Lead Neurotoxicity: Intervention/Prevention

January 22, 2007

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SPECIAL ARTICLE

Lead poisoning in childhood—comprehensive management and prevention

A symposium was held at Happy Hills Hospital in Baltimore on April 24, 1967, to call attention to the need for a cooperative community approach to the social, environmental, and psychological aspects of the problems of children with lead intoxication. Comprehensive care is just as urgent for the asymptomatic child with an increased body burden of lead as it is for the child with manifest acute plumbism. While chelation therapy for the acute toxic episodes of chronic lead poisoning is deservedly emphasized, hospitalization in a chronic disease facility which has a positive program of child and family rehabilitation serves an important role in the total care of the affected child. Experience in Baltimore and other large cities has shown that coordinated and sustained efforts by health departments, pediatricians, medical social workers, and child guidance workers are essential for an effective program for the prevention and treatment of childhood lead intoxication.

J Peds 73(6):942–950, 1968.

J. Julian Chisolm, Jr., M.D.,* and Eugene Kaplan, M.D.

BALTIMORE, MD.

THE JOURNAL OF PEDIATRICS

JULY 1968 *Volume 73 Number 1*

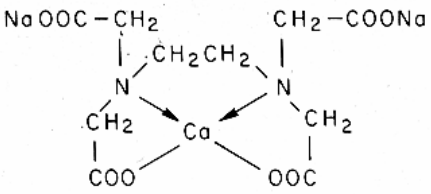
SPECIAL ARTICLE

The use of chelating agents in the treatment of acute and chronic lead intoxication in childhood

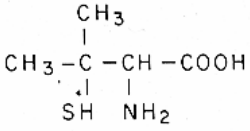
The toxicologic studies reported here provide supportive evidence that prompt institution of chelation therapy with the combination of 2,3-dimercapto-1-propanol (BAL) and edathamil calcium disodium (CaEDTA) together with appropriate supportive therapy can reduce substantially the mortality rate of acute encephalopathy in children with lead intoxication. Treatment of acute encephalopathy with EDTA alone is associated with a mortality rate of 25 per cent or greater; we have had no deaths in 24 cases of acute encephalopathy treated with BAL and EDTA. Biochemical data also indicate that the BAL-EDTA combination is superior to EDTA alone in the treatment of severe acute toxic episodes of plumbism. Evidence presented also suggests that long-term oral administration of d-penicillamine is safe and may be efficacious in the management of the chronic phase of lead poisoning. The rationale for the use of each of these 3 chelating agents is discussed.

J. Julian Chisolm, Jr., M.D.*

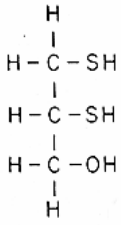
BALTIMORE, MD.



Calcium Disodium EDTA

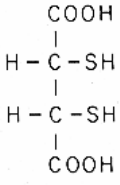


Penicillamine



2,3-Dimercaptopropanol

(BAL)



2,3-Dimercaptosuccinic acid

(DMS)

NATURE November 24, 1945 Vol. 156

BRITISH ANTI-LEWISITE (*BAL*)

By Prof. R. A. PETERS, F.R.S., Dr. L. A. STOCKEN

AND

Dr. R. H. S. THOMPSON

Department of Biochemistry, University Museum, Oxford

IN the first fortnight of the War (1939) fundamental research was initiated in the Oxford Department of Biochemistry by Peters and carried out under his direction by a group of workers as an extra-mural research with the support of and for the Chemical Defence Research Department, Ministry of Supply; the object was to find antidotes for vesicants, both arsenical such as lewisite ($CH.Cl:CH.AsCl_2$) and also those of the mustard gas type. In this brief review, the main facts are given about the discovery of the antidote to lewisite known as *BAL*, owing to its medical importance; more detailed papers based upon the original reports are being prepared. An attempt is made to include the more relevant work from elsewhere and also to focus the main stages in this discovery, as this may prove useful in planning future work of this type.

The Use of Chelating Agents for Accelerating Excretion of Radioelements*

By HARRY FOREMAN†

It has been demonstrated that certain chelating agents can be used to hasten the excretion of radioelements which have become deposited in the body. Specifically, the calcium chelate of ethylenediamine tetracetic acid has been shown to accelerate the urinary excretion of yttrium and plutonium. Similarly, Fe-3, a commercial chelating agent was found to accelerate the urinary excretion of plutonium. The results were produced whether the chelating agent was given shortly after or early after the radioelement was administered. The increased excretion of the plutonium was reflected in a lower Pu content in the tissues of the treated animals.

J Amer Pharm Assoc 42:629-632, 1953.

IN THE PAST, attempts to remove radioactive elements from the body have included: low calcium diets, parathormone, viosterol, ammonium chloride, calcium gluconate (1, 2), low phosphorus diets (3), and zirconium citrate (4). Of these, only zirconium citrate was shown to have an appreciable measure of effectiveness. The present study reports another approach to the problem of accelerating the excretion of radioelements, namely, the use of chelating agents.

in vivo application. It forms serum-soluble chelates which are not readily broken down in the body but are rapidly eliminated by the kidney. When administered as a neutral Na salt, EDTA combines avidly with serum calcium and produces death in hypocalcemia with relatively small doses, i. e., approximately two hundred mg./Kg. of body weight in rats. However, when administered combined with an equivalent weight calcium ion, a negative calcium balance is prevented and the compound is rendered relatively nontoxic. A

Vol. 154, No. 14 JAMA, 1954.

