CLINICAL ROUNDS

From the Massachusetts General Hospital

LEAD POISONING IN CHILDREN

Discussors

RALPH D. FEIGIN, M.D.

Senior Assistant Resident, Children's Service, Massachusetts General Hospital; Teaching Fellow in Pediatrics, Harvard Medical School

DANIEL C. SHANNON, M.D.

Senior Assistant Resident, Children's Service, Massachusetts General Hospital; Teaching Fellow in Pediatrics, Harvard Medical School

STEPHEN L. REYNOLDS, M.D.

Chief Resident, Children's Service, Massachusetts General Hospital; Teaching Fellow in Pediatrics, Harvard Medical School

LILIAN W. SHAPIRO, M.S.W.

Social Case Worker, Children's Service, Massachusetts General Hospital

Editorial Director

JOHN P. CONNELLY, M.D.

Chief, Ambulatory Division, Children's Service, Massachusetts General Hospital; Associate in Pediatrics, Harvard Medical School

Requests for reprints should be forwarded to John P. Connelly, M.D.; Chief, Ambulatory Division, Children's Service, Massachusetts General Hospital, Boston, Massachusetts 02114.

How does lead usually enter the body and what systems are usually involved?

What one symptom above all others should arouse the suspicion of lead poisoning?

In follow up of children with lead encephalopathy, frequently they have a lower I.Q. than their peers. What is the evidence for this?

Should the gastro-intestinal tract of children with lead poisoning be cleared of residual lead before treatment is instituted?

What public health measures are recommended if a case of lead poisoning is discovered?

DR. REYNOLDS: This child with lead poisoning was admitted recently to the Emergency Ward. We are going to discuss the case from two points of view; namely, metabolic and social. Dr. Shannon, the resident physician on the floor, will present the history.

DR. SHANNON: J. M., an 18-month-old boy, was brought to the Emergency Ward the evening of August 17, 1964 by his mother because of persistent vomiting and lack of response to Penicillin and Tetracycline given him by his private physician three days previously for otitis media and pharyngitis. On physical examination, the child was irritable, had symptoms of an upper respiratory infection with rhinorrhea, pharyngitis, right otitis media, and slight nucchal rigidity. A lumbar puncture was performed after the eye grounds were found to be normal. The opening pressure was 200 mm. of spinal fluid. The cerebrospinal fluid protein was 68 mg./100 ml. and

sugar, 65 mg./100 ml. Sixty-six polymorphonuclear and 20 mononuclear cells were seen on microscopic examination.

The mother was questioned retrospectively, and it was discovered that for two or three months prior to admission, the boy had been underactive, irritable and had occasionally vomited without adequate explanation. Since age nine months he had been mouthing many objects, especially the windowsills. About six months prior to admission, a physician reassured the mother that paint used today does not contain lead. Two to three months prior to admission, another physician reassured the mother about the impossibility of lead poisoning as long as he maintained a large milk intake.

While partially treated meningitis was a strong possibility in this case, the history prompted the house officer to obtain skull, knee and abdominal x-rays for signs of lead poisoning. X-rays of the skull (Fig. 1) revealed diastasis of the sutures; those of the knees (Fig. 2) revealed dense "lead lines" in the distal femur and proximal tibia; and an abdominal film (Fig. 3) showed scattered radiopacities in the gastro-intestinal tract, characteristic of lead ingestion, and dense lines in the iliac crest.

The total white blood count was 9,950 cells with 49 per cent mature polymorphonuclear cells, 4 band forms, and 47 per cent lymphocytes. A moderate hypochromia with moderate variation in size and shape and 40 per cent coarsely stippled red blood cells were seen on peripheral smear. The hemoglobin was 9.5 grams. Urinalysis showed a 1 + albuminuria reaction to heat and sulfosalicylic acid. The

