

TREATMENT OF ORGANIC LEAD (TETRAETHYL) INTOXICATION
WITH CALCIUM DIODIUM VERSENA TE
(ETHYLENEDIAMINETETRAACETIC ACID) (EDTA)

by

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The beneficial effects anticipated, and apparently realized to some extent from the administration of EDTA (ethylenediaminetetraacetic acid) in inorganic lead poisoning prompted its use in the treatment of three cases of organic lead poisoning seen recently in Panama.

For many years poisoning of this type has been confined almost entirely to workmen in the petroleum industry engaged in cleaning storage tanks that have contained leaded gasoline. The hazard of organic lead poisoning in this occupation resides primarily in the sludge which forms beneath the water bottom underlying the gasoline in a storage tank. In addition to varying amounts of gasoline, such sludge contains small quantities of decomposition products of tetraethyl lead, and may contain tetraethyl lead itself in concentrations which, occasionally, reach or even exceed 0.1 per cent. This sludge may be the source of dangerous concentrations of lead in the atmosphere within the tank under ordinary conditions of temperature. If workmen are exposed to such contaminated atmosphere without suitable protection for sufficient periods of time acute illness will result.

The length of time required for such exposure to give rise to serious lead poisoning will vary with the concentration of tetraethyl lead vapor in the air, but it is possible to breathe in and absorb a lethal dose of tetraethyl lead in half an hour. Under less severe conditions, a few hours of exposure on one day or on a number of successive days may induce a serious or fatal illness.

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The rapidity and severity of the onset of organic lead intoxication are directly related to the intensity and duration of the exposure. In the early stages of severe cases, and at all times in those in which the exposure has been minimal, the symptoms may be ill-defined, but they soon develop into a remarkably characteristic pattern in the severe case. The interval of time which elapses between exposure and the onset of illness may vary from several hours to a period of several days. In the severe cases, the severity of the exposure and the resultant illness tending to be inversely related to the rapidity of onset. When the exposure has continued intermittently for some time at a low level of intensity, recognizable symptoms may be delayed for a period of two or three weeks. When the exposure has been slight and of short duration, a true clinical picture may not develop, or may be difficult to detect or to differentiate from an anxiety state, particularly in men whose exposure can properly be regarded to have been negligible but yet has been had under conditions which the workman himself cannot differentiate from those which have caused serious or possibly fatal illness. In mild cases that result from a single or brief period of exposure, the symptoms usually regress rapidly, and recovery is complete within a week or so. In the more serious cases the illness progresses rapidly toward a state of acute mental disturbance, characterized by delirium, mania, convulsive seizures and coma. Visual and auditory hallucinations are usually present in these severe cases. Lucid periods may precede or follow these bouts of mania and delirium, and at this time the patient is usually depressed and apathetic. Relapses are commonly observed, although signs pointing to eventual recovery are usually apparent within a week or so after the onset of the acute illness. Prognosis as to life

should be guarded during the early stages in those cases exhibiting severe mental derangement. The prognosis for recovery is excellent once the critical stage has been passed, and complete restoration of physical and mental faculties occurs usually within the period of four to ten weeks. Any attempt to classify the illness in one category or another, or to attempt to relate the effectiveness of any special medication or therapeutic procedure, with respect to these symptoms, contributes little to an understanding of the clinical syndrome, since these patients at some time during their illness exhibit the features of all and frequently pass from one to the other or even from a relatively normal mental state to one of gross disturbance with amazing rapidity. The mental disturbance may subside at any time, with or without treatment.

The tank cleaning operations that resulted in the acute poisoning of a number of workmen in Panama extended over a period of two weeks.

Although several of the workmen complained of insomnia, bad dreams, restlessness and loss of appetite after the third day of work in the tanks, all continued to stay on the job until the cleaning operations were discontinued when 3 men failed to report for work. One of these men was admitted to the hospital the following day and died two days later. Another of these workmen, who had been subjected to the greatest severity of exposure, was seen by a physician on the day the tank cleaning work was stopped and was admitted to a local hospital for observation and treatment. At that time he seemed to be confused and semistuporous and complained of nausea, abdominal pain and vomiting. Later he became restless and was unable to sleep. He was disoriented and highly agitated, and at times fearful and depressed. He

vomited several times and complained of pain in the right inguinal region.