USE OF MONOCALCIUM DISODIUM ETHYLENE DIAMINE TETRA-ACETATE IN LEAD POISONING

Harriet L. Hardy, M.D., Hervey B. Elkins, Ph.D., Benjamin P. W. Ruotolo, M.D., John Quinby, M.D. and William H. Baker, M.D., Boston

The ideal clinical management of lead intoxication in human beings has not yet been achieved. Aub's original studies,[1] demonstrating that calcium and lead behave much the same way in the body, have provided successful therapeutic leads. During episodes of acute intoxication, calcium has been used to force lead from the

made colorimetrically with dithizone. Results of control analyses run on samples of normal urine to which known amounts of lead were added are shown in table 1. In most cases the recoveries were within the expected experimental error allowing for a normal variation of 1 mcg. in the blank.

Clinical Studies

Penicillamine, a New Oral Therapy for Wilson's Disease*

J. M. WALSHE

London, England

Amer J Med 21:487–495, 1956.

An increased concentration of copper in both the liver and brain of patients dying of Wilson's disease (hepatolenticular degeneration, H.L.D.) was noted by Haurowitz,[1] Lüthy[2] and Glazebrook.[3] These observations, all made on single cases, were confirmed and extended by Cumings[4] who reported a series of three patients who died of H.L.D. It is now known that, in addition to the excess copper in the tissues, there is an increased excretion of copper in the urine, a low plasma copper concentration and a very low level of ceruloplasmin, the copper-binding α globulin.[5] This last is believed to be the primary biochemical defect in Wilson's disease.

intensively than is conventionally advocated. Moreover, the degree of benefit that can occur depends on the amount of irreversible structural damage to the brain before treatment is started. Bearn divided his patients with H.L.D. into two groups, the BAL-sensitive and the BAL-resistant, the latter group consisted principally of patients who had the more acute forms of the disease. To the more chronic, or BAL-sensitive group, he gave 200 to 300 mg. of BAL twice daily for many months; some of these patients showed a striking and continued improvement. Unfortunately, in some patients severe toxic reactions to BAL may develop such as skin

TREATMENT OF LEAD-POISONING WITH ORAL PENICILLAMINE

BY

A. GOLDBERG, M.D., M.R.C.P., M.R.C.P.G.
Senior Lecturer

JACQUELINE A. SMITH, B.Sc.
Research Assistant

AND

ANN C. LOCHHEAD, B.Sc.
Research Assistant

University Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow

British Med Journal, 1963.

MEDICAL INTELLIGENCE

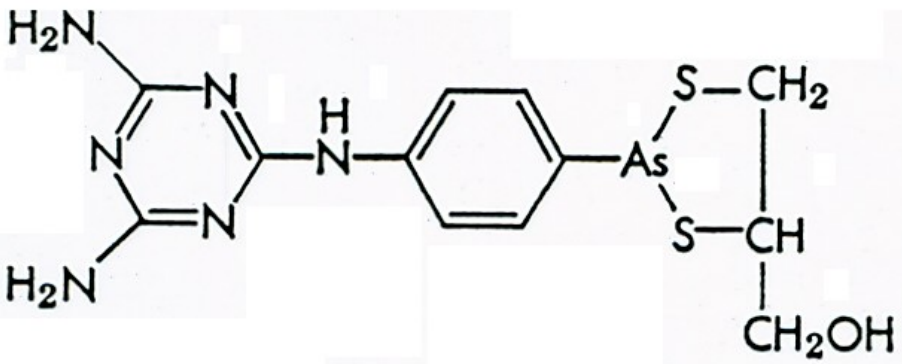
CURRENT CONCEPTS

Management of Increased Lead Absorption and Lead Poisoning in Children

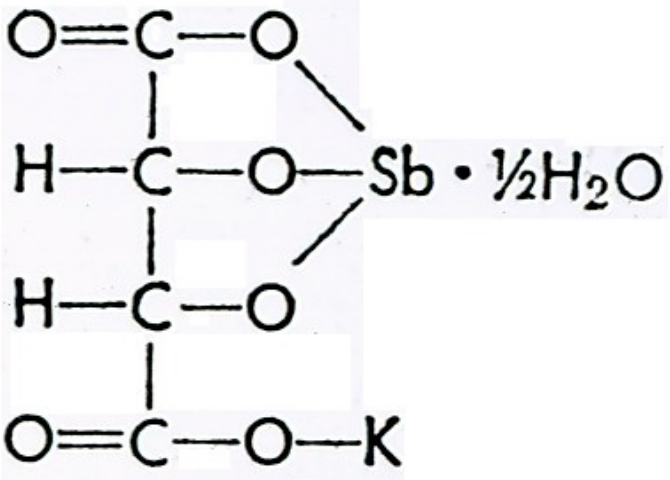
J. JULIAN CHISOLM, JR., M.D.

THE primary aim of treatment for plumbism in children is the prevention of injury to the nervous system. In the long run, societal steps to minimize adventitious lead absorption will be needed to obtain this goal. In practice today, therapeutic intervention at the subclinical stage of lead poisoning and close follow-up observation during the preschool years can do much to prevent the severe forms of residual nervous-system injury. At least 25 per cent of young children with acute lead determinations are of questionable accuracy and precision, the physician must, at present, rely more heavily on the other manifestations of plumbism.

