CDC uses a blood lead reference value (BLRV) of 3.5 micrograms per deciliter (µg/dL) to identify children with higher levels of lead in their blood compared to most children. This level is based on the 97.5th percentile of the blood lead values among U.S. children ages 1-5 years from the 2015-2016 and 2017-2018 National Health and Nutrition Examination Survey (NHANES) cycles. Children with blood lead levels at or above the BLRV represent those at the top 2.5% with the highest blood lead levels.

INCREASED LEAD ABSORPTION AND LEAD POISONING IN YOUNG CHILDREN

A STATEMENT BY THE

CENTER FOR DISEASE CONTROL

MARCH 1975

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
BUREAU OF STATE SERVICES
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I. Introduction

Significant advances in the management of children with lead poisoning, as well as a marked increase in program activities designed to prevent this condition, have been made since the Surgeon General's Statement, "Medical Aspects of Childhood Lead Poisoning," was issued in October 1970. The purpose of this statement is to reflect current knowledge by making revised recommendations regarding the screening, diagnosis, treatment, and follow-up of children for increased lead absorption and lead poisoning. Such activities for children will continue to be necessary until sources of lead are eliminated from their environment.

Terms used in the document are defined as follows:

> ***Lead poisoning*** exists when a child has: (1) a confirmed (two successive determinations) blood lead (Pb) equal to or greater than 80 micrograms per 100 milliliters (μg/100 ml) whole blood with or without symptoms; (2) erythrocyte protoporphyrin* (EP) level equal to or greater than 190 micrograms/100 milliliters (μg/100 ml) whole blood with or without symptoms; (3) or confirmed blood lead 50-79 μg/100 ml with compatible symptoms which cannot be explained otherwise or with associated abnormal erythrocyte protoporphyrin, ALA-d, urinary ALA, or urinary coproporphyrin levels or abnormal calcium disodium EDTA mobilization tests; or (4) EP level of 110-189 μg/100 ml with compatible symptoms which cannot be explained otherwise.
>
> ***Undue or increased lead absorption*** exists when a child has confirmed blood lead levels 30-79 μg/100 ml or an EP level of 60-189 μg/100 ml except where the elevated EP level is caused by iron deficiency.
>
> *Toxicity*, with respect to effects of lead in children, includes subclinical manifestations of biochemical derangements (such as increased erythrocyte protoporphyrin) as well as overt clinical manifestations (such as encephalopathy, Fanconi syndrome, etc.).

II. Background

While lead from lead-based paint is only one of several significant sources of lead in the environment, it is by far the most important "high dose" source and cause of lead poisoning in children.[1,2] Lead-based paint was commonly used on interior surfaces of housing units until the 1950's, and is still being used on exterior surfaces. While the ingestion of lead in paint peeling from indoor surfaces is well appreciated, lead-based paint on exterior surfaces accessible to children may also be the cause of an excessive lead burden. Dust and dirt may constitute "intermediate dose" sources of lead when contaminated by lead-based paint from interior or exterior surfaces or by auto emissions. Smelter dust may be a point source of excessive lead burden in localized instances. There are also a number of other sources of lead such as printed paper and canned foods. A variable percentage of ingested lead, 5-10 percent in adults,[3,4] but probably more in young children,[5,6] is very rapidly absorbed into the bloodstream.[4] Respiratory absorption of lead is dependent on particle size, but is generally much more complete than intestinal tract absorption.[3,7]

If lead uptake is not excessive, it is largely excreted in urine, bile, and sweat. If lead continues to be absorbed for a period of time at unusually high rates, tissue levels increase and result in toxic effects on soft tissues, significantly bone marrow, kidneys, and brain, and in deposition of large amounts of lead in bone. Blood lead levels then reflect the equilibrium between absorption, excretion, and soft tissue and bone pools. This balance appears to be influenced by dietary deficiency of iron and calcium[8,9] and by other unknown factors. Lead in soft tissues has serious, though largely reversible effects on heme production and renal function. Bone marrow is apparently the first organ system to be affected. Lead has even more serious and largely irreversible effects on the central nervous system. It is manifested by severe acute encephalopathy at one extreme and relatively mild neurological disability and possibly hyperactivity at a lower level of exposure.[10,11,12]

