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Lead Poisoning

Among the natural substances that man concentrates in his immediate environment, lead is one of the most ubiquitous. A principal cause for concern is the effect on children who live in decaying buildings

by J. Julian Chisolm, Jr.

Lead has been mined and worked by men for millenniums. Its ductility, high resistance to erosion and other properties make it one of the most useful of metals. The inappropriate use of lead has, however, resulted in outbreaks of lead poisoning in humans from time to time since antiquity. The disease, which is sometimes called "plumbism" (from the Latin word for lead) or "saturnism" (from the alchemical term), was first described by the Greek poet-physician Nicander more than 2,000 years ago. Today our concerns about human health and the dissemination of lead into the environment are twofold: (1) there is a need to know whether or not the current level of lead absorption in the general population presents some subtle risk to health; (2) there is an even more urgent need to control this hazard in the several subgroups within the general population that run the risk of clinical plumbism and its known consequences. In the young children of urban slums lead poisoning is a major source of brain damage, mental deficiency and serious behavior problems. Yet it remains an insidious disease: it is difficult to diagnose, it is often unrecognized and until recently it was largely ignored by physicians and public health officials. Now public attention is finally being focused on childhood lead poisoning, although the difficult task of eradicating it has just begun.

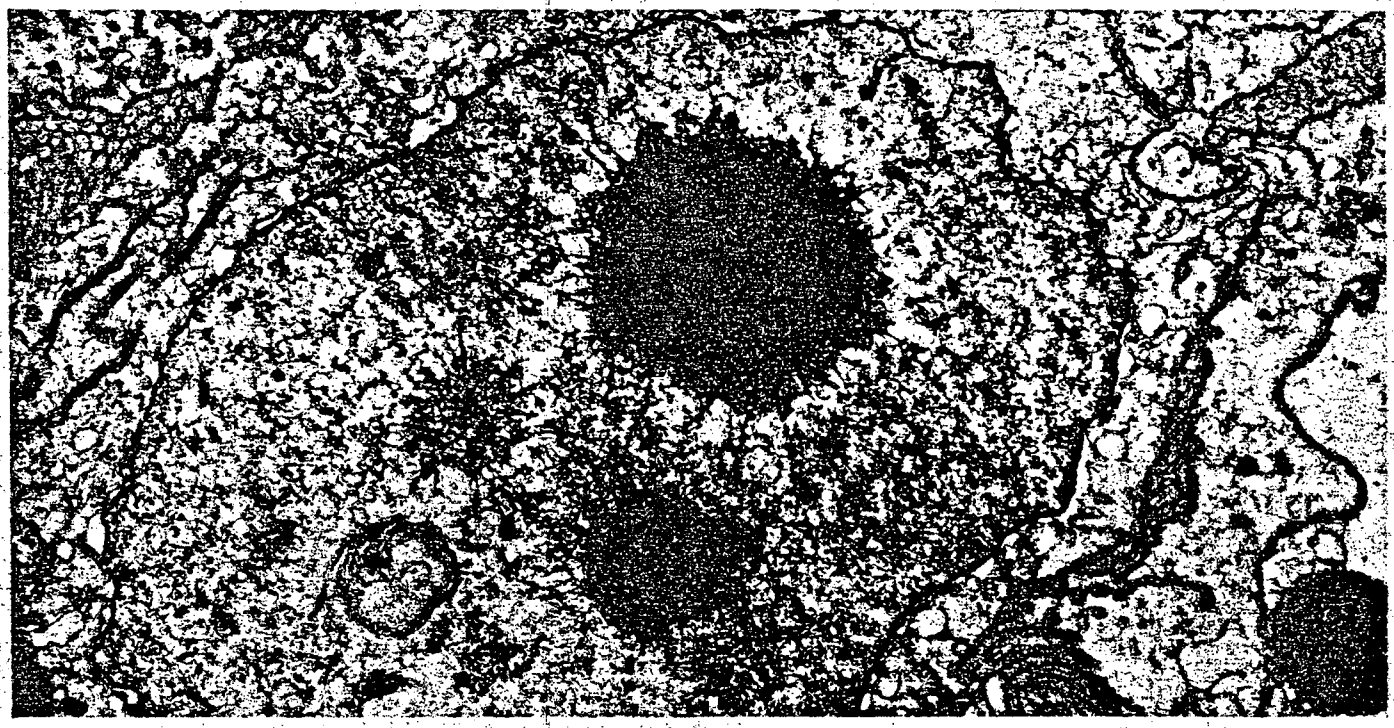
Symptomatic lead poisoning is the result of very high levels of lead in the tissues. Is it possible that a content of lead in the body that is insufficient to cause obvious symptoms can nevertheless give rise to slowly evolving and long-lasting adverse effects? The question is at present unanswered but is most pertinent. There is much evidence that lead wastes have been accumulating during the past century, particularly in congested urban areas. Increased exposure to lead has been shown in populations exposed to lead as an air pollutant. Postmortem examinations show a higher lead content in the organs of individuals in highly industrialized societies than in the organs of most individuals in primitive populations. Although no population group is apparently yet being subjected to levels of exposure associated with the symptoms of lead poisoning, it is clear that a continued rise in the pollution of the human environment with lead could eventually produce levels of exposure that could have adverse effects on human health. Efforts to control the dissemination of lead into the environment are therefore indicated.

The more immediate and urgent problem is to control the exposure to lead of well-defined groups that are known to be directly at risk: young children who live in dilapidated housing where they can nibble chips of leaded paint, whiskey drinkers who consume quantities of lead-contaminated moonshine, people who eat or drink from improperly lead-glazed earthenware, workers in certain small-scale industries where exposure to lead is not controlled. Of these the most distressing group is the large group of children between about one and three to five years of age who live in deteriorating buildings and have the habit of eating nonfood substances including peeling paint, plaster and putty containing lead. (This behavior is termed pica, after the Latin word for magpie.) The epidemiological data are still scanty: large-scale screening programs now in progress in Chicago and New York City indicate that between 5 and 10 percent of the children tested show evidence of asymptomatic increased lead absorption and that between 1 and 2 percent have unsuspected plumbism. Small-scale surveys in the worst housing areas of a few other cities reveal even higher percentages.

