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THE EFFECTS OF DIMERCAPROL AND PARATHYROID EXTRACT ON THE SUBACUTE DISTRIBUTION OF LEAD (ACETATE) IN RABBITS

BY

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It has been shown that dimercaprol (2 : 3-dimercaptopropanol, BAL) increases the excretion and alters the distribution of lead in rabbits when the dimercaprol is given less than twenty-four hours after intravenous administration of lead acetate (Ginsburg and Weatherall, 1948). This paper extends these observations to a later phase in the distribution of a single intravenous dose of lead. At this phase most of the lead remaining in the body was found in the bones. It seemed likely that dimercaprol would not have much effect on lead so deposited, and, at the suggestion of Professor J. H. Gaddum, the effect of parathyroid extract, which is believed to mobilize lead from bones (Hunter and Aub, 1927), was also examined, alone and in conjunction with dimercaprol.

METHODS

The procedure in these experiments followed that of Ginsburg and Weatherall (1948) with some modifications, as follows: Pb^{210} (radium D) was used as a tracer instead of Pb^{212} (thorium B), the short half-life of which made it useless for the present purpose. Radium E and radium F were removed from an equilibrium mixture of radium D, E, and F by displacement with nickel, added as foil to a solution in hydrochloric acid. A small quantity of the resulting solution of radium D and some dextrose were added to a solution of lead acetate so that the final solution contained 2.07 mg. Pb and 2–3 microcuries of radium D per ml. in 4 per cent (w/v) dextrose. Doses of 1.0 ml./kg. (i.e., 0.01 mM/kg.) were administered to rabbits of both sexes and various breeds by injection into the marginal vein of one ear at a rate of 2.0 ml. per min. After injection the rabbits were placed in metabolism cages and allowed food and water *ad libitum* from vessels placed outside windows in the cages so that spilt food or water did not dilute the urine nor contaminate the faeces. Faeces and urine were collected at first every second or third day, and later, during the period of treatment, daily. The animals were killed by a blow on the occiput 13 or 21 days after the injection of lead acetate. Solutions of dimercaprol for injection were freshly prepared in 66 per cent (v/v) aqueous propylene glycol. Both dimercaprol and parathyroid extract ("Parathormone" Lilly) were injected into the paravertebral muscles in doses as indicated below.

Ginsburg and Weatherall's (1948) procedure for taking and ashing samples of tissue was followed without modification. Samples of liver, epiphysis and diaphysis were routinely, and of bone marrow and kidney were sometimes, made in duplicate. Estimates of the concentration in other tissues were based on single samples. Before estimating their radioactivity, samples were allowed to stand for at least five weeks to allow an equilibrium mixture of radium D and E to form, because the counter used was not sufficiently sensitive to detect the low energy β-rays, emitted by the radium D, but counted the more energetic emission from radium E. The samples were diluted to a known volume, usually 10, 25, or 50 ml., and their activity was measured by means of an M.R.C. type 1 fluid Geiger-Müller counter. The total count per minute, corrected for the background count, with the counter used was linearly related to the amount of radioactive material present and was negligibly affected by variations in the density of the solution within the range involved in these experiments. The concentration and quantity of lead in tissues was calculated as before, except that the amount of lead in bone was assessed from the mean of the values in all the types of bone sampled, for reasons discussed below.

The standard error of the lead estimations, calculated from duplicate determinations made during the experiments, was ± 12.3 per cent. The total amount of lead accounted for in the entire animal and its excreta averaged 78 per cent of the dose, with a standard deviation of ± 12 per cent. The discrepancy between duplicate determinations is larger than in the earlier work, mainly if not entirely because much

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smaller quantities of radioactive tracer were used and the time of counting samples was not increased sufficiently to attain the same accuracy. The average fraction of the dose accounted for (78 instead of 90 per cent) is rather lower. The calculation of the total amount of lead in bone involves a particularly crude approximation, and in these experiments such a faulty approximation had a far larger effect than in the acute experiments where only 5 instead of 25 per cent of the dose was involved. The poorer recovery is clearly less satisfactory, but in the circumstances it does not appear to be so poor as grossly to invalidate the results obtained.