III. Screening

The primary goal of screening programs is to prevent symptomatic and asymptomatic lead poisoning and their sequelae. This can be achieved through the early detection of children with increased lead absorption or its metabolic effects, followed immediately by effective medical and environmental intervention before the child reaches the stage of overt lead poisoning. Screening is of no value without prompt, thorough, and ongoing medical and environmental follow-up of those children found to have increased lead absorption and/or lead poisoning.

All children ages 1 through 5 years (up to the sixth birthday) who live in, or frequently visit, poorly maintained housing units constructed prior to the 1960's should be screened at least once a year. Some day care centers or other sites where children spend a considerable amount of time may also be hazardous due to deterioration of surfaces with lead paint. Children in such sites should be screened as well. Priority should be given to children who are 1 through 3 years of age, have a history of pica, or are siblings of a child with increased lead absorption or lead poisoning. Although the reasons are not fully understood, children are at higher risk during the May-October period.[13] Ideally, children 1 to

*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 100 ml whole blood.

3 years of age who are at risk should be screened every 2 to 3 months during this period.

Screening tests for undue lead absorption and lead toxicity are essentially limited to various methods of blood lead determination and measurement of erythrocyte protoporphyrins.[14,15,16,17] Blood lead may be determined by a macro method or by one of many micro methods.

The blood lead level is the result of many factors and a single determination cannot indicate whether the observed level is increasing, decreasing, or stable. By any method, blood lead determination is an exacting laboratory procedure requiring constant attention to quality control. A micro test is usually employed in children since it requires only a sample of blood taken by finger stick. Blood lead determinations by a micro method are highly sensitive to contamination from lead on the skin during collection by finger stick. Thus, a blood lead test should be repeated on children whose initial blood lead levels are determined to be "elevated." If possible, an erythrocyte protoporphyrin test should be performed before further action is taken.

The erythrocyte protoporphyrin level can also be determined on a micro specimen. It is a simpler laboratory procedure, is not influenced by contamination of the specimen with lead, and is less subject to physiological fluctuation. More important, EP is a better index of potential toxicity from the body's lead burden and is usually elevated before clinical symptoms begin.[14,15,16,17]

Significant numbers of children with blood lead levels of 30 to 39 μg/100 ml have shown evidence of metabolic impairment as detected by EP testing. Recent evidence suggests that when blood lead levels and EP levels disagree, the EP level most reliably reflects a child's true clinical status. The EP provides a better estimate of soft tissue lead, adverse metabolic response and, hence, risk.[17,18]

However, tests for both EP and blood lead are acceptable as primary screening tests, because a negative result usually excludes lead intoxication. A positive result of either test cannot by itself establish the risk of lead poisoning. It must be realized that a percentage of elevated EP levels may be due to iron deficiency anemia and a percentage of elevated blood lead levels may be due either to external contamination of the sample by lead or to a transitory elevation from lead ingestion.

Both blood lead, a test of lead absorption, and erythrocyte protoporphyrin tests, a test of metabolic effect of lead, are necessary to fully evaluate and monitor children who are positive on screening by either method. This allows three possibilities for screening:

1. Initial screening with EP – all positive children tested for blood lead level.
2. Initial screening for blood lead level – all positive children tested for EP and repeat blood lead level.
3. Initial testing with both tests simultaneously.

The Center recommends that an EP test be used for screening for lead poisoning followed by blood lead level tests for all children with positive EP. This recommendation is made because of the greater ease and reproducibility of EP measurement and the added benefit of detecting children who may have iron deficiency. Laboratories performing these tests should participate in the Center's Proficiency Testing Program or an equivalent program to help insure accurate test results.

For uniformity, it is recommended that the results of blood lead be expressed in μg/100 ml of whole blood and the results of EP be expressed as equivalents of Free Erythrocyte Protoporphyrin (FEP) μg/100 ml of whole blood by the ethyl acetate-acetic acid HCl extraction method. The results of both EP and blood lead can be graded to establish a degree of hazard of lead intoxication.