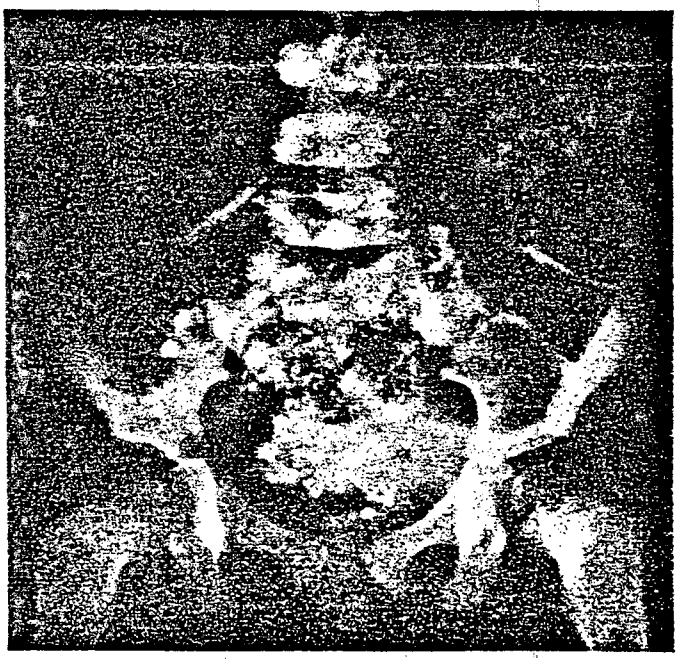
There is little doubt that childhood lead poisoning is a real problem in many of the older urban areas of the U.S. and perhaps in rural communities as well. Current knowledge about lead poisoning and its long-term effects in children is adequate to form the basis of a rational attack on this particular problem. The ubiquity of lead-pigment paints in older substandard housing and the prevalence of pica in young children indicate, however, that any effective program will require the concerted and sustained effort of each community. Furthermore, the continued use of lead-pigment paints on housing surfaces that are accessible to

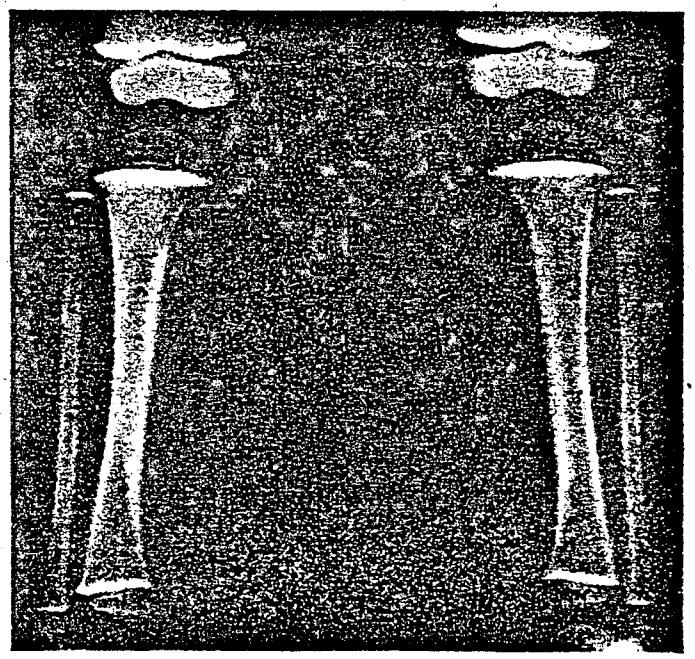
young children and will at some future date fall into disrepair can only perpetuate the problem.

Traces of lead are almost ubiquitous in nature and minute amounts are found in normal diets. According to the extensive studies of Robert A. Kehoe and his associates during the past 35 years at the Kettering Laboratories of the University of Cincinnati, the usual daily dietary intake of lead in adults averages about .3 milligram. Of this, about 90 percent passes through the intestinal tract and is not absorbed. Kehoe's data indicate that the small amount absorbed is also excreted, so that under "normal" conditions there is no net retention of lead in the body. In addition the usual respiratory intake is estimated at between five and 50 micrograms of lead per day. These findings must be recon-



EXCESS LEAD complexed with protein forms inclusion bodies in the nuclei of certain cells in lead-poisoned animals and man. In an electron micrograph made by Robert A. Goyer and his colleagues at the University of North Carolina School of Medicine the nucleus, of a cell from a proximal renal tubule of a lead-poisoned rat is enlarged 15,000 diameters. The large structure with a dense core and a filamentous outer zone is an inclusion body; below it to the left is a smaller one. The dark area below the large body is the nucleolus.





X-RAY PLATES may show evidence of lead ingestion or of an excessive body burden of the metal. The abdominal X ray (*left*) shows a number of bright opaque particles in the large intestine: bits of lead-containing paint that had been eaten by the 18-month-old subject. The X ray of the same child's legs (*right*) shows bright "lead lines": excess lead stored at the ends of the long bones.

cited with postmortem analyses, which indicate that the concentration of lead in bone increases with age, although its concentration in the soft tissues is relatively stable throughout life. The physiological significance of increasing storage in bone is not entirely clear, but it has caused considerable concern. It is quite clear that as the level of intake of lead increases, the rate of absorption may exceed the rate at which lead can be excreted or stored in bone. And when the rates of excretion and storage are exceeded, the levels of lead in the soft tissues rise. Studies in adults indicate that as the sustained daily intake of lead rises above one milligram of lead per day, higher levels of lead in the blood result and metabolic, functional and clinical responses follow [*see illustration on pages 22 and 23*]. The reversible effects abate when the rate and amount of lead absorbed are reduced again to the usual dietary range.

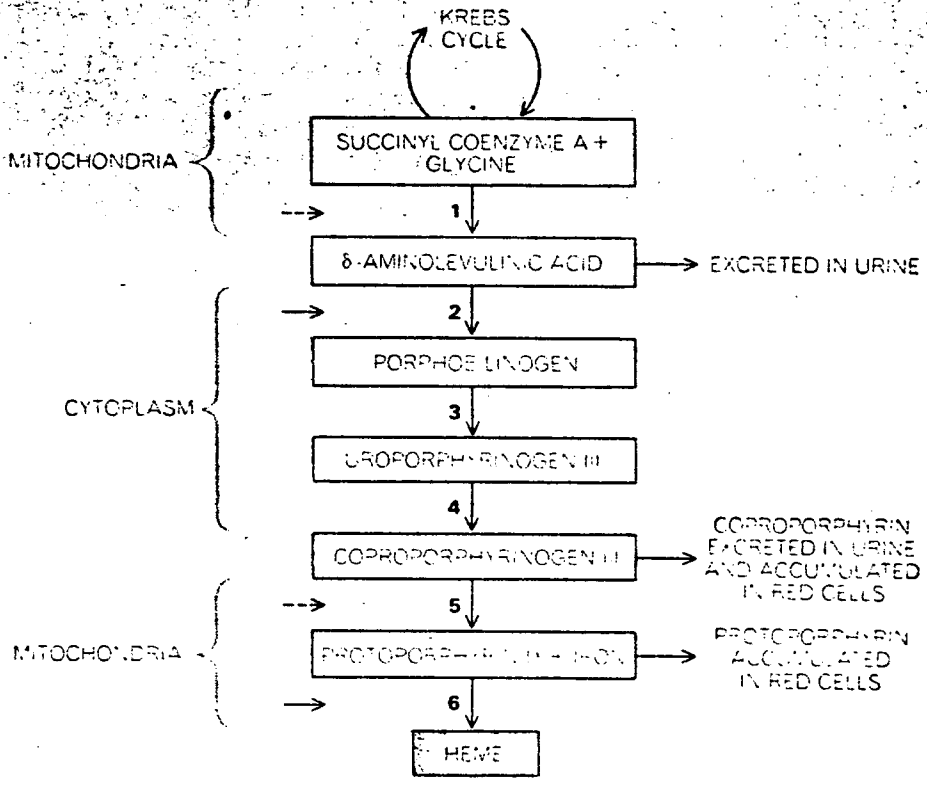
As far as is known, lead is not a trace element essential to nutrition, but this particular question has not been adequately examined. Some of the adverse effects of lead on metabolism have nonetheless been studied in considerable detail. These effects are related to the concentration of lead in the soft tissues. At the level of cellular metabolism, the best-known adverse effect of lead is its inhibition of the activity of enzymes that are dependent on the presence of free sulfhydryl (SH) groups for their activity. Lead interacts with sulfhydryl groups in such a way that they are not available to certain enzymes that require them. In the living organism, under most conditions, this inhibition is apparently partial. Inhibitory effects of lead on other aspects of cellular metabolism have been demonstrated in the test tube. Such studies are preliminary. Most of the effects reported are produced with concentrations of lead considerably higher than are likely to be encountered in the tissues of man, so that speculation about such effects is unwarranted at this point.

