tion of abnormal exposure provides an index of the period of time a patient will require careful medical supervision after exposure ends. Serial blood and urine lead determinations together with urine coproporphyrin (UCP) and δ-aminolevulinic acid (ALA) measurements provide the best index of soft tissue lead toxicity (3,11). Although measurements of δ-aminolevulinic acid dehydratase (ALAD) activity in vitro in hemolysates of blood and free erythrocyte protoporphyrin in peripheral blood can probably provide comparable information; they are not, at this writing, as well standardized as the other measurements. Administration of chelating agents rapidly reduces the lead content of soft tissues.

The most severe clinical manifestation of intoxication is acute encephalopathy, which is more frequent in children than in adults, carries a significant mortality and results in severe permanent brain damage in at least 25 per cent of survivors. Since one of the main goals of therapy is to prevent injury to the central nervous system, it is axiomatic that treatment must be started before classic signs of increased intracranial pressure make the diagnosis of encephalopathy obvious.

Accurate lead analyses may be difficult to obtain but are essential to proper treatment. Blood samples must be collected into lead-free equipment and analyzed by a laboratory experienced in lead determinations. Risks with respect to the acute adverse effects of increased lead absorption may be estimated in terms of current blood lead concentrations as follows: a) >40 μg Pb/100 g whole blood indicates undue lead exposure; b) 50–79 μg Pb/100 g indicates excessive absorption, is associated, in most instances, with metabolic evidence of impaired heme synthesis and may, in some instances, be associated with mild symptoms compatible with lead poisoning. Such cases require careful medical supervision and should be considered possible cases of plumbism, especially in anemic patients. Blood lead concentrations of more than 80 μg Pb/100 g whole blood indicate risks which in children are unacceptable; virtually all cases of severe acute lead poisoning, including those with acute encephalopathy, are associated with blood lead concentrations of 100 μg Pb/100 g whole blood or greater. At blood lead concentrations of more than 80 μg Pb/100 g whole blood, symptoms may be absent, but onset of severe acute illness is unpredictable.

CHILDHOOD LEAD INTOXICATION

Lead poisoning in childhood should be approached as a chronic disease because of the long-term high-dose type of exposure to which

Table 1. Environmental Exposure of Young Children to Lead in Urban Housing

Residence	No. of children	Children with: Abnormal urine* No.	%	Plumbism No.	%
Old housing	801	216	27	38	4.7
New housing project	105	3	—	0	0

* Concentration of both lead and coproporphyrin increased
[From Griggs et al (10)]

same household so that all preschool children should be tested for plumbism wherever an index case is found. Prospective screening programs are currently in operation in Chicago and New York. Recently, cases of severe lead poisoning have been traced to the contamination of juices (and other acidic beverages) stored in improperly lead-glazed earthenware vessels.

Prompt Diagnosis

An indirect epidemiologic approach is essential for prompt clinical diagnosis since a history of pica often is not elicited at the first clinic visit. We ask the following questions: a) Does the child live in or visit a house built prior to World War II? (A list of high-risk addresses should be posted in all pediatric clinics to aid physicians

Table 2. Uncommon Non-industrial Types of Potentially Hazardous Environmental Lead Exposure

Children	Adults	Children and adults
Toys and child furniture (beware of items repainted by relatives)	Bootleg whiskey	Improperly lead-glazed dishware and cookware
Lead toys and baubles*	Ceramic and pottery glazing in home	Soft well-water conveyed in lead pipes
Lead nipple shields	Home battery manufacturing	Ashes and fumes of painted wood and battery casings used for fuel in stoves and fireplaces
	Lead dust in shooting gallery (attendant at risk)	
	Artist's paint pigments (hand-mixing)	

* [Plastic beads, necklaces and jewelry coated with lead to simulate a pearl appearance, are sources, often unnoticed.—Ed.]