It must be noted that, in the case of EP, elevated levels (60-189 μg/100 ml) may be due to iron deficiency anemia, but extremely elevated levels (≥190 μg/100 ml) are due almost exclusively to lead intoxication. The only exception is the rare genetic disorder, erythropoietic protoporphyria, which is characterized by severe cutaneous photosensitivity.

Interpretation of Results

The children tested may be divided into four major lead poisoning categories, or classes, by combining the results of these two tests, as shown in the table. These categories indicate the degree of risk and, therefore, urgency of medical and environmental management based on both blood lead and EP measurement (μg/100 ml whole blood).

Test	Class I Normal	Class II Minimally Elevated	Class III Moderately Elevated	Class IV Extremely Elevated
Pb	≤29	30–49	50–79	≥80
EP	≤59	60–109	110–189	≥190

The ranges of blood lead and EP were chosen to represent an approximation of the equivalent degree of risk to the child and to predict the probability of need for medical management. Presently available experience indicates that in the majority of cases, the results of EP and blood lead will fall in the corresponding range. However, in a minority of cases, there will be discrepancy between the results of the blood lead and of the EP. In these cases, the result of the EP is most likely

to reflect the true status of the child. The estimate of the potential of lead intoxication should be upgraded when the EP level is more elevated than the blood lead and downgraded in the opposite case.

Some Class I children may be placed into two additional categories. Class Ia would include those children with iron deficiency anemia. Class Ib children appear, on the basis of present available experience, to have transient or declining blood lead elevations. Although the EP standard is based on tests involving several tens of thousands of children, this experience is more limited than that associated with blood lead. There may be need for revision of these standards when increased experience with EP measurements becomes available.

In addition, several combinations are not observed in practice when the blood lead is repeated. These combinations indicate that the first blood lead sample was contaminated.

The anticipated combinations of results of blood lead and EP are shown in the enclosed scheme as a suggested guideline to estimate the most likely degree of risk.

Test Results	EP ≤ 59	EP 60-109	EP 110-189	EP ≥ 190
Pb ≤ 29	I	Ia	Ia	EPP+
Pb 30-49	↓Ib	II	↑III	↑IV
Pb 50-79	*	↓II	III	↑IV
Pb ≥ 80	*	*	*	IV

EPP+ = Erythropoietic protoporphyria

* = combination of results is not generally observed in practice; when blood lead is repeated, the results will generally indicate contamination of the first specimen.

↓ = downgrading of the estimate of risk of lead intoxication suggested by blood lead is altered on the basis of the EP results.

↑ = upgrading of the estimate of risk of lead intoxication suggested by blood lead is altered on the basis of the EP results.

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 Tests After Screening

If screening tests indicate a child needs further evaluation, whether symptomatic or not, several diagnostic tests are readily available to the clinician, including:

1. Radiographic examination for long-bone "lead lines" or radiopaque material in the intestinal tract.
2. Calcium disodium EDTA mobilization tests should be reserved for asymptomatic patients only. The ideal method is the 24-hour excretion of lead after the administration of 50 mg/kg body weight of calcium disodium EDTA. The results are expressed as the ratio of micrograms lead excreted per milligram EDTA. A level greater than 1 is considered indicative of lead poisoning.[19] Alternatively, it may be necessary in some circumstances to measure only an 8-hour urine sample after a single dose of 50 mg/kg/EDTA. For this test, a level 1000 μg/liter under standard hydration is indicative of significant lead poisoning.[20]
3. δ ALAD – δ Amino levulinic acid dehydratase.

Under emergency conditions, the two following tests may help establish a presumptive diagnosis:

1. Semi-quantitative coproporphyrin examination of spot urine.[21]
2. Examination of urine for glucose and protein.

Other useful diagnostic tests that are not universally available include:

1. Urine output δ – ALA > 20μg/100 ml.[22]
2. Serum δ – ALA > 20μg/100 ml.[23]
3. Urinary coproporphyrin output 150μg/24 hour.[24]

It should be remembered that some of the above tests are useful only if they are positive since, in some instances, negative results would not rule out lead poisoning.