Results

Results are presented for the distribution and excretion of lead in nine rabbits, all of which received, by intravenous injection, a single dose of lead acetate containing 2.07 mg. of lead per kg. of body weight. Some of the rabbits were treated with dimercaprol or with parathyroid extract or with both, as indicated in Table III, and all were killed after thirteen or twenty-one days. Rabbits receiving no dimercaprol received instead similar injections of propylene glycol (66 per cent v/v in water). The parathyroid extract was given in the morning. The dimercaprol was given at the same time, though injected at a different site, and again four hours later, in order to cover the period in which the greatest mobilization of lead might be expected. The experiments were conducted in three groups, one of which consisted of rabbits 377 and 379, one of 378, 380, and 384, and one of 396, 397, 398, and 399. All the rabbits within a group were treated at the same time, and comparisons between rabbits in the same group are therefore less subject to incidental sources of variations than are comparisons between rabbits in different groups.

The excretion of lead before treatment was started is shown in Table I. It has been shown (Ginsburg and Weatherall, 1948) that, within twenty-four hours of giving lead, excretion occurs chiefly in the urine. In the present experiments, over a longer period, faecal excretion was usually two to three times greater. The amounts excreted appeared to depend to some extent on the quantity of excreta passed.

TABLE I

THE EXCRETION OF LEAD BY RABBITS AFTER THE INTRAVENOUS ADMINISTRATION OF LEAD ACETATE (2.07 MG. PB/KG.), BEFORE ANY FURTHER TREATMENT

Excreta were collected at 10 a.m. The period "Days 0–3" therefore ends at 10 a.m. on the third day after injection and the period "Days 3–5" runs from 10 a.m. on the third day to 10 a.m. on the fifth day. The excreta of rabbits 378, 380, and 384 were collected and estimated in bulk during the first fourteen days and so are not included in this table.

Rabbit No.:	Total quantity of excreta and concentration of lead in excreta											
	URINE											
	379*		377		398		396		397		399	
	ml.	μg./ml.	ml.	μg./ml.	ml.	μg./ml.	ml.	μg./ml.	ml.	μg./ml.	ml.	μg./ml.
Days 0–3 ...	162	0.44	194	0.50	220	0.99	280	1.27	131	2.36	165	0.97
,, 3–5 ...	178	0.16	286	0.19	97	0.82	192	0.57	38	1.41	67	0.63
,, 5–7 ...	42	0.37	56	0.17	198	0.29	182	0.38	126	0.71	246	0.33
,, 7–9 ...	36	0.42	—	—								
,, 9–11...	112	0.15	—	—	60	0.23	146	0.38	99	0.37	90	0.30
,, 11–13...	102	0.22	—	—	184	0.40	180	0.23	24	0.69	137	0.42
,, 13–14...	—	—	—	—	73	0.17	52	0.20	56	0.31	45	0.36
	FAECES											
	g.	μg./g.	g.	μg./g.	g.	μg./g.	g.	μg./g.	g.	μg./g.	g.	μg./g.
Days 0–3 ...	125	2.58	35	3.37	43	11.02	70	2.34	60	7.21	65	1.70
,, 3–5 ...	26	3.63	18	4.97	119	12.56	83	2.60	31	3.45	86	1.84
,, 5–7 ...	61	2.93	30	3.51	37	1.61	103	1.52	42	6.24	97	0.80
,, 7–9 ...	71	0.31	—	—	145	1.16	142	0.56	155	2.23	125	0.16
,, 9–11...	124	0.34	—	—								
,, 11–13...	40	0.17	—	—	155	0.58	100	0.40	181	0.98	89	0.63
,, 13–14...	—	—	—	—	68	0.13	45	0.63	42	0.89	50	0.49
	Total percentage of the dose excreted in 14 days											
Urine ...	—		—		10.8		16.9		12.3		9.2	
Faeces ...	—		—		36.1		17.1		32.7		8.0	

* Treated with propylene glycol on days 8–11.