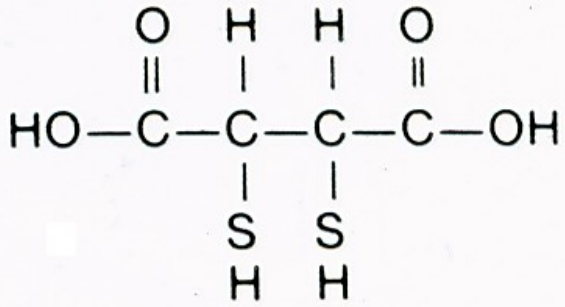
The pediatrician's responsibility is not limited to the supervision of brief courses of chelation therapy. Excessive intake of lead must be stopped. Effective plans for long-term management must be formulated within the constraints imposed by the social, behavioral and environmental conditions under which the affected child lives. On the one hand, there is the prevalence of pica in toddlers, a habit that is poorly understood and difficult to abate. On the other hand, there is pervasive exposure to "high-dose" sources of lead, principally old lead-pigment house paints and old putty.[5,6] At the time of the 1970 United States Census, there were 30,000,000 dwellings built before World War II, but still in use; about 7,000,000 were considered deteriorated or dilapidated. Studies[5,6] of such dwellings indicate that 90 per cent or more have potentially hazardous amounts of lead on surfaces accessible to young children. Surely, some time will be required to abate this environmental hazard to young children. These, then, are the constraints within which management must be planned today.



Melarsoprol



Antimony Potassium Tartrate



DMSA
(MESO-DIMERCAPTO SUCCINIC ACID)
SUCCIMER

2,3-Dimercaptosuccinic Acid: A New Agent for the Treatment of Lead Poisoning[1]

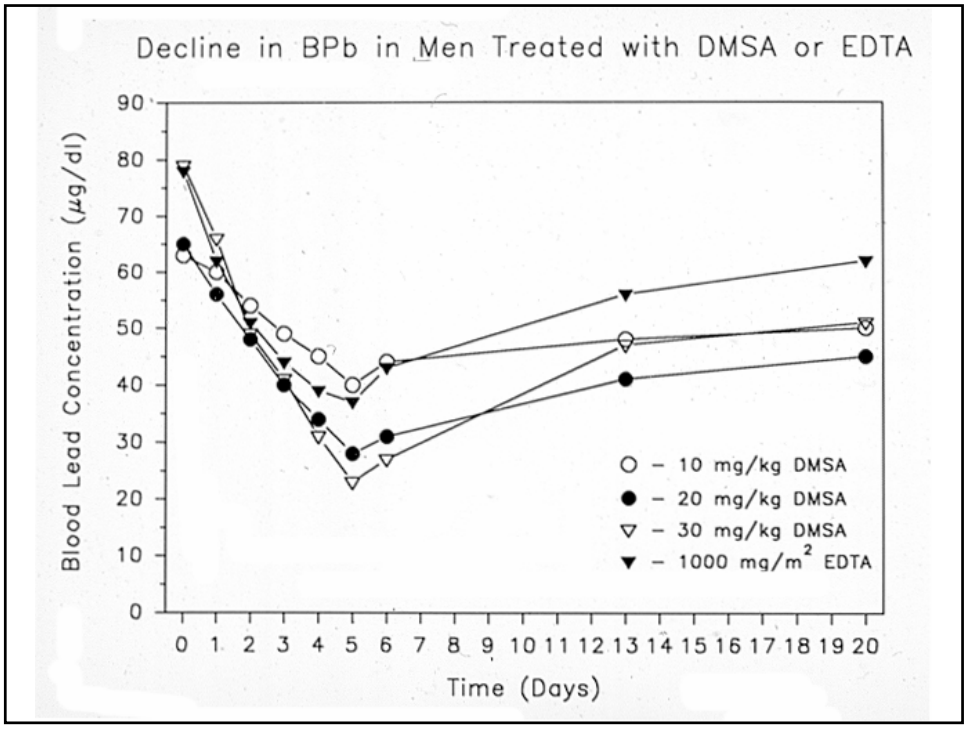
J. H. GRAZIANO, J. K. LEONG and E. FRIEDHEIM[2]

