MERCURY NEPHROSIS IN YOUNG CHILDREN

WITH SPECIAL REFERENCE TO TEETHING POWDERS CONTAINING MERCURY

BY

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Mercury poisoning occurs in acute and chronic forms. In acute mercury poisoning there is severe injury to the kidney. Although oedema is usually prevented by the violent diarrhoea which is present, the urine has a high content of albumin and shows a picture similar to that found in nephrosis. Histologically there is necrosis of the epithelial cells of the tubules, and toxic changes occur in the glomeruli. In chronic mercury poisoning the symptoms vary according to whether the mercury is in the form of inorganic or organic compounds or whether mercury vapours are produced (Leschke, 1934). Inhalation of organic compounds or metallic mercury vapours causes, above all, nervous symptoms, whereas the ingestion of mercury salts causes intestinal and renal disorders.

Individual sensitivity to mercury varies widely. The nephrotic syndrome in children is mentioned by Fanconi *et al.* (1947) as an occasional late manifestation of mercury poisoning resulting from worm powders containing calomel. The possibility of mercury nephrosis resulting from prolonged administration of mercury-containing compounds, such as most varieties of teething powders, has not, however, been recognized. These teething powders each weigh approximately 2 to 2.8 gr. (130–180 mg.), the weight varying with the brand, and contain 27% to 33% of calomel, the content of metallic mercury being 0.59 to 0.64 gr. (38–42 mg.). Over long periods, therefore, the amount of mercury administered is considerable, and, since the patients are usually infants or toddlers, it is not surprising that chronic mercury poisoning may result even in children who are not unduly sensitive to mercury.

During investigation of cases of pink disease, one patient with nephrosis was found by one of us (V.K.W.) to be excreting large amounts of mercury in the urine. On this evidence we decided to examine the urine for mercury in further cases of nephrosis. Five cases with an excess of mercury in the urine have been found during recent months.

Case 1

A boy aged 21 months was admitted to hospital on November 20, 1950, with a history suggestive of pink disease of five weeks' duration. He had been given teething powders each containing approximately 0.64 gr. (42 mg.) Hg in the form of calomel over a period of 18 months. At first three to four powders a week were given, but more recently one to two powders a month.

On examination both legs were swollen and puffy from the knee downwards, the oedema increasing over the dorsum of the feet. The urine was loaded with albumin. No casts were found. There was 1 red cell per high-power field The urine contained 102 γ Hg per 100 ml., and the serum cholesterol was 585 mg. per 100 ml. The diagnosis of nephrosis possibly due to chronic mercury poisoning was made. On December 3 treatment with dimercaprol (B.A.L.) was started, being completed on December 11. On the sixth day of treatment the urine contained 82 γ Hg per 100 ml. Ten days later the urine contained 98 γ Hg per 100 ml. During treatment the albuminuria decreased gradually, and after its completion was hardly detectable. The Esbach readings fell from 1.5 g. per litre to 0.02 g. per litre.

There was a dramatic improvement in his general condition, and he was discharged well on January 3, 1951. When seen in the out-patient department on March 5 the urine contained no mercury. He was seen at monthly intervals for a period of eight months, when, apart from a persistent sinus infection, he appeared well. There was no recurrence of the oedema and no albuminuria. Biochemical details are given in Table I.

TABLE I.—*Case 1*

Date	Blood Urea mg /100 ml.	Blood Cholesterol mg /100 ml	Serum Proteins			Plasma Chlorides mg /100 ml.
			Total g. %	Alb. g. %	Glob. g. %	
21/11/50 ..	25					
28/11/50 ..	—	585	6·64	2·60	4·04	658
1/3/51 ..		204	8·25	5·75	2·50	

Case 2

A girl aged 3½ years was admitted to hospital on January 15, 1951, with a history of swelling of the limbs and face for three days. The child had been off colour for six months with anorexia and loss of weight. During this time there had been attacks of diarrhoea, with the passage of four to five watery offensive stools daily and occasional abdominal pain. One week before admission the condition deteriorated and the child became oedematous.

On examination there was generalized oedema; the systolic blood pressure was 105 mm. Hg by palpation. The urine contained albumin (+ + +) but no blood; otherwise the examination was negative. When mercury was found in the urine the parents were interviewed again to discover its source. No teething powders containing mercury had been given, but the child had received three grey tablets daily for the past five months for "liver trouble." These tablets each contained ½ gr. (32 mg.) Hg—i.e., approximately 15 g. Hg had been taken in five months.