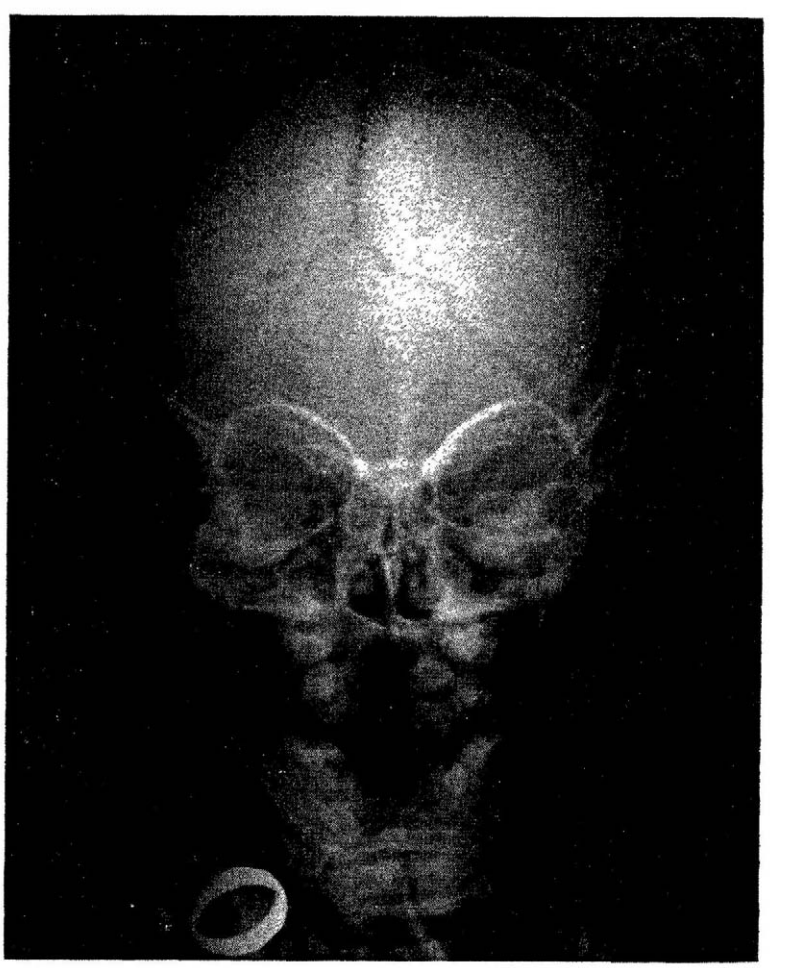


FIGURE 1.

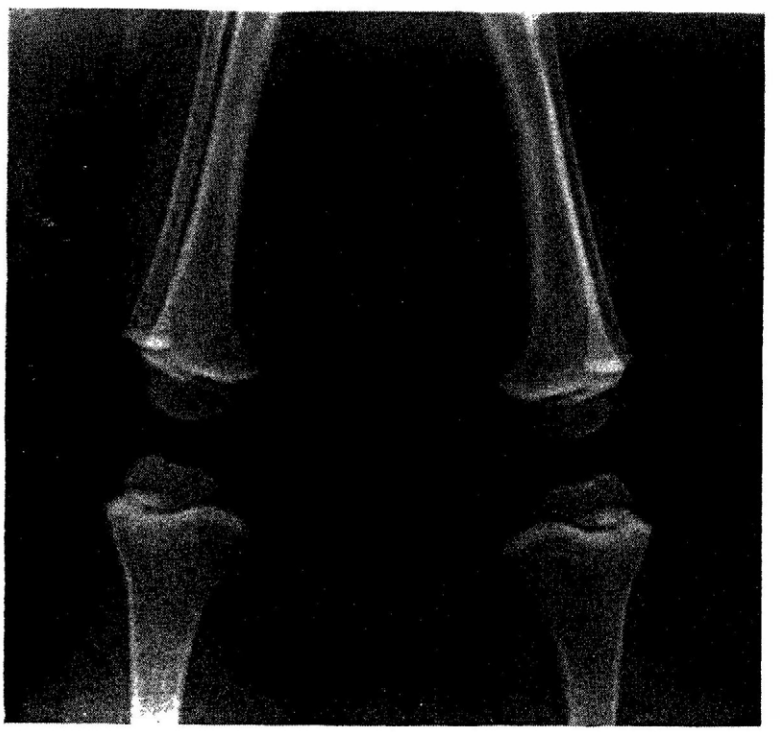


FIGURE 2.

child was then admitted with the presumptive diagnosis of lead poisoning.

In the hospital, blood, cerebrospinal fluid and throat cultures were obtained but no growth occurred. Viral studies were not performed. As a diagnostic and therapeutic maneuver, the child was begun on calcium (ethylene dinitrilo) tetraacetate (EDTA), 75 mg./Kg./24 hours and 24 mg./Kg./24 hours of dimercapral or British Anti-Lewisite (BAL) divided in six doses and given intramuscularly for five days. He excreted 7.2 mg. lead per 24 hours. During this initial course, he was observed at frequent intervals and showed no evidence of increasing intracranial pressure. On the contrary, his irritable disposition was noted to improve dramatically. After a five-day rest another course of treatment was given using only versenate during which he excreted 3.0 mg. of lead per 24 hours. A third and final course of treatment was accompanied by excretion of 5 mg. of lead per 24 hours. Therapy was then terminated and the child was returned home where he promptly began to look for painted surfaces to eat. At this time, oral iron was begun and after five days his pica stopped.