These diagnostic tests are appropriate for evaluation of children who are positive on screening, but they are not suitable for use as a screening method. The examination of peripheral blood smear for basophilic stippling is *not* considered useful for diagnosis due to its unreliability. Other tests, especially neurochemical ones, may become available for diagnostic purposes in the near future.

Children in Classes II, III, or IV may be either clinically symptomatic or asymptomatic. However, the statistical likelihood of clinical symptoms and permanent damage increases at least arithmetically with confirmed blood lead values above 30 μg and EP values above 60 μg/100 ml. It is for this reason that the increased lead absorption category is subdivided into Classes II and III to indicate relative urgency of action. Specific recommendations for disposition of children on

the basis of their screening test results are given in the following section.

V. Pediatric Management

Screening, pediatric management, and hazard control are equally important in caring for children at risk of lead poisoning. Pediatric management must include treating the child with undue lead absorption, in addition to following him until the risk of further damage is minimal. Guidelines for the management of children in various risk categories are outlined in this section.

Class IV

Class IV children, regardless of the presence or absence of clinical symptoms or of other laboratory findings, should be considered an unequivocal case of lead poisoning. Since the risk of acute lead encephalopathy is great, its onset unpredictable, and its course fulminant, these children should be hospitalized immediately for evaluation and chelation therapy. Severe and permanent brain damage may occur in as many as 80 percent of the children that develop acute encephalopathy.[25] Treatment before onset of encephalopathy will improve this grim prognosis.

Children in this group who are symptomatic, have intercurrent fever or dehydration, or are detected during summer months are at extremely high risk. This group of children, and in particular the younger child, should be given highest priority.

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

Chisolm, Coffin, and others[26,27,28] have described appropriate protocols for inpatient chelation therapy of children with lead poisoning. It is essential to consult such references before treating children in order to properly appreciate the inherent dangers, precautions, and rationale for such treatment.

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 also require long-term medical surveillance and care. "Rebound" of blood lead levels resulting from release of lead from tissue pools after an apparently successful course of chelation therapy should be anticipated. The need for repeated courses of chelation in some children – even after lead ingestion has ceased – should be recognized.

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 lead-poisoned children should use it in accordance with current FDA policy. In this manner, careful usage of the drug will be encouraged and useful data regarding its efficacy and safety may be obtained. In no case should it be used in children without, or in lieu of, control of lead hazard in their homes.

Reduction of lead intake is necessary for all children in Class IV, both as part of immediate therapy and as a part of the follow-up 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.

After hospitalization and removal of lead from their environments, children in Class IV are still at high risk and should be followed with blood lead and/or erythrocyte protoporphyrin determinations at 1-2 week intervals until those levels stabilize or show a continual decline for at least 6 months. Thereafter, they should be followed at 1-3 month intervals (at least 6-week intervals in summer months) until 6 years of age, or longer, to prevent repeated poisoning. Neurological and psychological assessment should be obtained at the time of diagnosis and in following years to detect any neurological or behavioral deviation 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.

Class III

Class III children who have compatible symptoms which cannot be explained otherwise or who have abnormal ALA-d, urinary ALA, or urinary coproporphyrin levels should be considered as having lead poisoning and recognized as candidates for urgent inpatient medical management. All children in this class should be further evaluated by history for otherwise unexplained symptoms or signs (pica, anorexia, vomiting, abdominal pain, behavioral change, irritability, speech disturbance, ataxia, seizures) with *selected* laboratory tests (complete blood count, radiography of long bones and intestinal tract, repeat EP and blood lead, semi-quantitative urine coproporphyrin, ALA-d quantitative urinary ALA, or coproporphyrin). A thorough physical and neurological examination is particularly indicated to exclude other illnesses in symptomatic children in this category.