Table 3. Laboratory Determinations Required for Diagnosis of Lead Intoxication in Children

Test	*Technical factors*	*Interpretation*
EMERGENCY TESTS FOR RAPID PRESUMPTIVE DIAGNOSIS		
Qualitative urinary coproporphyrin (UCP) test (2)	See Appendix p 612 for procedure; peroxide-free ether required–test urine within 10 min after voiding	Intense orange-red fluorescence (+++ or ++++) often associated with blood lead > 100 μg Pb/100 g whole blood and, therefore, is indication for immediate hospitalization and chelation therapy in symptomatic children even if all other presumptive tests negative–test may give misleading negative results initially in moribund patients and severely iron-depleted children not regenerating heme–moribund patients usually have glycosuria and other urine abnormalities
X-rays		
Flat plate of abdomen	Use KUB technique; look carefully in rectosigmoid area for radiopaque flecs when rest of intestine appears negative	Abdominal flat plate positive for radiopaque material in approx. 50% of symptomatic young children; rarely positive in adults
PA views of wrists and knees	Must be differentiated from growth arrest lines: "lead lines" at metaphyses are broad (>2 mm) continuous bands of increased density, whereas growth arrest lines appear as multiple narrow discrete lines; study films under bright light	Interpret bone films with respect to child's age: a) <2 yr: "lead lines" frequently absent in symptomatic cases b) 2–5 yr: "lead lines" usually present and may show "seasonal banding" c) >5 yr: "lead lines" rarely prominent. Width of "lead lines" reflect duration of increased lead absorption but is unrelated to symptoms
Hemoglobin, hematocrit, reticulocyte count, smear for morphology (basophilic stippled cell count)	Basophilic stippled cell count requires specialized technique not usually available in general hospital laboratories	Hb usually <10 g; findings as in untreated iron deficiency states except reticulocytes often increased; basophilic stippled cell counts in peripheral blood of children too variable to be helpful but basophilic stippling of normoblasts in bone marrow smears uniformly increased (>50%) in plumbism in children and adults–hematocrit required for interpretation of blood lead since 90% of lead in whole blood is attached to red blood cell surface, correct blood lead data for very low hematocrits

case. The rate of intravenous infusion is adjusted hourly until that rate is found which will maintain the rate of urine flow within basal metabolic limits (0.35 to 0.5 ml urine secreted/calorie metabolized/24 hr). This is equivalent to a daily urine output of 350 to 500 ml/sq m/24 hr. Children with encephalopathy behave as though their secretion of antidiuretic hormone is inappropriate; the above technique is essential to avoid excessive fluid administration which can further increase cerebral edema.

All oral intake is prohibited until the child is greatly improved. Body temperature is maintained at normal but not hypothermic levels by using a cooled oxygen tent, supplemented by cooling blankets when necessary. Oxygen is administered.

For the quick control of seizures, Valium® is effective. In patients with acute encephalopathy, control can be maintained thereafter during the first few days of treatment with repeated doses of paraldehyde. Barbiturates and diphenylhydantoin are better reserved for long-term anticonvulsant use. During the acute phase, one should not await frank seizures. Better control can be achieved if doses of paraldehyde are given whenever there is a significant increase in muscle tone or muscle twitching. Administration of paraldehyde should overlap the institution of long-term anticonvulsant therapy with barbiturates in order to prevent seizures from recurring during the early convalescent phase. Barbiturates should be avoided during the first few days because severely depressant amounts are often needed and even then may be ineffectual.

Chelation Therapy

After urine flow is established, which should require 2 to 3 hours at most, chelation therapy is started with 2,3-dimercaptopropanol (BAL) and edathamil calcium disodium (CaEDTA, calcium disodium versenate) in combination according to the dosage schedule shown in Table 4. This combination is used in all symptomatic patients.

In cases of acute encephalopathy, the usual 5-day course may be extended to 7 days if great clinical improvement has not occurred by the fourth day. In symptomatic patients without encephalopathy, who show a quick and dramatic clinical response, and in those asymptomatic patients with whole blood lead concentrations in the range of 100–200 μg Pb/100 g, BAL may be discontinued after 2 to 3 days and the dosage of CaEDTA may be reduced to 50 mg/kg/day, in divided doses, as either two 6-hour intravenous infu-

Table 5. Choice of Chelating Agents Based on Symptomatology and Blood Lead Concentration

