ARCHIVED: THIS DOCUMENT IS ARCHIVED FOR HISTORICAL PURPOSES AND IS NO LONGER BEING MAINTAINED OR UPDATED.

CDC now uses a blood lead reference value of 5 micrograms per deciliter to identify children with blood lead levels that are much higher than most children's levels. This new level is based on the U.S. population of children ages 1-5 years who are in the highest 2.5% of children when tested for lead in their blood.

This reference value is based on the 97.5th percentile of the National Health and Nutrition Examination Survey (NHANES)'s blood lead distribution in children.

This document was archived for historical purposes on July 30, 2020.

5A1

Preventing Lead Poisoning in Young Children

A STATEMENT BY THE
CENTER FOR DISEASE CONTROL
APRIL 1978

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL

CENTER FOR DISEASE CONTROL
CHILDHOOD LEAD-BASED PAINT POISONING PREVENTION ad hoc ADVISORY COMMITTEE

December 1, 1977 – March 1, 1978

The Childhood Lead-Based Paint Poisoning Prevention ad hoc Advisory Committee shall advise and make recommendations to the Secretary, the Assistant Secretary for Health, and the Director, Center for Disease Control, and his staff on amendments to the policy statement dated March 1975, "Increased Lead Absorption and Lead Poisoning in Young Children."

CHAIRPERSON

NEEDLEMAN, Herbert L. (M.D.)
Assistant Professor of Psychiatry
The Children's Hospital Medical Center
300 Longwood Avenue
Boston, Massachusetts 02115

EXECUTIVE SECRETARY

HOUK, Vernon N. (M.D.)
Director
Environmental Health Services Division
Bureau of State Services
Center for Disease Control, PHS
Atlanta, Georgia 30333

BILLICK, Irwin H. (Ph.D.)
Program Manager
Lead-Based Paint Program
Office of Policy Development and Research
Department of Housing and Urban Development
451 7th Street, S.W. – Room 8136
Washington, D.C. 20410

BUCHART, Ellen (R.N.)
Director of Nursing
Louisville-Jefferson County Health Department
P.O. Box 1704
Louisville, Kentucky 40201

CHADZYNSKI, Lawrence (R.S.)
Director
Lead Poisoning Control Program
Detroit Department of Health
Herman Kiefer Health Complex
1151 Taylor Street
Detroit, Michigan 48202

CHALLOP, Roger (M.D.)
Private Practice, Pediatrics
186 Audubon Avenue
Mt. Vernon, New York 10552

CHISOLM, J. Julian, Jr. (M.D.)
Senior Staff Pediatrician
Baltimore City Hospitals
4940 Eastern Avenue
Baltimore, Maryland 21224

CURRAN, Anita S. (M.D.)
Deputy Commissioner
New York City Department of Health
125 Worth Street
New York, New York 10013

DAVIDOW, Bernard (Ph.D.)
Assistant Commissioner for Laboratory Services
New York City Department of Health
Bureau of Laboratories
455 First Avenue
New York, New York 10016

FIELD, Patricia (Ph.D.)
Chief, Toxicology Section
Wisconsin State Laboratory
465 Henry Mall
Madison, Wisconsin 53706

GRAEF, John (M.D.)
Associate in Medicine
The Children's Hospital Medical Center
300 Longwood Avenue
Boston, Massachusetts 02115

GREENBERG, Nahman H. (M.D.)
Medical Director
Childhood Lead Poisoning Prevention Program
Chicago Department of Health
Richard J. Daley Center
Chicago, Illinois 60602

LIN-FU, Jane S. (M.D.)
Pediatric Consultant
Health Services Administration, PHS
Parklawn Building – Room 7-31
5600 Fishers Lane
Rockville, Maryland 20857

MELIA, Edward P. (M.D.)
Chief, Program Coordination Sectior
Maternal and Child Health Branch
California Department of Health
714 P Street
Sacramento, California 94918

PIOMELLI, Sergio (M.D.)
Professor of Pediatrics
Director of Pediatric Hematology
New York University Medical Center
550 First Avenue
New York, New York 10016

REIGART, J. Routt (M.D.)
Associate Professor
Department of Pediatrics and Preventive Medicine
Medical University of South Carolina
171 Ashley Avenue
Charleston, South Carolina 29403

ROBINSON, Betty
Community Outreach Supervisor
Lead Poisoning Prevention Project
Department of Human Resources
Room 812
1875 Connecticut Avenue, N.W.
Washington, D.C. 20009

SAYRE, James W. (M.D.)
Representing American Academy of Pediatrics
Associate Professor of Pediatrics
University of Rochester Medical Center
Box 631 – 601 Elmwood Avenue
Rochester, New York 14542

SOBOLESKY, Walter J.
Director, Childhood Lead Poisoning Prevention Program
Environmental Health Services
Department of Public Health
500 South Broad Street
Philadelphia, Pennsylvania 19146

WELCOME, Mary
Solicitor
City of Atlanta
165 Decatur Street
Atlanta, Georgia 30303

00-2629

Preventing Lead Poisoning in Young Children

A STATEMENT BY THE
CENTER FOR DISEASE CONTROL

APRIL 1978

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
BUREAU OF STATE SERVICES
ENVIRONMENTAL HEALTH SERVICES DIVISION
ATLANTA, GEORGIA 30333

I. Introduction

The detection and management of children exposed to lead is a rapidly changing field. Since the Surgeon General's statement "Medical Aspects of Childhood Lead Poisoning" (1970) and the subsequent statement by the Center for Disease Control (1975) were issued, considerable new data from clinical, epidemiological, and experimental studies have become available. These data have improved upon our knowledge of the extent of lead exposure, its sources, and the requirements for prompt and reliable identification and management of children at risk. The CDC recognizes that there will doubtless be further development in this field which may alter or redefine our current understanding.

The purpose of this statement is to reflect current knowledge by making revised recommendations regarding the screening, diagnosis, treatment, and followup of children with undue lead absorption and lead poisoning. The ultimate preventive goal is identification and removal of lead in the environment before it enters the child. Until this occurs, screening, diagnosis, treatment, and environmental management will continue to be necessary public health activities.

Definitions

The terms which follow in this section are arbitrarily defined for the purpose of this document.

Elevated blood lead level is defined as a confirmed blood lead 30 micrograms per deciliter (μg/dl) or greater.

Lead toxicity is defined as biochemical [e.g., erythrocyte protoporphyrin* (EP) equal to or greater than (≥) 50 μg/dl] or functional derangements caused by lead.

Undue lead absorption refers to excess lead in the blood with evidence of biochemical derangement in the absence of clinical symptoms. It is defined by confirmed blood lead levels of 30-69 μg/dl associated with EP levels of 50-249 μg/dl whole blood.

Lead poisoning is defined as existing whenever a child has any one or more of the following:

1. Two successive blood lead levels equal to or greater than 70 μg/dl with or without symptoms.
2. EP level equal to or greater than 250 μg/dl whole blood and a confirmed elevated blood lead level equal to or greater than 50 μg/dl with or without symptoms.
3. EP level greater than 109 μg/dl associated with a confirmed elevated blood lead level (≥ 30 μg/dl) with compatible symptoms.
4. Confirmed blood lead level greater than 49 μg/dl with compatible symptoms and evidence of toxicity (e.g., abnormal EP, calcium disodium EDTA mobilization test, urinary aminolevulinic acid excretion or urinary coproporphyrin excretion).

Iron deficiency exists when a child has insufficient iron available for erythropoiesis. This may be caused by inadequate ingestion, malabsorption, impaired transport, impaired utilization of iron, or blood loss. Iron deficiency may exist with or without frank anemia.

*Erythrocyte protoporphyrin (EP) results are expressed in equivalents of free erythrocyte protoporphyrin (FEP) extracted by the ethyl acetate-acetic acid-HCl method and reported in micrograms per deciliter whole blood. For the purpose of this document, zinc protoporphyrin and FEP are referred to as EP.

II. Background

As experience with lead screening has grown, awareness of the nature of the effects of lead on health has both broadened and deepened. In the past, medical attention has focused principally on the effects of severe exposure and resultant very high body burdens which are associated with classical signs and symptoms of intoxication. [1,2,3,4,5] It is now apparent that lesser levels of exposure result in important biochemical alterations. [6,7] A growing body of knowledge indicates that subtle effects of lead may be expressed in altered neuropsychological behavior of considerable significance, especially to the growing child (see Appendix A). These altered behaviors may be recognized by parents, teachers, and clinicians as attentional disorders, learning disabilities, or emotional disturbances which impair progress in school. [8,9,10] Because of the large number of children involved, these adverse effects would appear to be the main cause for societal concern.

Large scale screening studies of children without symptoms have demonstrated that the number of children found with undue lead absorption is greater than previously thought. It was once considered to be a problem primarily of the inner part of large cities in the so-called "Lead Belt" of the Northeast. However, when children under the age of 6 years who live in a hazardous environment containing excess lead are tested, 3 to 20 percent will be identified with elevated blood lead levels. This is true whether those children live in the East or West, North or South, or in a rural or urban setting. Thus, the magnitude of the problem is greater and the consequences more severe than previously thought.

At the same time, the multiple sources of lead have come under increasing scrutiny. Lead-based paint is the most important "high dose" source of lead and the most common cause of serious lead poisoning in children. [6,11,12] The total body burden of a given individual, however, is a complex sum of many different vectors, including air, dust, [13,14] dirt, and diet (see Appendix A).

A number of factors can affect the absorption of lead. Younger children absorb a greater proportion of the available lead than older ones. Both respiratory and alimentary absorption of lead are dependent on particle size. [6,15] Composition of the diet is important. Increased dietary fat and decreased dietary intake of calcium, iron, and possibly other nutrients enhance the absorption of lead from the intestine in experimental animals. [6,15,16,17] Absorbed lead is distributed throughout soft tissue and bone. Blood lead levels reflect the equilibrium between absorption, excretion, and sequestration in soft and hard tissue.

The tissues and organs most severely affected by lead are the bone marrow, kidney, and brain. One of the biochemical systems most sensitive to lead effects is the heme biosynthetic pathway. Among the earliest signs of impaired function is an elevated EP level which results from direct action of lead on the mitochondria. Because EP elevation is an early and reliable measure of functional impairment due to lead and because its determination avoids the problem of false high values due to contamination with lead, EP has become an important tool in early screening of asymptomatic children.

It is vital in following the text of this document that screening be separated from diagnosis. Screening means the application of detection techniques to large numbers of children considered asymptomatic in order to determine the degree of lead exposure and risk. Diagnosis, on the other hand, means the categorization of a given child appearing to have excess exposure to lead according to the severity of burden and toxicity in order to institute appropriate management. No child with suggestive symptoms of lead toxicity should be put through the screening process. He or she should be brought directly to medical attention.

The symptoms of lead poisoning are often vague. Among the milder symptoms and signs are fatigability, pallor, malaise, appetite loss, irritability, sleep disturbance, sudden behavioral change, and developmental regression. Of more serious import are clumsiness, ataxia, weakness, abdominal pain, persistent vomiting, constipation, and changes in consciousness which can presage encephalopathy. Children who display symptoms require urgent and thorough diagnostic evaluation and prompt treatment should the disease then be confirmed.

III. Screening

Goal

The goal of any childhood lead poisoning prevention effort is the prevention of undue lead absorption and lead poisoning. This requires the early detection of children with undue lead absorption followed by effective medical and environmental intervention before the child reaches the stage of overt lead poisoning. The achievement of this goal can be accomplished only by the implementation of the following:

1. A screening program structured to enroll the maximum number of children in need of followup while at the same time excluding children not unduly exposed.
2. A referral system that insures a comprehensive diagnostic evaluation of every child with a positive screening test.
3. A method of monitoring for quality and appropriateness of the treatment and followup of every diagnosed child.
4. A system to insure elimination of the source of the child's lead exposure.

