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UNANSWERED QUESTIONS IN METAL CHELATION

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Chelation for heavy metal intoxication has been practiced in various forms for approximately 40 y. The collective experience of clinicians and laboratory investigators is quite extensive. However, there are many questions that remain unanswered and need to be addressed.

One of the most fundamental questions is: "Does chelation improve the clinical outcome of intoxicated patients?" I have subtitled this: "Does excretion equal efficacy?", because the primary basis on which chelation has been used over the past four decades has been the demonstration that chelation can increase the urinary excretion of metals. This is particularly true of lead intoxication. Somewhat surprisingly, however, there is a paucity of data documenting efficacy in terms of clinical outcome. For instance, do more chelated individuals survive a severe intoxication than individuals who have not been chelated? Is there improvement or reversal in CNS deficits or renal damage in individuals who have undergone chelation compared to those

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that have not? Is there prevention or reversal of anemia in individuals who have undergone chelation? There is little information available to address these questions.

For the chelators British Anti-Lewisite (BAL) and ethylenediaminetetraacetic acid (EDTA), which have been entrenched in use since the 1950s, it is understandable that the Food and Drug Administration (FDA) did not require the pre-approval studies that might apply to a drug introduced today. However, how should we react to the FDA's approval of dimercaptosuccinic acid (DMSA, succimer), for use in childhood lead poisoning without any data that indicates it is superior to placebo with respect to human clinical outcomes? I would like to review the data that suggests or does not suggest that chelation has clinical efficacy, and then turn to the pharmacokinetic aspects that might indicate which patients are the prime candidates to receive chelation.

Let's begin our story where chelation began. That is World War II in England, in a British laboratory in which Stockton and Thompson were quite concerned over the possible use of dichlorovinyl arsine, known as lewisite, as a toxic agent in warfare. Lewisite is a very potent vesicant and a highly toxic multisystem agent. Dimercaprol (2,3 - dimercaptopropanol, British Anti-Lewisite, or BAL) is a disulfide that was initially prepared as a topical agent in oil to avert the toxicity of lewisite. When used in animals which were exposed topically to lewisite, BAL improved survival. Animals that were treated with BAL had 100% survival, while those treated with a monothiol, 2-mercaptoethanol, did not survive (1). Other experiments demonstrated that BAL prevented the decline in oxygen uptake associated with inhibition of pyruvate dehydrogenase by lewisite (1).

Animal studies have revealed a very important time dependence to the efficacy of BAL in averting the lethality of arsenic. One injection of BAL given five minutes after exposure to arsenic resulted in 100% survival, but multiple injections begun six hours after exposure were ineffective (2). Doctor Aposhian's lab found a similar pattern of time dependence for the efficacy of DMSA in treating lethal doses of sodium arsenite. In his laboratory, the survival rate was 79% when DMSA was administered at 60 min, but dropped to 55% when it was administered at 2 h (3). If DMSA had been given several hours later, survival would likely have declined further.

Is there human data that support the use of BAL in the treatment of arsenic intoxication? Lewisite was never used during World War II, but there was another scourge the soldiers suffered from and that was syphilis, perhaps encountered shortly after the victory. Many of the agents used to treat syphilis in the pre-penicillin era were organic arsenicals such as arsphenamine. Many of the patients who underwent treatment with these organoarsenical anti-syphilitic agents suffered side effects that were attributed to arsenic intoxication. The first clinical use of BAL in humans occurred in individuals suffering from a side effect known as arsenical dermatitis (4). An early report of 37 cases treated with BAL found the mean duration of arsenical dermatitis to be 21.5 days, compared to 62.5 days in untreated historical controls (5). In 1948, pediatricians in New Orleans reported the first case series of children treated with BAL for arsenic ingestion (6). The hours that patients were symptomatic, the hospital length of stay, and the death rate in patients treated with BAL was compared retrospectively to patients who had been admitted but never chelated. We can see from this chart (Table 1) that in the 111 patients not receiving BAL, there were three deaths, and an average length of stay of 4.2 d. About half of the patients were symptomatic on admission, and 29% remained symptomatic after 12 h. When Woody and Komentani began using BAL, they encountered no deaths in 42 patients. Patients had a shorter length of stay, and the 47% that were symptomatic on admission had no symptoms at 12 h (6). You can imagine the uncertainties in comparing one historical case series to another, but this is about as rigorous as the data ever gets in terms of clinical experience with BAL in the treatment of human arsenic intoxication.

The ability of BAL to avert peripheral neuropathy following acute arsenic intoxication has been variable. There are no controlled trials that have looked at this outcome. As with other clinical endpoints, most of the data which might support the use of BAL stem from case reports published over the past three decades. In some episodes of symptomatic acute arsenic poisoning with documented high urine arsenic levels, neuropathy has not occurred when BAL was begun within 24 h. However, in other cases, neuropathy or death has ensued despite early treatment. There is no evidence that established neuropathy is improved by the use of BAL. Nevertheless, the

TABLE 1

Treatment of Childhood Arsenic Ingestion with BAL: Comparison to Historical Controls

	N	Deaths	Avg LOS Days	Symptomatic (%) On Admit	at 12 h
Without BAL	111	3	4.2	46.2	29.3
With BAL	42	0	1.6	47.6	0

drug has been used without hesitation in individuals with arsenic intoxication. We have little else to rely on in terms of its value in human poisoning.