There was no disturbance in bowel function and the appetite was good. Physical examination at this time disclosed no significant findings with the exception of arterial hypotension. The body temperature was 98.6°, the pulse 80, the blood pressure 92/58, the respirations 24 and regular; there were no pulmonary rales, no abdominal tenderness, spasm or rigidity, and no significant alteration of reflexes.

The following day the blood pressure was 90/60, pulse 78, respirations 20. The patient was restrained in bed with ankle straps and wrist bands. He continued to be apprehensive and agitated, talking irrationally and more or less continuously. He refused all medication, was in great fear of being poisoned or killed and was highly suspicious of all doctors and nurses.

The condition of this man was most critical for the ensuing several days. He was irrational and the victim of hallucinations. He cried out occasionally, struggled almost continuously against the restraining straps, moved his head and eyes constantly and became violent and abusive without apparent provocation. He complained repeatedly of the taste of gasoline and of the sensation of burning discomfort in his throat.

For the first time, on the twelfth day after his admission to the hospital, he began to have fleeting periods of lucidity during which he recognized his mother and brother. However, he became agitated readily, talked loudly and irrationally and was always in fear of being killed. A few days later he began to exhibit longer periods of rational behavior, when he would answer questions readily and sensibly, and follow the instructions of the nurse and orderly.

From this time on, aside from short periods of agitation and apprehension, his daily improvement was apparent to everyone. He was allowed to sit in a chair, and all physical restraint was removed. Convalescence proceeded without interruption, but constant attendance by a male nurse was continued in order to avert any acts of violence or irrationality which might develop out of relapses. Such relapses commonly occur in such cases and must always be guarded against.

Laboratory Data (On admission)

Hemogram - RBC 5,180,000, Hb 14.5 g. (Sahli), WBC 9,950

Differential: Polymorphonuclear Neutrophils 61
Lymphocytes 37
Monocytes 1
Eosinophiles 2

No abnormality of erythrocytes, no punctate basophils. Coagulation time 2 minutes, 35 seconds Prothrombin Content 100%

Fragility Test - Hemolysis begins at 0.44%, complete at 0.54%

Blood Chemistry	Mg. Per 100 ml.
Urea Nitrogen	13
Glucose	110
Calcium	10
Inorganic Phosphate	3.5

Urinalysis

Specimen clear, amber, sp. gr. 1.022, pH 5.5, albumin negative, sugar negative. Microscopic: No red cells, no casts, few leucocytes and epithelial cells.

Numerous tests were carried out in this case as well as in all others of the group and all of the results were within the normal range.

The case as described was one of several which varied in pattern and in degree among themselves. The early fatal outcome of one man's illness had

served to demonstrate the grave character of the exposure, and every reason presented itself for making use of any therapy which offered hope of benefit. Ethioopropanol therapy had been employed in a few cases, previously, and had been well tolerated, while calcium disodium versenate had been used with seemingly beneficial effects by others in cases of inorganic lead poisoning. The latter was made available* in limited amount, and so was employed to that extent, while the former, also, was given in a few instances.

Three from a group of six critically ill patients were selected for treatment with calcium disodium versenate. Comprehensive clinical laboratory tests (red and white cell and differential counts, Hb, hematocrit, bleeding, clotting and prothrombin time, urinalysis (including urobilinogen), serum calcium, phosphorus, total serum protein, B/C ratio, glucose, urea N, non-protein nitrogen, bilirubin) were carried out prior to, during and after treatment in each case. The results of these tests were within normal range in every instance. Calcium Disodium Versenate was given in daily intravenous doses of 1 gram per thirty pounds of body weight. The administration of the compound gave rise to no demonstrable untoward effects at any time.

