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EDATHAMIL CALCIUM-DISODIUM (VERSENATE) IN TREATMENT OF LEAD POISONING IN CHILDREN

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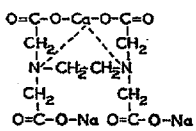
THE TREATMENT of both acute and chronic lead poisoning in children has been unsatisfactory; acute encephalopathy leading to death or gross mental defect in a high proportion of instances, while the less dramatic forms of infantile plumbism have frequently been followed by failure of orderly cerebral maturation.[1] Various methods of treatment, such as surgical decompression, measures directed at depositing circulating lead in the skeleton, deleading with sodium citrate or dimercaprol (BAL), have had little influence on the outcome. Recent publications have suggested that edathamil calcium-disodium (calcium disodium ethylenediaminetetraacetic acid; Ca EDTA; calcium versenate) is an effective agent in safely and rapidly removing lead from the body.*

The drug is a chelating agent of the following structual formula:



It is soluble in water and the usual watery intravenous solutions such as liquid dextrose and isotonic sodium chloride solution. It forms un-ionized soluble very stable complexes with metallic ions, the two nitrogen atoms supplying a resonating bond each, helping to attach the metallic ion more firmly to the complex. In vitro, in a general way, heavier metallic ions tend to replace lighter metallic ions from the central position; thus calcium displaces magnesium, and copper, calcium; lead, copper, and uranium, lead. In living tissue, however, competing substances interfere with this series; beryllium and copper are bound more tightly by tissue than by edathamil and cannot be removed from the body; cobalt and nickel, on the other hand, can be quickly and quantitatively removed from living animals by edathamil.

Lead occupies an intermediate position. Given simultaneously with lead, edathamil protects the animal from large doses, but it is still possible to cause lead

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Edathamil used in these studies was supplied by the Riker Laboratories, Inc.

From the Department of Pediatrics, Harvard Medical School, and the Children's Medical Center.

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* References 2 and 3.

poisoning by using still larger doses of lead edathamil. Given to animals already given lead, the metal is well removed from most of the soft tissues but the store in the skeleton is only slightly reduced. There is also some tendency of the lead content of the bone marrow to increase.[4]

The drug is absorbed irregularly from the gastrointestinal tract, where it forms complexes with whatever metallic ions are present. Since these usually include small amounts of lead, the lead content of the urine increases, but it is thought that this increase is secondary to increased lead absorption.[5] This point seems not to be adequately explored as yet. Gastrointestinal symptoms, especially diarrhea, have accompanied the use of the drug by mouth.[3]

The drug is generally used in doses of 1 gm. per 15 kg. body weight per day, divided into two doses, administered intravenously in 250 cc. of 5% liquid dextrose solution, each dose being given over a period of one to two hours. Not more than 5 gm. per 15 kg. body weight should be given in any one week, and not over 10 days of consecutive treatment should be given until more is known of the possible toxic effects of the drug. In the Children's Hospital the drug has been used for three days, followed by a three-day rest period, two or three courses being given each patient.

METHOD AND MATERIALS

Five children with lead poisoning have been treated with edathamil. Diagnostic criteria have comprised three types of information: first, chemical identification of a source of lead; second, the establishment of a constellation of symptoms clinically diagnostic of lead poisoning, and, third, the demonstration of an abnormally great 24-hour excretion.

Paint samples were obtained by one of us (C. M.) from chewed interior paint in tenements occupied by the families. In most instances several layers of paint were involved, but it appeared that chrome green and chrome yellow were the offending sources. It was necessary in obtaining paint samples to scrape or sandpaper the paint down to bare wood to insure adequate sampling. The fact that the paint had been chewed was also established by the house visit.

The clinical diagnosis of lead poisoning depended on establishing three of the major symptoms or signs of lead poisoning. These were considered to be (1) secondary anemia with basophilic stippling of the red cells; (2) coproporphyrinuria †; (3) glycosuria in the presence of a normal blood sugar; (4) x-ray evidence of condensation of the zones of provisional calcification at the metaphyses of the shafts of the long bones; (5) clinical signs of involvement of the peripheral or central nervous system with or without increase in cells or total protein or both in the spinal fluid; (6) vomiting, cramps, and constipation. Since none of these symptoms or signs are peculiar to lead poisoning, the combination of at least three of these symptom groups was required to form a diagnostic constellation.