Treatment with dimercaprol was started on January 25, 36 mg. being given intramuscularly four-hourly for 48 hours and 36 mg. daily for 10 days. The child became extremely ill and dehydrated as a result of vomiting and diarrhoea, and required energetic treatment with intravenous plasma and saline during the next few days. The oedema rapidly subsided, and 11 days after dimercaprol was started the albumin had completely disappeared from the urine. The diarrhoea gradually subsided and the stools became formed on March 5. Before treatment the urine contained 200 γ Hg per 100 ml. The albumin precipitate was separated and mercury estimations were done on the precipitate and the filtrate. Nearly all the mercury (175 γ) was found in the precipitate—only 25 γ in the filtrate. After four days' treatment with dimercaprol the urine contained 150 γ per 100 ml.

TABLE II.—*Case 2*

Date	Blood Urea mg./100 ml.	Serum Cholesterol mg./100 ml.	Serum Proteins			Plasma Chlorides. mg. NaCl per 100 ml.	Plasma CO_2 Vols. %	Urea Clearance. % Average Normal Function
			Total g. %	Alb. g. %	Glob. g. %			
20/1/51 ..	25	640						
27/1/51 ..	24		4·09	1·03	3·06			
31/1/51 ..						459	38	
7/2/51 ..		260				503	57	63
8/2/51 ..		210						

(130 γ in precipitate; 20 γ in filtrate). After 12 days' treatment the urine contained 28 γ per 100 ml. Eleven days later the mercury in the urine was 20 γ per 100 ml., and a fortnight later it was 8 γ. The child made an uninterrupted recovery. Other biochemical investigations are shown in Table II.

Case 3

Ten days before the admission to hospital of a boy aged 11 months the mother noticed that his eyelids were swollen in the morning. Four days later the feet and ankles began to swell, and in a few days the abdomen became swollen. The child was admitted to hospital on July 20, 1951. There had been no diarrhoea or vomiting. On examination there was generalized oedema, and the urine contained albumin (+ + +) (Esbach, 14 g./litre). Hyaline and granular casts were present and there were more than 50 red cells in the centrifuged deposit. On admission no inquiry had been made about mercury. On recalling the parents it was found that the child had been given one teething powder on alternate days for the past five months. These powders each contained approximately 0.64 gr. (42 mg.) Hg in the form of calomel, so that about 3.1 g. Hg had been given in that period. Treatment with dimercaprol was started on July 28, 20 mg. being given intramuscularly four times daily for two days, 20 mg. twice daily for one day, and 20 mg. daily for 10 days. There was marked diuresis, and the loss of weight which occurred is shown on the Chart.

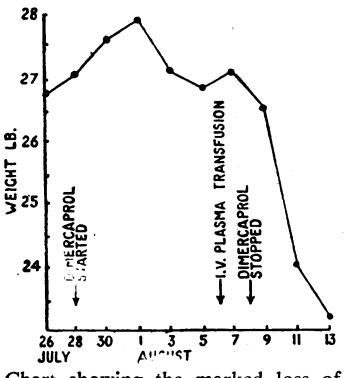

Chart showing the marked loss of weight which followed treatment of Case 3 with dimercaprol.

Before treatment the urine contained 75 γ Hg per 100 ml. A few days after dimercaprol was started the mercury content rose to 120 γ per 100 ml. Seven days later the urine contained 28 γ Hg. Three weeks later it contained 9 γ Hg. The child was given two intravenous plasma transfusions, one during the course of treatment with dimercaprol and the second a week later. During the five days after dimercaprol was stopped the child lost about 3½ lb. (1.59 kg.) in weight and the oedema was much diminished. A few days later the oedema recurred to some extent, but a fortnight afterwards no oedema could be detected though the urine still contained some albumin (Esbach, 1 g./litre). In view of the persistent slight albuminuria and the fact that the mercury content of the urine had risen to 24 γ per 100 ml. a further course of dimercaprol was started on September 24. Two days after this course was begun the urine contained 260 γ Hg per 100 ml., and six days later 58 γ Hg. As the child had had a patch test (in which a small amount of ointment containing 13% calomel was applied to the skin for 48 hours) we felt it necessary to find out if this test had affected the amount of mercury excreted. A similar patch test (mercury content approximately 5,000 γ) was applied to a normal baby of the same age for 48 hours. This baby's urine contained no mercury before the patch test, but 24 hours after its application the urine contained 6 γ per 100 ml. Twenty-four hours later the urine contained 2 γ. Four days later no mercury was detected, but two days later the urine contained 4 γ Hg. These tests are not strictly comparable, since the normal baby was not receiving dimercaprol. In neither case was the skin test positive. About 21 days after the second course of dimercaprol the urine became free of albumin and the child was discharged well.