Samples of the blood and urine of all of the patients were obtained for analysis for lead. Difficulties were encountered in carrying out a program of sampling, because of the distance from the source of supply in the Laboratory in Cincinnati, and while these and other difficulties introduced discrepancies into the observations, considerable numbers of data were obtained ultimately, and are illustrated below by individual cases.

* supplied for clinical trial by Elker Laboratories, Inc., Los Angeles, California

TREATMENT OF ACUTE TETRAETHYL LEAD INTOXICATIONCase **██████** - Age 21

Intense intermittent exposure.

Severe poisoning.

Seen by physician after a period of about 2 weeks spent working in and around tanks.

In semistupor, complaining of nausea and vomiting.

<u>Date</u> 1952	<u>Time</u>	<u>Blood</u>		<u>Urine</u>
		<u>Mg. Pb Per 100 Grams</u>		<u>Mg. Pb Per Liter</u>
		<u>Spectrographic</u>	<u>Dithizone</u>	
8-8 through 8-13 - Treatment with Dithiopropanol (BAL) *				
8-12	10:50 A. M.	0.06	0.075	
8-13	8:00 A. M.			4.5
8-13	10:00 A. M.	0.07	0.06	
Treatment with Dithiopropanol Discontinued				
8-14 through 8-21 - Treatment with Calcium Disodium Versenate (EDTA)				
8-14	2:10 P. M.	-	0.07	
8-14	3:00 P. M.			1.5
8-14	4:45 P. M.			
8-14	4:55 P. M.			1.0
8-15	2:30 P. M.			7.9
8-16	11:00 A. M.	0.07	0.06	
8-17	11:30 A. M.			1.5
8-18	7:50 P. M.			0.93
8-19	11:00 A. M.	0.08	0.06	
8-20	1:45 A. M.			0.99
8-21	3:30 A. M.			0.60
Treatment with Calcium Disodium Versenate (EDTA) Discontinued				
8-22	1:00 A. M.			0.30
8-23	7:00 A. M.			0.13
8-27	9:00 A. M.			0.30
9-12		0.05	0.05	0.03
9-12				0.31
9-13				0.32
9-14				0.29
9-15		0.05	0.05	
9-19				0.15
9-20				0.08
9-20				0.05
9-22				0.05
10-30		0.06	0.05	0.07
11-1				0.09
11-1		0.04	0.05	0.13

*Containers for the collection of specimens of blood and urine were not available at the time treatment with BAL was instituted.

TREATMENT OF ACUTE TETRAETHYL LEAD INTOXICATION

Case [REDACTED] - Age 24

Engaged in tank cleaning operations for twelve days.
 Slight to moderate intermittent exposure.
 Mild poisoning.
 Seen by physician on fifth day after stopping work.
 Chief complaint, insomnia.

<u>Date</u> <u>1952</u>	<u>Time</u>	<u>Blood</u>		<u>Urine</u>
		<u>Mg. Pb Per 100 Grams</u>		<u>Mg. Pb Per Liter</u>
		<u>Spectrographic</u>	<u>Dithizone</u>	
8-12	12:30 P. M.	0.08	0.06	
8-12	1:00 P. M.			0.03

8-14 through 8-18 - Treatment with Calcium Disodium Versenate (EDTA)

8-14	1:45 P. M.	-	0.06	
8-15	8:00 A. M.			0.20
8-15	8:00 A. M.			0.15
8-15	9:00 A. M.			0.11
8-15	11:10 A. M.			0.46
8-15	11:30 P. M.			0.52
8-16	10:30 A. M.	-	0.04	
8-16	11:20 P. M.			0.28
8-17	1:40 P. M.			0.05
8-18	12:40 A. M.			0.07
8-18	8:25 A. M.			0.12
8-18	11:00 A. M.	0.05	0.04	
8-18	8:15 P. M.			0.08

Treatment with Calcium Disodium Versenate Discontinued

8-19	10:30 A. M.			0.22
8-19	8:00 P. M.			0.09
8-20	12:20 P. M.			0.08
8-21	8:00 A. M.			0.09
8-22	3:00 A. M.			0.05
8-23	1:45 A. M.			0.09
9-11	11:00 A. M.	0.06	0.03	
9-12				0.07
9-13		0.08	0.06	

TREATMENT OF ACUTE TETRAETHYL LEAD INTOXICATION

Case [REDACTED] - Age 28

Bank Cleaning.