DR. REYNOLDS: I think it is worthwhile to comment on the importance of the history in this case. The admitting physician asked the mother, "Does your child eat anything else but food?" This is a good question in that it is open-ended and does not preclude the description of what the child eats. Her answer, "Oh yes, he eats paint," was elicited because the question was open-ended. Dr. Feigin will discuss the metabolic aspects of the case.

DR. FEIGIN: This child has many features of lead poisoning that are quite typical. He is 18 months of age; 90 per cent of cases tend to occur in the 15 to 36-months age group. This child presented in August; lead poisoning tends to become symptomatic in April through September, or the warmer months of the year in the temperate climate. The explanation for this is not known at this time despite considerable investigation. There is frequently, as there was in this child, a concurrent viral or bacterial infection. Some of these children may have what appears to be febrile seizure at a fever of 100° or 101° F. rectally. The occurrence of the seizure with such a low grade fever should alert the phy-

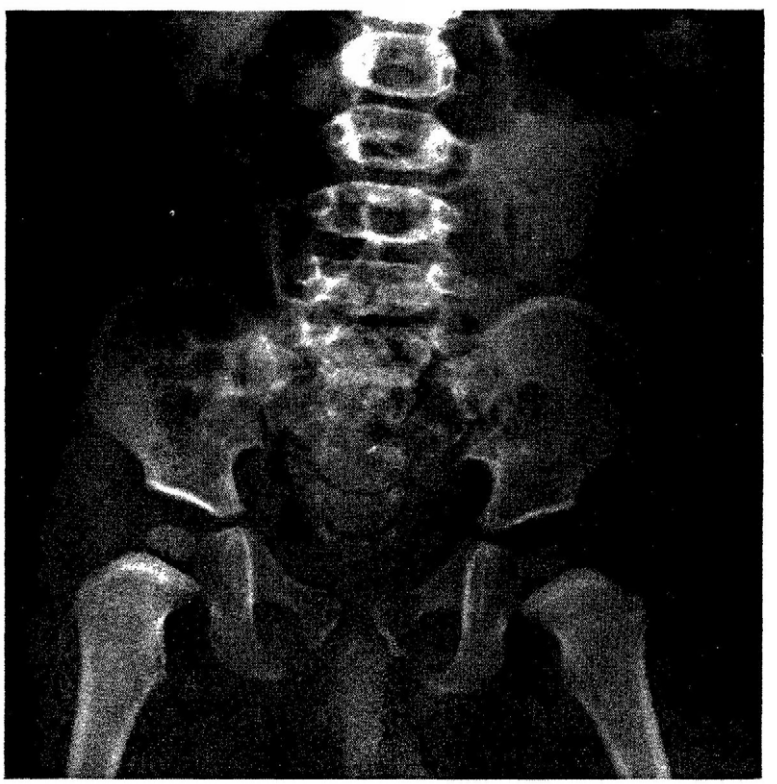


FIGURE 3.

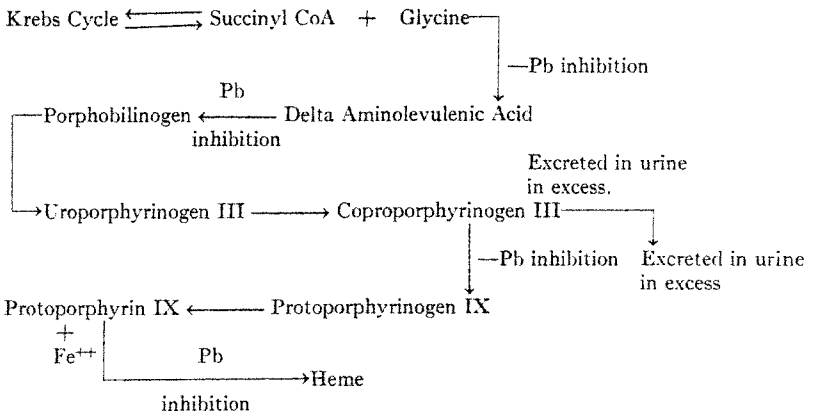
sician to investigate for this possibility. It is difficult to distinguish cases such as this one from meningitis. Sometimes children will be treated for both conditions until a firm diagnosis can be established. If one child in a family has been discovered with lead poisoning, it is advisable to check the other children even if the mother denies the history of pica since several of the published series on this subject note a 30 per cent incidence of simultaneous lead poisoning among siblings. The siblings in this family were found free of lead.