TABLE III.—*Case 3*

Date	Blood Urea mg./100 ml.	Serum Cholesterol mg./100 ml.	Serum Proteins		
			Total g.%	Alb. g.%	Glob. g.%
20/7/51	26	520	4·40	1·58	2·82
22/7/51					
10/8/51	33				
27/8/51	42				
3/9/51	28				
24/9/51	24				

Case 4

Two weeks before his admission to hospital the mother of a boy aged 12 months noticed that his eyelids were swollen. Two days before admission the abdomen, penis, and legs became swollen. For a week little urine had been passed and there was marked thirst. There had been no diarrhoea. The child was admitted on September 14, 1951. On examination there was generalized oedema and the urine contained albumin (+ +). Scanty hyaline casts were present and a few red cells. This child had been given one teething powder on alternate days for the past six months. These powders each contained approximately 0.64 gr. (42 mg.) Hg in the form of calomel—i.e., approximately 3.8 g. Hg had been taken in six months. On September 20 the urine contained 52 γ Hg per 100 ml. No dimercaprol was given in this case. On admission the child's weight was 26 lb. 14 oz. (12.2 kg.). The oedema decreased rapidly, and in the course of 10 days cleared completely. On October 4 his weight was 20 lb. 12 oz. (9.4 kg.). A week later the weight was 19 lb. 12 oz. (9 kg.), and the general condition was greatly improved. Nine days later vomiting and diarrhoea occurred for a few days. On October 24 the urine contained 44 γ Hg per 100 ml. Microscopy of urine was negative and no albumin was present. The infant was discharged well on October 25 and without any renal abnormality. He has since remained well. Other biochemical investigations are shown in Table IV.

TABLE IV.—*Case 4*

Date	Blood Urea mg./100 ml.	Serum Proteins		
		Total g.%	Alb. g.%	Glob. g.%
17/9/51	30			
19/9/51		6·48	3·06	3·42
15/10/51 ..		6·74	4·20	2·54

Case 5

We are indebted to a colleague for the following case history.

A child aged 19 months was admitted to hospital with generalized oedema which had been present for three days and with marked albuminuria. Despite routine treatment for a month the oedema and albuminuria persisted unabated. At this point the possibility of a mercury nephrosis was raised, and an interview with the parents uncovered the fact that one teething powder had been given daily for three to four months before admission. Each powder contained approximately 0.56 gr. (36 mg.) Hg. Urine for mercury estimation, obtained with difficulty, was found to contain 22 γ Hg per 100 ml. Unfortunately the child deteriorated rapidly and died before treatment with dimercaprol could be started. Permission for necropsy was refused. We believe that this was a case of mercury nephrosis.

The method used for the mercury estimations was essentially that of Milton and Hoskins (1947). The mercury content of the urines of 12 normal children was estimated by the same method for use as controls. In nine of these no mercury was found in the urine. One had 1 γ Hg per 100 ml. of urine and the other two had 3 γ Hg.

Discussion

The mercurial compounds given to these children are in common use, but the danger of causing nephrosis by their prolonged ingestion is not recognized. In three of the cases

no inquiry had been made about the administration of mercury compounds at the first interview with the parents, so that the possibility that mercury was the cause of the nephrosis would not have come to light had our suspicions not been previously aroused. Our experience with Case 3 shows that a considerable amount of mercury may remain in the body for long periods and that more than one course of dimercaprol may be necessary to eliminate it adequately. If the treatment with dimercaprol is instituted promptly complete recovery of renal function is possible. Cast 4 shows that in some cases spontaneous recovery may occur when the intake of mercury is stopped, though its excretion may continue for relatively long periods. On the other hand, Case 5, in which no dimercaprol was given, proved fatal.

In view of these findings we urge that mercury compounds should be eliminated from all teething powders and that other mercury compounds, such as grey pills, be used with care, and prolonged administration be avoided in young children. Teething powders not containing mercury are free of the risks we have described.

Summary

Five cases of mercury nephrosis are described. Complete recovery in a short period in three cases treated with dimercaprol is reported. Of two cases not treated with dimercaprol one patient recovered and one died.

We are indebted to the resident medical and nursing staffs who have cared for these children while in hospital, to Miss J. Summerscales for assistance with the mercury estimations, and to Miss P. M. Gorse for routine biochemistry in some of the cases.

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FATAL HYPOKALAEMIC ALKALOSIS WITH TETANY DURING LIQUORICE AND P.A.S. THERAPY

BY

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This is a report on a patient who, while receiving treatment for tuberculous meningitis, developed unexplained electrolyte abnormalities, from which she died. Papers published subsequently have thrown light on the mechanism of her death.