Screening is of no value without prompt, thorough, and ongoing medical and environmental followup of those children found to have undue lead absorption or lead poisoning.

Target Population

The screening effort should be focused on asymptomatic children known or suspected to have been unduly exposed to lead. The target population for screening is children from 1 year of age until their sixth birthday who live in or frequently visit poorly maintained housing units constructed prior to the 1960's or who are exposed to other hazardous lead sources (e.g., residence near lead smelters and processing plants or roadways with heavy motor vehicle traffic, attendance at day-care centers or other institutions where lead-based paint had been found, etc.). Priority should be given to children 12 to 36 months of age, those who have a history of pica, or who have siblings with undue lead absorption or lead poisoning. Pica, the repetitive ingestion of nonfood substances, is prevalent in preschool children, especially those less than 3 years of age. Excessive mouthing of foreign objects is also prevalent in this age range.[18]

Screening Schedule

Children included in the target population are at risk throughout the year and should be screened at least once per year. Children are at higher risk during the May-October period.[19] Ideally, children 12 to 36 months of age who are at risk should be screened every 2 to 3 months during this period.

It is important to realize that negative screening tests in children from a hazardous environment do not rule out subsequent exposure. Children known to be at risk should therefore be rescreened at regular intervals until they reach the age of 6 years or until their hazardous exposure is known to have been terminated.

Screening Methods

Currently, the most useful screening tests are EP and blood lead determinations.[20,21,22,23] Samples of venous or capillary blood* may be used for both tests, but capillary samples are more widely used because of the relative ease of collection.

Blood lead and EP represent different parameters of undue lead absorption or poisoning. Blood lead reflects absorption while EP measures the adverse metabolic effects of lead on heme synthesis.[24] While there is usually a close correlation between the two measurements, one may be elevated without concomitant increase of the other. Studies have indicated that when such discrepancies exist, EP provides a better indicator of the risk of lead poisoning and of the urgency of diagnostic evaluation. At blood lead levels below 50 μg/dl, the EP better identifies children with rising blood lead levels and may not detect those children with stable or declining blood lead levels. Current evidence suggests that these latter children are at low risk.[25] Moreover, EP levels reflect individual responses to lead toxicity and are usually elevated before clinical evidence of poisoning appears.[20,21,22,26,27] Another advantage of EP over blood lead is that it is unaffected by contamination with environmental lead and does not show wide fluctuations due to sporadic exposure to lead or changes in the child's physiologic state (infections, acidosis, etc.).

*Capillary blood may be transported in the liquid state in an appropriate anticoagulant containing container or in the dry state on filter paper.

EP is also elevated in iron deficiency states,[28] and increased EP levels may precede the appearance of anemia. Iron deficiency should therefore be ruled out before an elevated EP level can be attributed to the toxic effects of lead. However, undue lead absorption and iron deficiency do coexist, and the latter tends to potentiate lead toxicity.

Iron deficiency is generally associated with moderately increased EP levels (50-249 μg/dl) while markedly elevated values (≥300 μg/dl) are usually due to lead toxicity. The only known exception is erythropoietic protoporphyria,[29,30] a rare genetic disorder characterized by severe cutaneous photosensitivity and very high EP levels.

EP may be measured by fluorometry after extraction from the red cells or by direct measurement of its fluorescence in intact red cells.[31,32] This metabolite is present in the red cells as zinc protoporphyrin, but zinc is removed by the extraction procedure, leaving the EP "free." Measurement of zinc protoporphyrin and EP after extraction reflects essentially the same compound. For uniformity, it is recommended EP be expressed as equivalents of free erythrocyte protoporphyrin (FEP) μg/dl of whole blood by the ethyl acetate-acetic acid-HCl extraction method.

Unlike EP, blood lead is specific for lead absorption. Wide fluctuations in blood lead values can be due to physiologic variations or sporadic acute lead exposure. Measurements of blood lead, particularly when done on capillary samples, are highly sensitive to contamination with environmental lead. Therefore, only low blood lead values can be considered valid; high values must be confirmed. If capillary samples are used for blood lead analysis, at least two specimens should be collected so that high values may be confirmed on the duplicate sample.

Laboratories performing these blood lead and EP determinations should participate in the Proficiency Testing Program of the Center for Disease Control or an equivalent program to help insure accurate test results.

Screening Schemes

There are three possibilities for the screening scheme:

1. Initial screening with EP, followed by blood lead measurement in positive children.
2. Initial screening with blood lead, followed by EP measurement and repeat blood lead in positive children.
3. Initial screening with both EP and blood lead.

The difficulty of performing venipuncture at many screening sites and environmental contamination of capillary samples seriously limit the use of blood lead determinations as the initial test in large scale screening efforts. The children at greatest risk are those with adverse metabolic effects of lead and not those with a moderately elevated blood lead level without adverse metabolic effects.[25] For the above reasons, and due to the availability of simple methods for its determination,[32] the EP measurement as the initial test will allow for greater numbers of children to be screened with less unnecessary followup.

The Center for Disease Control recommends that an EP test be used for screening for lead poisoning followed by blood lead measurements for all children with an elevated EP. This recommendation is made because the EP has the following advantages:

1. Ease of measurement.
2. Results not affected by environmental lead.
3. Greater cost effectiveness.
4. Value in separating those children with rising blood lead levels from those with stable or declining blood lead levels.
5. Reflection of individual's metabolic response to lead.
6. Added benefit of detecting children who may have iron deficiency.

Since the major cost incurred in the screening process is finding the child, sufficient blood must be obtained at that time for EP as well as blood lead and hematocrit (Hct) or hemoglobin (Hgb). This will eliminate a second visit to obtain additional samples. If the EP determination is less than or equal to (≤) 49 μg/dl whole blood, the remainder of the sample may be discarded.

When EP is the primary screening tool, two approaches are possible:

1. EP measured onsite. Under this plan, children do not leave the screening site until the result of the EP is known. Children found to have EP values of < 49 μg/dl may be discharged to routine followup. For those with values of ≥ 50 μg/dl, blood specimens should then be taken, if possible by venous sample, for laboratory analysis of blood lead and Hct or Hgb. If venipuncture is not possible, separate capillary samples for two blood lead analyses and Hct and Hgb should be obtained.
2. EP measurement offsite. Under this plan, blood samples are collected at the screening site and sent to the laboratory for analysis. Thus, sufficient sample should always be collected initially not only for EP but also for confirmatory tests. The remainder of specimens from those children whose EP levels are < 49 μg/dl may be discarded. For those specimens with EP values of ≥ 50 μg/dl, blood lead and Hct or Hgb should be determined.

If screening is being performed as part of a comprehensive health care program in areas where the prevalence of undue lead absorption is presumably low, obtaining duplicate capillary samples for blood lead determinations on all children may be excessively costly. If venous blood has not been obtained, it may be preferable for the program to recall those children whose EP is > 50 μg/dl for blood lead determination.

Interpretation of Screening Results

A single screening test, either EP or blood lead, cannot be used to categorize children for priority of followup. Both EP and blood lead values must be used to determine the potential risk of lead poisoning in children screened.

Children may be divided arbitrarily in four classes based on their EP and blood lead screening results (Table I). This classification merely suggests the relative risk of lead poisoning and the priority for medical evaluation and environmental intervention. *It should not be used as a diagnostic classification.* Moreover, the table should be used as a general but not as a rigid guideline. For example, the urgency for followup is greater for a 2 year old child whose EP is 109 μg/dl and blood lead is 49 μg/dl than for a 5½ year old child whose EP is 50 μg/dl and blood lead is 30 μg/dl. Yet both children fall into Class II. Since a certain range of both EP and blood lead values is used in the classification, children whose EP and blood lead values fall into the upper range of a class should be given priority over those at the lower range, and young children 12 to 36 months old should be dealt with more urgently than older ones.

Class IV children are at urgent risk of lead poisoning and should be provided immediate medical evaluation. In no case should they be evaluated later than 48 hours after the results of the studies are known; if possible, this should take place within 24 hours. Class III children are at high risk, Class II are at moderate risk, and Class I children at low risk.

Some Class I children may be placed into two additional categories. Class Ia are children with iron deficiency, and Class Ib are children who appear to have transient, stable, or declining blood lead levels and are at low risk for lead poisoning.[25] The trend of exposure should be determined by repeat testing of these children.

The results of EP and blood lead will usually fall in the corresponding range. However, in some cases, there will be discrepancies. In these cases, the result of the EP should be used in establishing the priority for medical evaluation. When the EP value is significantly greater than the blood lead would predict, this finding is most likely due to the combination of iron deficiency and undue lead absorption.

The screening effort should be focused on asymptomatic children. However, children may be found to be symptomatic only after screening has been done. In such cases, these children should be referred for immediate evaluation regardless of the classification.

TABLE I

RISK CLASSIFICATIONS FOR ASYMPTOMATIC CHILDREN

[To Reflect Priority for Medical Evaluation from the Screening Results.
Not to be used for Diagnostic Purposes]

Test Results	Erythrocyte Protoporphyrin (μg/dl Whole Blood)			
Blood Lead (μg/dl)	<49	50-109	110-249	>250
Not done	I	*	*	*
<29	I	Ia	Ia	EPP+
30-49	Ib	II	III	III
50-69	**	III	III	IV
>70	**	**	IV	IV

EPP+ = Erythropoietic protoporphyria – Although rarely iron deficiency may cause EP elevations to 300 μg/dl.

* = Blood lead necessary to estimate risk.

** = Combination of results not generally observed in practice; if observed, retest with venous blood immediately.

NOTE: Diagnostic evaluation should be provided more urgently than the classification would otherwise indicate in the following cases:

1. Children with any symptoms compatible with lead poisoning.
2. Children under 36 months of age.
3. Children whose blood lead and EP values place them in the upper part of a particular class.

It must be emphasized the suggested guidelines refer to the interpretation of screening results, but the final diagnosis and disposition rest on a more complete medical and laboratory examination of the individual child.

IV. Diagnostic Evaluation

Screening tests are not diagnostic. Therefore, every child with positive screening tests should be evaluated individually to determine the seriousness of the exposure. At the initial diagnostic evaluation, if the screening test was done on capillary blood, blood lead must be repeated on venous blood for confirmation of screening test results. Additional blood may be necessary for such tests as complete blood counts, serum iron, total iron binding capacity, and serum ferritin if available. The amounts necessary for these tests, which usually exceed the amount obtainable by capillary sample, can be obtained during a single venipuncture.

Hematologic tests assist the clinician in evaluating the relative contributions of increased lead body burden and iron deficiency to the degree of elevation in EP that is found. A blood lead measurement is absolutely essential if EP is used as the sole screening test.

After confirmatory venous blood lead and EP tests, the diagnostic evaluation should include the following:

1. Detailed history to include the presence or absence of clinical symptoms, child's mouthing activities, existence of pica, nutritional status, family history of lead poisoning, possible source of exposure, and previous blood lead or EP determinations.
2. Physical examination.
3. Nutritional status and hematologic evaluation for iron deficiency. Not only does concurrent iron deficiency contribute to an elevated EP[28], but there is evidence that it may enhance lead absorption and toxicity.[17,33]
4. Confirmatory diagnostic tests.

An initial plan for management requires that all of these interacting factors be taken into account. The initial plan should be modified as indicated by long-term trends in lead absorption, exposure, and clinical status.