The clearest manifestation of the inhibitory effect of lead on the activity of sulfhydryl-dependent enzymes is the disturbance it causes in the biosynthesis of heme. Heme is the iron-containing constituent that combines with protein to form hemoglobin, the oxygen-carrying pigment of the red blood cells. Heme is also an essential constituent of the other respiratory pigments, the cytochromes, which play key roles in energy metabolism. The normal pathway of heme synthesis begins with activated succinate (produced by the Krebs cycle, a major stage in the conversion of food energy to biological energy) and proceeds through a series of steps [*see illustration below*]. Two of these steps are inhibited by the presence of lead; two others may also be inhibited, but at higher lead concentrations.

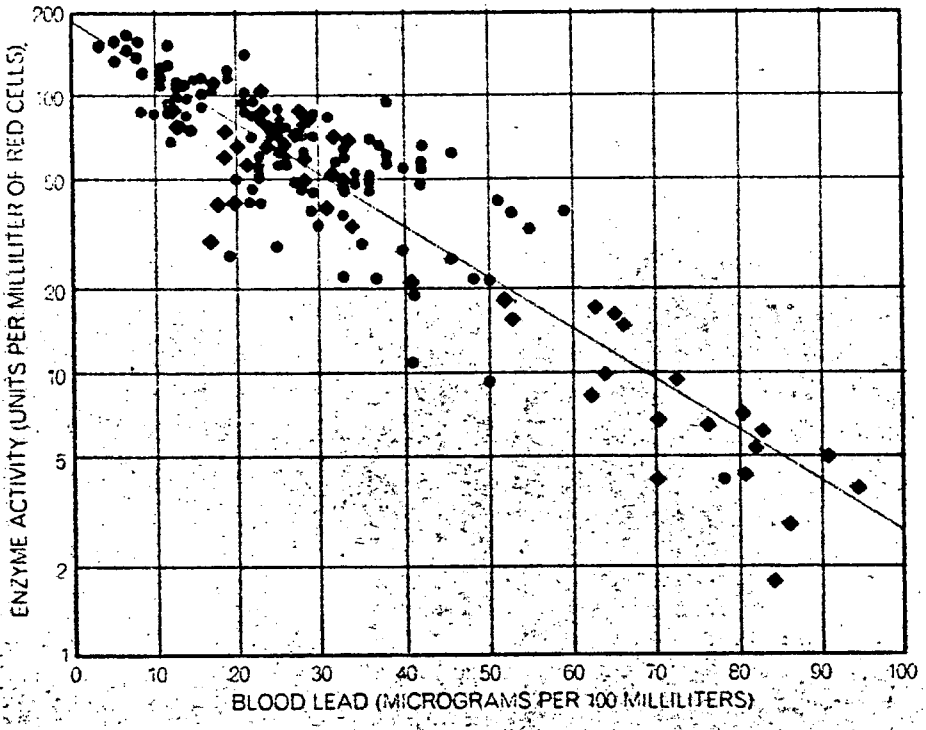
Lead is implicated specifically in the metabolism of delta-aminolevulinic acid (ALA) and in the final formation of heme from iron and protoporphyrin. Both of these steps are mediated by enzymes that are dependent on free sulfhydryl groups for their activity and are therefore sensitive to lead. The two steps at which lead may possibly be implicated are the formation of ALA and the conversion of coproporphyrinogen to protoporphyrin. Although the exact mechanism is not known, coproporphyrin (an oxidized product of coproporphyrinogen) accumulates in the urine and the red cells in lead poisoning. Whatever the mechanisms, the increased excretion of ALA and coproporphyrin is almost al-

PATIENTS	LEAD OUTPUT (MILLIGRAMS PER 24 HOURS)		
	MEAN	MEDIAN	RANGE
UNEXPOSED CONTROLS	.132	.157	.012–.175
HOUSEHOLD CONTROLS	.832	.651	.067–1.93
INCREASED LEAD ABSORPTION, NO SYMPTOMS	2.16	1.11	.116–9.60
LEAD POISONING, WITH AND WITHOUT BRAIN DAMAGE			
DURING EXPOSURE:	44.0	27.0	5.040–104.0
AFTER TREATMENT:	.362	.240	.062–0.850

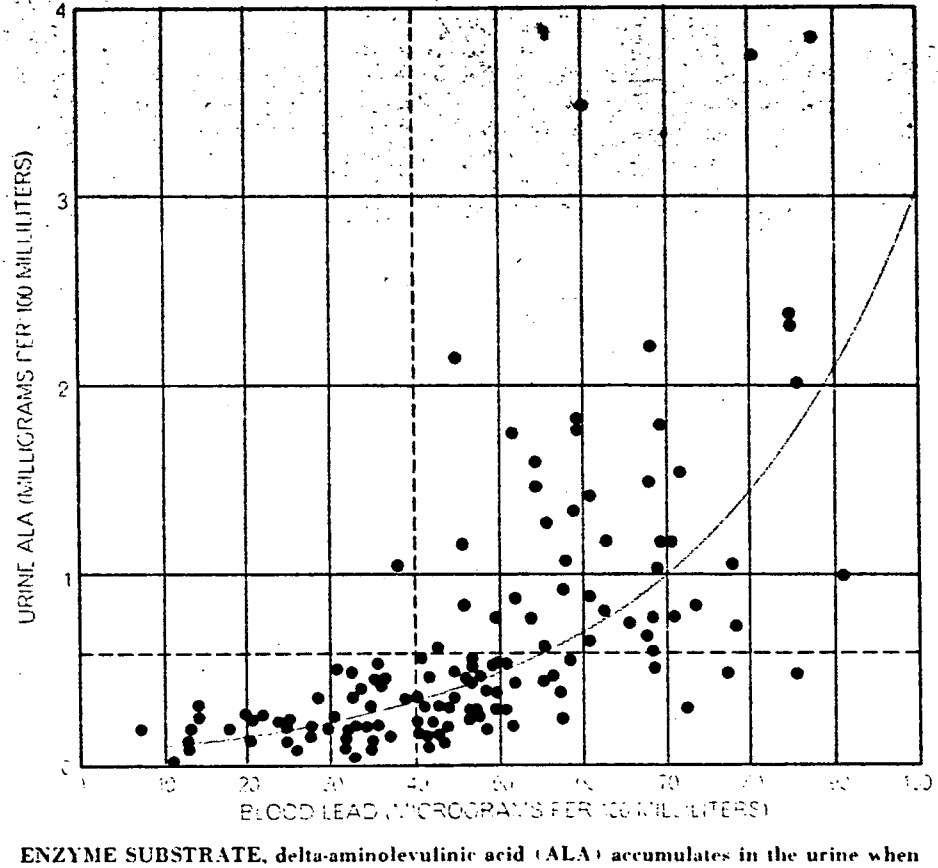
EXCRETION OF LEAD in feces is an index of exposure to lead. These results of a study by the author and Harold E. Harrison illustrate the massive exposures seen in lead poisoning. Unexposed controls were children with no known exposure to lead. The other groups were children with increased lead absorption (high blood lead), children with lead poisoning and members of their households with neither high blood values nor overt symptoms.