In four instances toxic levels of lead excretion, i. e., over 80 γ per 24 hours, as measured by a modified Fairhall method,[6] were demonstrated. It has been shown in another article that lead poisoning can exist in the presence of a normal level of excretion.[6] Urine samples were collected with precautions to prevent contamination with lead. Since the combination of lead and edathamil was too stable to allow the estimation of the lead in the urine by the Fairhall method, a modification of the method developed by the Massachusetts Division of Industrial Hygiene ‡ was used. A 5 cc. sample of urine was digested with 5 cc. of concentrated nitric acid in a porcelain crucible and ashed in a furnace at 500 C. The resulting ash was dissolved in 10 cc. of 1 N hydrochloric acid, the crucible being rinsed with a second 10 cc. of acid and the analysis carried on as recommended in the directions from the state laboratory beginning after the process of digestion.

† Qualitative coproporphyrin tests were done by acidifying urine with dilute sulphuric acid, extracting with ether, and observing the presence or absence of pink fluorescence in the ether layer on exposure to ultraviolet light (Wood's lamp).

‡ Elkins, H. B.: Personal communication to the authors.

In this method the quantitation of lead was made by direct colorimetric methods. Limitation of the accuracy of the method was due to the fact that the dithizone solution in itself was intensely colored and that the color changes produced in it by the addition of small amounts of lead were so slight as to preclude accurate measurement. An error of ± 25% seemed inherent in the method when applied to amounts of lead below 50 γ, but with larger amounts accuracy increased. All analyses were made in duplicate and averaged. For the purpose of indicating the very large increases in lead excretions found after the use of edathamil the method seemed adequate. Rubin and others[7] have recently published observations on the treatment of lead poisoning in human beings with edathamil calcium-disodium and have included in their article a discussion of methods of analysis of urine containing lead edathamil.

The patients were all seen in the Children's Hospital, Boston, and treated there. During the past six months seven patients with lead poisoning have presented themselves; of these, however, two were in extremis when they arrived at the hospital and died within two or three hours. They will not be further considered.

RESULTS

The clinical findings and sources of lead as well as the pretreatment level of lead excretion per 24 hours are presented in the Table. Adequate sources of lead were demonstrated in four instances. Patient 5 had the habit of picking flecks of paint

Pertinent Findings on Admission of Five Patients Selected for Edathamil Treatment

Patient	Lead in Paint Chewed, %	Anemia with Stippling	Copro-porphyrin in Urine	Glycosuria	Constipation with Cramps	X-Ray Changes in Bones	Encephalopathy	Spinal Fluid Abnormalities	24-Hr. Urine Lead, γ
1	12	X	X	X	X	0	X	X	200
2	21	X	X	X	X	X	X	X	152
3	18	X	X	X	X	X	X	X	156
4	18	0	X	X	0	X	0	X	228
5	?	X	X	0	X	X	0	0	34

off the outside of houses up and down the street and eating them. There was no assurance of which paint she had eaten, and adequate sampling seemed impossible. All save Patient 5 excreted clearly toxic amounts of lead. Patient 5 excreted an amount well within the normal range, but, as shown previously,[6] this fact does not exclude lead poisoning. Clinically all showed a constellation of symptoms indicative of lead poisoning.

The chemical results of treatment are shown in Figures 1 to 5. In each instance an increase in lead output in the urine varying between tenfold and fortyfold was produced, and in each instance a very rapid amelioration of symptoms occurred. Patient 1, who was suffering from coma and convulsions when treatment began, was sitting up feeding herself 36 hours after the institution of treatment with edathamil and began to talk in 48 hours. None of the others was so severely ill, but all were free of abdominal complaints promptly, and mild confusion seen in Patient 3 was improved the following day.