Lead may enter the body through the gastro-intestinal tract, the skin, or the lungs. There have been epidemics of acute lead intoxication in children who have participated in the burning of lead storage batteries and inhaled the fumes. More commonly, a child acquires his lead poisoning in a more chronic fashion from ingestion of paint from cribs or from house paint which even today contains lead. There may be ten or 15 coats of paint on the walls in some of the older homes, and the child will eat down to the lower coats which do contain a good deal of lead. Lead poisoning in childhood may also occur from the ingestion of water going through old lead pipes.

The signs and symptoms of lead intoxication usually involve three main organ systems: gastro-intestinal, hematologic, and the central nervous system. The kidneys are also affected but usually not to an extent that permits their involvement to be clinically discernable.

The one symptom, above all others, that should arouse the suspicion of lead poisoning is a history of pica. It has been estimated that only 10 per cent of parents admit pica at the time the child is first brought for evaluation and the diagnosis of lead poisoning made. When a retrospective history is taken, this percentage rises dramatically. Gastro-intestinal symptoms include recurrent vomiting such as was found in this patient, but vague abdominal pain and constipation may be early symptoms. Only rarely will a child present with a board-like abdomen which is so typical of lead colic in the adult. Some mothers note that the

TABLE 1. *Steps in Heme Biosynthesis**



* From Chisholm, J. J. Jr.: Disturbances in the biosynthesis of heme in lead intoxication. J. Pediat. 64: 174–186, 1964.

child has black stools. These are probably secondary to lead sulfide which can be precipitated in the stool. Although a lead line on the gums is quite common in adults, it is not a frequent finding in childhood lead intoxication.

As mentioned, the hematologic system may be involved. Occasionally, the only clinical sign of a child with chronic lead poisoning will be pallor due to anemia. The anemia is thought to be due to an interruption in the incorporation of protoporphyrin into heme [1] (Table 1). Basophilic stippling is felt to be one of the hallmarks of lead poisoning but is not commonly seen. It is believed that the stippling is due to ineffective incorporation of ribonucleic acid into red cell synthesis. One may see an eosinophilia which is unrelated to lead poisoning. This is thought to be present because children with pica frequently ingest dirt and, with the dirt, theoretically ingest a parasite, such as ascaris or toxocara canis. It is for this reason we make a careful search for intestinal parasites in our lead intoxicated patients.

The symptoms of central nervous system involvement can include drowsiness, lethargy, clumsiness, repetitive falling, ataxia, convulsions and coma. The convulsions follow no particular pattern and may be focal or generalized.

In lead poisoning with encephalopathy, one generally finds an increased cerebrospinal fluid pressure and an elevated protein ranging between 50 and 70 mg./100 ml. although values as high as 200 mg./100 ml. or more have been reported. The older literature makes no mention of the cell counts in lead poisoning. More recent studies note that a slight pleocytosis is present, usually lymphocytic. I know of no data concerning the range of the total cerebrospinal fluid cellular count or the number of polymorphonuclear leukocytes which may be present. In reviewing a number of cases seen at Boston City Hospital during the past four years, the average cell count was found to be between 4 and 15 cells with a predominance of lymphocytes. There were two severely affected children, one with 29 polymorphonuclear leukocytes and other with 59 polymorphonuclear leukocytes in the initial spinal fluid determination, both of whom had encephalopathy. During the past week, Dr. Chisholm from Johns Hopkins Hospital and Dr. Byers from Boston Children's Hospital were contacted. They felt that although it is not the usual presentation, they too had seen cases similar to the one under discussion and claimed that a polymorphonuclear count this high was not inconsistent with a diagnosis of lead poisoning.

There is a 25 per cent mortality in children who have lead encephalopathy. Of the remaining children, approximately 40 per cent have electroencephalographic changes and have generalized or focal seizures. An additional

25 per cent have behavioral problems or a suggestive diminution in their I.Q. In a follow up study [2] of children with lead poisoning encephalopathy, the average I.Q. five years after their encephalopathy was 80 points. Children who had lead poisoning without encephalopathy five years later had an average I.Q. of 87 points. The control group in this study consisted of patients who had a history of pica but from substances other than paint and who had no symptoms of lead poisoning. They had an average I.Q. of 97 points.