Tests

In addition to confirmatory and serial EP and blood lead determinations, the following tests may be useful if available in assessing the patient's lead absorption status:

1. **Flat Plate of Abdomen**
   Radiologic examination (flat plate) of the abdomen may reveal radiopaque foreign material but only if such material has been ingested during the preceding 24 to 36 hours. In view of the sporadic nature of lead ingestion, this examination is significant only if positive, but does not rule out lead poisoning if negative. When positive, it indicates recent ingestion of large amounts of lead.
2. **X-ray of Long Bone**
   Radiographic examination for bands of increased density at the metaphyses of the growing long bones. Bands of increased density (colloquially referred to as "lead lines") are usually measured in posterior-anterior x-ray views of the distal ends of the radius and ulna and the knee (distal femur, proximal tibia and fibula). Bands of increased density, when present, reflect disturbance in the deposition of bone mineral and indicate past exposure. Their width and intensity reflect prolonged previous lead absorption but do not indicate current ingestion. They are seldom seen in children under 24 months of age. Negative tests do not rule out lead poisoning.
3. **Calcium Disodium EDTA Mobilization Test***
   Children who are symptomatic or whose blood lead exceeds 70 μg/dl should not receive a provocative chelation test. Instead, appropriate chelation therapy should be instituted. It is particularly useful when the screening tests indicate that the child has undue lead absorption (*not lead poisoning as defined*), and there is some question as to whether chelation therapy is indicated. Its use should be given serious consideration. This test provides an index of the mobile or potentially toxic fraction of the total body lead burden.[24] Operationally, it most directly demonstrates whether chelation therapy will provoke a significant diuresis of lead.

*Sodium EDTA which does not contain calcium should *not* be used under any circumstance.

The ideal method is to administer calcium disodium EDTA with added procaine by deep intramuscular injection in two doses of 500 milligrams per square meter (mg/m^2) of body surface area per dose given at 12-hour intervals. Urine is collected for 24 hours with "lead-free" apparatus* after the initial injection.[34] A single dose, followed by a 24-hour collection of urine, will also suffice.[35] In either case, results are expressed as the ratio of μg of lead excreted per milligram of calcium disodium EDTA injected. A ratio (μg Pb/mg CaEDTA) > 1 is indicative of a fivefold increase in the mobile or a potentially toxic fraction of the total body lead burden.[24] Correlation studies suggest that such levels are associated with a significantly increased risk of toxicity due to lead.[24]

Practical considerations make this test difficult in young children. Alternatively, a single intramuscular dose of 50 milligrams per kilogram (mg/kg) of body weight of calcium disodium EDTA (maximum dose 1,000 mg) followed by quantitative 6- to 8-hour collection of urine is more convenient.[36] Under these conditions, an excretion ratio (μg Pb/mg CaEDTA) of > 0.5 or lead content greater than 1 mg per liter is considered "positive".

*Special "lead-free" collection apparatus must be used for valid test results. The laboratory performing the analysis may supply the proper collection apparatus. It is preferable that urine be voided directly into polyethylene or polypropylene bottles which have been subjected to the usual cleaning procedures, followed by washing in 1 percent nitric acid, followed by copious rinses with deionized, distilled water. For children who are not toilet trained, double compartment plastic pediatric urine collectors may be used. Urine collected in this manner should be transferred directly in the urine collection bottles. Appropriate preservation of the collected urine with hydrochloric acid will stabilize not only lead but also ALA.[38]

4. **Increased excretion of δ-aminolevulinic acid in urine (ALA-U)**[35]
   ALA-U greater than 3 mg/m^2 for 24 hours is considered a significant deviation from normal.
5. **Increased excretion of coproporphyrin in urine (CPU)**
   A strongly positive semiquantitative urinary coproporphyrin test is associated with blood lead concentrations >100 $\mu g/dl$.[37]
6. **Inhibition of δ-aminolevulinate dehydratase (ALA-D) activity, as assayed in vitro in circulating erythrocytes**
   This test is limited in its availability but if available is useful. Reduction of ALA-D activity to 15 to 20 percent of normal for the method[38,39] is generally considered positive; however, the reader is advised to consult the references cited.
7. **Examination of red cells for basophilic stippling**
   Since basophilic stippling is not universally found in chronic clinical lead poisoning and is relatively insensitive to lesser degrees of lead toxicity, this is *not* considered useful in diagnosis.

CAUTION:
If lumbar puncture is necessary to rule out meningitis or other serious disease, it should be performed cautiously and only after careful search for signs and symptoms of increased intracranial pressure.

Since trends are important, serial measurements of blood lead and EP (and other tests as indicated) are far more valuable in diagnosis and management than data obtained at a single point in time.[25]

V. Clinical Management

The classification system described under the screening section is to be modified by the results of the diagnostic evaluation. In this manner, after all information is available to the clinician, the child's true risk classification is established. Clinical management includes reduction of the child's lead exposure, general pediatric care, family education for all, chelation therapy for some when appropriate, and correction of nutritional deficiencies where they exist. The plan for clinical management requires that all of the interacting factors of lead absorption, exposure, age, and clinical status be taken into account. In addition, the child must be followed until the risk of further damage is minimal. Reduction in ingestion of lead is the single most important factor in pediatric management. The family of the child with undue lead absorption or lead poisoning must be fully informed of the condition and what clinical and environmental actions to expect.

Treatment of lead poisoning requires a clear understanding of the pathophysiological effects of lead in the human body. The physician and others caring for the child must recognize that lead poisoning is usually a chronic disease, related generally to the chronic ingestion and absorption of excess quantities of lead. Body stores of excess lead may be quite large and are quite inefficiently removed by chelation therapy. Acute illness is only a period of acute decompensation in this chronic disease process and should be viewed as such. Treating during a phase of acute illness will relieve symptoms but is only the initial phase of care.

The cornerstones of clinical management are careful clinical and laboratory surveillance of the child with major reduction of lead exposure to prevent further accumulation of lead. This also allows spontaneous excretion of previously absorbed lead. Chelation therapy will not be necessary for most children. Suggestions for the clinical management of children are outlined in this section and are dependent upon the risk determinations made during diagnostic evaluation.

For the purposes of clinical management, the risk categories are defined as follows:

Urgent Risk – Children with confirmed lead poisoning as defined, regardless of the presence or absence of clinical symptoms.

High Risk – Children whose repeat EP and confirmatory venous blood lead levels fall in the same range as Class II and Class III of the screening tests but who also have a positive CaEDTA mobilization test or other confirmatory diagnostic tests. Class III children who have not had confirmatory diagnostic tests should be considered high risk until evidence is available to place them in another risk category.

Moderate Risk – Children whose repeat EP and venous blood lead levels fall into the same range as Class II of the screening tests but whose other confirmatory diagnostic tests are negative.

Low Risk – Children whose repeat EP and venous blood lead levels fall into Class I of the screening tests. These children are usually not given other diagnostic tests.

The above categorization is arbitrary and allows individualization. For example, a 20-month old child with persistent pica whose environmental lead hazard cannot be controlled satisfactorily, even if his/her repeat EP and venous blood lead levels fall in the range of Class II and other diagnostic tests are negative, may nonetheless be considered High Risk.

URGENT RISK

Children with confirmed lead poisoning as defined, regardless of the presence or absence of clinical symptoms, should be treated with the same intensity as children with frank neurologic manifestations. The higher the confirmed venous blood lead, the greater the need for chelation therapy. Severe and permanent brain damage may occur in as many as 80 percent of children who develop acute encephalopathy.[2] Treatment before onset of encephalopathy will improve this grim prognosis.

Chisolm [3,40] and Coffin et al[4] have described appropriate protocols for inpatient chelation therapy of children with lead poisoning. Multiple courses of chelation therapy may be necessary. It is essential to consult such references before treating children in order to properly appreciate the inherent dangers, precautions, and rationale for such treatment. Special attention should be given to the proper use of British anti-lewisite (BAL) in the treatment scheme with calcium disodium EDTA.

Penicillamine is *not* recommended as the initial treatment for children in this category.

The chronicity of lead poisoning and undue lead absorption as a medical problem for the individual child must be emphasized. Children who require chelation therapy will require long-term medical surveillance and care. A transitory elevation of the EP may also be observed during and immediately after chelation therapy. After an apparently successful course of therapy with calcium disodium EDTA incorporating BAL as necessary, the "rebound" phenomenon may be observed. The blood lead level, having dropped during treatment, almost invariably rises again. This phenomenon reflects reequilibration of stored lead and is not a reason to interrupt treatment. The decision to repeat chelation therapy is based on the blood lead level after the "rebound" has occurred.

Reduction of lead intake is urgent for all children in this category, both as part of immediate therapy and as a part of the followup preventive procedure. Children receiving chelation therapy should not be released from the hospital until lead hazards in their homes and elsewhere in their environment are controlled or suitable alternative housing arranged. Thus, the appropriate public agency in the community must be notified immediately to initiate environmental investigation and intervention.

After hospitalization and removal of lead from their environments, these children are still at high risk and should be followed with blood lead and/or erythrocyte protoporphyrin determinations at 1 to 2 week intervals until those levels show a continual decline for at least 6 months or stabilize. Thereafter, they should be followed at 1 to 3 month intervals (at least 6-week intervals in summer months) until 6 years of age or older to prevent repeated poisoning.

Neurological and psychological assessment should be obtained at the time of diagnosis and in following years so that proper therapy and school placement can be instituted. Additional clinical and laboratory evaluation should be conducted when indicated to assess other sequelae of lead poisoning, such as renal, myocardial, and metabolic disorders.

HIGH RISK

Many children in the high risk category will have been given a calcium disodium EDTA mobilization test to determine the utility of chelation therapy. If the calcium disodium EDTA mobilization test suggests the need for chelation therapy, inpatient chelation should be performed if feasible. Under some conditions, it may be possible to treat the children without urgent risk factors as outpatients. However, this should be reserved for centers capable of providing closely monitored outpatient care and followup supervision. Particular emphasis should be placed on the "rebound" phenomenon and environmental intervention and monitoring. In addition, the parents should be cooperative and demonstrate that they are able to follow instructions. In such circumstances, calcium disodium EDTA may be administered according to Sachs'[41] protocol.

Penicillamine, though receiving increasing attention for the treatment of lead poisoning in children, is not licensed by the Food and Drug Administration (FDA) for this purpose. Therefore, any physician or program wishing to use this drug as a chelating agent for children should use it in accordance with current FDA policy. In no case should it be used in children without or in lieu of control of lead hazard in their homes since data from studies of animals indicate it may increase the absorption of lead.[42]

High risk children should be followed with blood lead and/or erythrocyte protoporphyrin determinations at least monthly, especially in the summer, until the sources of lead in their environment have been removed and until their blood lead and/or erythrocyte protoporphyrin levels have declined for 6 months and stabilized. Thereafter, they should be followed at 1 to 3 month intervals (at least 6-week intervals in the summer) until 6 years of age or older in order to detect repeated lead exposure and prevent poisoning. Careful neurological and psychological assessment is advised to detect any behavioral or neurological deviation early so that proper therapy and school placement can be instituted.

MODERATE RISK

Based upon present evidence, children in this category generally will not require chelation therapy. Reduction of lead intake from all sources and careful monitoring of the child will usually suffice.

Until the lead hazards are eliminated from their environment, these children should be followed at monthly intervals in summer and otherwise at 2-month intervals until at least 6 years of age. After they are no longer exposed to lead hazards, they should be evaluated at 3-month intervals. Such followup should continue until the child is at least 36 months of age or until the blood lead/erythrocyte protoporphyrin levels return to normal.