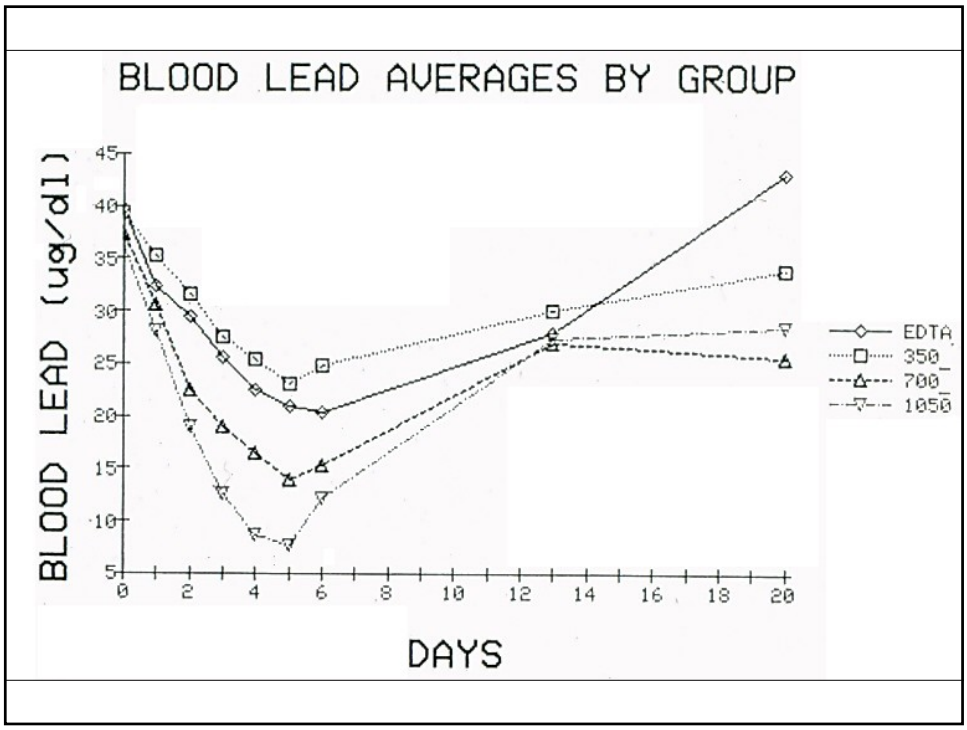
The Development of DMSA (Succimer) as a Treatment for Childhood Lead Poisoning

- 1974: Animal model of Pb poisoning developed; begin screening candidate drugs
- 1977: DMSA identified as a potential antidote for Pb in an animal model
- 1982: Clinical trials begin at Columbia Univ.
- 1990: New Drug Application submitted
- 1991: FDA approval for use in children
- SEVENTEEN YEARS!
- What could have expedited this process?

What Could Have Expedited This Process?

- Higher throughput drug screening models
- Help in partnering with a pharmaceutical firm interested in an orphan drug
- The development of a network of sites involved in studies of children's environmental health, with access to potential study participants
- Funding for additional clinical trial sites

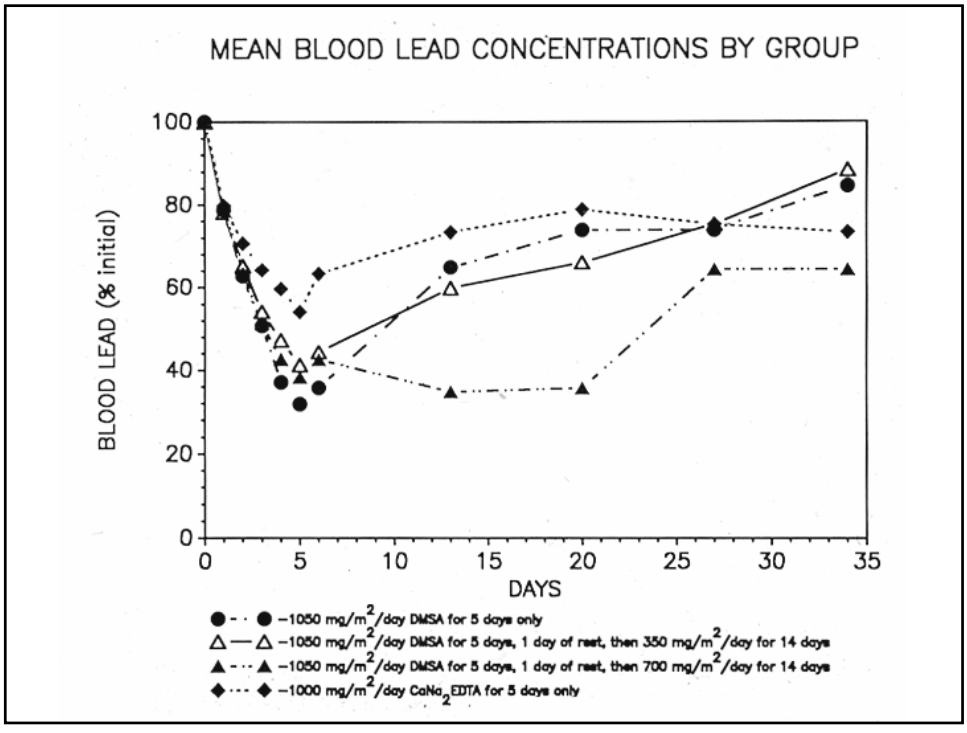

Decline in BPb in Men Treated with DMSA or EDTA
Blood Lead Concentration (µg/dl)
Time (Days)
○ – 10 mg/kg DMSA
● – 20 mg/kg DMSA
▽ – 30 mg/kg DMSA
▼ – 1000 mg/m² EDTA