Sonkin [3] recently reported a greyish stippling found around the optic disc in some of the cases of lead poisoning which may be seen when looking at the eye grounds with the ordinary ophthalmoscope. Other ocular findings which have been reported include an optic neuritis, ocular muscle paralysis, central visual disturbances and ptosis. The lead neuropathy occurring in adults but infrequently seen in childhood usually consists of some sensory loss or muscle weakness.[4]

Analysis of the urine may reveal glycosuria, albuminuria, acetonuria, and amino aciduria. The amino aciduria has been extensively studied by Dr. Chisholm at Johns Hopkins Hospital.[5] He has demonstrated that there is generalized amino aciduria in lead poisoning, very similar to that seen in Fanconi's syndrome or in renal tubular acidosis. He feels that this is a primary manifestation of the disease and is not the result of versenate or BAL therapy.

The urine of a lead poisoning suspect can be analyzed for coproporphyrins. At this hospital, quantitative coproporphyrins can be obtained on a 24-hour urine. It is probably of more immediate benefit, however, to do a qualitative coproporphyrin determination since this is bedside procedure and can aid in the diagnosis on admission. A qualitative coproporphyrin determination involves taking 5 cc. of urine and acidifying it to pH 4 with glacial acetic acid. This can be checked with nitrazine paper. Five cubic centimeters of urine is then added to an equal amount of ether. The mixture is shaken in a separatory funnel and the ether layer saved. After a few drops of 1.5 normal hydrochloric acid have been added to this layer, a Woods light is shined on it. A pink fluorescence will be seen if there are coproporphyrins present. This pink fluorescence can be graded from 1 to 4 + when compared to commercially available standards.

There are some children in whom the diagnosis of lead poisoning is strongly suspected but difficult to confirm with a simple 24-hour urine lead level. In these cases, we resort to the versenate stimulation test devised by Whitaker *et al.*[6] This consists in the administration of 75 mg./Kg. of body weight of versenate for one day with the simultaneous collection of a 24-hour urine. The established normal values are shown on Table 2. The post drug levels provide a clear-cut differentiation of the child with lead poisoning from the normal.

Treatment consisted first of removing the child from the lead environment. This is usually accomplished in childhood by hospitalizing the patient. The second and equally important part of treatment is drug therapy. For a number of years versenate (Calcium EDTA) has been utilized. The recommended dosage is 75 mg./Kg. of body weight per day given by the intramuscular route, either in four or six divided doses mixed with 1 or 2 per cent Procaine. A five-day course of therapy is given. The child is then observed off therapy for five to seven days. In many cases another course of versenate will be necessary.

TABLE 2. *Versenate Stimulation Test*

	Pre-test—24-hour urine lead excretion		Post-test—24-hour urine lead excretion	
	Range	Average	Range	Average
Normal	0–160 mcg./liter	15 mcg./liter	4–405 mcg./liter	165 mcg./liter
Lead Poisoning Suspect	0– 35 mcg./liter	14 mcg./liter	608–1,570 mcg./liter	995 mcg./liter

During the first 24 to 48 hours of versenate administration, there may be an exacerbation of symptoms. Greengard *et al.*[7] have proposed that this occurs because versenate will promote absorption of whatever lead remained in the gastro-intestinal tract with a resultant increase in its total body stores. Since the chelate is not irreversible, lead may be released into the tissues before excretion can occur, producing an exacerbation of symptoms. To avoid this, he suggested that the patient who is hospitalized have saline enemas until the gut is cleared and that versenate therapy be withheld for 12 to 24 hours. Although this hypothesis is of interest, there is no concrete evidence that the chelating agent increases the absorption of lead present in the gastro-intestinal tract. It has been my personal experience that during the time necessary to cleanse the child's gastro-intestinal tract, some of these children rapidly develop increasing symptoms of encephalopathy. Our present regimen is to give the saline enemas simultaneously with the versenate therapy.

In the last year and a half, we have been using BAL in combination with versenate at a dosage of 24 mg./Kg./24 hours given every four hours intramuscularly for two to five days.[8] If lead encephalopathy is present, we frequently also use intravenous urea in a dose of 1 to 1.5 grams per kilo of body weight to reduce cerebral edema. This may have to be repeated once or twice during the course of the day. In some centers, an operative decompression procedure is done, but the mortality rate seems to be high. At present, we recommend this only when medical management of the cerebral edema is failing.