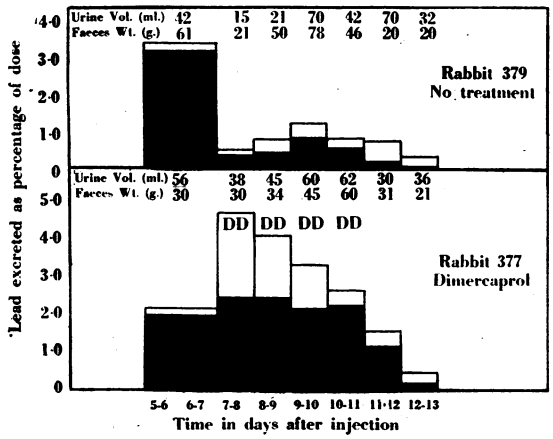

FIG. 1.—The effect of dimercaprol on the excretion of lead in the urine and faeces 8–11 days after the intravenous administration of lead acetate (2.07 mg. Pb/kg.). Ordinates: Amount of lead excreted as a percentage of the dose administered (1 per cent = 20.7 μg. Pb/kg. body weight). Abscissae: Number of days after the injection of lead acetate. D = 12.5 mg./kg. dimercaprol injected intramuscularly. ▭ Urinary excretion. ■ Faecal excretion.

The effects of the treatments on the elimination of lead in the urine and faeces are shown in Figs. 1 and 2. When dimercaprol was administered seven days after the lead (377), a tenfold increase in the urinary excretion of lead occurred during the first day of treatment, after which the amount fell progressively during subsequent days of treatment. The faecal lead also increased, although probably not significantly. In the rabbits treated with dimercaprol on the fifteenth and subsequent days after the administration of lead (378 and 396) there was an increase in the concentration of lead in the urine and faeces. This was accompanied by a diminution in the quantity of excreta, so that there was no increase in the total amount of lead excreted. A slight fall of doubtful significance occurred in the total amount of lead excreted by the rabbits treated with parathyroid extract or with dimercaprol and parathyroid extract, probably owing to the diminution in the quantity of excreta which also occurred in these rabbits. Rabbit 399 developed acute retention of urine during the days preceding death, when over 400 ml. of urine was found in the bladder. No cause for this retention was apparent, but it accounts for the large amount of lead recorded as excreted on the twenty-first day.

TABLE II

THE CONCENTRATION OF LEAD IN THE BLOOD CELLS OF RABBITS POISONED WITH LEAD ACETATE DURING TREATMENT WITH DIMERCAPROL AND PARATHYROID EXTRACT

	μg. Lead per g. of blood cells		
Rabbit No.	378	384	380
Treatment (details as in Table III) ...	Dimercaprol	Parathyroid extract	Dimercaprol and parathyroid extract
Immediately before treatment	0.16	0.50	0.18
3 hours after first dose	<0.05	0.26	0.07
24 hours after first dose	0.09	0.20	<0.07
3 days after end of treatment (i.e., at death)	0.19	0.21	0.07