BIOSYNTHESIS OF HEME, a constituent of hemoglobin, is inhibited by lead, resulting in accumulation of intermediates in the synthetic pathway. Of six steps in the pathway, the first and the last two take place in mitochondria, the others elsewhere in the cell cytoplasm. Lead inhibits two steps (*solid colored arrows*) and may inhibit two others (*broken arrows*).



CORRELATION between blood lead and the activity of delta-aminolevulinic acid dehydrase, an enzyme inhibited by lead, was shown by Sven Hernberg and his colleagues at the University of Helsinki. The vertical scale is logarithmic. The values are well correlated, as indicated by the straight regression line, over a wide range of blood-lead levels in groups with different lead exposures: students (*black dots*), automobile repairmen (*black squares*), printshop employees (*colored dots*) and lead smelters and ship scrappers (*colored squares*).



ENZYME SUBSTRATE, delta-aminolevulinic acid (ALA) accumulates in the urine when lead inhibits enzyme activity. Stig Selander and Kim Cramér found that a decrease in lead below about 30 micrograms does not produce a comparable decrease in ALA, suggesting that an enzyme reserve may be involved. Broken lines show presumed normal values.

ways observed before the onset of symptoms of lead poisoning, and the presence of either is therefore important in diagnosis.

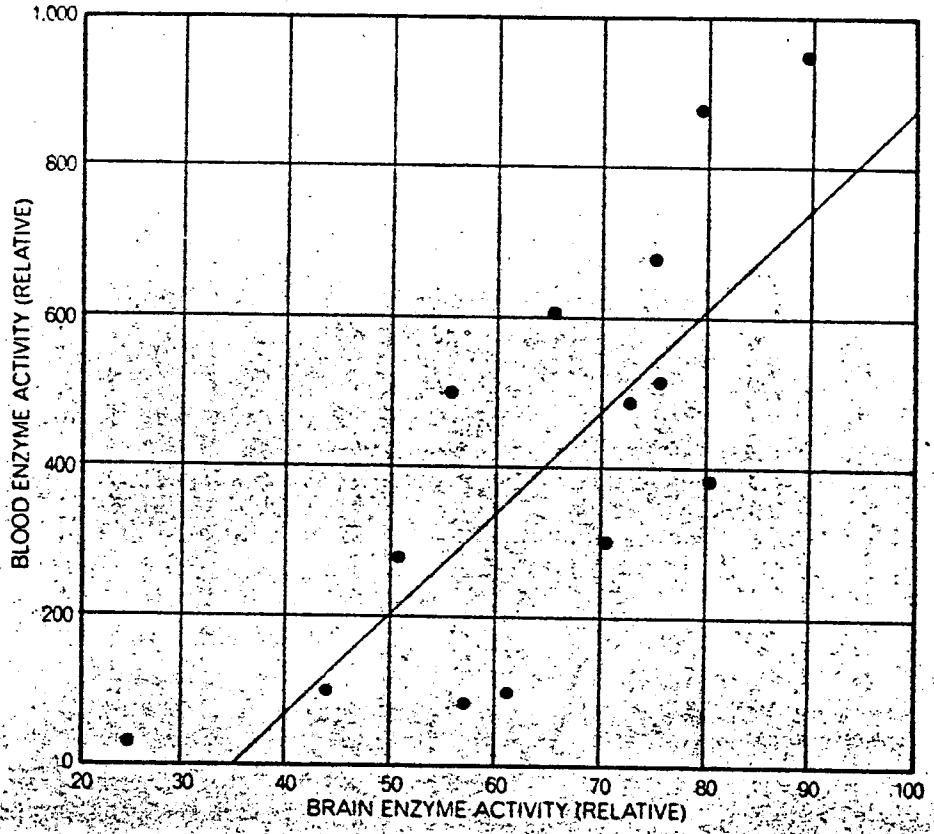
The enzyme that catalyzes ALA metabolism is ALA dehydrase. A number of investigators, including Sven Hernberg and his colleagues at the University of Helsinki and Abraham Goldberg's group at the University of Glasgow, have studied the extent to which varying levels of lead in the blood inhibit ALA-dehydrase activity in red blood cell preparations in the laboratory. They have shown a direct relation between the concentration of lead in blood and the activity of the enzyme. Moreover, they find that there seems to be no amount of lead so small that it does not to some extent decrease ALA-dehydrase activity; in other words, there appears to be no threshold for this effect [*see top illustration at left*]. If that is so, however, one would expect to see a progressive increase in the urinary excretion of the enzyme's substrate, ALA, beginning at very low blood-lead levels. This does not seem to be the case. Stig Selander and Kim Cramér in Sweden, correlating blood-lead and urine-ALA values, found that the first measurable increase in urine ALA is observed only after blood lead rises above approximately 30 micrograms of lead per 100 milliliters of whole blood [*see bottom illustration at left*]. The apparent inconsistency between the effect of lead on the activity of an enzyme in the test tube and the accumulation of the enzyme's substrate in the body might be explained by the presence of an enzyme reserve. This hypothesis is consistent with the functional reserve exhibited in many biological systems.

Almost all the information we have on the effect of lead on the synthesis of heme comes from observations of red blood cells. Yet all cells synthesize their own heme-containing enzymes, notably the cytochromes, and ALA dehydrase is also widely distributed in tissues. The observations in red blood cells may therefore serve as a model of lead's probable effects on heme synthesis in other organ systems. Even so, the degree of inhibition in a given tissue may vary and will depend on the concentration of lead within the cell, on its access to the heme synthetic pathway and on other factors. For example, J. A. Millar and his colleagues in Goldberg's group found that ALA-dehydrase activity is inhibited in the brain tissue of heavily lead-poisoned laboratory rats at about the same rate as it is in the blood [*see illustration on opposite page*]. When these workers used amounts of lead that produced an aver-

age blood-lead level of 30 micrograms per 100 milliliters of blood, the level of ALA-dehydrase activity in the brain did not differ significantly from the levels found in control rats that had not been given any added lead at all. It is now established experimentally that lead does interfere with heme synthesis in tissue preparations from the kidney, the brain and the liver as well as in red cells but the concentrations of lead that may begin to cause significant inhibition in these organs are not yet known.