Clinical presentation	*Chelating agent**	*Comment*
A. CHILDREN		
1. All symptomatic cases	BAL-CaEDTA (IM)	Any symptoms in children call for at least one 5-day course
a. Acute encephalopathy	BAL-CaEDTA (IM)	First course 5–7 days; give second 5-day course if blood lead >80 μg Pb/100 g whole blood 14–21 days after first course; transfer patient to convalescent hospital for 3–6 mo course of oral D-penicillamine
b. Intoxication without encephalopathy	BAL-CaEDTA (IM)	First course 5 days only; indication for second course same as above; follow with oral penicillamine (3–6 mo) if blood lead >60 μg Pb/100 g whole blood and long bone X-rays show prominent "lead lines"
2. Asymptomatic cases		
a. Blood lead >100 μg Pb/100 g whole blood	BAL-CaEDTA (IM)	Choice for first course indicated by blood lead; follow with oral D-penicillamine as above (section 1b)
<100 μg Pb/100 g whole blood	CaEDTA only (IM)	
3. Long-term followup care		
a. Intercurrent infection, demineralizing disorders	CaEDTA only (IM)	Give 3-day course whenever significant increase in UCP and/or ALA occurs even if no increase in blood lead occurs
b. Recurrent ingestion	BAL-CaEDTA (IM) or CaEDTA only (IM)	Choice same as for asymptomatic cases above (section 2a)
c. Long-term chelation	D-Penicillamine* (oral)	Do not use any chelating agent orally if risk of residual lead in bowel. Use oral penicillamine under conditions precluding risk of hazardous environmental lead exposure for followup after initial therapy with parenteral BAL-CaEDTA or CaEDTA only
B. ADULTS		
1. Symptomatic cases		
a. Acute encephalopathy	BAL-CaEDTA (IM)	Same as for children
b. Abdominal syndromes (muscle pain, weakness, colic)	BAL-CaEDTA (IM)	Course of 3–5 days followed by oral D-penicillamine until urine lead <500 μg Pb/24 hr or 2 mo, whichever is less
	CaEDTA only (IV)	Use if patient intolerant of BAL. Do not infuse total daily dose in less than 6 hr

(continued)

enhances the absorption of lead from the gut; on the contrary, there is evidence, in animals, that BAL enhances the excretion of lead through the intestinal tract. Neurosurgical operations for the relief of increased intracranial pressure are contraindicated. There is no decisive evidence concerning the effectiveness of steroids in combatting cerebral edema in lead encephalopathy. In view of evidence in animals which shows that steroids enhance the renal toxicity of CaEDTA, these compounds are not used by the author. Repeated doses of mannitol appear safest and most efficacious for the relief of persistent cerebral edema, as indicated by persistent deep unconsciousness.

Asymptomatic Children

Asymptomatic children should be separated from their environmental lead sources promptly. Usually this entails brief hospitalization for diagnostic study, preliminary evaluation of environmental lead sources, and protection of the child until temporary safe residence is found. The laboratory tests in Table 3 are performed and chelation therapy is given according to the doses in Table 4 and the indications in Table 5. If the UCP test gives a 3–4+ result we do not await the results of blood lead analysis but begin BAL-CaEDTA immediately. This policy is based upon past clinical experience; the condition of young children with plumbism can deteriorate precipitously even in the hospital. It is safer to start chelation therapy promptly and then stop if blood lead determinations later prove the initial diagnosis in error.

Recently we have been using penicillamine on an investigational basis; it has been administered orally for periods of 1–6 months to 32 children without serious side-effects. The treatment is started in the hospital and completed in a convalescent home or inspected lead-free temporary foster home. It is possible with this drug to maintain blood lead concentration within the normal range during early convalescence.

Precautions with Chelating Agents

The main toxic effects of BAL are nausea and vomiting which can be avoided if oral intake is withheld. Due to the formation of a toxic BAL-iron complex medicinal iron may not be given concurrently.

CaEDTA is not metabolized in the body; virtually all of this com-

procedures used by the Baltimore City Health Department for detection (12) and eradication (14) of hazardous lead sources in the home are published elsewhere. The family is evaluated with respect to the need for psychiatric consultation to assist in bringing the child's pica under control. If the home is too deteriorated to permit adequate repair, the family is assisted by the medical social worker to find new safe housing. Modern public housing areas are preferred. In no instance should affected children be allowed to remain in the home while the necessary repair work is in progress. The procedures necessary to find a safe location for the child often require several weeks. During this time it is our policy to transfer the patient to a convalescent home.

Children recovering from acute encephalopathy usually exhibit severe behavioral abnormalities during the first 3 to 6 months of convalescence. It is our practice to transfer all such patients to a convalescent children's home and to administer oral penicillamine during this period. These institutions usually have an active child life program which can be most beneficial in terminating the child's pica and in revealing new areas of interest to him.