All children in the Urgent, High, and Moderate Risk categories may have concomitant nutritional deficiencies. These deficiencies may increase the child's risk from lead by increasing the absorption, retention, and toxicity.[6,16,17,43] All children in these risk categories should receive a careful nutritional evaluation, including appropriate laboratory tests. In addition to the care provided for undue lead absorption or lead poisoning, appropriate nutritional therapy should be provided. It may be particularly important to correct iron deficiency and maintain an adequate calcium intake when increased lead absorption is found.[44]

LOW RISK

These children did not have significant evidence of undue lead absorption at the time of testing. However, they require periodic rescreening until they reach their sixth birthday. Children whose EP elevation is not caused by lead absorption should receive appropriate medical attention and care for the medical condition determined to be responsible for the elevated EP. Children with elevated blood lead in the absence of toxicity should be evaluated at monthly intervals until a determination is made that the child does not have undue lead absorption. This decision can generally be made within 3 months.

In conclusion, clinical management of lead poisoning must include appropriate treatment, adequate followup, environmental intervention, and family education. Chelation therapy is indicated for some children with undue lead absorption. Though indiscriminate chelation is unwise, withholding or delaying chelation therapy is also unwise when it is indicated. The physician providing clinical management must know the current status of the child's environment. The optimal frequency of followup is dependent on many factors including the child's age, environmental status, and trend of laboratory results.

VI. Environmental Evaluation and Lead Hazard Abatement

Environmental investigation and intervention should begin as soon as lead poisoning or undue lead absorption status is confirmed. Lead hazards must be identified and removed from the environments of children with lead poisoning and undue lead absorption. Priorities for action should be determined by the child's risk classification. Children who require hospitalization and chelation therapy are at highest risk of permanent neurologic damage from a recurrent episode and continued high level exposure. Therefore, children in the Urgent and High Risk categories should receive first priority for environmental investigation and intervention. The next priority is given to the environment of children in the Moderate Risk category.

The identification of lead hazards and the reduction of lead intake of these children is as much a medical necessity as is clinical management. The effectiveness of environmental intervention is judged by the response of the child and not by the services performed. Environmental management is *not* successful *or* complete until the child's EP and blood lead levels have declined and stabilized for at least 6 months. The identification and removal of one source of lead exposure does not necessarily mean that the child's exposure to lead has ended.

Lead-based paint on interior and exterior surfaces is usually the most important single source of lead for severely poisoned children. However, there are other sources which contribute to the child's total lead body burden. Lead contained in air, dust, and soil may also constitute a hazard for children. Lead in food and food supplements, household utensils, ceramic pottery, and printed matter may serve as contributory sources. The burning of leaded materials, remodeling of old homes,[45] automotive emissions, and some industrial sources located near residences or schools contribute to airborne lead and lead in dust and soil. Lead in dust and soil is becoming increasingly suspect as a source of lead exposure for young children, especially that within 3 feet of the house's foundation, inside the house,[13] along heavily traveled roadways, or on vacant lots where housing has been removed.[46-53]

It is also important to consider the occupation of the parents and associates. Workers in lead-related industries[45] can bring home lead-rich dust on the work clothing, shoes, and hair. Lead poisoning in children has been traced to these sources.

Although the child's home usually contains the source of his lead exposure, this is not always the case. Hazards may also exist in other places where the child spends or has spent a considerable amount of time, e.g., prior residences and homes of relatives and friends. Investigators should consider all sources of lead and should appropriately sample all potential hazards for their lead content. These sources other than lead-based paint must be reduced or removed, or the child removed from the source.

Portable x-ray fluorescence analyzers can be used in identifying lead-based paint hazards. These instruments can measure lead content in painted surfaces within ± 0.2 mg/cm^2. Readings of 0.7 mg/cm^2 should be considered positive. It is important to note the lead analyzer is a probability sampling device and repeated readings are necessary for proper reliability.

A lead-based paint hazard exists when (a) XRF reading is positive and (b) the surface being tested is reachable and chewable or contains damaged paint (cracking, chipping, loose, chewed). Lead-based paint on intact walls, ceilings, or other surfaces not accessible to the child does not constitute an immediate hazard. Inspectors should obtain measurements on any interior or exterior surface that may constitute a lead hazard. This includes walls, doors, window frames, baseboards, guardrails, fences, and siding. Outside inspection should encompass garages and other adjacent structures as well as the main building.

After the lead hazards are identified, parents and landlords must be advised on the extent of the problem and what must be done to eliminate it. The investigator should recommend methods for eliminating the hazard. This should include repair and housekeeping measures that can be undertaken immediately, safeguarding the child until permanent abatement can be completed. It is extremely important that the physician providing medical care to the child be informed of the results of the environmental investigation and the course of intervention that has been recommended. If surfaces containing lead-based paint are identified that do not constitute an immediate hazard, the owner, landlord, and occupant

should be notified and informed that the surface, if properly maintained, does not present an immediate hazard.

The following outlines some common methods for reducing lead-based paint hazards.

PHASE I – EMERGENCY INTERVENTION

Emergency measures provide temporary intervention and immediate control of lead hazards until permanent hazard reduction is completed. Emergency hazard abatement includes scraping off and removing all peeling, flaking, chewed, and readily accessible lead-based paint. All children must be removed from the dwelling and adults must take due precaution during these activities. Covering with adhesive-backed paper, masking tape, or similar materials may also be used.

Families should be instructed on methods of maintaining these areas free of loose and flaking paint until the hazard is permanently reduced. Housekeeping techniques such as thorough sweeping and wet mopping floors to remove dust are essential to maintain temporary intervention.

Emergency intervention must be provided for all children, particularly those who are hospitalized or undergo chelation therapy. They are at highest risk of permanent body damage from repeated exposure.

PHASE II – PERMANENT HAZARD REDUCTION

Permanent lead hazard reduction measures are intended to reduce to a minimum the possibility of the identified lead sources causing a problem again. Permanent hazard abatement consists of the removal or permanent covering of the lead hazards. Occupants should be advised of the proposed actions to be taken and the possible dangers during abatement procedures. All children must be removed from the dwelling, and adults must take due precaution during these activities. In addition to the workers following the usual good industrial hygienic practices, approved respirators and protective clothing should be worn. Lead-containing materials removed during this process must be disposed of in a safe manner.

Wall coverings, use of heat, sanding and scraping, and liquid paint removers are the most frequently used methods for permanent hazard abatement. These methods are outlined below:

Wall Coverings

This method is the safest to use. In many cases, it is the most acceptable and least expensive. It is most often used for large interior areas. Acceptable wall coverings include wallboard, hardboard, fiberglass, plywood paneling, or a similar fire-resistant durable material. These materials must be firmly applied by nailing, cementing, or gluing to prevent their removal by a small child or by normal wear. The application must be vermin proof and in certain areas of the dwelling, fire retardant (e.g., next to furnaces, stoves, and in common hallways).

Heat

This method uses heat from gas fired torches, infrared lamps, or other heat sources to *soften* the paint so that it can be scraped off easily. It may produce lead fumes which are toxic if inhaled in concentrated amounts. Even small concentrations over a sufficient length of time can pose a hazard. It should be done only by experienced persons with an awareness of the potential danger of igniting the surface, adjacent wall areas, or nearby combustibles.

Scraping And Sanding

All lead-based paint that is chipping, loose, peeling, or chewed or that is readily accessible to children should be scraped off. Any remaining painted surface is then sanded down to the base material, patched, sealed, and repainted with nonlead-containing materials. This method requires the most physical labor and is expensive.

While scraping and sanding is being done, large amounts of lead dust and particles become airborne, thereby temporarily increasing the lead hazard in the immediate environment. Tarpaulins or plastic floor coverings could be used during the process to collect the waste products. Similar procedures must be used for exterior surfaces to avoid soil contamination. Careful cleanup procedures including dusting, wet mopping, and washing must be used in the interior.

Liquid Paint Removers

Solvents are generally used for small areas such as window sills and doors. Most solvents evaporate rapidly and are flammable and toxic. They should be used with the utmost caution. Proper protective equipment, coverings, and clothing must be used. The work area must be well ventilated at all times.

The approach described above is reasonable and workable in the environmental management activities for children with lead poisoning or undue lead absorption. Ideally, it would be most desirable to develop a communitywide code enforcement program to completely eliminate all lead-based paint hazards in housing. But until such time as societal commitment exists, lead hazard identification and abatement for children with undue lead absorption or lead poisoning must be the responsibility of the appropriate governmental unit where the child lives.

VII. Health Education

The community and especially parents of preschool children who live in older, deteriorating neighborhoods should be informed at every available opportunity of the need to have their children screened periodically for lead poisoning. Basic preventive measures should be emphasized, such as regular sweeping and removal of accessible paint flakes and dust to reduce potential lead hazards in the child's environment. The danger of ingesting paint chips, dust, and soil should be stressed. Older siblings of children at high risk should also be educated to the sources and risks of lead poisoning, as they often provide a major contribution to the younger child's care.

If a child is screened and does not have undue lead absorption, there is still a risk and rescreening is required, particularly during the summer months, until the sixth birthday. Until hazard-free housing is available for all, periodic screening and the practice of basic intervention measures will reduce the risk of lead poisoning.

The educational process should start when the child is screened and should be reinforced by physicians, nurses, environmentalists, and aides each time the child is seen. Where a child is found to have undue lead absorption, education of the family is essential to successfully follow the child. The family of the child with undue lead absorption or lead poisoning must be fully informed of the condition and what clinical and environmental actions to expect. The parents' responsibility is to see that the child is not exposed to lead hazards in the future. This can only occur when they have a full understanding of the child's condition, its cause, and the possible result of lead poisoning.

VIII. Reporting of Lead Poisoning and Undue Lead Absorption

Presumptive and confirmed cases of lead poisoning and undue lead absorption should be considered a notifiable condition which must be reported to the appropriate health agency by primary care physicians and by persons in charge of screening programs. All laboratories performing blood lead or erythrocyte protoporphyrin determinations also should report abnormal findings.

