excreted during treatment of lead poisoning. All cases were treated with penicillamine given by mouth. A detailed report of this treatment will be given in a separate paper.

Material

Fifteen workers are included in the study. Thirteen of these had been working in the scrap-metal industry, chiefly engaged on ship-breaking, an employment which can give a very high level of lead exposure unless elaborate precautions are taken. The remaining two worked in a well supervised storage battery plant, where precautions against lead intoxication appeared to be good. In both of these cases poisoning resulted from abnormal circumstances.

Methods

All patients were admitted to hospital during treatment and co-operated well both in connexion with treatment and the collection of urine. The dosage of penicillamine varied between 750 and 1,500 mg. a day. The total dosage was between 9 and 30 g. and was administered over 13 to 29 days.

As an indication of the clinical degree of lead intoxication we have, like King and Thompson (1961), tried to assess the symptoms on a numerical scale as follows:

General symptoms (tiredness, headache, irritability, etc.)	1-5
Haematological signs (Hb < 12g. %, leucopenia, stippled cells)	1-3

Indigestion (loss of appetite, metal-taste, loss of weight)	1-5
Lead colic (in combination with constipation and/or diarrhoea)	1-5
Neurological and muscle symptoms (cramps, paraesthesiae, etc.)	3-5

The grading was performed by the same clinician in all cases. Although there must be a degree of subjectivity about this grading, we think there is some value in using a numerical scale to indicate the degree of clinical intoxication; it certainly assists in relating the clinical state to the laboratory data.

The following laboratory examinations were performed: determination of haemoglobin, white blood cell count, differential cell count, basophilic stippling, and the excretion of lead, ALA, coproporphyrin, and creatinine in urine. For a punctate basophil count, the blood smear was fixed for two minutes in methyl alcohol. It was then stained for 30 minutes in a mixture of Löffler's methylene blue (one part) and distilled water (two parts). Fifty microscopical fields were counted, each containing roughly 200 red blood cells. The number of stippled cells is given per 10,000 red blood cells. Lead in urine was determined according to Bessman and Layne (1955) as modified by Haeger-Aronsen (1960), ALA in urine according to Mauzerall and Granick (1956), coproporphyrin as described by Haeger-Aronsen (1960), and creatinine according to Jaffe (1886).

ALA, lead, and coproporphyrin were expressed in amount/100 ml. urine as well as the amount/g. creatinine. As the creatinine output for an individual is more or less constant, excretion/g. creatinine is more exact and eliminates the errors of inadequate

collection of urine and varying amounts of diuresis. This is especially important when determinations are made on urine samples voided during the day.

As normal values we have employed those given by Haeger-Aronsen (1960):

ALA	
1.52 mg./g. creatinine	S.D. 0.59
0.29 mg./100 ml. urine	S.D. 0.14
Lead	
8.6 µg./g. creatinine	S.D. 5.6
1.4 µg./100 ml. urine	S.D. 0.9
Coproporphyrin	
38 µg./g. creatinine	S.D. 24
7 µg./100 ml. urine	S.D. 4

Results

All the patients had stippled cells in the peripheral blood. The number varied from 1 to 73 per 10,000 red blood cells. Four patients had less than 5 per 10,000 red blood cells, which we consider to be the highest normal value. No correlation was found between the number of stippled cells and the other laboratory tests or the clinical degree of lead intoxication.

The other results are given in the Table and in Figures 1 to 6. The Table shows the degree of clinical intoxication, initial values for ALA, lead, and coproporphyrin in the urine, and the output of lead after a total dosage of 9 g. penicillamine. Figures 1 to 3 demonstrate the correlation between the initial values for ALA, lead, and coproporphyrin, and Figs. 4 to 6 the correlations between these values and the amount of lead excreted during treatment with a total amount of 9 g. penicillamine.