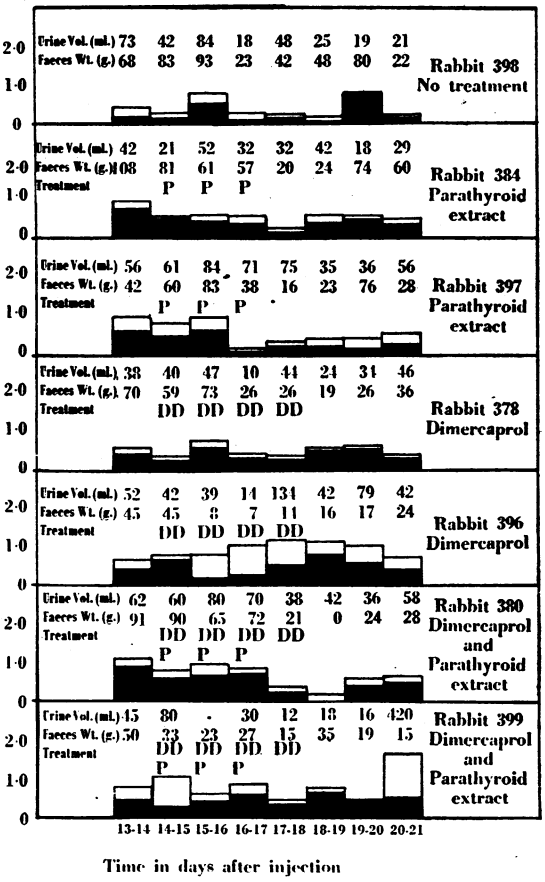

FIG. 2.—The effect of dimercaprol and parathyroid extract on the excretion of lead in the urine and faeces 15–18 days after the intravenous administration of lead acetate (2.07 mg. Pb/kg.). Ordinates, abscissae, and symbols as in Fig. 1. P = 8 units/kg. parathyroid extract injected intramuscularly.

TABLE III

THE EFFECT OF TREATMENT WITH DIMERCAPROL AND PARATHYROID EXTRACT ON THE CONCENTRATION OF LEAD IN THE TISSUES OF RABBITS THIRTEEN AND TWENTY-ONE DAYS AFTER THE INTRAVENOUS ADMINISTRATION OF LEAD ACETATE (2.07 MG. PB/KG.)

	Micrgrammes of lead per gramme fresh weight of tissue								
Time after giving lead ...	13 days		21 days						
Treatment with parathyroid extract	None	None	None	None		8 u./kg./day on days 15, 16, and 17		8 u./kg./day on days 15, 16, and 17	
Treatment with dimercaprol ...	None	12.5 mg./kg. twice daily, days 8–11	None	12.5 mg./kg. twice daily, days 15–18		None		12.5 mg./kg. twice daily, days 15–18	
Rabbit No. ...	379♀	377♂	398♂	378♀	396♂	384♂	397♀	380♀	399♂
Init. wt., kg. ...	1.40	1.50	2.02	1.90	1.82	1.70	2.06	1.90	2.02
Final wt., kg. ...	—	—	1.90	1.60	1.65	1.80	1.80	1.80	—
Plasma	0.06	0.02	<0.16	<0.09	<0.22	<0.10	<0.13	<0.05	<0.16
Blood cells ...	2.25	0.72	0.62	0.19	0.34	0.21	<0.27	0.07	0.35
Spleen	—	3.44	<0.64	0.30	<1.30	<0.90	<0.83	<0.23	<1.50
Bone marrow ...	9.8	6.0	3.50	<0.25	7.0	4.6	4.2	1.10	2.70
Liver	3.0	4.1	1.9	0.62	2.0	3.3	2.2	4.7	1.4
Bile	<1.54	0.87	<0.64	1.0	<2.9	0.33	<1.0	0.59	<2.21
Pancreas ...	<0.17	0.19	—	<0.08	—	<0.45	—	<0.15	—
Colon	0.07	0.14	<0.07	0.01	<0.10	0.03	<0.08	0.01	<0.12
Colon contents ...	0.34	0.29	<0.30	0.03	<0.12	0.04	<0.15	0.11	—
Kidneys	0.63	1.68	0.67	0.16	0.45	0.53	0.55	0.27	0.50
Adrenals ...	<1.45	<0.48	—	<1.14	—	<2.07	—	<0.87	—
Gonads	<0.95	0.50	—	<0.64	—	<0.64	—	<0.55	—
Seminal vesicles...	—	—	—	—	—	<0.11	—	—	—
Uterus	<0.16	—	—	<0.04	—	—	—	<0.06	—
Lungs	0.42	0.14	<0.13	0.83	1.86	0.02	0.34	<0.02	0.20
Skeletal muscle ...	0.02	0.05	<0.09	<0.01	<0.09	<0.02	0.13	<0.01	<0.07
Diaphysis ...	9.0	5.3	5.1	3.8	2.6	7.0	3.5	4.4	1.4
Epiphysis ...	9.6	12.6	12.9	5.7	8.0	10.9	5.2	3.5	2.5
Ribs	7.6	10.3	19.0	6.7	9.7	10.0	7.8	6.4	1.5
Vertebrae ...	11.9	11.5	—	6.2	—	10.0	—	5.4	—
Skull vault ...	9.8	15.0	12.8	10.4	5.5	7.8	5.0	12.5	2.6
Brain	<0.09	0.17	<0.13	0.12	<0.12	0.10	0.15	<0.02	0.11
Skin	0.12	0.10	0.20	0.11	<0.15	0.10	<0.14	0.10	0.30