Severe intermittent exposure for two weeks.

Severe poisoning.

Admitted to hospital on fourth day after stopping work.

Agitated, garrulous, confused, visual and auditory hallucinations.

Date <u>1951</u>	Time <u>Time</u>	Blood		Urine
		Mg. Pb Per 100 Grams		Mg. Pb Per Liter
		<u>Spectrographic</u>	<u>Dithizone</u>	
8-2	1:00 A.M.			0.49
8-12	10:00 A.M.	0.06	0.06	
8-12	1:21 A.M.			0.30
8-13 through 8-20 - Treatment with Calcium Disodium Versenate (EDTA)				
8-13	9:45 A.M.	0.04	0.02	
8-14	2:30 P.M.	0.04	0.02	
8-15	1:00 P.M.			0.35
8-16	10:25 P.M.			0.77
8-16	1:20 P.M.			0.20
8-16	1:45 A.M.			1.05
8-16	10:30 A.M.	0.03	0.05	
8-17	1:20 P.M.			1.09
8-17	9:00 A.M.			0.33
8-17	1:45 P.M.			0.24
8-17	4:40 P.M.			0.45
8-18	8:00 A.M.			0.45
8-18	3:55 A.M.			0.59
8-19	11:15 A.M.	0.05	0.05	
8-20	7:30 A.M.			0.25
Treatment with Calcium Disodium Versenate Discontinued				
8-21	5:30 A.M.			0.22
8-22	9:00 A.M.			0.24
8-23	9:30 A.M.			0.24
8-24	9:30 A.M.			0.28
8-27	5:30 A.M.			0.21
9-11		0.03	0.03	
9-12				0.08
9-13				0.05
9-15		0.03	0.04	0.03
9-17				1.05
9-19				0.29
9-20				0.08
9-22				0.04
10-10		0.05	0.04	0.03
11-1				0.05
11-2		0.03	0.04	0.07

TREATMENT OF ACUTE TETRAETHYL LEAD INTOXICATION

Case [REDACTED] - Age 36

Engaged in tank cleaning.

Severe intermittent exposure for two weeks.

Severe poisoning.

Admitted to hospital for observation on fourth day after stopping work, agitated, confused, disoriented.

Sudden onset of convulsive seizure and delirium.

<u>Date</u>	<u>Time</u>	<u>Blood</u>		<u>Urine</u>
		<u>mg. Pb Per 100 Grams</u>		<u>mg. Pb Per Liter</u>
		<u>Spectrographic</u>	<u>Dithizone</u>	

8-12 through 8-23 - Treatment with Dithiopropanol (DAPL)

8-12	11:00 A. M.	0.07	0.07	0.32
8-12	1:55 P. M.			2.5
8-13	2:30 A. M.	0.08	0.08	
8-13	2:15 P. M.			2.34
8-14	8:00 A. M.			1.8
8-14	10:20 A. M.	0.05	0.05	
8-17	6:20 A. M.			1.1
8-18	7:10 A. M.			1.7
8-18	10:10 A. M.			1.9
8-18	11:00 A. M.	0.06	0.04	
8-19	10:10 A. M.	0.03	0.04	
8-19	12:00 Noon			0.30
8-20	11:05 A. M.			1.72
8-21	12:25 A. M.			1.35
8-22	7:00 A. M.			2.63
8-23	1:20 A. M.			1.14

Treatment with Dithiopropanol Discontinued

9-11		0.04	0.06	
9-13		0.06	0.04	
9-13				0.13

TREATMENT OF ACUTE TETRAETHYL LEAD INTOXICATION

Case [REDACTED] - Age 36

Tank cleaning.

Severe intermittent exposure for two weeks.

Severe poisoning.

Admitted to hospital on fourth day after stopping work.