Only in the blood is it as yet possible to see a direct cause-and-effect relation between the metabolic disturbance and the functional disturbance in animals or people. In the blood the functional effect is anemia. The decrease in heme synthesis leads at first to a decrease in the life-span of red cells and later to a decrease in the number of red cells and in the amount of hemoglobin per cell. In compensation for the shortage, the blood-forming tissue steps up its production of red cells; immature red cells, reticulocytes and basophilic stippled cells (named for their stippled appearance after absorbing a basic dye) appear in the circulation. The presence of stippled cells is the most characteristic finding in the blood of a patient with lead poisoning. The stippling represents remnants of the cytoplasmic constituents of red cell precursors, including mitochondria. Normal mature red cells do not contain mitochondria. The anemia of lead poisoning is a reversible condition: the metabolism of heme returns to normal, and the anemia improves with removal of the patient from exposure to excessive amounts of lead.

The toxic effect of lead on the kidneys is under intensive investigation but here the story is less clear. In acute lead poisoning there are visible changes in the kidney and kidney function is impaired. Again the mitochondria are implicated: their structure is visibly changed. Much of the excess lead is concentrated in the form of dense inclusions in the nuclei of certain cells, including those lining the proximal renal tubules. Robert A. Goyer of the University of North Carolina School of Medicine isolated and analyzed these inclusions and found that they consist of a complex of protein and lead [*see upper illustration on page 16*]. He has suggested that the inclusions are a protective device: they tend to keep the lead in the nucleus, away from the vulnerable mitochondria. Involvement of the mitochondria is also suggested by the fact that lead-poisoned kidney cells consume more oxygen than normal cells in laboratory cultures, which indicates that their energy metabolism is affected.

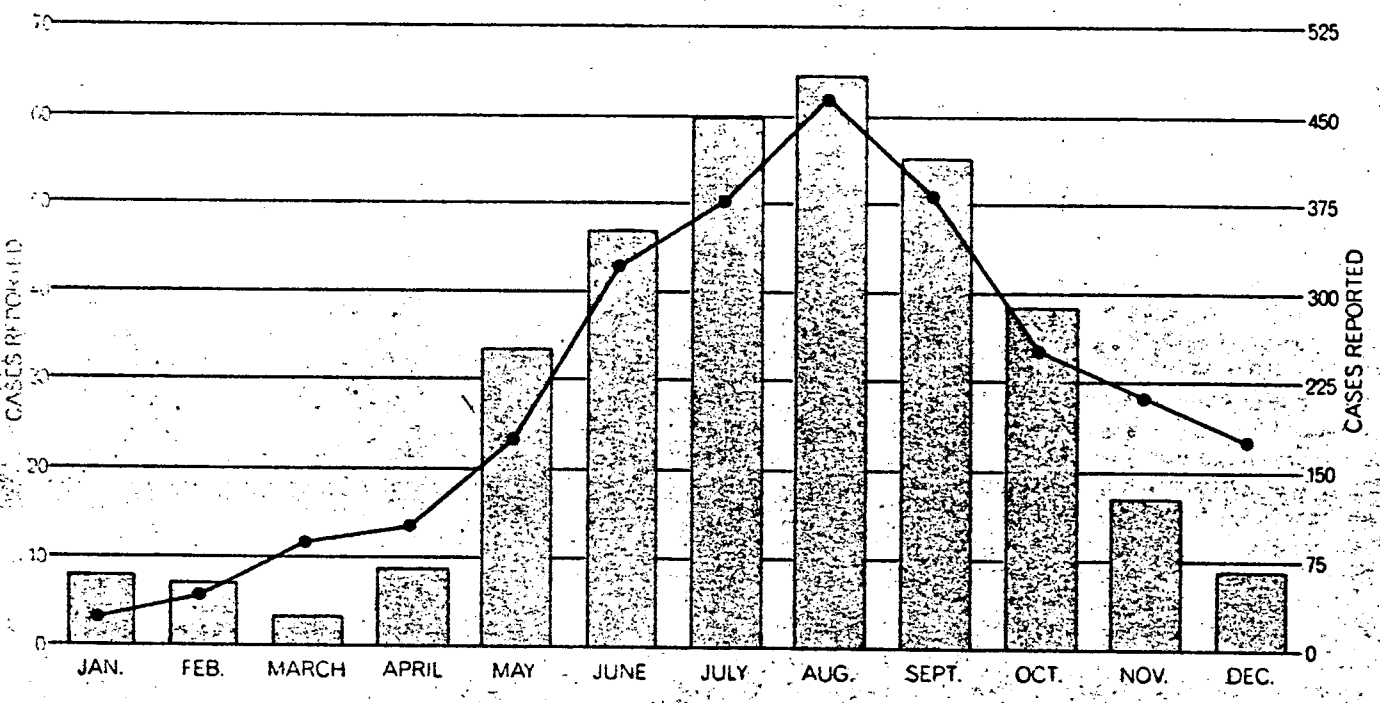


CORRELATION between the activity of ALA dehydrase in the blood and in the brain of normal rats (*black dots*) and lead-poisoned rats (*colored dots*) suggests that the enzyme may be implicated in brain damage, according to J. A. Millar and his colleagues. These data are for severely poisoned rats; in others with blood-lead values of about 30 micrograms per 100 milliliters of blood, brain enzyme activity was not significantly less than in controls.

Kidney dysfunction, apparently due to this impairment in energy metabolism, is expressed in what is called the Fanconi syndrome: there is an increased loss of amino acids, glucose and phosphate in the urine because the damaged tubular cells fail to reabsorb these substances as completely as normal tubular cells do. The excessive excretion of phosphates is the important factor because it leads to hypophosphatemia, a low level of phosphate in the blood. There is some evidence that, when phosphate is mobilized from bone for the purpose of maintaining an adequate level in body fluids, lead that is stored with relative safety in the bones may be mobilized along with the phosphate and enter the soft tissues where it can do harm. The effect of acute lead poisoning on the kidney can be serious but, like the effect on blood cells, it is reversible with the end of abnormal exposure. Furthermore, the Fanconi syndrome is seen only at very high levels of lead in blood (greater than 150 micrograms of lead per 100 milliliters of blood) and only in patients with severe acute plumbism.

In the central nervous system the toxic effect of lead is least understood. Little is known at the metabolic level; most of the information comes from clinical observation of patients and from postmortem studies. Two different mechanisms appear to be involved in lead encephalopathy, or brain damage: edema and direct injury to nerve cells. The walls of the blood vessels are somehow affected so that the capillaries become too permeable; they leak, causing edema (swelling of the brain tissue). Since the brain is enclosed in a rigid container, the skull, severe swelling destroys brain tissue. Moreover, it appears that certain brain cells may be directly injured, or their function inhibited, by lead.