Coproporphyrinuria, usually very persistent in lead poisoning, disappeared in from 7 to 10 days after the beginning of treatment. In one patient it was not adequately investigated.

Spinal fluid total proteins in the three patients in whom second lumbar punctures were done had returned to normal in 5 to 18 days. Again, relevant observation was not made in one patient.

In none of these patients was there any clear-cut change in the hemoglobin, red blood cell count, or platelets during hospitalization. In two patients a mild increase in reticulocytes, from 1.1% and 0.8% to 3.6% and 2.1%, respectively, occurred during hospitalization. In no patients was there a clear change in the level of hemoglobin in the two or three months following treatment, but two of the patients continued to chew paint in spite of all attempts to prevent it.

Patient 1, who had epilepsy controllable with phenobarbital following recovery from acute encephalopathy, tended to have convulsions whenever edathamil was given unless the dose of phenobarbital was increased from 60 mg. to 120 mg. daily.

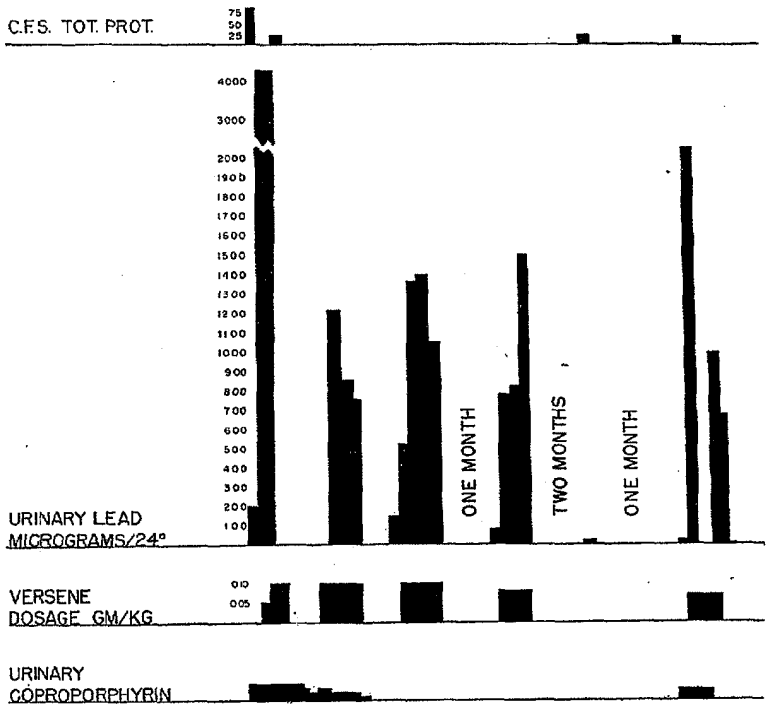

Fig. 1 (Case 1).—Urinary excretion of lead in micrograms per 24 hours before and during edathamil treatment, correlated with total protein in spinal fluid and urinary coproporphyrin.

Periods ranging from five months to two months have elapsed since the completion of the first course of treatment in these patients. Two continued to chew painted wooden surfaces in spite of efforts by parents, social workers, and others to substitute healthier satisfactions. The habits of these children point to the necessity of removing the lead from the child's environment by stripping off all suspect paint from woodwork within range of the child's chewing or removing the child from the paint by finding new quarters in a housing project with brick walls and newly painted inside trim.

Patient 1 apparently gave up pica after her first admission, for no clear reason. She has since had two rather acute upper respiratory infections with mild fever and acute cervical lymphadenopathy. In relation to both of these coproporphyrinuria returned, but none of the other signs of lead poisoning reappeared. During one of these episodes, 24-hour lead excretion was found to be 13 γ, well in the normal range. Because the coproporphyrinuria suggested tissue damage, this child was treated three months and five months after the original courses, and large excretion of lead resulted.