The effects of the treatments on the concentration of lead in the blood cells are shown (for three rabbits) in Table II. After the first treatment with dimercaprol, or parathyroid extract, or both, the concentrations of lead in the blood cells fell by one-half to two-thirds. They remained low during treatment and afterwards, if anything, tended to rise. The counts were very low and were prolonged to give an accuracy of only ±25 per cent, so that even the initial fall is barely significant. The corresponding samples of plasma contained no lead, or too little to be detected—i.e., less than 0.3–0.4 microgramme per gramme in the samples taken before death and less than 0.1 microgramme per gramme in the samples taken at death.

The concentration of lead in microgrammes per gramme of wet weight of tissue and the percentage of the dose found at death (i.e., three days after the end of treatment) in various organs and calculated for various tissues are shown in Tables III, IV, and V. In the previous paper in this series, Ginsburg and Weatherall (1948) calculated the amount of lead in bone from the concentration in diaphyses, because the concentration of lead in the bone marrow was much higher and it was uncertain to what extent the marrow present in the interstices of the cancellous bone of the samples of epiphyses was raising the concentration there. In the present experiments the concentration of lead in the epiphyses was much higher than the concentration in either marrow or diaphyses, and

TABLE IV

THE EFFECT OF TREATMENT WITH DIMERCAPROL AND PARATHYROID EXTRACT ON THE DISTRIBUTION OF LEAD IN RABBITS THIRTEEN AND TWENTY-ONE DAYS AFTER THE INTRAVENOUS ADMINISTRATION OF LEAD ACETATE (2.07 MG. PB/KG.)