TABLE

URINARY OUTPUT OF ALA, LEAD, COPROPORPHYRIN, AND CREATININE DURING FIRST DAY AFTER ADMISSION TO HOSPITAL AND TOTAL LEAD OUTPUT IN URINE DURING TREATMENT WITH 9 g. PENICILLAMINE

Case No.	Clinical Degree of Intoxication*	ALA		Lead			Coproporphyrin		Creatinine mg./100 ml. urine	Urine ml./24 hrs.
		mg./g. creatinine	mg./100 ml. urine	µg./g. creatinine	µg./100 ml. urine	mg./9 g. PCA	µg./g. creatinine	µg./100 ml. urine		
1	4+3+3+2+0=12	42.6	5.8	140	19	19.5	90	12.3	136	625†
2	3+2+4+0+3=12	37.1	5.2	485	68	17.1	550	77.0	140	1270
3	2+3+4+1+3=13	36.7	6.6	339	61	20.5	—	—	180	990
4	2+3+1+2+3=11	33.9	5.6	133	22	14.2	490	81.0	163	600†
5	2+3+4+2+0=11	32.5	4.4	170	23	13.1	—	—	135	1320
6	2+2+4+3+0=11	31.5	5.4	235	40	13.5	257	43.7	170	1150
7	2+1+2+2+3=10	23.8	1.9	200	16	7.5	315	25.2	80	1900
8	3+1+1+0+3=8	21.9	3.2	227	33	7.4	481	70.2	146	530†
9	1+2+3+3+3=12	19.3	2.6	44	6	13.3	—	—	135	1390
10	0+2+0+0+0=2	13.0	1.3	110	11	6.7	30	3.0	100	1700
11	2+1+2+2+0=7	11.6	1.7	82	12	6.6	284	36.2	146	1500
12	0+1+2+0+0=3	10.3	1.3	253	32	8.2	230	29.0	126	1450
13	1+2+1+0+0=4	6.4	0.4	125	7	4.3	99	5.6	56	2000
14	1+1+0+0+0=2	5.8	0.1	88	11	3.4	66	8.2	125	1070
15	1+1+1+0+0=3	3.4	0.7	51	10	2.8	84	16.2	194	900

*See text.

†Urinary volume over 12 hrs. (7 a.m. to 7 p.m.)

Figs. 1 to 6.—Relations between initial urinary concentrations of ALA, lead, and coproporphyrin and the amount of lead excreted during treatment with a total dosage of 9 g. penicillamine.