Patient 3 also had an acute upper respiratory infection a month after her original two courses of edathamil; her blood, which had been free of stippled cells, again

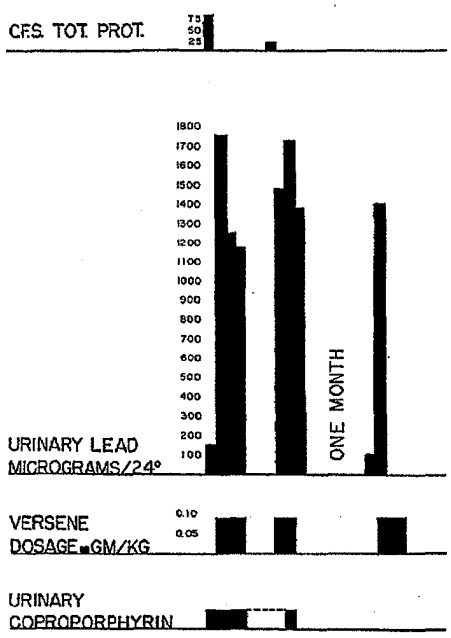

Fig. 2 (Case 2).—Urinary excretion of lead in micrograms per 24 hours before and during edathamil treatment, correlated with spinal fluid total protein and urinary coproporphyrin. (The dotted line in the coproporphyrin figure indicates that no observations were made on the indicated days.)

showed stippling, her urine showed small amounts of coproporphyrin, and abdominal cramps and constipation again developed. She and her twin sister, who had no signs of infection or plumbism, were both treated again. Both had urinary lead outputs in the high-normal range prior to treatment, but Patient 3, with infection, immediately excreted large amounts of lead when given edathamil, whereas her sister, who remained free of infection, showed a much slower rise in rate of lead excretion and smaller total excretion.

These observations support the hypothesis that during infection lead is transported from the skeleton to the soft tissues and indicate that infection in a child

with recent lead poisoning should be regarded as a serious health hazard, requiring treatment in hospital with edathamil. Such episodes may well contribute to the failure of normal intellectual maturation described by Byers and Lord.[1]

CONCLUSIONS

Edathamil calcium-disodium appears to be a safe agent for rapidly eliminating large amounts of lead from the body.

Much of the lead removed probably comes from the soft tissues.

Clinical evidence of plumbism rapidly clears with such treatment.

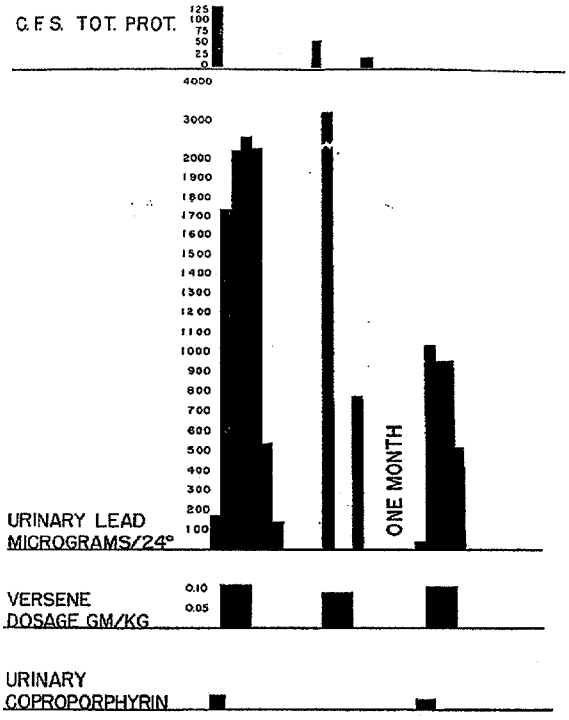

Fig. 3 (Case 3).—Urinary excretion of lead in micrograms per 24 hours before and during edathamil treatment, correlated with spinal fluid total protein and urinary coproporphyrin.

After treatment most children will again indulge in pica, and removal of all lead paint from their environment is of great importance.

After treatment with edathamil, lead remains in the skeleton, from which it is excreted over a prolonged period.

Metabolic stress, such as fever, acidosis, or alkalosis, tends to increase the rate of release of lead from the skeleton and its transportation to soft tissues, thus producing recurrent episodes of lead poisoning.