BLOOD LEAD AVERAGES BY GROUP
BLOOD LEAD (ug/dl)
DAYS
EDTA
350
700
1050

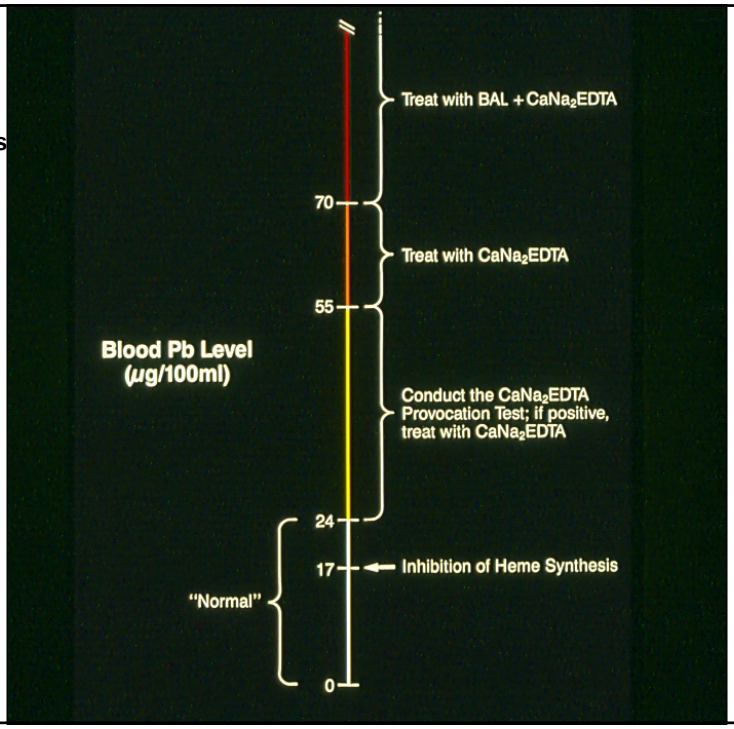
Dose-response study of oral 2,3-dimercaptosuccinic acid in children with elevated blood lead concentrations

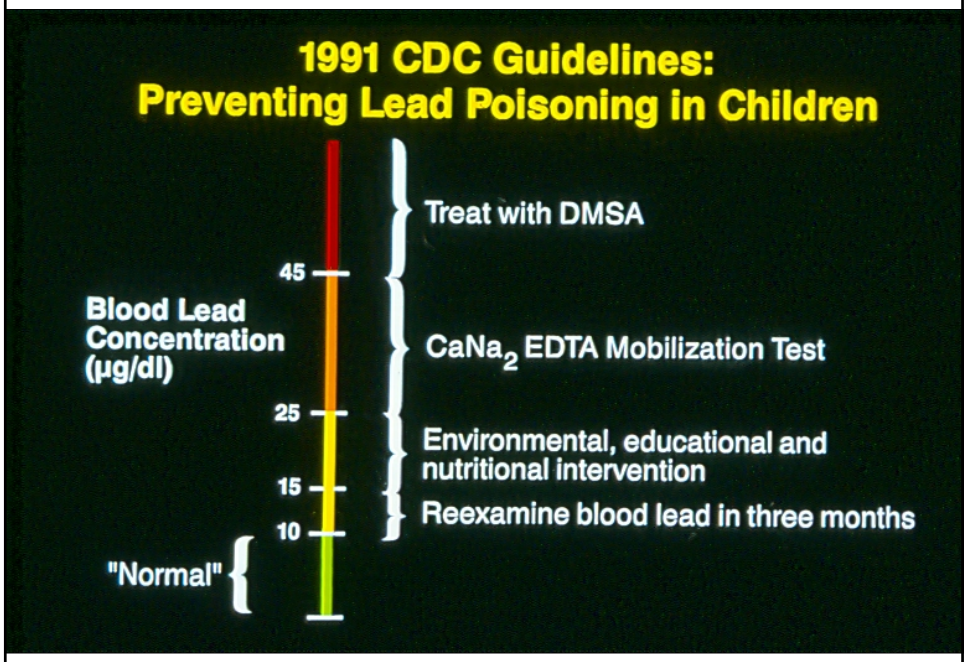
Joseph H. Graziano, PhD, Nancy J. Lolacono, MPH, and Patricia Meyer, MPH

From the Departments of Pharmacology and Pediatrics, Columbia University College of Physicians and Surgeons and Babies Hospital, New York