	Percentage of dose in entire organ or tissue								
Time after giving lead ...	13 Days		21 Days						
Treatment with parathyroid extract	None	None	None	None		8 u./kg./day on days 15, 16, and 17		8 u./kg./day on days 15, 16, and 17	
Treatment with dimercaprol ...	None	12.5 mg./kg. twice daily, days 8–11	None	12.5 mg./kg. twice daily, days 15–18		None		12.5 mg./kg. twice daily, days 15–18	
Rabbit No. ...	379♀	377♂	398♂	378♀	396♂	384♂	397♀	380♀	399♂
Init. wt., kg. ...	1.40	1.50	2.02	1.90	1.82	1.70	2.06	1.90	2.02
Final wt., kg. ...	—	—	1.90	1.60	1.65	1.80	1.80	1.80	—
Plasma	0.12	0.06	<0.30	<0.24	<0.45	<0.22	<0.30	<0.11	<0.31
Blood cells ...	3.11	0.62	0.86	0.20	0.45	0.24	<0.30	0.08	0.48
Spleen	—	0.12	<0.02	0.01	0.02	<0.02	0.02	<0.01	<0.02
Bone marrow ...	9.6	5.8	3.3	<0.38	6.8	4.4	4.0	0.99	2.5
Liver	3.8	6.0	2.2	0.70	2.0	4.5	2.8	5.4	1.3
Pancreas ...	<0.01	0.03	—	<0.01	—	<0.01	—	<0.01	—
Colon	0.03	0.07	<0.02	0.01	<0.02	0.01	<0.02	0.01	<0.02
Colon contents ...	0.18	0.12	<0.04	0.01	<0.05	0.01	<0.04	0.04	—
Kidneys	0.24	0.55	0.18	0.04	0.14	0.16	0.13	0.07	0.14
Adrenals ...	<0.02	<0.01	—	<0.01	—	<0.06	—	<0.01	—
Gonads	<0.01	0.06	—	<0.01	—	<0.02	—	<0.01	—
Lungs	0.08	0.03	<0.02	0.02	0.26	0.01	0.05	<0.01	0.03
Skeletal muscle ...	0.50	1.25	<2.2	<0.68	<2.3	<0.58	3.3	<0.28	<1.8
Bone	26.0	29.2	35.8	19.2	18.7	27.4	15.7	18.7	5.7
Brain	<0.02	0.04	<0.02	0.02	<0.02	0.02	0.03	<0.01	0.02
Skin	0.70	0.52	1.2	0.61	<0.87	0.60	<1.00	0.57	1.8
Injected ear ...	3.86	15.2	0.23	0.02	0.14	0.41	0.02	0.59	33.3
Total in carcass†	50%	63%	44%	21%	29%	39%	26%	26%	45%
Excreted:									
Urine, days 0–14	5.9*	(10.7)*	10.8	11.3	16.9	11.8	12.3	14.9	9.2
Urine, days 14–21	—	—	1.1	0.8	3.2	0.8	1.7	1.3	3.1
Faeces, days 0–14	23.0*	(19.3)*	36.1	33.9	17.1	28.9	32.7	27.1	8.0
Faeces, days 14–21	—	—	5.7	2.7	3.6	2.7	2.0	3.1	4.9
Total excreted ...	29%	30%	54%	49%	41%	44%	49%	45%	25%
Total accounted†	79%	93%	98%	70%	70%	83%	75%	71%	70%

* Days 0–13. † Including items shown in Table V.

clearly a larger part of the entire dose had been taken up at the ends of the bones. The total amount of lead in bone has therefore been estimated from the mean concentration in all the types of bone consistently sampled, without weighting for the relative proportions of the different types. Large inaccuracies are probably so introduced, and the figures are useful only as a rough check that a reasonable fraction of the entire dose has been accounted for.

In the first pair of rabbits (377 and 379), the concentration of lead in the wall of different parts of the alimentary canal above the rectum was fairly uniform, and therefore in subsequent experiments only one portion of the intestine, the colon, was sampled. The rest of the alimentary canal was the largest amount of tissue not examined in the later animals; but probably did not include more than 1 or 2 per cent of the dose.

TABLE V

THE CONCENTRATION OF LEAD AND THE PERCENTAGE OF THE DOSE OF LEAD IN CERTAIN ADDITIONAL TISSUES OF RABBITS THIRTEEN DAYS AFTER THE INTRAVENOUS ADMINISTRATION OF LEAD ACETATE (2.07 MG. PB/KG.) WITHOUT AND WITH TREATMENT WITH DIMERCAPROL