The effects I have been discussing are all those of acute lead poisoning, the result of a large accumulation of lead in a relatively short time. There are chronic effects too, either the aftereffects of acute plumbism or the result of a slow buildup of a burden of lead over a period of years. The best-known effect is chronic nephritis, a disease characterized by a scarring and shrinking of kidney tissue. This complication of lead poisoning came to light in Australia in 1929, when L. J. J. Nye became aware of a pattern of chronic nephritis and early death in

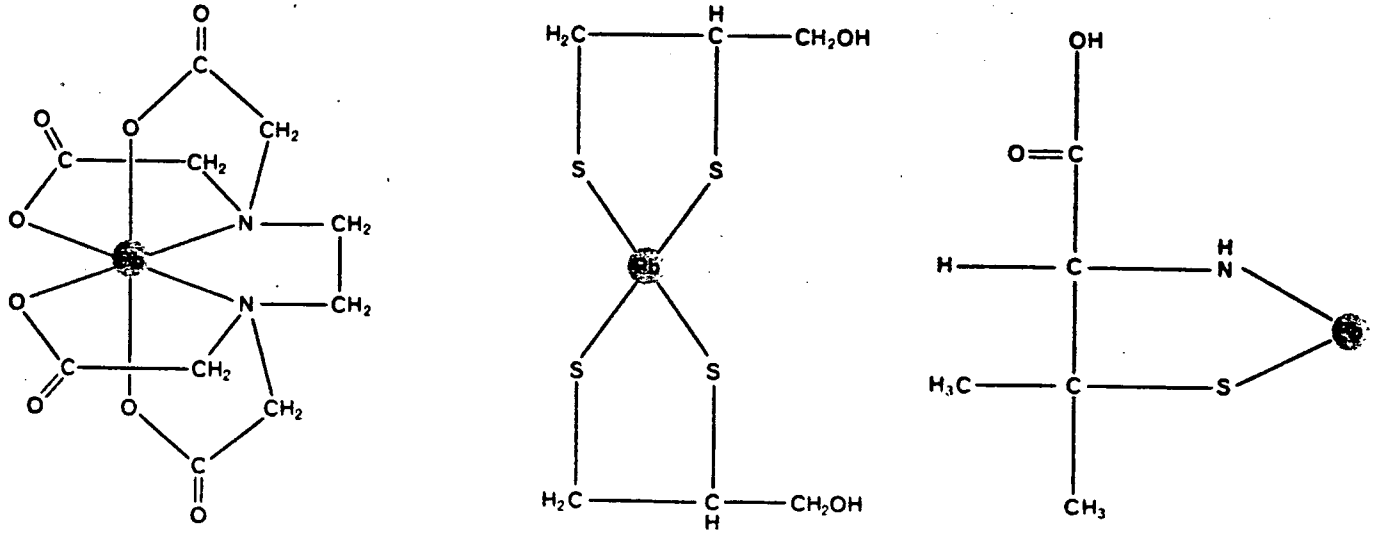


SEASONAL PATTERN of lead-poisoning cases is striking. The bars show the average number of cases reported monthly in Baltimore from 1931 through 1951 (*numbers at left*). Curve shows cases reported monthly in New York City last year (*numbers at right*).

the state of Queensland. Investigation revealed that Queensland children drank quantities of rainwater that was collected by runoff from house roofs sheathed with shingles covered with lead-pigmented paint. In 1954 D. A. Henderson found that of 352 adults in Queensland who had had childhood lead poisoning 15 to 40 years earlier, 165 had died, 94 of chronic nephritis. Chronic lead nephropathy, which is sometimes accompanied by gout, is also seen in persistent, heavy moonshine drinkers and in some people who have had severe industrial exposure. In all these cases, however, the abnormal intake of lead persists for more than a decade or so before the onset of nephropathy. Most of the patients have a history of reported episodes of acute plumbism, which suggests that they have levels of lead in the tissues far above those found in the general population. Furthermore, there is the suspicion that factors in addition to lead may be involved.

The other known result of chronic overexposure to lead is peripheral nerve disease, affecting primarily the motor nerves of the extremities. Here the tissue damage appears to be to the myelin sheath of the nerve fiber. Specifically, according to animal studies, the mitochondria of the Schwann cells, which synthesize the sheath, seem to be affected. Various investigators, including Pamela Fullerton of Middlesex Hospital in London, have found that conduction of the nerve impulse may be impaired in the peripheral nerves of industrial workers who have had a long exposure to lead but who have no symptoms of acute lead poisoning.

These findings and others raise serious questions. It is clear that a single attack of acute encephalopathy can cause pro-



CHELATING AGENTS used in treating lead poisoning bind lead atoms (*Pb*) firmly in one or more five-member chelate rings. Diagrams show lead chelates formed by EDTA (*left*), BAL (*middle*) and d-penicillamine (*right*). The last structure is still hypothetical.

and mental retardation and other forms of neurological injury that is permanent. Similarly, in young children repeated bouts of symptomatic plumbism can result in permanent brain damage ranging from subtle learning deficits to profound mental incompetence and epilepsy. Can a level of absorption that is insufficient to cause obvious acute symptoms nevertheless cause "silent" brain damage? This question remains unanswered, in part because of the difficulty in recognizing mild symptoms of lead poisoning in children and in part because the experimental studies that might provide some answers have not yet been undertaken.

POPULATION	EXPOSURE (MICROGRAMS PER CUBIC METER OF AIR)	MEAN BLOOD LEAD (MICROGRAMS PER 100 GRAMS)
RURAL U.S.	0.5	16
URBAN U.S.	1.0	21
DOWNTOWN PHILADELPHIA	2.4	24
CINCINNATI POLICEMEN	2.1	25
CINCINNATI TRAFFIC POLICEMEN	3.6	30
LOS ANGELES TRAFFIC POLICEMEN	5.2	21
BOSTON AUTOMOBILE TUNNEL EMPLOYEES	6.3	30

RESPIRATORY EXPOSURE to lead is reflected in the mean blood-lead values of various groups, according to John R. Goldsmith and Alfred C. Hexter of the California Department of Public Health. Groups apparently exposed to more lead in the air have generally higher blood-lead values; whether these indicate higher body burdens of lead is not known.

Classical plumbism—the acute disease—is seen today primarily in children with the pica habit. Before discussing these cases in some detail I shall briefly take up two other current environmental sources of lead: earthenware improperly glazed with lead and lead-contaminated alcoholic beverages.