References

1. Zarkowsky, H. S. The Lead Problem in Children: Dictum and Polemic. *Curr. Probl. Pediatr.* 6: 1: 1976.
2. Perlstein, M.A. and Attala, R. Neurologic Sequelae of Plumbism in Children. *Clin. Pediatr.* 5: 292: 1966.
3. Chisolm, J.J., Jr. The Use of Chelating Agents in the Treatment of Acute and Chronic Lead Intoxication in Childhood. *J. Pediatr.* 73: 1: 1968.
4. Coffin, R., et al. Treatment of Lead Encephalopathy in Children. *J. Pediatr.* 69: 198: 1966.
5. Byers, R.K. and Lord, E.E. Late Effects of Lead Poisoning on Mental Development. *Am. J. Dis. Child.* 66: 471: 1943.
6. Committee on Toxicology. Recommendations for the Prevention of Lead Poisoning in Children. National Academy of Sciences, National Research Council, Washington, D.C., July 1976.
7. Lead, Environmental Health Criteria 3, United Nations Environment Programme and the World Health Organization, Geneva, Switzerland, 1977.
8. Perino, J. and Ernhart, C.B. The Relation of Subclinical Lead Level to Cognitive and Sensorimotor Impairment in Black Preschoolers. *J. Learn. Disabil.* 7: 616: 1974.
9. de la Burdé, B. and Choate, M.S. Early Asymptomatic Lead Exposure and Development at School Age. *J. Pediatr.* 87: 638: 1975.
10. Albert, R.E., Shore, R.E., Sayers, A.J., Strehlow, C., et al. Follow-up of Children Overexposed to Lead. *Environ. Health Persp.* 7: 33: 1974.
11. Lin-Fu, J. S. Undue Absorption of Lead Among Children – A New Look at an Old Problem. *N. Engl. J. Med.* 286: 702: 1972.
12. Bridbord, K. Human Exposure to Lead from Motor Vehicle Emissions. U.S. DHEW, PHS, CDC, NIOSH, Pub. 77-145, 1977.
13. Sayre, J.W., Charney, E., Vostal, J. and Pless, I.B. House and Hand Dust as a Potential Source of Childhood Lead Exposure. *Am. J. Dis. Child.* 127: 167: 1974.
14. Vostal, J.J., Taves, E., Sayre, J.W. and Charney, E. Lead Analysis of House Dust: A Method for the Detection of Another Source of Lead Exposure in Inner City Children. *Environ. Health Persp.* 7: 91: 1974.
15. Rabinowitz, M.B., Wetherill, G.W. and Kopple, J.D. Kinetic Analysis of Lead Metabolism in Healthy Humans. *J. Clin. Invest.* 58: 260: 1976.
16. Barltrop, D. and Khoo, H.E. The Influence of Nutritional Factors on Lead Absorption. *Postgrad. Med. J.* 51: 795: 1975.
17. Six, K.M. and Goyer, R.A. The Influence of Iron Deficiency on Tissue Content and Toxicity of Ingested Lead in the Rat. *J. Lab. Clin. Med.* 79: 128: 1972.
18. Barltrop, D. The Prevalence of Pica. *Am.J. Dis. Child.* 112: 116: 1966.
19. Blanksma, L.A., et al. Incidence of High Blood Lead Levels in Chicago Children. *Pediatrics* 44: 661: 1969.
20. Kammholz, L.P., et al. Rapid Protoporphyrin Quantitation for Detection of Lead Poisoning. *Pediatrics* 50: 625: 1972.
21. Piomelli, S., et al. The FEP (Free Erythrocyte Porphyrins) Test: A Screening Micromethod for Lead Poisoning. *Pediatrics* 51: 254: 1973.
22. Sassa, S., et al. Studies in Lead Poisoning. I. Microanalysis of Erythrocyte Protoporphyrin Levels by Spectrofluorometry in the Detection of Chronic Lead Intoxication in the Subclinical Range. *Biochem. Med.* 8: 135: 1973.
23. Chisolm, J.J., Jr. and Brown, D.H. Micro-scale Photofluorometric Determination of "Free Erythrocyte Porphyrin" (Protoporphyrin IX). *Clin. Chem.* 21: 1669: 1975.
24. Chisolm, J.J., Jr. Heme Metabolites in Blood and Urine in Relation to Lead Toxicity and Their Determination. *Adv. Clin. Chem.* 20:225:1978, O. Bodansky, ed., Academic Press, N.Y.
25. Reigart, J.R. and Whitlock, N.H. Longitudinal Observations of the Relationship Between Free Erythrocyte Porphyrins and Whole Blood Lead. *Pediatrics* 57: 54: 1976.
26. Piomelli, S. A Micromethod for Free Erythrocyte Porphyrins: The FEP Test. *J. Lab. Clin. Med.* 81: 932: 1973.
27. Stockman, J.A., III, Weiner, L.S., Simon, G.E., Stuart, M.J. and Oski, F.A. The Measurement of Free Erythrocyte Porphyrin (FEP) as a Simple Means of Distinguishing Iron Deficiency from β-Thalassemia Trait in Subjects with Microcytosis. *J. Lab. Clin. Med.* 85: 113: 1975.
28. Piomelli, S., Brickman, A. and Carlos, E. Rapid Diagnosis of Iron Deficiency by Measurement of Free Erythrocyte Porphyrins and Hemoglobin: The FEP/Hemoglobin Ratio. *Pediatrics* 57: 136: 1976.
29. DeLeo, V.A., Poh-Fitzpatrick, M., Mathews-Roth, M. and Harber, L.C. Erythropoietic Protoporphyria – 10 Years Experience. *Am. J. Med.* 60: 8: 1976.
30. Mathews-Roth, M.M. Erythropoietic Protoporphyria – Diagnosis and Treatment. *N. Engl. J. Med.* 297: 98: 1977.
31. Lamola, A.A., Joselow, M. and Yamane, T. Zinc Protoporphyrin (ZPP): A Simple, Sensitive, Fluorometric Screening Test for Lead Poisoning. *Clin. Chem.* 21: 93: 1975.
32. Blumberg, W.E., Eisinger, J., Lamola, A.A. and Zuckerman, D.M. The Hematofluorometer. *Clin. Chem.* 23: 270: 1977.
33. Kaplan, M.L., et al. Inhibitory Effect of Iron on the Uptake of Lead by Erythrocytes. *Life Sci.* 16: 1545: 1975.
34. Chisolm, J.J., Jr., Barrett, M. B. and Harrison, H.V. Indicators of Internal Dose of Lead in Relation to Derangement in Heme Synthesis. *Johns Hopkins Med. J.* 137: 6: 1975.
35. Chisolm, J.J., Jr., Mellits, E.D. and Barrett, M.B. Interrelationships Among Blood Lead Concentration, Quantitative Daily ALA-U and Urinary Lead Output Following Calcium EDTA. *Effects and Dose-Response Relationships of Toxic Metals*, G.F. Norberg, ed., Elsevier, Amsterdam, Netherlands. 1976.
36. Graef, J.W. Outpatient Use of a Six-Hour Lead Mobilization Test in Chelation Therapy. *Pediatr. Res.* 10: 330: 1976.
37. Benson, P.F. and Chisolm, J.J., Jr. A Reliable Qualitative Use Coproporphyrin Test for Lead Intoxication in Young Children. *J. Pediatr.* 56: 759: 1960.

38. Granick, J.L., Sassa, S., Granick, S., Levere, R.D. and Kappas, A. Studies in Lead Poisoning. II. Correlation Between the Ratio of Activated to Inactivated δ-Aminolevulinic Acid Dehydratase of Whole Blood and the Blood Lead Level. *Biochem. Med.* 8: 149: 1973.

39. Burch, H.B. and Siegel, A.L. Improved Method for Measurement of delta-Aminolevulinic Acid Dehydratase Activity of Human Erythrocytes. *Clin. Chem.* 17: 1038: 1971.

40. Chisolm, J.J., Jr. Treatment of Lead Poisoning. *Modern Treatment* 8: 593: 1971.

41. Sachs, H.K., et al. Ambulatory Treatment of Lead Poisoning: Report of 1,155 Cases. *Pediatrics* 46: 389: 1970.

42. Jugo, S., Maljković, T. and Kostial, K. Influence of Chelating Agents on the Gastrointestinal Absorption of Lead. *Toxicol. Appl. Pharmacol.* 34: 259: 1975.

43. Ziegler, E.K., Edwards, B.B., Jensen, R.L., Mahaffey, K.R. and Fomon, S.J. Absorption and Retention of Lead by Infants. *Pediatr. Res.* 12:29:1978.

44. Sorrell, M., Rosen, J.F., and Roginsky, M. Interactions of Lead, Calcium, Vitamin D, and Nutrition in Lead-Burdened Children. *Arch. Environ. Health* 32: 160: 1977.

45. Tola, S., Hernberg, S. and Vesanto, R. Occupational Lead Exposure in Finland. VI. Final Report. *Scand. J. Work Environ. Health* 2: 115: 1976.

46. Hanken, L., et al. Lead on Wrappers of Specialty Foods as a Potential Hazard for Children. *Clin. Pediatr.* 13: 1064: 1974.

47. Crosby, W.H. Lead-Contaminated Health Food Associated with Lead Poisoning and Leukemia. JAMA 237: 2627: 1977.

48. Angle, C.R. and McIntire, M.S. Lead: Environmental Sources and Red Cell Toxicity in Urban Children. *NTIS* PB-249 061/3WP: 92: 1975.

49. Angle, C.R., et al. Lead in Air, Dustfall, Soil, Housedust, Milk and Water; Correlation with Blood Lead of Urban and Suburban School Children. *Trace Substances in Environmental Health – VIII.* D.H. Hemphill, ed. Univ. Missouri, Columbia. 1974.

50. Butler, J.D. and MacMurdo, S.D. Interior and Exterior Atmospheric Lead Concentrations of a House Situated Near an Urban Motorway. *Int. J. Environ. Studies* 6, No. 2-3: 181: 1974.

51. Lepow, M.L., et al. Investigations into Sources of Lead in the Environment of Urban Children. *Environ. Res.* 10: 415: 1975.

52. Kosowski, M.A. and Kosowski, W.J. Lead in the Environment: Sources of Danger. *Can. Med. Assoc. J.* 114: 474: 1976.

53. Landrigan, P.J., Gehlbach, S.H., Rosenblum, B.F., Shoults, J.M., Candelaria, R.M., Barthel, W.F., et al. Epidemic Lead Absorption Near an Ore Smelter. The Role of Particulate Lead. *N. Engl. J. Med.* 292: 123: 1975.

Reprinted with permission by the
U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
from NEW ENGLAND JOURNAL OF MEDICINE, Vol. 297, No. 17, Oct. 27, 1977

Appendix A

EXPOSURE TO LEAD: SOURCES AND EFFECTS

by Herbert L. Needleman, M.D.

Reducing exposure to lead and its consequences to health continues to be an important unfinished task in the public-health area. Recent recognition of lead in some glassware decorations has focused attention on the many sources of lead in the human environment and raises for re-examination the definition of critical thresholds for measurable health effects.

The early work of Massachusetts physicians such as Drs. McKann, Blackfan, Aub, and Byers led to an enriched understanding of the serious consequences of childhood lead poisoning. More recent data indicate that the sources of lead for children are multiple, and that body lead burdens below those associated with clinical symptoms can affect biochemical functions, and neuropsychologic performance.

The increased vulnerability of young children to lead is a well accepted clinical maxim. Increased absorption of lead across the child's gut has been demonstrated by Alexander et al.[1] and is supported by studies in the immature rodent by Kostial et al.[2] At the same internal dose of lead (as measured by blood lead concentration), children have recently been shown to have more impairment in heme synthesis than adults, as measured by free erythrocyte protoporphyrin.[3]

Because anemia is a long recognized effect of lead exposure, and blood is a tissue readily available for study, initial studies of the biochemical changes associated with lead have centered on the heme pathway. Additional studies have demonstrated that lead affects other heme enzymes, notably cytochrome P-450 in the liver.[4] Red-cell D-amino levulinic acid dehydrase (D ALA-D), an enzyme necessary for the conjugation of levulinic acid into porphobilinogen, is inhibited at lead levels as low as 10 μg per deciliter.[5] Millar et al. have shown that brain levels of D ALA-D in the rodent parallel peripheral blood levels, suggesting that oxidative metabolism in the brain may be affected at blood levels as low as 20 μg per deciliter.[6]

Lead inhibits brain adenyl cyclase at low concentrations in cerebellar preparations[7] and in nigrostriatal preparations.[8] Lead has also been shown to inhibit pancreatic adenyl cyclase.

Interference with globin synthesis[9] and collagen synthesis[10] has also been demonstrated at relatively low concentrations of lead. In the heme pathway itself, lead acts at a number of sites. In addition to the previously-cited inhibition of red-cell D ALA-D, lead acts on the red-cell mitochondrion. Here, it interferes with the incorporation of iron into the tetrapyrrole ring, resulting in its replacement by zinc. Consequently, increased levels of zinc protoporphyrin or its extraction product, free erythrocyte protoporphyrin, occur in persons with elevated blood lead levels. Recent studies indicate that this effect begins at 15 μg per deciliter.[11] Increased urinary amino levulinic acid excretion begins to appear at blood lead levels of 40 μg per deciliter.[12]

For the young child, the most important target organ is the brain. The catastrophic effects of lead encephalopathy and the protean symptoms of lead poisoning have caused many clinicians to ask whether lesser levels of lead than those producing frank encephalopathy result in subtler forms of brain injury.