1985 CDC guidelines





The NEW ENGLAND JOURNAL of MEDICINE

THE EFFECT OF CHELATION THERAPY WITH SUCCIMER ON NEUROPSYCHOLOGICAL DEVELOPMENT IN CHILDREN EXPOSED TO LEAD

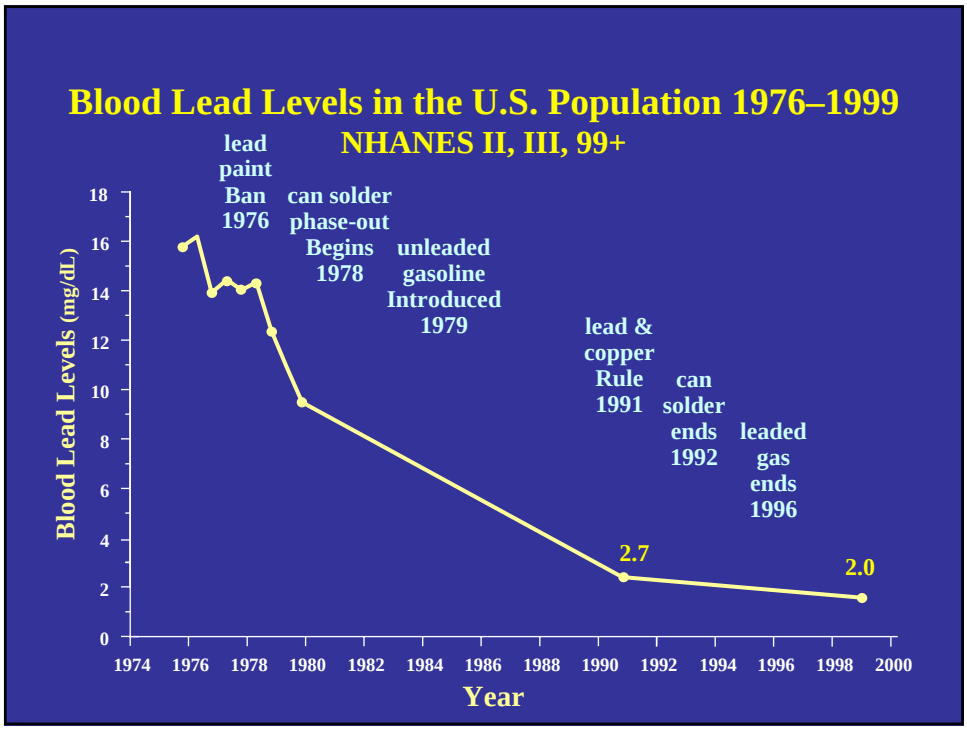
WALTER J. ROGAN, M.D., KIM N. DIETRICH, PH.D., JAMES H. WARE, PH.D., DOUGLAS W. DOCKERY, PH.D., MIKHAIL SALGANIK, PH.D., JERILYNN RADCLIFFE, PH.D., ROBERT L. JONES, PH.D., N. BETH RAGAN, B.A., J. JULIAN CHISOLM, JR., M.D., AND GEORGE G. RHOADS, M.D., FOR THE TREATMENT OF LEAD-EXPOSED CHILDREN TRIAL GROUP*

ABSTRACT

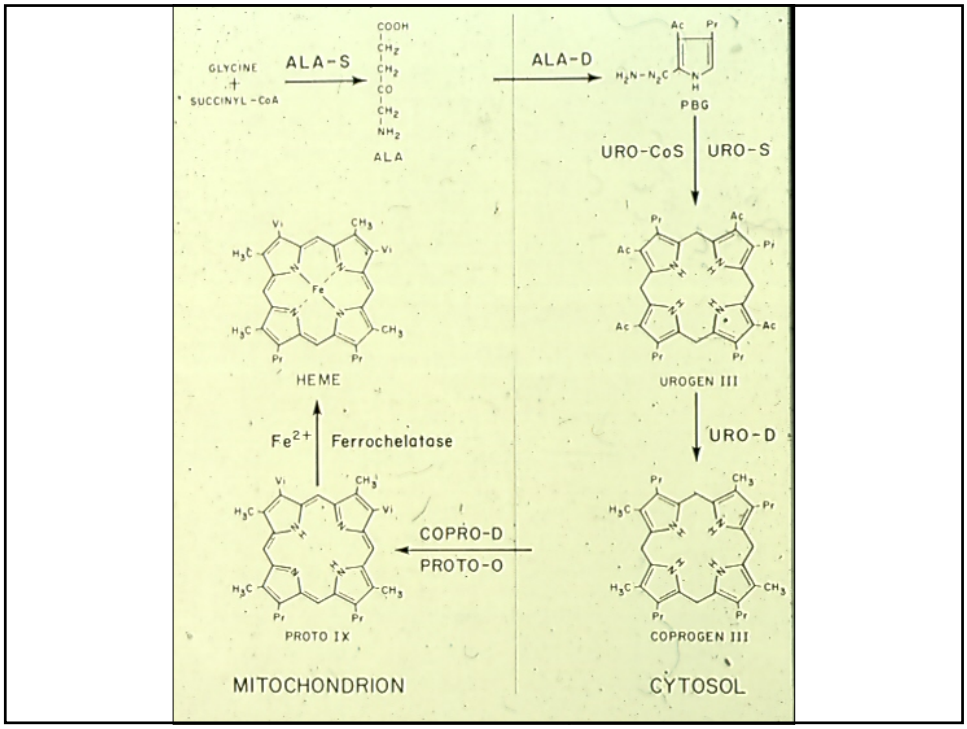
Background Thousands of children, especially poor children living in deteriorated urban housing, are exposed to enough lead to produce cognitive impairment. It is not known whether treatment to reduce blood lead levels prevents or reduces such impairment.