Michael Klein and his colleagues at McGill University recently reported two cases of childhood lead poisoning, one of which was fatal, that they traced to an earthenware jug in which the children's mother kept a continuously replenished supply of apple juice. The slightly acidic juice was leaching lead out of the glaze, the thin layer of glassy material fused to the ceramic surfaces of the jug. The investigators thereupon tested 117 commercial earthenware food and beverage containers and 147 samples made with 49 different commonly used glazes in the McGill ceramics laboratory. Excessive amounts of lead—more than the U.S. maximum permissible amount for glazes of seven parts per million—were leached out of half the vessels. (The maximum permissible amount should probably be reevaluated, since past methods of testing have not taken account of such variables as the quantity of the food or beverage consumed, its acidity, the length of time it is stored and whether or not it is cooked in the pottery.) As the McGill report points out, the danger of poisoning from lead-glazed pottery has been rediscovered periodically since antiquity. The Greeks knew about the danger but the Romans did not; they made the mistake of storing wine in earthenware. James Lind, who in 1753 recommended lemon or lime juice as a preventive for scurvy, also warned that the juices should not be stored in earthenware jugs. Now the index of suspicion has fallen too low: one physician poisoned himself recently by drinking a cola beverage (and 3.2 milligrams of lead) every evening for two years from a mug his son had made for him. Do these cases represent isolated occurrences? How many other people are similarly exposed? Clearly the first step is the testing of earthenware and a reevaluation of its fabrication and use for food and drink.

In the manufacture of moonshine whiskey, lead solder is used in the tubing of distillation units. Moreover, discarded automobile radiators that contain lead often serve as condensers. Lead is therefore found in most samples of confiscated moonshine. Lead encephalopathy, nephritis with gout and other lead-related conditions have been reported in moonshine consumers, largely in the southeastern part of the U.S. The problem of diagnosis is complicated by the fact that the symptoms of acute alcoholism and acute lead poisoning are similar in many ways. (Again there is a historical record. The McGill report noted that the Massachusetts Bay Colony forbade rum distillation in leaded stills in 1723 in an effort to prevent "dry gripes," an intestinal condition. In 1767 Sir George Baker blamed "the endemic colic of Devonshire" on the use of lead-lined troughs in the making of apple cider.)

Childhood lead poisoning in the U.S. is seen almost exclusively in children of preschool age who live in deteriorated housing built before 1940 (when titanium dioxide began to replace lead in the pigment of most interior paints). The causative factors are commonly a triad: a dilapidated old house, a toddler with pica and parents with inadequate resources (emotional, intellectual, informational and/or economic) to cope with the family's needs. The three factors interact to increase the likelihood that the child will eat chips of leaded paint. A chip of paint about the size of an adult's thumbnail can contain between 50 and 100 milligrams of lead, and so a child eating a few small chips a day easily ingests 100 or more times the tolerable adult intake of the metal! In one study conducted some years ago at the Baltimore City Hospitals and the Johns Hopkins Hospital, Harold E. Harrison and I found that the average daily fecal excretion of lead by children with severe plumbism was 44 milligrams. In a group of normal unexposed children we found a daily fecal lead excretion of less than .2 milligram of lead. In other words, pica for leaded paint results in genuinely massive exposures. And when the abnormal intake ceases, it may be several months or years before blood-lead levels return to normal.

The repeated ingestion of leaded-paint chips for about three months or longer can lead to clinical symptoms and eventually to the absorption of a potentially lethal body burden of lead. During the first four to six weeks of abnormal ingestion there are no symptoms. After a few weeks minor symptoms such as decreased appetite, irritability, clumsiness, unwillingness to play, fatigue, headache, abdominal pain and vomiting begin to appear. These, of course, are all quite nonspecific symptoms, easily ignored as behavior problems or blamed on various childhood diseases. In a few weeks the lassitude may progress to intermittent drowsiness and stupor; the vomiting may become persistent and forceful;

brief convulsions may occur. If the exposure to lead continues, the course of the disease can culminate abruptly in coma, intractable convulsions and sometimes death.

This picture of fulminating encephalopathy is commonest in children between 15 and 30 months of age; older children tend to suffer recurrent but less severe acute episodes and are usually brought to the hospital with a history of sporadic convulsions, behavior problems, hyperactivity or mental retardation. The symptoms tend to wax and wane, usually becoming more severe in summer. (Some 85 percent of all lead-poisoning cases are reported from May through October. This remarkably clear seasonal pattern is still not understood. It may be due at least in part to the fact that the ultraviolet component of sunlight increases the absorption of lead from the intestine.)

The symptoms of even acute encephalopathy are nonspecific, resembling those of brain abscesses and tumors and of viral and bacterial infections of the brain. Diagnosis depends, first of all, on a high level of suspicion. To make a positive diagnosis it is necessary to show high lead absorption as well as the adverse effects of lead. This requires the measurement of lead in blood and other specialized tests. Mild symptoms may be found in the presence of values of between 60 and 80 micrograms of lead per 100 milliliters of blood. As the blood-lead level rises above 80 micrograms the risk of severe symptoms increases sharply. Even in the absence of symptoms, in children blood-lead levels exceeding 80 micrograms call for immediate treatment and separation of the child from the source of lead.

Treatment is with potent compounds known as chelating agents (from the Greek *chēlē*, meaning claw): molecules that tend to bind a metal atom firmly, sequestering it and thus rendering it highly soluble [see "Chelation," by Harold F. Walton; SCIENTIFIC AMERICAN, June, 1953]. Chelating agents remove lead atoms from tissues for excretion through the kidney and through the liver. With chelating agents very high tissue levels of lead can be rapidly reduced to levels approaching normal, and the adverse metabolic effects can be promptly suppressed. Initially two agents are administered by injection: EDTA and BAL. (EDTA, or edathamil, is ethylenediaminetetraacetic acid; BAL is "British Anti-Lewisite," developed during World War II as an antidote for lewisite, an arsenic-containing poison gas.) After the lead level has been reduced another agent, d-penicillamine, may be administered orally as a follow-up therapy.

Before chelating agents were available about two-thirds of all children with lead encephalopathy died. Now the mortality rate is less than 5 percent. Unfortunately the improvement in therapy has not substantially reduced the incidence of brain damage in the survivors. Meyer A. Perlstein and R. Attala of the Northwestern University Medical School found that of 59 children who developed encephalopathy, 82 percent were left with permanent injury: mental retardation, convulsive disorders, cerebral palsy or blindness. This high incidence of permanent damage suggests that some of these children must have had recurrent episodes of plumbism; we have found that if a child who has been treated for acute encephalopathy is returned to the same hazardous environment, the risk of permanent brain damage rises to virtually 100 percent. In Baltimore, with the help of the Health Department and through the efforts of dedicated medical social workers, we are able to make it an absolute rule that no victim of lead poisoning is ever returned to a dangerous environment. The child goes from the hospital to a convalescent home and does not rejoin his family until all hazardous lead