This controversial question is made more difficult by the often close association of lead exposure with poverty and its attendant troubles, by the lack of sensitive clinical indicators during the peak exposure period in early childhood, and by problems in reliably measuring past exposure in older children — epidemiologic issues that are not peculiar to lead. It is not surprising that some investigators have found neuropsychologic deficits in children with low level exposure whereas others have not. Among the studies of low level lead and brain function, two are acknowledged by many as more rigorous and controlled. Burdé and Choate followed children identified as lead exposed, and controls matched on socioeconomic status and race, and found that the exposed group had a higher incidence of gross and fine motor dysfunction, irritability and impaired cognition at the age of four years. When the children were retested at seven to eight years of age the incidence of dysfunction had not decreased. This finding suggested that the deficit was fixed.[13] Perino and Ernhart studied black preschoolers with blood leads greater than 50 or less than 30 μg per deciliter.[14] Controlling for socioeconomic status, the authors reported a statistically significant deficit on the McCarthy scales of mental development. Al-

Further information may be obtained from Herbert L. Needleman, M.D., Children's Hospital Medical Center, 300 Longwood Ave., Boston, MA 02115 ([617] 734-6000, ext. 3400).

though the correlation between parental and child IQ in the low-lead group was 0.52, in the high-lead group the correlation was 0.1. This finding suggests that another factor, presumably lead, disturbed the parent–child IQ correlation.

The effects of lead exposure during pregnancy deserve close consideration. Because lead crosses the placenta, it has been found in the umbilical-cord blood of newborns.[15] It has also been shown to be associated with severe reproductive damage in occupationally exposed women, and to be teratogenic in the laboratory animal. In Glasgow, Moore et al. identified 77 retarded and normal children matched for socioeconomic status and geography. The mother's residence during pregnancy was visited, and a first-flush water sample obtained. No normal children came from homes with a high content of lead in the water, although 11 of 64 retardates did. The discovery of blood samples on file from old phenylketonuria cards allowed retrospective blood lead determinations to be made on some of these subjects. Blood lead levels in retardates in the first week of life were significantly higher than in normal controls.[16] Wibberly reported higher placental lead levels in malformed and stillborn than in normal infants.[17]

The sources of lead for children are many and ubiquitous. Although new paint for household use will soon contain less than 0.06 per cent lead, thousands of houses have paint that contains well over 1 per cent. Many of these surfaces are flaking and peeling. Those that are not often chalk and contribute to lead in dust. Air-borne lead of small particle size is readily absorbed through the lung; large particles fall out into dust and are swallowed by children. The largest contribution to lead in the atmosphere is automobile emissions. Foodstuffs contribute a substantial amount of lead to the daily intake, much of which is added to the food during processing. Water may be a source in areas where the mineral content is low, the water acidic, and old leaded pipes still in place. Newsprint and some ceramic tableware may contain lead. Decorative decals and glazes on the exterior of some glasses contain considerable amounts of lead. This lead, leachable by dilute acids, can also flake off the glass, and represents a potential hazard for some children.

Although the relative contribution of each source varies with an individual's age, habits and circumstances, rough estimates can be constructed as guidelines. Dietary lead provides 50 to 250 μg per day external dose, of which 20 to 100 μg is absorbed by children. Urban dust contains lead in concentrations between 1000 and 5000 μg per gram. The ordinary hand-to-mouth activity of children transfers considerable quantities of dust-borne lead to the gut. Ingestion of 100 mg of dust containing 1000 ppm of lead would add 100 μg of external dose, of which 40 μg would be absorbed. Urban air lead levels range between 2 and 5 μg per cubic meter, but can be higher at selected sites and at peak traffic periods. Children have higher metabolic rates, are generally more active, and therefore have higher respiratory volumes relative to body size. Air-borne lead could provide an internal dose of between 16 and 40 μg per day for an adult, and 8 to 20 μg per day for a child. Paint, of course, provides lead in the highest concentration for children with pica. One single paint flake containing 1 per cent lead delivers an external dose of 10,000 μg.

Clearly, the lead burden of a given person is a sum of the multiple sources experienced by that person. The importance of one source should not be played off against another if effective prevention is to be obtained. Lead should be discovered first in the environment before it gets into children, and then removed. Effective housing inspection and abatement are complex, difficult and often contentious enterprises. They must, however, be pursued. Removing lead from air and dust are urgent public-health goals.

Each source has its own control or abatement cost, and each has a vested interest. The costs of removing lead from the environment are formidable, and many who identify themselves as realists say that society cannot support these costs.

The worth of the human brain is incalculable. The value we assign to it will be defined by the intensity with which we pursue or avoid the protection of its optimum development. Excess lead in the human environment is man-made and is, therefore, preventable by man.

References

1. Alexander FW, Delves HT, Clayton BE: The uptake and excretion by children of lead and other contaminants, Environmental Health Aspects of Lead. Edited by D Barth, A Berlin, R Engel, et al. Luxembourg, Commission of the European Communities, Center for Information and Documentation, 1973, pp 319-330
2. Kostial K, Simonović I, Pisonić M: Lead absorption from the intestine in newborn rats. Nature 223:564, 1971
3. Roels H, Buchet J-P, Lauwerys R, et al: Impact of air pollution by lead on the heme biosynthetic pathway in school-age children. Arch Environ Health 31:310-316, 1976
4. Alvares AP, Leigh S, Cohn J, et al: Lead and methyl mercury: effects of acute exposure on cytochrome P-450 and the mixed function oxidase system in the liver. J Exp Med 135:1406-1409, 1972
5. Hernberg S, Nikkanen J, Mellen G, et al: α-Aminolaevulinic acid dehydrase as a measure of lead exposure. Arch Environ Health 21:140-145, 1970
6. Millar JA, Battistini V, Cumming RLC, et al: Lead and δ-aminolaevulinic acid dehydratase levels in mentally retarded children and in lead-poisoned suckling rats. Lancet 2:695-698, 1970
7. Nathanson JA, Bloom FE: Lead-induced inhibition of brain adenyl cyclase. Nature 255:419-420, 1975
8. Walton KG, Baldessarini R: Effects of Mn^{2+} and other divalent cations on adenylate cyclase activity in rat brain. J Neurochem 27:557-564, 1976
9. Ali MAM, Quinlan A: Effect of lead on globin synthesis in vitro. Am J Clin Pathol 67:77-79, 1977
10. Vistica DT, Ahrens FA, Ellison WR: The effects of lead on collagen synthesis and proline hydroxylation in the Swiss mouse 3T6 fibroblast. Arch Biochem Biophys 179:15-23, 1977

11. Piomelli S, Seaman C, Zullow D, et al: Metabolic evidence of lead toxicity in "normal" urban children. Clin Res 25:459A, 1977

12. Selander S, Cramer K: Interrelationships between lead in blood, lead in urine, and ALA in urine during lead work. Br J Ind Med 27:28-39, 1970

13. de la Burdé B, Choate MS: Early asymptomatic lead exposure and development at school age. J Pediatr 87:638-642, 1975

14. Perino J, Ernhart CB: The relation of subclinical lead level to cognitive and sensorimotor impairment in black preschoolers. J Learn Dis 7:26-30, 1974

15. Rom WN: Effects of lead on the female and reproduction: a review. Mt Sinai J Med 43:542-552, 1976

16. Moore MR, Meredith PA, Goldberg A: A retrospective analysis of blood-lead in mentally retarded children. Lancet 1:717-719, 1977

17. Wibberly DG, Knera AK, Edwards H, et al: Lead in human placentae from normal and malformed births. J Med Genet (in press)

Appendix B

Comments on "Treatment of Lead Poisoning"
***Modern Treatment*, Vol. 8, No. 3, August 1971**
by J. Julian Chisolm, Jr., M.D.

January 1978

The following article on the treatment of lead poisoning was first prepared in 1967 and revised slightly in 1971. Although the basic principles of clinical management remain unchanged, newer information suggests that the various risk categories in children, according to blood lead groups, should be revised as follows: Currently, 30 μg Pb/dl whole blood is considered the upper limit of normal in children, not 40 μg, as previously stated. Where the original text refers to 60 and 80 μg Pb/dl whole blood, 50 and 70 μg Pb/dl whole blood, respectively, should be substituted. Correction of blood lead concentration according to hematocrit, as originally suggested, is probably inappropriate, although still somewhat controversial. Calculation of dosage of chelating agents on the basis of body surface area, rather than body weight, is pharmacologically preferable. In particular, this change will minimize overdosage in older children. These changes are reflected in the revisions of Tables 4 and 5, which are attached.

Table 4. Revised Dosage Schedule for Chelating Agents, January 1978

Drug	*Dosage*	*Route*	*Schedule*
BAL-CaEDTA in combination (BAL = 2, 3-dimercaptopropanol available as BAL in Oil for IM use only. EDTA = edathamil calcium disodium ($CaNa_2$ EDTA, Versenate); available in 20% sol. to be diluted for IV administration)*	BAL = 500 mg/m^2/24 hr given in divided dose q4h CaEDTA = 1500 mg/m^2/24 hr given in divided dose q4h	IM IM	For first dose, inject BAL only. Beginning 4 hr later and every 4 hr thereafter, inject BAL and CaEDTA simultaneously at separate *deep* IM sites; usual course = 5 days (30 doses). (See text for indications for 3- and 7-day courses.) In adults, continuous 24 hr IV infusion of CaEDTA may be preferred
CaEDTA only (therapeutic)	1000 mg/m^2/24 hr	Children: deep IM Adults: Continuous slow IV. Concentration of EDTA in 5% D/W or NS should not exceed 0.5%	Children: In divided doses every 8 to 12 hr for 3-5 days Adults: Infuse total daily dose in 12-24 hr (min. safe infusion time is 8 hr) Max course is 5 days All: Allow minimum rest period of 2 days between courses. Rest periods of 2-3 wk are both safer and more efficient in promoting lead diuresis
CaEDTA mobilization test (diagnostic)	500 mg/m^2 to max dose of 1 gm	Give as single IM injection or infuse IV over 1 hr period (0.5% in 5% D/W)	Collect urine quantitatively for lead analysis for 24 hr if renal function normal; 3-4 day collection required in renal insufficiency (6)
Oral D-penicillamine (ββ-dimethylcysteine; available as Cuprimine in 250-mg capsules. Investigational drug in USA; see recommendations of AMA Council on Drugs for precautions in use (1))	600 mg/m^2/day	Oral	Young children: Give on *empty* stomach as single early morning dose, 2 hr before breakfast. For young children unable to swallow capsules, empty contents of capsule into small amount of chilled fruit or fruit juice immediately prior to administration Adults: Give on empty stomach 2 hr apart from meals. May be given in divided dose 2 or 3 times a day.

*Suggested preparation of calcium disodium EDTA for intramuscular injection: Use procaine hydrochloride crystal, 80 to 100 mesh USP and calcium disodium EDTA, 20% solution, 5 ml ampules for intravenous use. Add 0.3 g crystalline procaine hydrochloride to 12 vials of calcium disodium EDTA (60 ml). Scrub, rinse and steam sterilize all vials and stoppers. Use freshly-distilled and filtered water passed through a 0.22 micron Millipore filter. After crystals of procaine hydrochloride are dissolved directly in the calcium disodium EDTA, the entire solution is passed through a 0.22 micron filter and transferred, under aseptic conditions, into vials containing 5 ml each. Final concentration in the intramuscular preparations are: Calcium disodium EDTA 200 mg/ml and procaine hydrochloride 0.5%.