	μg. Lead per g. fresh weight of tissue		Percentage of dose in entire organ or tissue	
Rabbit No. ...	379	377	379	377
Treatment ...	Propylene glycol	Dimercaprol	Propylene glycol	Dimercaprol
Stomach ...	0.07	0.18	0.06	0.10
Stomach contents ...	0.07	0.07	0.11	0.16
Small intestine	<0.07	0.14	<0.10	0.10
Small intestine contents ...	0.14	0.02	0.04	0.02
Caecum ...	0.11	0.22	0.13	0.53
Caecum contents ...	0.27	0.34	0.63	2.25
Rectum ...	0.04	0.15	0.01	0.04
Rectum contents ...	0.66	0.32	0.44	0.11
Heart ...	<0.18	<0.15	<0.02	<0.02
Bladder ...	1.18	<0.43	0.05	<0.02
Spinal cord...	0.38	0.67	0.05	0.09
Eyes... ...	<0.12	<0.15	<0.03	<0.03

Of the lead which remained in the body, regardless of treatment and apart from that which had not been injected cleanly and remained at the site of injection (notably in rabbits 377 and 399), 50 to 95 per cent was found in the bones. No other single tissue accounted for more than a few per cent of the dose, and only the liver and bone marrow contained more than 2 per cent consistently. Similarly the highest concentrations were found in the bones, bone marrow, and liver, which generally contained 2–15 microgrammes of lead per gramme of tissue. Other tissues rarely contained more than 1 microgramme per gramme. The concentration in blood cells, lungs, kidneys, bile from the gall bladder, and skin tended to be above 0.1 microgramme per gramme, whereas those in skeletal muscle, the alimentary canal, and brain tended to be below this level.

General inspection of the results shows no striking differences between differently treated animals. The concentrations in bone were somewhat higher in the untreated rabbits than in any others. Interpretation of this difference is confused by the great variability of the concentration in different bones, by the large deposit of lead at the site of injection in one rabbit (399), and by variation in the amount of lead excreted before treatment was started. The total amount of lead accounted for tended to be low when the concentration of lead in the bones was low; that is, as here calculated, there was no completely corresponding increase in the amount of lead outside the skeleton in the treated animals, and the evidence that appreciable quantities of lead are removed from the bone by any of the treatments is unconvincing. Other tissues showed no consistent differences which could be related to the treatments.

Discussion

The distribution of lead in the untreated rabbits of this series showed no unexpected features. As has generally been found in rabbits (Kisskalt and Friedmann, 1914; Lomholt, 1924; Kehoe and Thamann, 1933), the excretion of lead, even after parenteral administration, was greater in the faeces than in the urine after the first day or two, and the combined excretion amounted to about half the total dose in three weeks. The rate of excretion roughly followed an exponential curve, and had reached a very low level at the end of these experiments. Even if there was no further decrease in the rate of excretion after three weeks, it would have taken a period of the order of a hundred days to excrete the rest of the lead in the body. This residual lead was, as expected, mainly in the bones; and the bone marrow and liver were the only other tissues in which concentrations usually exceeded 1 microgramme per gramme. Little attention has hitherto been paid to the bone marrow as distinct from bone (cf. Ginsburg and Weatherall, 1948), and the persistence of lead in the marrow is clearly interesting in relation to the mechanism by which lead produces anaemia. The present figures for the concentration in muscle are lower than those of Kisskalt and Friedmann (1914) and of Kehoe and Thamann (1933), even allowing for the difference in dosage: but when the small quantities of lead involved are considered, the differences are not striking nor surprising. In the central nervous system the discrepancies are larger. Kehoe and Thamann's method was unreliable (Kehoe, Thamann, and Cholak, 1935) and their figures are very variable and may be disregarded. Kisskalt and Friedmann consistently found concentrations several hundredfold higher than those reported here. With quantities of the order involved, the reliability of their method is perhaps questionable. In more acute poisoning, Weyrauch (1931) failed to detect any lead in the brain of rabbits sixteen hours after the intravenous injection of lead nitrate (12 mg. Pb/kg.), though the sensitivity of his method was not sufficient to exclude concentrations of the order quoted here: and Ginsburg and

Weatherall (1948) found slightly higher figures at six and twenty-four hours after injection than the present ones. On the whole it appears unlikely that concentrations of lead much exceeding 0.1 microgramme per gramme of tissue occur in the brains of rabbits after the intravenous injection of salts of lead.