Such metabolic stresses in children who have had lead poisoning within a year should be treated promptly with edathamil.

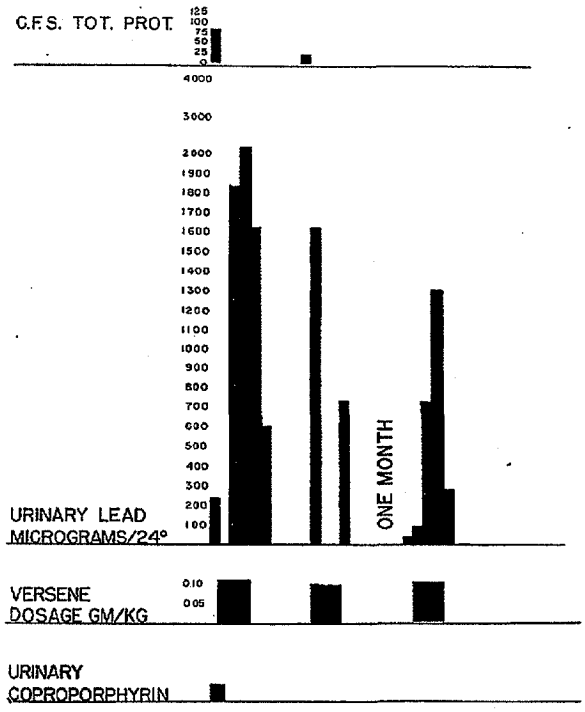

Fig. 4 (Case 4).—Urinary excretion of lead in micrograms per 24 hours before and during edathamil treatment, correlated with spinal fluid total protein and urinary coproporphyrin.

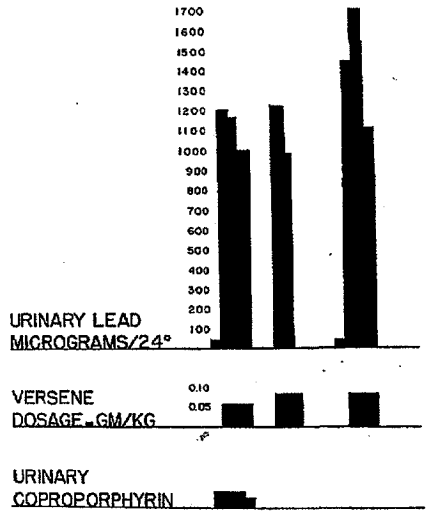

Fig. 5 (Case 5).—Urinary excretion of lead in micrograms per 24 hours before and during edathamil treatment, correlated with urinary coproporphyrin. Spinal fluid was normal at all examinations.

Since completion of this manuscript an excellent article on this subject by Karpiniski and others [8] has been published. Analyses for urinary excretion of lead following edathamil treatment, measured by two different methods, gave results in general accord with ours. The chemistry and pharmacology of the drug are well discussed, as are methods of analysis.

REPORT OF CASES

CASE 1 (No. 391197).—L. E., a girl aged 4½ years, was the first child of healthy parents. She had been developmentally slow, walking at 16 months and talking at 2½ years. For five or six months she had chewed on various wooden objects, including window sills, the paint from which showed 12% lead by weight. For three months she had complaints of abdominal cramps, constipation, vomiting, and weight loss; three weeks before admission her legs became weak and she had stopped walking. Two weeks before admission coma and convulsions had developed and she was admitted to another hospital, where no diagnosis was made.