Table 5. Revised Choice of Chelating Agents Based on Symptomatology and Blood Lead Concentration, January 1978

Clinical Presentation	*Chelating agent**	*Comment*
A. CHILDREN		
1. Symptomatic cases		
a. Acute encephalopathy	BAL-CaEDTA(IM)	First course 5-7 days; give second 5-day course if blood lead rebounds to >70 μg Pb/dl whole blood 14-21 days after first course; transfer patient to convalescent facility for 2-6 mo course of oral D-penicillamine
b. Intoxication without encephalopathy (classical clinical plumbism without increased intercranial pressure or ataxia)	BAL-CaEDTA(IM)	First course 5 days only; indication for second course same as above; follow with oral D-penicillamine (2-6 mo) if blood lead >50 μg Pb/dl whole blood. Longer courses may be needed when long bone x-rays show prominent "lead lines." If symptoms abate within 24 hr, BAL should be stopped 48 hr later. If initial blood lead <70 μg Pb/dl whole blood, BAL usually not indicated
2. Asymptomatic cases		
Blood lead >100 μg Pb/dl whole blood	BAL-CaEDTA(IM)	Choice of first course based on initial blood lead. Evidence of metabolic toxicity should be demonstrated.
70-99 μg Pb	BAL-CaEDTA(IM)	When Pb-B exceeds 70 μg, EP generally > 250. Give CaEDTA 5 days, but limit BAL to first 48 hr
50-69 μg Pb	CaEDTA(IM)	EP generally > 110. Give CaEDTA 3-5 days; follow with D-penicillamine, especially if long bone x-rays positive.
3. Long-term followup		
a. Intercurrent infection, demineralizing bone disorders	CaEDTA only(IM)	Give 3-day course whenever significant increase in UCP and/or ALA occurs, even though no increase in either blood lead or EP occurs.
b. Recurrent ingestion	BAL-CaEDTA(IM) or CaEDTA only (IM)	Choice same as for asymptomatic cases above (section 2)
c. Long-term chelation	D-penicillamine* (oral)	Do not use any chelating agent orally if risk of residual lead in bowel. Following initial therapy with parenteral BAL-CaEDTA or CaEDTA only, use oral D-penicillamine only when the risk of continued hazardous environmental lead exposure is precluded.

*Precautions: D-penicillamine contraindicated in penicillin-sensitive individuals. CaEDTA-intramuscular preparation contains procaine.

Reprinted with permission by the
U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
from *Modern Treatment*, Vol. 8, No. 3, August 1971

Treatment of Lead Poisoning

J. JULIAN CHISOLM, Jr, MD

From the Department of Pediatrics, John Hopkins University School of Medicine, and the Baltimore City Hospitals, Baltimore

THE CRUCIAL ASPECT OF THERAPY in all age groups is prompt termination of undue lead exposure, defined as exposure to lead from sources other than those found in normal uncontaminated food, beverage and ambient air. When indicated, the use of chelating agents must be considered an adjunct to the prevention of continued dangerous environmental lead exposure. The rationale of this therapeutic approach is based upon our knowledge of the absorption, metabolism and excretion of lead in man (13). Inorganic lead compounds are poorly absorbed into the body from the gastrointestinal tract so that repetitive ingestion of small amounts is usually far more hazardous than single massive exposure (see p 610). Plumbism, thus, results from the accumulation over a period of weeks, months, or years of an excessive body burden of lead. This burden is distributed between bone and soft tissues, with the major portion being stored in bone. There is no known significant toxicity associated with the portion that has been well incorporated into the matrix of bone. Rather, the acute toxic effects of lead are apparently associated with increments in the lead concentration in soft tissues. Under conditions of prolonged, but perhaps intermittent excessive exposure and absorption of inorganic lead salts, the clinical course is one of recurrent, acute symptomatic episodes which, in turn, appear to be associated with sharp increments in the concentration of lead in various soft tissues.

Once abnormal absorption is terminated, virtually all of the lead remaining in the body is gradually shifted to bone. The studies of Kehoe in human adult volunteers indicate that it takes at least twice as long to excrete a given burden of lead as it does to accumulate it. Since chelating agents probably do not remove significant quantities of lead which have been incorporated into the matrix of bone, they cannot be expected to accelerate this process. Estimates of the dura-

Supported in part by United States Public Health Service Grant 5 R01 EC 00201-18 from the National Institute for Occupational Safety and Health.

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

children might be subject, especially in old deteriorated housing. Effective therapy calls for solutions to three difficult problems: a) early diagnosis and treatment of acute toxic episodes, b) permanent separation of the child from environmental lead sources, and c) prevention of pica. Most children with plumbism require close medical supervision until they reach school age and some need care much longer. The comprehensive therapeutic program described here requires the coordinated long-term efforts of physician, pediatric psychiatrist, medical social worker, child guidance personnel, health department personnel, and visiting public health nurses.

Once minor symptoms of poisoning are present, acute encephalopathy can develop with unpredictable and startling rapidity, especially during the summer months. For this reason, *any child with symptoms that suggest plumbism or blood lead concentrations >80 μg Pb/100 g of whole blood should be treated as a medical emergency and hospitalized immediately.* Delay is one of the main reasons for poor therapeutic results. Early diagnosis depends upon a high index of suspicion a knowledge of the epidemiology of plumbism and the interpretation of specific emergency laboratory tests.

Epidemiology

The vast majority of cases of childhood plumbism in the United States today are found in children who reside in old, deteriorating urban housing. Recent studies in Baltimore, Maryland revealed that 50 to 70 per cent of the old houses in selected slum areas contain dangerous quantities of flaking lead pigment paints (14). The interior wood work, painted plaster and wallpaper of houses built prior to 1940 and still in use may contain layers of lead pigment paints which have never been removed. Several tiny flakes of such paint may contain 100 mg or more of lead; the safe daily intake of lead is <0.5 mg (13). Table 1 summarizes the results of a prospective home survey of preschool children in Cleveland, Ohio (10). A comparable situation exists in most of the large cities of the continental United States, particularly those east of the Mississippi River. It is abundantly clear from these data that young children in substandard urban housing should be screened periodically for plumbism. Table 2 lists unusual sources of lead.

Repetitive ingestion of small quantities of lead in paint apparently must continue for 3 months or longer before a potentially lethal quantity of lead is absorbed into the body. For practical purposes one must assume that ingestion begins by one year of age in children who live in urban slum areas. Multiple cases are often found in the

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

Residence	No. of children	Children with Abnormal urine* No.	%	Children with 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.]

not familiar with the city. b) How long has the child been walking or crawling? If the child lives in or visits a house built prior to 1940, has been ambulatory for three months or longer, and has any symptom suggestive of plumbism he receives the emergency laboratory determinations listed in Table 3. *Provisional diagnosis and the decision to hospitalize the patient and institute chelation therapy must be made at the first clinic visit.*

Symptoms that suggest early lead intoxication are: anorexia, apathy, anemia (hemoglobin <10 g), hyperirritability and other behavioral disturbances, clumsiness, loss of recently acquired developmental skills and sporadic vomiting. The onset of encephalopathy is heralded by gross ataxia, persistent and forceful vomiting, periods of lethargy or stupor interspersed with lucid intervals and finally coma and intractable convulsions. Any of these symptoms, together with one or more positive presumptive laboratory tests (Table 3), calls for immediate hospitalization and institution of chelation therapy. Young children with pica, behavioral disorders, convulsions, mental retardation and symptoms suggestive of cerebral degenerative diseases should also receive these tests (4).

It is unusual for all tests to be positive in a given case. The quickest presumptive test in children is the qualitative UCP test which is described in Appendix 1. Technical and interpretive considerations for each test are included in Table 3. Lumbar puncture should be avoided unless essential for differential diagnosis which includes tuberculous meningitis, various encephalitides, and other causes of increased intracranial pressure (eg, tumor). If lumbar puncture is attempted, the least amount of cerebral spinal fluid should be collected dropwise, and never allowed to spurt out; 1 ml is more than sufficient. In acute lead encephalopathy the fluid shows normal sugar content, mild pleocytosis and a moderate increase in protein content. Attempts to obtain fluid by ventricular tap are not warranted and usually fail.

TREATMENT

Supportive Measures

It is our policy to treat all symptomatic children as potential cases of acute encephalopathy and, hence, to begin treatment immediately. Adequate urine flow should be established first. As soon as the child with encephalopathy is admitted to the hospital, a continuous intravenous infusion of 10 per cent dextrose in water (10 to 20 ml/kg body weight) is administered over a period of 1 to 2 hours. If this

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

Table 3 (Continued)

Test	Technical factors	Interpretation
Urinalysis	UCP test takes precedence; use general reagents for reducing sugars (ie, Clinitest)	Glycosuria (+ or ++) found in very chronic or very severe cases; very acute and severe cases often show proteinuria, hematuria, cellular casts, and leukocytes in sediment (important findings in critical patients if UCP test negative)
		SPECIFIC DIAGNOSTIC TESTS
Whole blood lead	Special lead-free needle, syringe and sample container must be used and often supplied by laboratory performing analysis; 10 ml lead-free B-D Vacutainer commercially available. Draw enough blood (10 ml usually required) as insufficient samples may yield erroneously high results	Normal unexposed children: 15–40 μg Pb/100 g whole blood Undue exposure: >40 μg/100 g whole blood suggests lead intake from sources other than normal uncontaminated diet Mild symptoms may be present: 60–80 μg Pb/100 g whole blood Symptoms may be absent, but risk of encephalopathy great: >100 μg Pb/100 g whole blood
Urine lead output	Use lead-free collection apparatus supplied by laboratory performing analysis, this test of limited value because quantitative 24-hr collection required in young children	Result may be misleading (ie, pretreatment values often within normal limits (>80 μg Pb/24 hr) in acute encephalopathy). Consider excretion >1.5 mg Pb/24 hr during first 24 hr of chelation therapy diagnostic of plumbism in symptomatic cases

fails to initiate urination, mannitol (1 to 2 g/kg body weight) is infused intravenously as a 20 per cent solution at a rate of 1 ml/min. Once urine flow is established, further intravenous fluid therapy is restricted to basal water and electrolyte requirements and to a minimum estimate of the quantities needed for convulsive activity, and fever and the replacement of deficits due to vomiting and dehydration. Careful parenteral fluid therapy is vital to survival and is best monitored by measuring the rate of urine flow. This may require indwelling bladder catheterization in unconscious children, a risk which must be carefully weighed by the attending physician in each

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 4. Dosage Schedule for Chelating Agents

Drug	Dosage	Route	Schedule
BAL-CaEDTA in combination (BAL = 2,3-dimercaptopropanol available as BAL in Oil for IM use only. EDTA = edathamil calcium disodium ($CaNa_2EDTA$, Versenate); available in 20% sol. to be diluted for IV administration. For IM add procaine to 20% sol. to give conc. of procaine of 0.5%)	Children: BAL = 4 mg/kg/dose	IM	For first dose, inject BAL only Beginning 4 hr later and every 4 hr thereafter, inject BAL and CaEDTA simultaneously at separate deep IM sites; usual course = 5 days (30 doses). (See text for indications for 3-and 7-day courses.)
	CaEDTA = 12.5 mg/kg/dose	IM	
	Adults: BAL = 2.5 mg/kg/dose	IM	
	CaEDTA = 8.0 mg/kg/dose	IM	
CaEDTA only (therapeutic)	50 mg/kg/24 hr	Young children: Deep IM	Young children: in divided doses every 8 to 12 hr for 3–5 days
	2 g/day (mild case)	Adults: Continuous slow IV Concentration of EDTA in 5% D/W or NS should not exceed 0.5%)	Adult: Infuse total daily dose in 12–24 hr (min safe infusion time is 8 hr) Max course is 5 days.
	3–4 g/day (cautiously in severe cases)		All: Allow minimum rest period of 2 days between courses. Rest periods of 2–3 wk are both safer and more efficient in promoting lead diuresis.
EDTA mobilization test (diagnostic)	25 mg/kg to max dose of 1 gm	Give as single IM injection or infuse IV over 1 hr period (0.5% in 5% D/W)	Collect urine quantitatively for lead analysis for 24 hr if renal function normal; 3–4 day collection required in renal insufficiency (6)
Oral D-penicillamine (ββ-dimethylcysteine; available as Cuprimine in 250-mg capsules. Investigational drug in USA; see recommendations of AMA Council on Drugs for precautions in use (1))	Children: 30–40 mg/kg/24 hr	Oral	Children: Given in divided doses twice a day
	Adults: 500–750 mg/24 hr	Oral	Adults: Given in divided doses twice or three times a day
			All: Give on empty somach 1½ hr before meals; for young children unable to swallow capsules, empty contents of capsule into small amount of fruit or fruit juice immediately prior to administration

*An updated version of this table appears on page 20.