Careful follow-up is continued after the child returns home. We encourage enrollment in a nursery school or "Head Start" program to provide continued stimulation for the child. Many of the mothers of children with plumbism show multiple maternal inadequacies and require constant support. During the first year after acute intoxication intercurrent infections may be associated with biochemical evidences of increased soft tissue lead toxicity (increased UCP and ALA) (3) requiring chelation therapy (Table 5). Long-term administration of penicillamine on an outpatient basis cannot be recommended at present. Serial blood leads should be obtained at bimonthly intervals or more frequently as indicated. Values in excess 60 μg Pb/100 g whole blood during convalescence call for repeat courses of CaEDTA or penicillamine in the hospital. Values >100 μg Pb/100 g whole blood almost certainly indicate recurrent lead ingestion which calls for review of the psychodynamic aspects of the case and recheck of environmental lead sources. The families at greatest risk move with the greatest frequency. This close surveillance should be maintained until blood lead returns to and remains within the normal range (15–40 μg Pb/100 g whole blood). Phenobarbital and/or diphenylhydantoin (Dilantin®) are adequate for the control of seizures that follow lead encephalopathy. Recurrence of seizures without recurrent lead ingestion is usually indicative of a lapse in anticonvulsant medication. Both seizures and behavioral disturbances tend to abate

Table 6. Laboratory Tests Used in Industrial Medicine to Monitor Occupational Exposure to Inorganic Lead

Test	General population (nonexposed)	Lead workers: Increased absorption (worker healthy)	Lead workers: Dangerous absorption (may be symptomatic)
Blood lead (μg Pb/100 g whole blood)	<40	55–80	>80
Urine lead† (μg Pb/liter)	<80	<150	>200
Hemoglobin (g/100 ml whole blood)	>13	>13	<13
Urine coproporphyrin* (μg/liter)	<250	<500	>800
Qualitative test†	0 to ++	+++	++++
Urine*‡ δ-aminolevulinic acid (mg/liter)	<6	<13	>19

* Based on analysis of overnight urine (first morning voiding), but same data applicable to 24-hour urine collections which are preferable.

† Technique of Benson and Chisolm described in this article (2)

‡ Method of Mauzerall and Granick (*J Biol Chem* 219:435, 1956); subtract 2 mg/liter from each ALA value if method of Urata and Granick (*J Biol Chem* 238:811, 1963) used.

in UCP so that values <800 μg UCP/24 hr cannot be considered diagnostic of plumbism (11). Table 7 shows pyrrole excretion patterns in diseases sometimes confused with plumbism. The combination of increased ALA and UCP is specific for plumbism (11). Findings

Table 7. Patterns of Increased Pyrrole Excretion in Urine of Acute Symptomatic Patients*

Disease	Pyrroles: ALA	PBG†	UUP	UCP
Lead intoxication	+++	0	±	+++
Acute intermittent porphyria	++++	++++	+ to ++++	+ to +++
Acute hepatitis (toxic and infectious types)	0	0	0	+ to +++
Acute alcoholism	0	0	±	+ to +++

* 0 = Normal; + to ++++ = degree of increase; ALA = δ-aminolevulinic acid; PBG = porphobilinogen; UUP = urine uroporphyrin; UCP = urine coproporphyrin

† Qualitative Watson-Schwartz test for PBG

from all industrial operations. As control procedures improve it is likely that acceptable limits of "safe" occupational exposure (Table 6) will be lowered (16). The presence of chronic renal, bone or other metabolic diseases are indications for terminating further occupational exposure to lead. Upon termination of exposure, medical followup should be continued in all patients for a period of time equivalent to twice the duration of abnormal exposure. Chelating agents should not be administered orally in the presence of continued, hazardous exposure. Oral EDTA increases the absorption of lead from the intestine. Comparable data for penicillamine are not available.

Intoxication Due to Organic Lead Compounds

Intoxication due to tetraethyl lead and tetramethyl lead presents a special problem (15). Exposure is limited entirely to the manufacture, transport, and handling of these compounds in the petroleum industry up to the point where the concentrated material is mixed into gasoline as an antiknock additive. Cleaning and repairing of tanks used for storage of leaded gasoline may also be hazardous. The number of workers at risk is limited. Illness begins acutely with insomnia, wild and terrifying dreams, emotional instability and hyperactivity, and may progress to frank toxic psychosis. The hematologic abnormalities of inorganic lead poisoning are not found. Urinary lead excretion is very elevated but blood lead is only slightly high. No specific therapy is available. Chelating agents are not used. Heavy and prolonged sedation with short-acting barbiturates in hospital provide the most effective therapy available. Fluid and electrolyte balance must be carefully maintained and may be difficult due to the patient's hyperactivity. Convalescence may be prolonged and punctuated by recurrence of irrational behavior. The disease carries a mortality rate of approximately 20 per cent.

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