DR. SHANNON: Why two physicians advised the mother not to be concerned about this child's pica because of alleged absence of lead from paint prompted us to contact the City of Boston Health Department about the current laws governing lead-containing paint. It seems that the law only states that no paint containing lead shall be used to paint the interior of a dwelling. It says nothing about manufacturing paint with lead in it. Although paint used for interiors, in fact, usually does not contain lead, what happens, however, is that people in the lower socio-economic strata are more likely to buy the less expensive outside paint which may contain lead and use it on the interior of their homes. These people are also more likely to live in dwellings that have four to six coats of paint on the woodwork, the base coat(s) containing significant amounts of lead.

A visit was made to the home of this child. The father had just recently repainted the woodwork with inside "lead-free" paint, which on analysis contained 4 mg. per cent lead. A full-thickness sample of the paint from the windowsills on which the patient had been chewing was obtained and shown to contain 13 mg. per cent lead. A sample of the lowermost coat of paint contained 40 mg. per cent lead.

Regarding the late effects of lead encephalopathy, Dr. Feigin has already mentioned one study demonstrating subsequent retarded mental development in children. Kanner[8] states that in 30 patients he has followed, nearly all had low I.Q.'s and 16 of the 30 were severely retarded. Byers[9] studied 20 cases of mild lead poisoning and found a very high incidence of learning problems. Mellins[10] studied 21 cases and found more than 90 per cent were retarded. Moncreif *et al.*[11] recently cited a rather high incidence of lead in the brains of retarded children at autopsy.

Of interest to the practitioner is a study in the form of a questionnaire administered to parents entering a Baltimore clinic.[12] One of the questions asked was, "Does your child eat ashes or dirt?" Only one parent of 784 answered yes. When the parents were asked the same question by a physician, 171 responded yes. The psychological background of children with pica has been the subject of many studies. There is still some disagreement as to whether pica is a primary symptom or whether mild retardation predisposes to pica. Most investigators do agree that these children have a high incidence of infant feeding problems. The patient under discussion was described as a "bottle baby," drinking milk excessively, and eating only cereal and carbohydrates. A preponderance of anxious, rigid mothers who are dependent and unable to

give of themselves to their child has also been noted.

The realistic approach to lead intoxication should emphasize the prevention or at least the early recognition of the problem.

DR. REYNOLDS: We have asked Mrs. Shapiro, the ward social worker, to tell us what she has learned about the preventive public health measures usually taken in problems of this kind.

MRS. SHAPIRO: After interviewing the parents of this child, I called a number of health agencies to ascertain what corrective and preventive measures are being taken in these cases, and was directed to the Boston Health Department. Cases of lead poisoning are reported to the Boston Health Commissioner. After receiving the letter of notification, the district health nurse is sent to the home to inspect the apartment and to make suggestions to the parents. One of her main objectives is to acquaint the family with preventive technics to avoid further lead poisoning. The City Health Commissioner also sends a district health commissioner to evaluate the apartment. The Health Commissioner may, if necessary, bring some pressure to bear on the landlord to comply with his suggestions. A lawsuit may be initiated, but this is rarely effective.

DR. REYNOLDS: There is a study from Chicago in a current public health bulletin [13] in which investigators are able to define areas in which the incidence of lead poisoning is markedly elevated. From personal experience, both Dr. Shannon and I recall that these areas are in the poorer residential neighborhoods where buildings are being torn down, where there is a great influx of migrant populations primarily from the South; and where the landlords are doing very little to maintain the property.

A PHYSICIAN: In spite of the fact that there are many areas of this city where there are older houses, we do not see many patients with lead poisoning from these locales. The question, I think, boils down to why children have pica. One of the reasons set forth is that these children are iron deficient and are searching for iron.

DR. FEIGIN: Even if iron deficiency anemia is demonstrated in these children in the absence of clinical necessity, we do not give iron during BAL and EDTA treatment because the resultant dimercapral-iron complex is very toxic. We wait, as in this case, and provide the iron after completion of treatment.

A PHYSICIAN: How many courses of therapy did you give the boy to de-lead him?

DR. FEIGIN: Two. One course of therapy given to a child who can excrete this much lead in the first 24-hour urine is usually not sufficient. Even though the child clinically appears well at this time, he may present again with the same symptoms unless additional courses of treatment are given.

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