*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		Choice for first course indicated by blood lead; follow with oral D-penicillamine as above (section 1b)
>100 μg Pb/100 g whole blood	BAL-CaEDTA (IM)	
<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)

*An updated version of this table appears on page 21.

Table 5 (Continued)

Clinical presentation	Chelating agent*	Comment
c. Painless peripheral neuropathy (including wrist and foot drops)	D-Penicillamine (oral)	1–2 mo course depending on clinical response and lead diuresis. Give BAL-CaEDTA 3–5 days initially if blood lead >100 μg Pb/100 g whole blood
2. Asymptomatic Cases		
a. Blood lead >100 μg Pb/100 g whole blood	BAL-EDTA (IM)	3–5 day course followed by oral penicillamine as above
80–100 μg Pb/100 g whole blood	Penicillamine (oral)	Remove from exposure and give brief course as above
3. Long-term Chelation	Penicillamine (oral)	Same as for children but limit course to 2 mo
4. Organic Lead Compounds (tetraethyl lead, tetramethyl lead)	Not recommended	Treatment supportive; see text

* Precautions: D-penicillamine contraindicated in penicillin-sensitive individuals. CaEDTA-intramuscular preparation contains procaine.

sions or two intramuscular injections at 12-hour intervals during the succeeding 2 to 3 days of the total five-day course. While this approach can reduce the number of injections during a five-day course, it probably also somewhat reduces the diuresis of lead. Immediate followup of initial parenteral chelation therapy with oral D-penicillamine virtually always obviates the need for repeated courses of parenteral chelation therapy. Some of the toxic effects of lead may be intensified if CaEDTA is given alone in the presence of very high tissue concentrations of lead (3). The addition of BAL to CaEDTA minimizes these toxic effects, greatly accelerates urinary lead excretion and causes a significantly more rapid decrease in blood lead concentration (4). Medicinal iron should not be given concurrently with BAL. The patient should remain in the hospital or convalescent home until chelation therapy is completed according to indications in Table 5.

Other Measures

No time should ever be wasted in attempts to evacuate residual lead from the bowel by enema. Such attempts are futile, and in cases of encephalopathy the attendant delay jeopardizes the child's life. There is no evidence that parenteral administration of BAL-CaEDTA

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-

pound is excreted unchanged by the kidney (7). CaEDTA must, therefore, be withheld during periods of anuria. The dosage should not exceed 50 mg/kg body weight/day except in the BAL-CaEDTA combination. When EDTA is administered by intermittent intramuscular injection according to the schedules given in Table 4, the following side effects have been observed in occasional patients: proteinuria, microscopic hematuria and large epithelial cells in the urinary sediment, hypercalcemia, and fever. These untoward reactions are most frequently observed toward the end of a second or subsequent course of therapy and call for immediate cessation of CaEDTA administration. More severe reactions have been reported during intravenous administration and are most likely to occur when the total daily dose is administered in less than 12 hours (8). Safe administration of this drug requires the following determinations on the 1st, 3rd, and 5th day of each course of therapy: serum electrolytes, blood urea nitrogen, calcium, phosphorus, alkaline phosphatase measurements in blood, and routine urinalysis. The patient should also be monitored for irregularities of cardiac rhythm. [Nephrosis, which is usually reversible, and hypokalemia are two of the more serious side-effects of CaEDTA.—Ed.] D-Penicillamine is a degradation product of penicillin. There has been considerable experience with this drug in the treatment of lead intoxication in Europe (9) but at the present time it is available in the United States on an investigational basis only. It is contraindicated in persons with a history of penicillin sensitivity. The following adverse side-effects of penicillamine have been reported (1): a) transient eosinophilia, b) erythematous skin rashes, c) superficial extravasations of blood, d) fever, e) prolonged bleeding time, f) leukopenia, agranulocytosis and thrombocytopenia, and g) nephrotic syndrome. Patients receiving this drug must be monitored with weekly urinalyses and blood counts (1). Adverse side effects of D-penicillamine are apparently dose-related: Serious reactions (ie, nephrotic syndrome) have been reported in patients receiving 1 to 2 g or more per day. Observations in this clinic indicate that dosages not exceeding 30 to 40 mg/kg/day in children have not been associated with serious side effects. In adults, dosages of 1 to 1.5 g are effective in the treatment of lead poisoning.

Convalescent and Long-term Care

The first precept of convalescent and long-term care is: *no child is ever returned to a leaded house.* All cases are referred to medical social service and reported to local public health authorities. The

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

as puberty approaches. Behavior abnormalities due to lead intoxication can be greatly intensified by persistently abnormal mother-child relationships. This long-term program may seem unnecessarily difficult and tedious, but it is essential if permanent brain damage is to be minimized.

ADULT LEAD INTOXICATION

The management of plumbism in adults differs from that in children in: a) types of hazardous exposure and measures for their control and b) interpretation of certain laboratory data. Principles for the use of chelating agents are essentially the same as in the child. Encephalopathy is rare in adults; in the United States today it usually results from the consumption of lead-contaminated illicit liquor (moonshine, "white lightening") which can present quite a diagnostic problem in the chronic alcoholic. The other clinical syndromes are well described elsewhere (15).

The following industries present the greatest occupational hazard: lead smelting, storage battery manufacturing, ship breaking, automotive body painting, painting, printing, and pottery glazing. Some phases of the following industries also present risk: petroleum, cable construction, ceramics, ammunition, radiation shielding, and noise and vibration control. In any industrial process the hazard lies in exposure to dust of inorganic lead salts and to fumes resulting from heating or burning of lead. These hazards can be largely controlled by proper ventilation, damp-dusting in the "dusty trades," automation of hazardous steps and use of respirators and protective clothing by exposed workmen (15). Protective clothing must be changed and hands washed before eating. Food should be eaten in a safe place separate from the work area. The physician must determine whether adequate occupational safety procedures are available to and being used by the patient. Nonindustrial types of exposure are listed in Table 2.

The laboratory parameters used in industry for medical supervision of occupational exposed workers are summarized in Table 6. The limits for "safe" occupational exposure have been set arbitrarily and are based on the observation that symptoms rarely occur in the absence of complicating illness unless these limits are exceeded. Quantitative data are preferable; in emergencies the interpretation of the presumptive tests in Table 3 for children are generally applicable to adults, with the exception of bone X-rays which are of no value in adults.

A variety of diseases are associated with two- to threefold increases

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

suggestive of acute nephritis (hematuria, casts, proteinuria) may be present in acute plumbism; cautious administration of BAL-CaEDTA is indicated in such cases. The CaEDTA mobilization test (Table 4) is helpful in difficult diagnostic problems, particularly in the presence of renal insufficiency and in the absence of recent lead exposure (6).

Treatment

The identification and control of hazardous exposure is mandatory for effective therapy. Indications for chelation therapy are presented in Table 5 and dosage in Table 4. In adults, the following maximum daily doses of CaEDTA should not be exceeded: in patients with encephalopathy, 7.5 g; in patients with intoxication but without encephalopathy, 4.0 g. Adverse side effects of drugs are discussed above. Supportive therapy for acute encephalopathy in adults is the same as that for children.

Experience with BAL-CaEDTA combination in adults is limited. I have observed very prompt relief of symptoms and metabolic abnormalities in a few adults with encephalopathy, severe colic, and profound muscle pain and weakness who received combined BAL-CaEDTA. Goldberg has reported good response to oral penicillamine alone (1.0 to 1.5 g daily for 3 to 5 days) in mildly symptomatic cases. European experience during the past 10 years with D-penicillamine in adults has been good. Oral therapy has the advantage of home administration and avoids painful injections.

It is the author's personal opinion that combined BAL-CaEDTA followed by oral penicillamine is indicated whenever blood lead exceeds 100 μg Pb/100 g whole blood even in the absence of obvious symptoms. Metabolic evidence of lead toxicity is universally present and the risk of symptomatic episodes is considerable when blood lead exceeds 100 μg Pb/100 g whole blood. This recommendation is not universally accepted. At issue is the question of whether treatment of lead intoxication should be limited solely to symptomatic episodes. The recommendations given in Table 5 are based upon the concept that chelating agents should be used in conjunction with control of environmental exposure to reduce soft tissue lead content to levels not associated with significant metabolic evidence of toxicity (4,11). This approach can greatly reduce the incidence of acute toxic episodes and quite possibly, the incidence of serious sequelae.

Vicarious lead hazards should be entirely eliminated. Unfortunately, increased occupational exposure cannot, as yet, be entirely eliminated

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.

References

1. AMA Council on Drugs: Copper chelating agent, penicillamine (Cuprimine). JAMA 189:153, 1964
2. Benson PF, Chisolm JJ Jr: A reliable qualitative urine coproporphyrin test for lead intoxication in young children. J Pediat 56:759, 1960
3. Chisolm JJ Jr: Disturbances in the biosynthesis of heme in lead intoxication. J Pediat 64:174, 1964
4. *Idem:* The use of chelating agents in the treatment of acute and chronic lead intoxication in childhood. J Pediat 73:1, 1968

5. Coffin R, Phillips JL, Stapes WI, Spector S: Treatment of lead encephalopathy in children. J Pediat 69:198, 1966
6. Emmerson BT: Chronic lead nephropathy: the diagnostic use of calcium EDTA and the association with gout. Australian Ann Med 12:310, 1963
7. Foreman H, Finnegan C, Lushbaugh CC: Nephrotoxic hazard from uncontrolled edathamil calcium-disodium therapy. JAMA 160:1042, 1956
8. Foreman H: Toxic side effects of ethylenediaminetetraacetic acid. J Chron Dis 16:319, 1963
9. Goldberg A, Smith JA, Lochhead AC: Treatment of lead-poisoning with oral penicillamine. Brit Med J 1:1270, 1963
10. Griggs RC, Sunshine I, Newill VA, Newton BW, Buchanan S, Rasch CA: Environmental factors in childhood lead poisoning JAMA 187:703, 1964
11. Haeger-Aronsen B: Studies on urinary excretion of aminolevulinic acid and other heme precursors in lead workers and lead-intoxicated rabbits. Scand J Clin Lab Invest 12:Suppl 47:1, 1960
12. Kaplan E, Shaull RS: Determination of lead in paint scrapings as an aid in the control of lead paint poisoning in young children. Amer J Public Health 51:64, 1961
13. Kehoe RA: Metabolism of lead in man in health and disease (The Harben Lectures, 1960). J Roy Inst Public Health 24:81, 101, 129, 177, 1961
14. Schucker GW, Vail EH, Kelley EB, Kaplan E: Prevention of lead paint poisoning among Baltimore children. Public Health Rep (Wash) 80:969, 1965
15. Symposium on Lead. Arch Environ Health 8:199–354, 1964
16. Selander S, Cramer K: Interrelationships between lead in blood, lead in urine, and ALA in urine during lead work. Brit J Indust Med 27:28, 1970

17J4544478

Notes