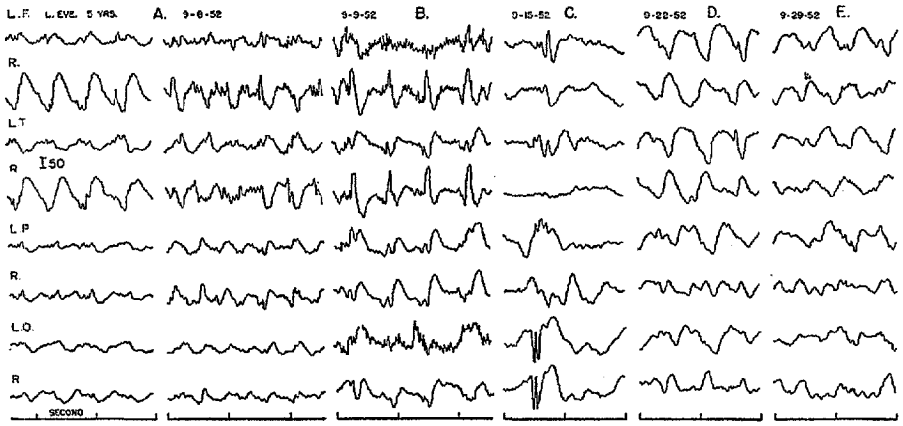

Fig. 6 (Case 1).—Successive electroencephalograms. Treatment with edathamil began on Sept. 17, 1952, between samples *C* and *D*. Calibration with 50 beside it indicates 50 μv.

On admission to the Children's Hospital she exhibited coma and generalized convulsions but no edema of the optic discs. Tendon reflexes were not obtainable. The hemoglobin level was 9 gm. per 100 cc., and the red cells showed hypochromia and stippling on smear. Reticulocytes numbered 0.8% of red cells. Urine examination showed glycosuria and coproporphyrinuria. Cerebrospinal fluid showed a total protein of 89 mg. per 100 cc. and 160 lymphocytes per cubic millimeter. X-rays of the long bones did not show changes compatible with lead poisoning. An electroencephalogram showed diffuse slowing and right temporal spike focus (Fig. 6*A*). A pneumoencephalogram was normal. Her weight was 16 kg. A 24-hour urine sample showed 202 γ of lead. She was treated with 0.5 gm. of edathamil calcium-disodium twice daily, and on the first day her urinary lead excretion rose to 4,210 γ per 24 hours. Figure 1 describes her subsequent courses. Spinal fluid was examined on the eighth day of treatment and showed no leucocytes and a total protein of 19 mg. per 100 cc. Forty-eight hours after beginning of edathamil therapy the patient was talking and feeding herself.

The patient developed epilepsy, with a diffusely abnormal electroencephalogram (Fig. 6*B*), a few weeks after treatment. The convulsions were controllable with phenobarbital, 60 mg. daily, but when the patient was readmitted for edathamil treatment control of the convulsions was incomplete on 120 mg. of phenobarbital a day.

Three months and five months after discharge she had upper respiratory infections, cervical adenitis, and fever. With each of these episodes coproporphyrinuria returned and convulsions became more frequent.

Reticulocyte counts varied from 0.8 to 5.4% at various times in her course, being at their highest in the few days following her first course of edathamil.

Thymol turbidity and cephalin flocculation tests were negative one month after her first course of treatment. Total serum bilirubin was 0.8 mg. per 100 cc.

CASE 2 (No. 392968).—K. T., a girl aged 1 year and 10 months, was the third child of healthy parents. She and her siblings had shown pica of a moderate sort for some months, but in the two months prior to admission the patient had chewed paint extensively from window sills in the old tenement where the family lived. For three weeks she had complained of vomiting and was constipated. Weakness of her legs had been apparent for a week or two, and she had vomited before breakfast repeatedly.

Physical examination showed a talkative overactive immature girl who was pale and could not lift her feet up steps. Her knee jerks were hyperactive, and there was a positive Babinski sign on the left. Her urine showed glycosuria and coproporphyrinuria. Her hemoglobin was 7.6 gm. per 100 cc., and the red cells showed hypochromia and stippling on smear. Reticulocytes were 1.1% of the red cells. Cerebrospinal fluid showed no leucocytes but a total protein of 72 mg. per 100 cc. X-rays of the long bones were consistent with heavy-metal ingestion. Samples of paint from the chewed window sills showed 21% lead by weight. The patient's weight was 1,200 gm. A 24-hour collection of urine showed 151 γ of lead, a figure well in the toxic range.