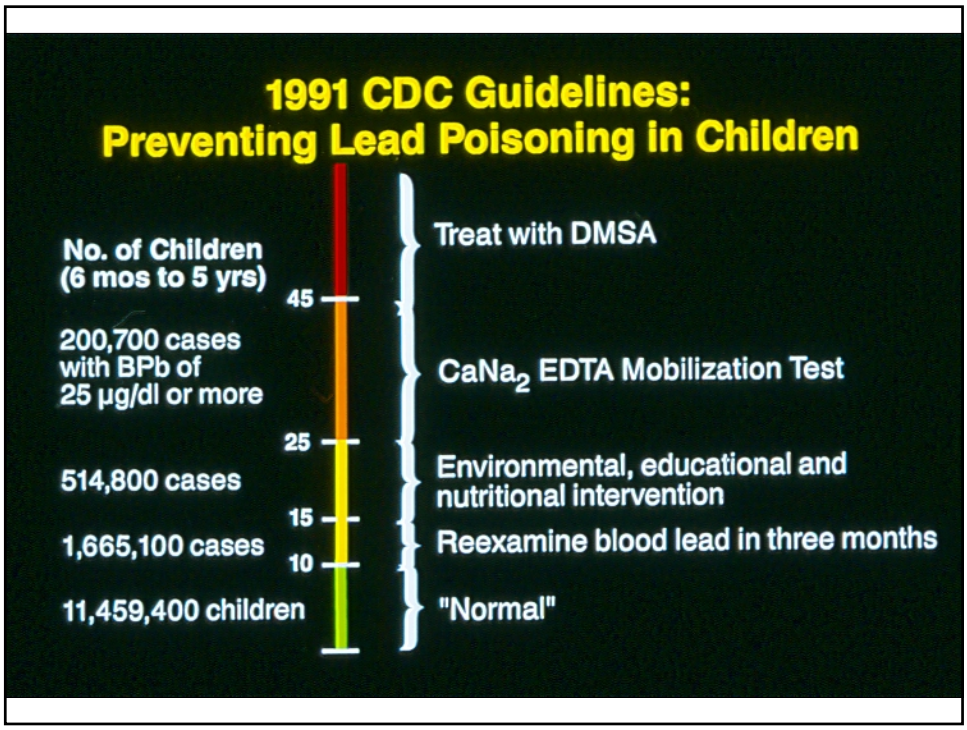
Methods We enrolled 780 children with blood lead levels of 20 to 44 μg per deciliter (1.0 to 2.1 μmol per liter) in a randomized, placebo-controlled, double-blind trial of up to three 26-day courses of treatment with succimer, a lead chelator that is administered orally. The children lived in deteriorating inner-city housing and were 12 to 33 months of age at enrollment; 77 percent were black, and 5 percent were Hispanic. Follow-up included tests of cognitive, motor, behavioral, and neuropsychological function over a period of 36 months.

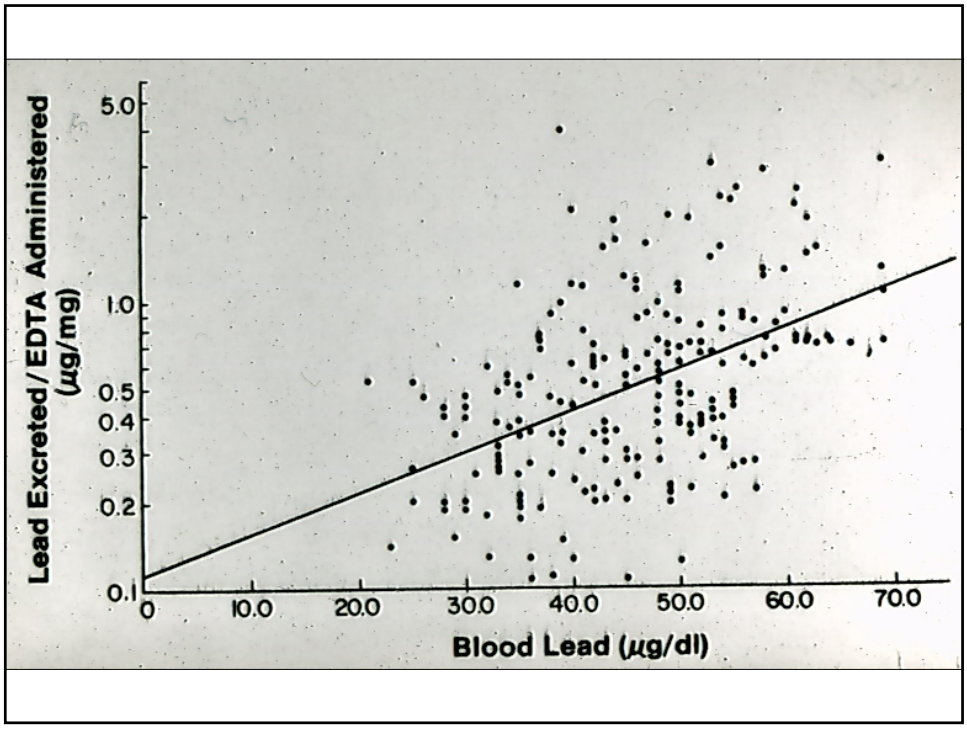
In 1991, the Food and Drug Administration licensed succimer (dimercaptosuccinic acid), the first approved oral lead chelator, for use in children with blood lead levels of at least 45 μg per deciliter (2.2 μmol per liter).[7] Succimer reduced blood lead levels at least as well as parenteral treatment with edetate calcium disodium in children with levels of 30 μg per deciliter (1.4 μmol per liter) or higher.[8] Also in 1991, universal screening of children for elevated blood lead levels was recommended by the Centers for Disease Control (CDC),[9] and the threshold of concern was lowered from 25 μg per deciliter (1.2 μmol per liter) to 15 μg per deciliter (0.7 μmol per liter) — a level associated with cognitive impairment but not symptoms of lead poisoning. However, the CDC made no specific recommendation about chelation therapy in children with blood lead levels of 20 to