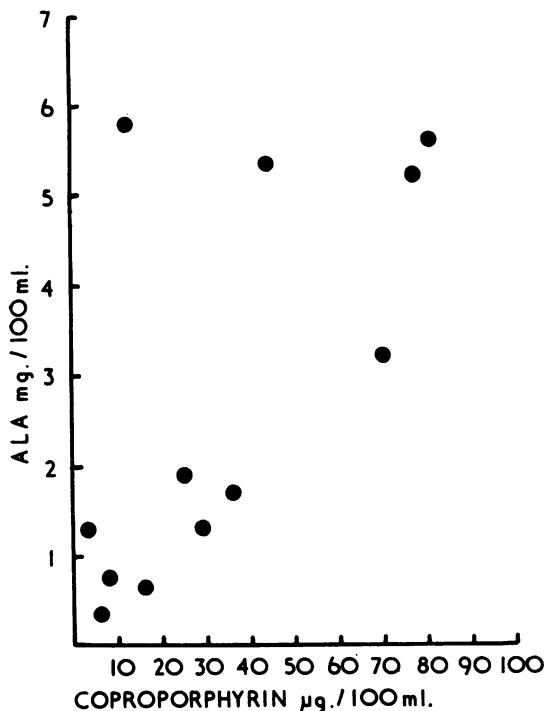


FIG. 1.— $n = 12$; $r = 0.65$; $P < 0.05$

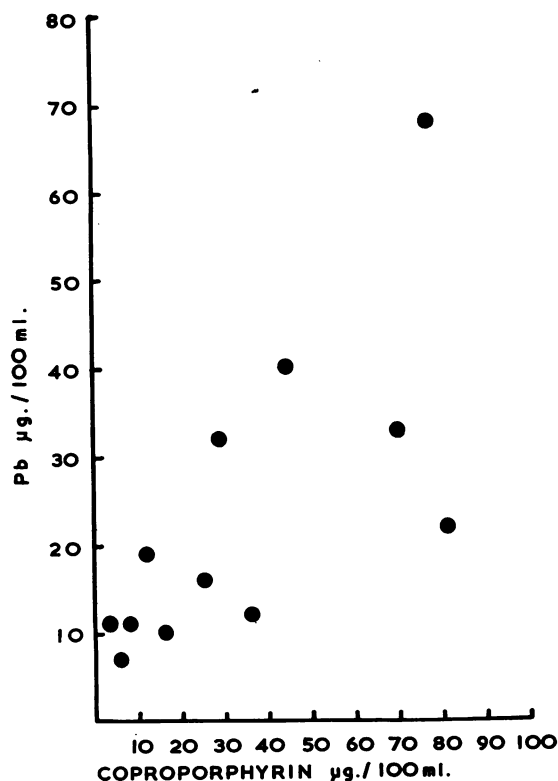


FIG. 3.— $n = 12$; $r = 0.72$; $P < 0.01$

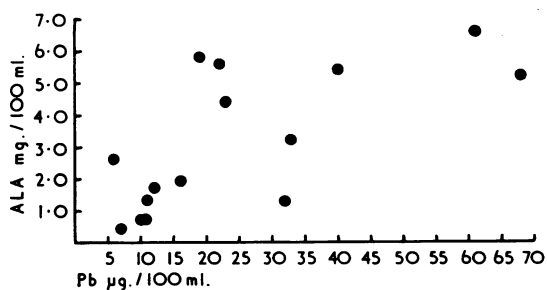


FIG. 2.— $n = 15$; $r = 0.68$; $P < 0.01$

Discussion

The Table shows that the mode of expression of concentrations of different substances in urine may be of importance. Thus, patient 13, with a diuresis of 2 l./24 hr., had a normal initial value for ALA (mg./100 ml. urine) whereas the value for ALA (mg./g. creatinine) was clearly pathological. This applies also to the output of coproporphyrin for this patient. It is clearly preferable to use the latter form

of expression, but the advantages must be weighed against the disadvantages of having to determine creatinine in urine.

Considering that the output of coproporphyrin in several cases was normal in spite of pathological values for the output of ALA and lead, it is not surprising to find a rather weak correlation between ALA and coproporphyrin. The correlation is better between lead and coproporphyrin, and between ALA and lead, but there is a great individual spreading of the figures. Our findings correspond better with those of de Kretser and Waldron (1963) than with those of Haeger-Aronsen (1960).

It is particularly important to relate the laboratory findings to clinical manifestations of lead poisoning, and for this purpose the quantities of ALA in urine show by far the best correlation. The lack of correlation between symptoms and the urinary output of lead and of coproporphyrin is evident and confirms the observation of Tanis (1955) in children poisoned by lead. It further confirms the experience of Griggs and Harris (1958) and of Moncrieff, Koumides, Clayton, Patrick, Renwick, and Roberts (1964) but is contrary to the experience of Zielhuis (1961), who