Edathamil calcium-disodium, 0.5 gm., was given in 250 cc. of 5% dextrose in water every 12 hours over two three-day periods. Lead excretion rose to a peak of 1,753 γ per 24 hours on the first day of edathamil treatment and was high, as shown in Figure 2, in relation to each dose of edathamil. Collection was continued for 24 hours after the edathamil therapy had been stopped, and lead excretion continued in the same high range.

On readmission a month later the patient had still been chewing lead paint from the window sills, as it had not been removed by the family. At this time her blood showed a hemoglobin level of 10 gm. per 100 cc., no stippled cells, and 3.6% reticulocytes. A 24-hour collection of urine prior to treatment showed 105 γ of lead. Coproporphyrin was present in the urine. She was given a third three-day course of edathamil treatment, but because of cystitis urine collection could not be made.

CASE 3 (No. 396376).—E. St. C., twin sister of Patient 4, was 16 months of age when admitted to the hospital because of vomiting, constipation, and unsteadiness of gait of about one week's duration. She had walked at 12 months and had a vocabulary of several words prior to her admission. Physical examination showed a somewhat apathetic pale unsteady child who weighed 1,000 gm.

The hemoglobin level was 9 gm. per 100 cc. with a moderate number of stippled red cells on smear. The patient had mild glycosuria, and her urine was strongly positive for coproporphyrin. X-rays of the long bones showed condensation of the zones of provisional calcification consistent with lead poisoning. Her spinal fluid showed 21 leucocytes per cubic millimeter and a total protein of 131 mg. per 100 cc. Examination of paint samples chewed by the patient and her sister showed 18% lead by weight. A 24-hour urine collection showed 156 γ of lead.

Edathamil was administered, 0.5 gm. every 12 hours for three days. Lead excretion rose, as measured by the dithizone colorimetric method, to 1,711, 2,126, and 2,432 γ on each of the days during which edathamil was administered. For the next two days lead excretion continued at a high rate, 2,184 and 533 γ per 24 hours, respectively, and on the third day after edathamil treatment it fell to zero.

On the third day after cessation of edathamil treatment her mental state was alert; her spinal fluid showed 12 cells and a total protein of 56 mg. per 100 cc. Her urine contained no qualitatively demonstrable coproporphyrin.

A second course of edathamil in the same dosage was given four days later. In the first 24 hours 3,075 γ of lead was excreted in the urine; further measurements were not made because of hematuria, which seemed to be caused by the indwelling catheter. The day after treatment was finished, the spinal fluid showed 1 leucocyte per cubic millimeter and a total protein of 28 mg. per 100 cc.

The baby was readmitted six weeks later for a third course of treatment because of an upper respiratory infection of four or five days' duration with fever and vomiting. She had, according to the mother, eaten no paint since discharge. She was pale, with a hemoglobin level of 9.8 gm. per 100 cc., and approximately 0.2% red cells showed basophilic stippling. Her urine showed a faintly positive test for coproporphyrin. A 24-hour collection of urine showed an output of 35 γ per 24 hours.

Edathamil was again administered, 0.5 gm. intravenously twice per 24 hours for three days. Urinary lead excretion during the three days of treatment was 1,026, 962, and 965 γ per 24 hours, respectively, and on the following day was 532 γ.

CASE 4 (No. 397207).—B. St. C., twin sister of Patient 3, was admitted at 16 months of age because she had chewed the same paint as Patient 3. She had walked at 11 to 12 months and was using one or two words, though not as many as her sister. She had no symptoms of lead poisoning. On physical examination she was pale and alert, and her weight was 1,200 gm. Her hemoglobin level was 9.0 gm. per 100 cc.; the red cells showed achromia but no stippling. Her urine contained small amounts of glucose and was strongly positive for coproporphyrin. X-rays of her long bones showed condensation of the zones of provisional calcification. Her spinal fluid showed no cells but contained 85 mg. per 100 cc. of total protein. A 24-hour urine sample showed 228 γ of lead.

Edathamil was administered intravenously, 0.5 gm. at 12-hour intervals for three days. The first day's urine collection was lost, but on the second and third days she excreted 1,875 and 2,017 γ, respectively, and on the two days after cessation of edathamil therapy, 1,610 and 596 γ per 24 hours, respectively.