As noted before, lumbar puncture is unwise due to the risk of increased intracranial pressure. If lumbar puncture is necessary to rule out meningitis or other

serious disease, it should be performed cautiously and only after a careful search for signs and symptoms of increased intracranial pressure.

Children in Class III who are symptomatic or present laboratory evidence of subclinical lead poisoning should be treated and followed as Class IV children.

Most asymptomatic children in Class III should be given a calcium disodium EDTA mobilization test to determine the potential utility of chelation therapy. If the calcium disodium EDTA mobilization test suggests the need for further chelation therapy, inpatient chelation should be performed, if feasible. Under some conditions, it may be possible to treat asymptomatic children without high risk factors as outpatients. This should be reserved for centers capable of providing excellent outpatient care and adequate follow-up supervision with particular emphasis on the "rebound" phenomenon and close environmental monitoring. In addition, the parents should be reasonably cooperative and demonstrate that they are able to follow instructions. In such circumstances, calcium disodium EDTA may be administered according to Sach's[20] protocol.

Class III children without symptoms or laboratory evidence of lead poisoning should be followed with blood lead and/or erythrocyte protoporphyrin determinations. These tests should be performed at least monthly, especially in summer, until the sources of lead in their environment have been removed, and until their blood lead and/or erythrocyte protoporphyrin levels have stabilized or declined for 6 months. Thereafter, they should be followed at 1-3 month intervals (at least 6-week intervals in the summer) until 6 years of age or longer 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.

Class II

Class II children should be considered as having increased lead absorption if there is no evidence of iron deficiency.[16] However, it must be remembered that both conditions, iron deficiency and increased lead absorption, may coexist. The higher the results of blood lead and EP, the greater is the statistical likelihood of lead toxicity. Further evaluation by history, selected laboratory tests, and in some instances EDTA mobilization test, is indicated in many of these children.

Children in Class II generally will not require chelation therapy, but those who have EP levels in this range because of iron deficiency should obviously be treated for that condition. Otherwise, reduction of lead intake from all sources and careful monitoring should suffice.

Class II children without evidence of lead poisoning should be evaluated at 3-month intervals after it is determined that they are no longer exposed to lead hazards. Such follow-up should continue until the child is at least 3 years of age, or until the blood lead/erythrocyte protoporphyrin levels return to normal. Regardless of age, these children should be followed more frequently after their first screening. Those who continue to be exposed in their homes, or elsewhere, should be followed at monthly intervals in summer and 1-2 month intervals thereafter until at least 6 years of age or until their blood lead/erythrocyte protoporphyrin levels return to normal.

Class I

Class I children did not have significantly increased lead absorption at the time of testing. They require no further evaluation except for routine rescreening until they reach their sixth birthday. Children in Class Ia should receive appropriate medical attention and care for iron deficiency anemia. Class Ib children 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, pediatric management of lead poisoning must include appropriate treatment and adequate follow-up. Chelation therapy is indicated for some children with undue lead absorption. Though indiscriminate chelation is unwise due to the poorly explored potential hazards, withholding or delaying chelation therapy is also unwise when it is indicated. The optimal frequency of follow-up visits is dependent on many factors including the child's age, status of housing, trend of laboratory results, and parental resources available. Since these factors must be weighed against health resources available, the recommendations concerning follow-up can only serve as a guide. The following table is a summary of the recommendations.

Summary of Recommended Follow-Up

Frequency	Diagnostic Category						
	IV**	III*	II	Ia	Ib	I Age 12 – 36 months	I Age > 36 months
1 – 2 weeks	XX						
4 weeks		XX			XX		
6 weeks	X (in summer)	X (in summer)					
3 months	X (after six mos. stable)		XX	Arrange treatment of iron deficiency	X (until blood lead normal)	XX	
1 year		X (after 1st yr. of follow-up)		Follow as Group I		X	XX

* Symptomatic or treated patients in Group III should be followed as Group IV.
** After hospitalization has been completed.
X Minimal
XX Optimal

VI. Hazard Control

Significant sources of lead must be identified and removed from the environments of children who have lead poisoning or who have absorbed hazardous amounts of lead. It is essential to recognize that the home of the affected child may not be the source of his lead exposure. Consideration must be given to the possibility of lead exposure from a prior residence, poorly maintained day care centers, homes of friends or relatives, or any other premises where the child spends a considerable period of time. In this context, it is important to remember that while lead-based paint is the most important source of lead for most poisoned children, it is not the only source. Attention to dust, dirt, canned foods, and canned milk is indicated in some instances.