Case Report

A girl aged 15 received a full course of streptomycin for miliary tuberculosis with tuberculous meningitis, and was discharged from hospital on February 24, 1950, having made a satisfactory recovery. She was seen at intervals as an outpatient, and gained weight and strength. On May 27 she was readmitted with a recurrence of the meningitis, and was treated with intramuscular and intrathecal streptomycin and sodium *para*-aminosalicylate (P.A.S.). The P.A.S. was given in a mixture containing 2 g. of sodium *para*-aminosalicylate and 12 min. (0.72 ml.) of ext. glycyrrh. liq. *B.P.*, and the dose was increased gradually to 20 g. daily. About 595 ml. of ext. glycyrrh. liq. was taken over the whole period. The meningitic symptoms showed signs of improvement, but on August 3 she complained of stiffness of her arms and legs, and there was twitching of the face. Later in the day she was reported to have had two epileptic attacks.

There were no further attacks during the next two weeks, during which phenobarbitone was prescribed, but stiffness was still a complaint. About August 24 muscular cramps occurred, and it was plain that she was having severe tetany, with carpopedal and facial spasm, and slight respiratory difficulty. There was no evident hyperpnoea. The serum calcium was found to be low (7.5 mg. per 100 ml.), and plasma alkali reserve 82 vols. CO_2 per 100 ml. The urinary calcium was normal as judged by Sulkowitch's reagent. Repeated administration of calcium gluconate intravenously had only a transient effect on the attacks of tetany, which increased in duration, and Trousseau's sign was constantly positive. On August 27 the electrocardiogram showed ST depression as occurs in hypokalaemia. On three occasions generalized convulsions with opisthotonos occurred during severe attacks of tetany. She gradually became weaker, with rapid shallow respirations, and died on September 2. The biochemical findings on the last two days of life were those of a hypochloraemic hypokalaemic alkalosis, and are shown in the Table.

Date	Plasma CO_2 Vols./100 ml.	Serum K mg./100 ml.	Plasma Cl mg./100 ml.	Serum Ca mg./100 ml.	Serum Na mg./100 ml.	Serum Inorganic Phosphorus mg./100 ml.
Aug. 25	82		374	7·5		
,, 26	82		410			
,, 28	82	13	386	8·5	345	3·7
,, 30			386	8·5		
,, 31	92	13	421		345	

On August 28 the serum alkaline phosphatase was 5 K.-A. units. On August 31 the serum albumin was 2·1 g.% and globulin 3 g.%.

At the post-mortem examination there was evidence of active tuberculous meningitis.

Discussion

One month after this patient had died, Borst *et al.* (1950) showed that liquorice had a deoxycortone-like action, and Strong (1951) has reported that two patients with tuberculosis who received P.A.S. flavoured with liquorice developed tetany with similar electrolyte findings to those of my patient. Also, Strong was informed by Cayley, who had recorded the development of hypokalaemia in three patients having P.A.S. (Cayley, 1950), that liquorice had also been given in his cases.

There seems to be good circumstantial evidence that liquorice was responsible for the electrolyte changes shown by these patients and the fatal case here recorded. The tetany seems to have been less severe in the cases reported by Strong than in the present case. His patients, although having cramps and positive Trousseau's sign, had a negative Chvostek's sign, but my patient had facial, carpopedal, and laryngeal spasm, with convulsions. The low serum calcium was due to the hypoalbuminaemia (2.1 g. of albumin per 100 ml.). The presence of a normal urinary calcium, as estimated by Sulkowitch's reagent, suggests that the diffusible calcium was normal in amount in the serum. Thus the tetany was unrelated to the low serum calcium.

Hypochloraemic hypokalaemic alkalosis is found in Cushing's syndrome and can be produced in man by cortisone, but the only evidence I can find of its production by D.C.A. is recent work by Seldin *et al.* (1951). These workers suggest, as a result of experiments, that D.C.A. has no direct effect on the renal excretion of potassium, but that a potassium diuresis may follow D.C.A. administration as a passive consequence of sodium retention. They were able to produce a hypochloraemic hypokalaemic alkalosis by D.C.A. if sodium was given freely, and in fact my patient was receiving the sodium salt of P.A.S., and was later given intravenous sodium chloride because of the hypochloraemia. Tetany is not mentioned by these workers, nor in reports of cortisone toxicity, and in fact the low serum potassium would make the occurrence of tetany unlikely. Tetany in