When this collection was completed, her spinal fluid total protein was found to be 9 mg. per 100 cc., and coproporphyrin could not be demonstrated in her urine.

A second course of treatment was given, beginning three days later, and on the first day of treatment she excreted 1,629 γ of lead. Collections were then omitted because of mild cystitis during the subsequent two days, but during the first 24 hours after cessation of edathamil treatment she excreted 728 γ of lead.

Six weeks later she was readmitted with her sister, who had an upper respiratory infection and whose laboratory tests showed signs of lead poisoning. Patient 4, save for hemoglobin of 10 gm. per 100 cc., had none of the clinical evidences of lead poisoning. A 24-hour collection of urine showed 38 γ of lead.

In the ensuing three days she received 1 gm. of edathamil intravenously each day; her urinary excretion of lead rose to 106, 737, and 1,304 γ, respectively, in each successive 24 hours and during the first 24 hours without edathamil was still 298 γ.

CASE 5 (No. 392564).—A. H., a girl aged 2½ years, was admitted to the hospital because of vomiting and attacks of abdominal pain. There was a clear history of the ingestion of flakes of paint from the outsides of houses in the neighborhood. Many neighboring women had sent the child home on finding paint flakes in her month. She had apparently sampled the paint on several houses about the homes of each of her playmates. Samples of the paint from her own home showed no lead, and no lead was found in the drinking water.

Her physical examination showed nothing remarkable save for moderate pallor. Laboratory examination showed a hemoglobin level of 9.5 gm. per 100 cc., moderate achromia, and a few stippled red cells on smear. Her urine showed no glucose but abundant coproporphyrin. Her spinal fluid was normal. X-rays of the long bones showed condensation of the lines of provisional calcification in the metaphyses consistent with lead poisoning. Her weight was 16 kg. A 24-hour urine sample showed 34 γ of lead, a value in the normal range.

With a probable source of lead, abdominal complaints, anemia with stippling, coproporphyrinuria, and consistent x-ray evidence, it seemed best to regard this as a case of lead poisoning in spite of the normal urinary output of lead, and treatment was decided upon.

Edathamil, 0.5 gm., was given intravenously every 12 hours for three days. Urinary lead output rose to 1,203, 1,158, and 994 γ per 24 hours on each day. After three days rest the dose of edathamil was increased from 0.6 to 0.9 gm. per kilogram by giving 0.5 gm. of edathamil every eight hours. On this dosage urinary lead output was 994, 858, and 1,216 γ per 24 hours. Twenty hours after the second course the urine showed no coproporphyrin.

One week later the patient was readmitted with vomiting, slight fever, and acetonuria. Her pica had continued at home.

On physical examination her liver edge was palpable at the costal margin. Thymol turbidity, cephalin flocculation, and serum bilirubin values were all normal.

Her urinary output of lead was 32 γ per 24 hours. Edathamil was again given, at a rate of 0.75 gm. twice a day for three days, and the urinary outputs of lead were 1,440, 1,748, and 1,102 γ, respectively. At the end of this course of treatment liver-function tests showed thymol turbidity, 0; thymol flocculation, ± 1 minute; bilirubin, 0.06 mg. per 100 cc.; total bilirubin, 0.6 mg. per 100 cc.; cephalin flocculation, 1+.

She returned home and was symptom-free for four months. While housed in the winter she had not been observed to exhibit pica, but when she went outdoors to play in March the pica recurred, and three weeks or so later she was readmitted with a recurrence of her abdominal complaints. Her liver was no longer palpable. She now weighed 18 kg. Her hemoglobin level was 9.8 gm. per 100 cc.; no stippled cells were seen on smear. Her urine showed no sugar but was strongly positive for coproporphyrin. She was given edathamil, 0.5 gm., intravenously twice a day for three days. Because of hematuria from the catheter no further urinary collections were made. Twenty-four hours after the last dose her urine no longer showed coproporphyrin.

She has remained well since and has been moved to a new neighborhood, where the houses are of brick veneer construction.

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