Children who require hospitalization and chelation therapy are at highest risk of permanent damage from a recurrent episode. Therefore, their environment has the first priority for hazard abatement. The next priority is given to the environment of those children in Class III.

Careful control of dust and flaking paint may be sufficient for the environments of children in Class Ib and II until the environments of the children at higher risk (e.g., Class IV and III) have been made safe.

If resources permit, a more aggressive hazard reduction action should be considered for those Class II children with greater risk factors. Immediate environmental investigation and corrective action should be started as soon as increased lead absorption status is confirmed. While these activities must usually be implemented by or through local governmental agencies, the attending physician must quickly notify the appropriate agency. That agency should insure that lead hazards are abated and that the child is not re-exposed to significant sources of lead. Hazard control is greatly facilitated by enactment and enforcement of specific local ordinances regarding lead-based paints.

VII. Education of Parents of Children at Risk

Parents of preschool children who live in high risk areas should be informed at every available opportunity of the need to have their children screened and re-screened for lead poisoning. A child without increased lead absorption is still at risk even after a negative report and this should be emphasized to the parents. Older siblings of children at high risk should also be informed of the sources and risks of lead poisoning, as they often provide a major portion of the younger children's caretaking.

Eating paint chips is dangerous; regular sweeping and removal of accessible paint flakes and dust could reduce this danger. Until safe housing is available for all, this simple knowledge can reduce the potential hazard and prevent undue lead ingestion in some of these children.

Where a child is found to have increased lead absorption, education of the parents is essential to successfully follow the child. The parents will be responsible to see that the child is not exposed to lead hazard in the future.

VIII. Reporting of Lead Poisoning and Increased Lead Absorption

Presumptive and confirmed cases of lead poisoning and increased lead absorption (children in Classes IV, III, II) 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 should report elevated findings. This would facilitate a more meaningful analysis of the problem at the local and national levels and contribute to prevention of the condition in the future.

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Treatment of Lead Poisoning

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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-

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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 ω 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.	Abnormal urine* %	Plumbism No.	Plumbism %
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 sedmiment (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 ($\beta\beta$-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

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

Clinical presentation	*Chelating agent*[a]	*Comment*
A. CHILDREN		
1. All symptomatic cases	BAL-CaEDTA (IM)	Any symptoms in children call for at least one 5-day course
a. Acute encephalopathy	BAL-CaEDTA (IM)	First course 5–7 days; give second 5-day course if blood lead >80 μg Pb/100 g whole blood 14–21 days after first course; transfer patient to convalescent hospital for 3–6 mo course of oral D-penicillamine
b. Intoxication without encephalopathy	BAL-CaEDTA (IM)	First course 5 days only; indication for second course same as above; follow with oral penicillamine (3–6 mo) if blood lead >60 μg Pb/100 g whole blood and long bone X-rays show prominent "lead lines"
2. Asymptomatic cases		
a. Blood lead >100 μg Pb/100 g whole blood	BAL-CaEDTA (IM)	Choice for first course indicated by blood lead; follow with oral D-penicillamine as above (section 1b)
<100 μg Pb/100 g whole blood	CaEDTA only (IM)	
3. Long-term followup care		
a. Intercurrent infection, demineralizing disorders	CaEDTA only (IM)	Give 3-day course whenever significant increase in UCP and/or ALA occurs even if no increase in blood lead occurs
b. Recurrent ingestion	BAL-CaEDTA (IM) or CaEDTA only (IM)	Choice same as for asymptomatic cases above (section 2a)
c. Long-term chelation	D-Penicillamine[a] (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)

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)	*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.

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