	I NO DEMONSTRABLE EFFECTS	II MINIMAL SUBCLINICAL EFFECTS DETECTABLE	III COMPENSATION	IV FUNCTIONAL INJURY (SHORT, INTENSE EXPOSURE)
METABOLIC EFFECTS	NORMAL	URINARY ALA MAY INCREASE	INCREASE IN SEVERAL METABOLITES IN BLOOD AND URINE	FURTHER INCREASE IN METABOLITES
FUNCTIONAL EFFECTS: BLOOD	NONE	NONE	REDUCED RED CELL LIFE-SPAN, INCREASED PRODUCTION	REDUCED RED CELL LIFE-SPAN WITH OR WITHOUT ANEMIA (REVERSIBLE)
KIDNEY FUNCTION	NORMAL	NORMAL	SOMETIMES MINIMAL DYSFUNCTION	FANCONI SYNDROME (REVERSIBLE)
CENTRAL NERVOUS SYSTEM	NONE	NONE	?	MINIMAL TO SEVERE BRAIN DAMAGE (PERMANENT)
PERIPHERAL NERVES	NONE	NONE.	?	POSSIBLE DAMAGE
SYMPTOMS	NONE	NONE	SOMETIMES MILD, NONSPECIFIC COMPLAINTS	ANEMIA, COLIC, IRRITABILITY, DROWSINESS. IN SEVERE CASES, MOTOR CLUMSINESS, CONVULSIONS AND COMA
RESIDUAL EFFECTS	NONE	NONE	NONE KNOWN	RANGE FROM MINIMAL LEARNING DISABILITY TO PROFOUND MENTAL AND BEHAVIORAL DEFICIENCY, CONVULSIVE DISORDERS, BLINDNESS

EFFECTS OF LEAD are associated in a general way with five levels of exposure and rates of absorption of the metal. Level I is associated with blood-lead concentrations of less than 30 micrograms of lead per 100 milliliters and Level II with the 30–50 microgram range. Level III, at which compensatory mechanisms apparently minimize or prevent obvious functional injury, may be associated with concentrations of between 50 and 100 micrograms. Level IV is usually associated with concentrations greater than 80 micrograms but impairment may be evident at lower levels, particularly if compensatory responses are interfered with by some other disease state.

sources have been removed or the family has been helped to find lead-free housing. Cases of permanent brain damage nevertheless persist. It appears that even among children who suffer only one episode, are properly treated and are thereafter kept away from lead, at least 25 percent of the survivors of lead encephalopathy sustain lasting damage.

Clearly, then, treatment is not enough; the disease must be prevented. Children with increased lead absorption must be identified before they become poisoned. Going a step further, the sources of excessive lead exposure must be eliminated.

Baltimore has taken a "case-finding" approach to these tasks. Free diagnostic services were established by the city Health Department in the 1930's. Physicians took advantage of the services, and increasing numbers of cases were discovered. Since 1951 the removal of leaded paint has been required in any dwelling where a child is found with a blood-lead value of more than 60 micrograms. The number of cases reported each year rose for some time as diagnostic methods and awareness improved, but recently it has leveled off. In order to reach children before they are poisoned, however, more is required than case-finding; what is needed is a screening program that examines entire populations of children in high-risk areas of cities. Chicago undertook that task in the 1960's. Last year New York City inaugurated a new and intensive screening program in which children are being tested for blood lead in hospitals and at a large number of neighborhood health centers; an educational campaign has been launched to bring lead poisoning and the testing facilities to public notice. As in Baltimore, a blood-lead finding of more than 60 micrograms results in an examination of the child's home. If any samples of paint and plaster contain more than 1 percent of lead, the landlord is ordered to correct the condition by covering the walls with wallboard to a height of at least four feet and by removing all leaded paint from wood surfaces; if the landlord does not comply, the city undertakes the work and bills him. Before the new program was begun New York was screening about 175 blood tests a week; by the end of the year it was doing about 2,000 tests a week. Whereas 727 cases of lead poisoning were reported in the city in 1969, last year more than 2,600 were reported. As Evan Charney of the University of Rochester School of Medicine and Dentistry has put it, "the number of cases depends on how hard you look."

Screening is complicated by technical difficulties in testing both children and dwellings. The standard dithizone method of determining blood lead requires between five and 10 cubic centimeters of blood taken from a vein—a difficult procedure in very small children—and the analysis is time-consuming. What is needed is a dependable test that can be carried out on a drop or two of blood from a finger prick. A variety of approaches are now being tried in several laboratories in order to reach this goal; as yet no microtest utilizing a drop or two of blood has been proved practical on the basis of large-scale use in the field. Several appear to be promising in the laboratory, so that field testing in the near future can be anticipated. As for the checking of dwellings, the standard method is laborious primarily because it requires the collection of a large number of samples. Several different portable instruments are under development, including an X-ray fluorescence apparatus that gives a lead-content reading when it is pointed at a surface, but these devices have not yet been proved reliable in the field.

Since World War II the incidence of lead poisoning (usually in the form of lead palsy) among industrial workers, which was once a serious problem, has been reduced by various control measures. The danger is now limited primarily to small plants that are not well regulated and to home industries.

There is increasing concern over environmental lead pollution. Claire C. Patterson of the California Institute of Technology has shown that the levels of lead in polar ice have risen sharply since the beginning of the Industrial Revolution. Henry A. Schroeder of the Dartmouth Medical School has shown that the burden of lead in the human body rises with age, and that this rise is due almost entirely to the concentration of lead in bone. Although man's exposure to lead in highly industrialized nations may come from a variety of sources, the evidence points to leaded gasoline as the principal source of airborne lead today. These observations have occasioned much speculation. It is nonetheless clear that a further rise in the dissemination of lead wastes into the environment can cause adverse effects on human health; indeed, concerted efforts to lower the current levels of exposure must be made, particularly in congested urban areas.

At the moment there is no evidence that any groups have mean blood levels that approach the dangerous range. Some, however, do have levels at which a minimal increase in urinary ALA, but nothing more, is to be expected. This includes people whose occupation brings them into close and almost daily contact with automotive exhaust. These observations emphasize the need to halt any further rise in the total level of exposure. A margin of safety needs to be defined and maintained. This will require research aimed at elucidating the effects of long-term exposure to levels of lead insufficient to cause symptoms or clear-cut functional injury. With regard to respiratory exposure, it is still not clear what fraction of the inhaled particles reaches the lungs and how much of that fraction is actually absorbed from the lung. Still another important question is the storage of lead in bone. Can any significant fraction of lead in bone be easily and quickly mobilized? If so, under what circumstances is it mobilized? There are more questions than answers to the problems posed by levels of lead only slightly higher than those currently found in urban man. Much research is required.

With regard to childhood lead poisoning, however, we know enough to act. It is impermissible for a humane society to fail to do what is necessary to eliminate a wholly preventable disease.

V
FUNCTIONAL INJURY (CHRONIC OR RECURRENT INTENSE EXPOSURE)
INCREASE ONLY IN CASE OF RECENT EXPOSURE
POSSIBLE ANEMIA (REVERSIBLE)
CHRONIC NEPHROPATHY (PERMANENT)
SEVERE BRAIN DAMAGE, PARTICULARLY IN CHILDREN (PERMANENT)
IMPAIRED CONDUCTION (MAY BE CHRONIC)
MENTAL DETERIORATION, SEIZURES, COMA, FOOT OR WRIST DROP
MENTAL DEFICIENCY (OFTEN PROFOUND), KIDNEY INSUFFICIENCY, GOUT (UNCOMMON), FOOT DROP (RARE)

What one can say is that the risk of functional injury increases as the concentration of lead in the blood exceeds 80 micrograms per 100 milliliters. The residual effects persist after blood-lead levels return to normal.