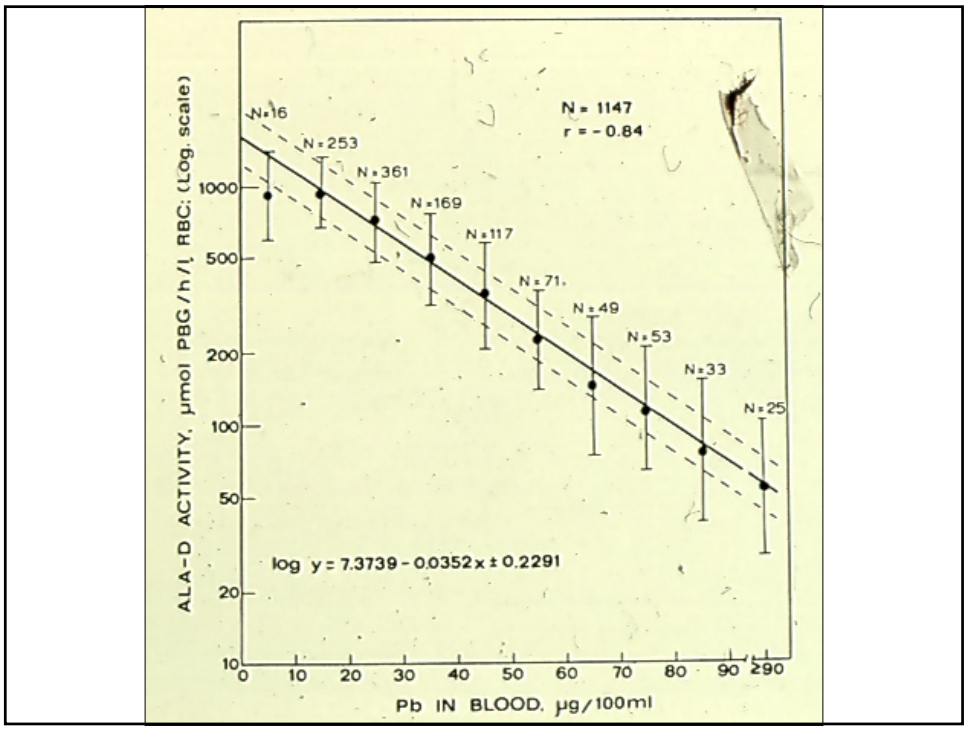


Thank You!


GLYCINE
+
SUCCINYL-CoA
ALA-S
ALA
ALA-D
PBG
URO-CoS
URO-S
UROGEN III
URO-D
COPROGEN III
COPRO-D
PROTO-O
PROTO IX
Fe2+
Ferrochelatase
HEME
MITOCHONDRION
CYTOSOL


1991 CDC Guidelines:
Preventing Lead Poisoning in Children
No. of Children
(6 mos to 5 yrs)
45
200,700 cases
with BPb of
25 µg/dl or more
25
514,800 cases
15
1,665,100 cases
10
11,459,400 children
Treat with DMSA
CaNa2 EDTA Mobilization Test
Environmental, educational and
nutritional intervention
Reexamine blood lead in three months
"Normal"


Lead Excreted/EDTA Administered (µg/mg)
5.0
1.0
0.5
0.4
0.3
0.2
0.1
0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
Blood Lead (µg/dl)


ALA-D ACTIVITY, µmol PBG/h/l RBC; (Log. scale)
N = 1147
r = - 0.84
N=16
N=253
N=361
N=169
N=117
N=71
N=49
N=53
N=33
N=25
log y = 7.3739 - 0.0352x ± 0.2291
1000
500
200
100
50
20
10
0
10
20
30
40
50
60
70
80
90
≥90
Pb IN BLOOD, µg/100ml

0022-3565/85/2353-0665$02.00/0
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

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Use of 2,3-Dimercaptopropane-1-Sulfonate in Treatment of Lead Poisoning in Children[1]

J. J. CHISOLM, JR. and DAVID J. THOMAS

The Kennedy Institute for Handicapped Children and the Department of Pediatrics, School of Medicine, The Johns Hopkins University, Baltimore, Maryland

Accepted for publication September 16, 1985

ABSTRACT

2,3-Dimercaptopropane-1-sulfonate (DMPS) is a water-soluble metal complexing agent. Administration to lead-poisoned children of 5-day courses of 200 or 400 mg of DMPS per m^2 surface area per day given p.o. in divided doses resulted in a significant decline in the concentration of lead in blood. DMPS treatment did not significantly alter the concentrations of zinc or copper in plasma. Urinary excretion of lead, zinc and copper was increased by DMPS administration and these increases were sustained throughout the 5-day course of treatment. No significant changes in hepatic, renal or hematological function were found in DMPS-treated children and no side effects attributable to DMPS were noted. It is concluded that a 5-day course of DMPS given p.o. may be safe and effective in the treatment of asymptomatic lead poisoning in children.

CLINICAL TOXICOLOGY, 30(4), 493-504 (1992)

BAL, EDTA, DMSA AND DMPS IN THE TREATMENT OF LEAD POISONING IN CHILDREN

J. Julian Chisolm, Jr., M.D.

Lead Poisoning Program, Kennedy Institute
Baltimore, Maryland