The effects of treatment were small. Eight days after the injection of lead acetate, dimercaprol increased the urinary excretion so that in all about an extra 4 per cent of the dose was excreted Fifteen days after the injection, the effect of dimercaprol, if any, did not exceed 2 per cent of the dose. Germuth and Eagle (1948) observed larger increments in the urinary excretion of lead by rabbits up to eleven days after the last dose of lead, but they had administered several doses of 200 mg. lead acetate subcutaneously and their rabbits therefore had a depot from which lead was almost certainly being continuously absorbed and was in addition possibly mobilized by dimercaprol. Even so, as here, successive doses of dimercaprol had a rapidly diminishing effect on urinary excretion, and any increase in faecal excretion was obscured by a diminished output of faeces. During treatment the amount of lead in the blood cells decreased, and three days after treatment the concentration of lead in the cells was highest in the untreated animal of each set. The difference in concentrations corresponded to a difference of about 2.5 per cent of the dose in the shorter experiments and about 0.5 per cent in the longer ones, and so was not far from accounting for all the extra lead excreted. As indicated above, the bones may also have contributed a little. A decreased concentration of lead in the bones of rabbits poisoned with large amounts of lead and treated with dimercaprol has been reported by Lusky, Braun, and Laug (1948), but no quantitative details were given. In the present experiments the variation between identically treated rabbits was generally larger than any changes attributable to treatment, and so attempts precisely to account for the small movements of lead which may have occurred are unprofitable. The data of Ryder, Cholak, and Kehoe (1947) and of Telfer (1947) suggest that dimercaprol has rather more effect on the lead of the blood cells and urine in man than in rabbits.

The changes after parathyroid extract were also minimal. There was no increase in the excretion of lead and, if anything, a reduction in the concentration of lead in the blood cells. It does not appear that, with the doses used in the rabbit, parathyroid extract has any appreciable effect on the distribution of lead once most of the lead is deposited in the bones. Consequently the rationale of using dimercaprol and parathyroid extract together was not fulfilled, and the negative results of the combination must be attributed to the lack of action of the parathyroid extract alone. This lack of action was a little surprising. However, the literature about the action of parathyroid extracts on lead metabolism is conflicting. An increase in the concentration of lead in the blood of rabbits (Teisinger, Joachim, and Kodicek, 1938) and of man (Schmitt and Taeger, 1937) has been reported, but an increase in that of the latter has not been confirmed (Teisinger, 1938), and the rise in blood lead in Schmitt and Taeger's patient was accompanied by far less increased excretion of lead than in the cases observed by Hunter and Aub (1927). Almost any interpretation can be put on these findings, and we have failed to find in the literature any complete account of the influence of parathyroid extracts on the distribution of lead in experimental animals. Further observations are clearly desirable to establish whether in any circumstances parathyroid extracts really effect the mobilization of lead from bones.

Summary

1. The distribution of lead in the tissues of rabbits thirteen and twenty-one days after the intravenous injection of lead acetate (2.07 mg. Pb/kg.) has been studied by use of the isotope Pb^{210} (radium D). Some of the rabbits were treated with dimercaprol, or parathyroid extract, or both, for some days during the week before they were killed.

2. Apart from a transient increase in the urinary excretion of lead after dimercaprol, none of the treatments caused any substantial change in the distribution or the excretion of lead.

3. About 50 per cent of the dose of lead was excreted in twenty-one days, predominantly in the faeces. The bones contained about 25 per cent of the dose twenty-one days after injection. The bone marrow and the liver were the only other tissues which consistently contained more than 1 per cent.

4. Treatment with dimercaprol and parathyroid extract appears to have no useful effect in rabbits subacutely poisoned with lead, but confirmation of this finding in other species is desirable.

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