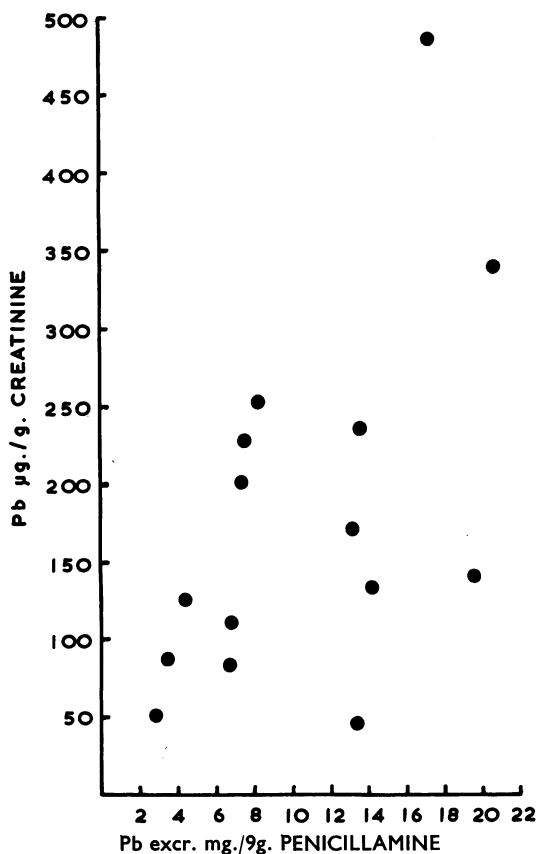


FIG. 4.— $n = 15$; $r = 0.54$; $P < 0.05$

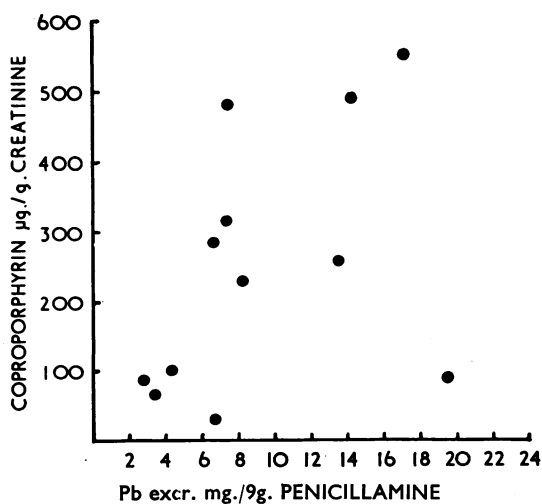


FIG. 5.— $n = 12$; $r = 0.43$; N.S.

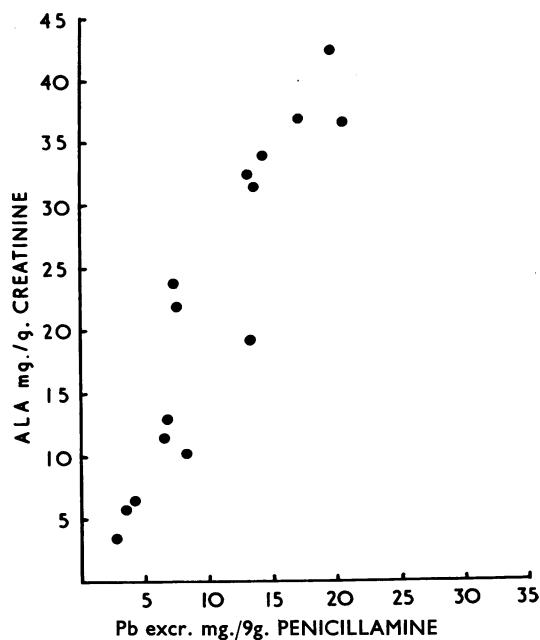


FIG. 6.— $n = 15$; $r = 0.92$; $P < 0.001$

considered that normal coproporphyrin values in urine ruled out lead intoxication.

We have also tried to compare the various laboratory findings with the amount of lead excreted in the urine during treatment with 9 g. penicillamine as a more or less objective measure of lead intoxication. Figures 4 to 6 show that there is a good correlation between this figure and the initial ALA value ($r = 0.92$; $P < 0.001$) but not with either of the other laboratory indices (lead and coproporphyrin in urine). These findings suggest that treatment with penicillamine is directed against the metabolically active lead fraction and that the size of the fraction could be calculated from the initial values of the ALA output.

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