Excited, confused, muscular twitching face, arms, and legs; auditory and visual hallucinations.

Date	Time	Blood		Urine
		Mg. Pb Per 100 Grams <u>Spectrographic</u>	<u>Estimation</u>	

Supportive and Relative Treatment Only

8-12	10:00 A.M.	0.07	0.04	
8-12	2:20 P.M.			0.70
8-13	10:00 A.M.	0.08	0.03	
8-14	12:00 Noon			0.60
8-14	2:00 P.M.	0.07	0.03	
8-15	3:20 P.M.			1.00
8-16	8:30 A.M.			0.62
8-16	9:00 A.M.			0.30
8-16	10:30 A.M.		0.06	
8-16	1:00 P.M.			0.33
8-16	3:30 P.M.			0.31
8-17	8:30 A.M.			0.23
8-17	1:00 P.M.			0.25
8-17	2:45 P.M.			0.27
8-17	4:55 A.M.			0.16
8-17	11:30 P.M.			0.22
8-17	11:30 A.M.		0.06	
8-19	1:35 P.M.			0.13
8-19	7:00 P.M.			0.21
8-20	10:20 A.M.			0.17
8-21	8:00 A.M.			0.14
8-22	5:00 A.M.			0.18
8-23	7:35 A.M.			0.20
9-11	11:00 A.M.	0.06	0.08	
9-12				0.08
9-13		0.04	0.04	

TREATMENT OF ACUTE TETRAETHYL LEAD INTOXICATION

Case - Age 22

Engaged in tank cleaning for one week.

Intermittent brief exposure.

No clinical signs of poisoning.

Results of repeated analyses of samples of blood and urine within the normal range.

Many subjective complaints, including dizziness, weakness, nausea, insomnia, loss of appetite.

<u>Date</u>	<u>Time</u>	<u>Blood</u>		<u>Urine</u>
		<u>Mg. Pb Per 100 Grams</u>		<u>Mg. Pb Per Liter</u>
		<u>spectrographic</u>	<u>Diethizone</u>	

No Treatment Given - No significant Exposure to Tetraethyl Lead

8-13	11:30 P.M.	0.06	0.04	0.07
8-14	1:03 P.M.	0.04	0.04	
8-16	9:20 P.M.			0.03
8-16	12:10 P.M.	0.04	0.04	0.08
8-18				0.10
8-18		0.04	0.04	0.07
8-18		0.04	0.04	0.08
8-17		0.03	0.04	0.10
8-18				0.06
8-18				0.05
8-17				0.03
8-20				0.06
8-21				0.05

The analytical data obtained in two other cases of tetraethyl lead poisoning are presented for comparison with the group that was treated with calcium disodium versenate. Repeated doses of diethylenetriamine (DET) were administered by intramuscular injection to one of these patients. The other received only supportive and symptomatic therapy.

A case of anxiety neurosis that developed in a member of the group who had negligible exposure is included here to demonstrate the normal levels of the analytical results.

Notwithstanding the fact that complete recovery will follow in the majority of cases of tetraethyl lead intoxication with prompt institution and faithful maintenance of good nursing care, adequate physical restraint and symptomatic sedative and supportive therapy, the illness is often grave, and it tends to persist with apparent remissions until much of the absorbed lead has been eliminated from the body. Any agent that will reduce the severity and shorten the course of the illness would be useful. The basis for the therapeutic use of calcium disodium versenate lies in the beneficial effects that may follow the formation of a chemically inert complex in the soft tissues of the body and in the increased excretion of lead which follows. That the latter occurs following the absorption of tetraethyl lead, as well as inorganic compounds of lead is gratifying, and offers hope that a beneficial effect can be achieved by this means.

While it is obvious that no valid conclusions can be drawn as to the useful therapeutic effects of calcium disodium versenate from a review of these cases, it may be said that the drug was well tolerated. No harmful effects of any kind were observed. No significance may be attached to

transient periods of clinical improvement in association with increase in the elimination of lead, since such episodes have been observed frequently in cases in which no specific therapeutic agent had been administered.

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