What about mercury? Here again our use of BAL is based on early studies conducted in the 1940s. BAL was used to treat a series of patients who presented at Johns Hopkins after attempting suicide by ingestion of mercuric bichloride. Small tablets of this compound were widely available over the counter as a laundry disinfectant. Ingestion of these tablets was apparently a common way of attempting suicide. Longcope and Luetscher compared the clinical outcome of patients treated with BAL within four hours of ingestion of greater than 1 g of mercuric chloride to historical controls from the preceding decade who had not been treated with BAL. In the group of 86 patients not treated with BAL, the mortality rate was 31.4%, compared to zero deaths among the 41 patients that were treated with BAL (7). Most of the untreated individuals who expired from mercury poisoning died of renal insufficiency. Others succumbed to severe hemorrhagic gastroenteritis. With publication of this paper, BAL was adopted into use for mercury intoxication. I am unaware of any similar case series or controlled trial that may have been performed in the subsequent 40 y.

What about lead? With the enthusiasm and interest generated by the use of BAL in the treatment of arsenic and mercury poisoning, it was natural that early investigators would turn to its use in lead poisoning. Studies at that time found that BAL increased the urinary excretion of lead both in rabbits and humans. In rats, it increased the urinary as well as the fecal

excretion of lead. However, it was noted in some lab investigations that BAL actually increased the toxicity of lead. For example, this data (Table 2), shows the effect of BAL on the survival of rabbits poisoned with lead acetate 240 mg/kg subcutaneously for 5 d (8). The control animals did not receive BAL and their mean survival was 26 days. However, as one started administering BAL, survival dropped off dramatically. This dampened the enthusiasm for the use of BAL in lead poisoning. In addition, there were case reports in the early 1950s suggesting that use of BAL as a single agent in the treatment of human lead intoxication did not result in a dramatic response. Because of this, it did not gain widespread use. Instead, use of calcium disodium EDTA, first reported in 1952 (9), became more popular. What the early reports established was that calcium EDTA did produce a dramatic increase in the urinary excretion of lead. Calcium EDTA also tended to reverse inhibition of aminolevulinic acid (ALA) dehydratase, an enzyme particularly sensitive to the effects of lead. Because of these two findings, the drug began to be used widely.

Where, however, are the data from animal systems demonstrating that chelation, aside from just increasing urinary lead excretion and rejuvenating the enzyme ALA dehydratase, was able to actually increase survival or produce other beneficial effects? Roderer studied the survival of unicellular algae cell cultures grown either in the presence of lead or without the presence of lead, and with or without the addition of a chelator (Figure 1) (10). Inorganic lead alone decreased survival of the algae. At the highest dose, EDTA alone was also toxic. This may have been due to zinc chelation by the EDTA. When EDTA was added to inorganic lead, there was a protective effect. Interestingly, EDTA increased the cytotoxicity of inorganic lead, and BAL increased the cytotoxicity of both inorganic lead and organic lead.

What models exist in mammals that demonstrate a benefit, in terms of survival, from the use of chelators in lead poisoning? In searching the literature, one finds a paper by Hofmann and Segewitz which reported the percent survival of rats dosed with lead at either 20 mg/kg or 50 mg/kg i.p. for 5 d (Table 3) (11). Some of these animals were then treated with either calcium DTPA, which is an analog of EDTA, D-penicillamine, or

TABLE 2

Effect of BAL on Survival of Rabbits Poisoned with Lead Acetate*

Dose of BAL (mg/kg) per injection	Total	Mean survival (d)
0	0	26
5	100	15
10	200	12
20	400	3

*240 mg/kg sc x 5 d

dimercaptopropane sulfonate (DMPS), a dithiol somewhat similar to DMSA. At the lower dose of lead, survival was approximately the same in the control group and the groups treated with chelators. At the higher doses of lead, we again see that none of the chelators was effective. The slight increase in percent survival with D-penicillamine was not statistically significant. The chelator dose, 100 μmol/kg, was somewhat low compared to a typical human regimen. On a weight basis, the DMPS dose was approximately 18 mg/kg/d, compared to 30 mg/kg/d that has been used in humans. Likewise, the DTPA dose was equivalent to 30-40 mg/kg/d of EDTA, also somewhat lower than the highest doses used in humans. It should be noted that at these doses the chelators did increase the urinary output of lead and did diminish urinary excretion of ALA, but when it came to survival, no benefit occurred.

It's also worth noting that the chelators in Hofmann's study were no different from placebo in preventing or reversing the decline in hemoglobin associated with lead intoxication (Figure 2) (11). This is an important endpoint to examine considering that much of the literature has cited the ability of EDTA or other chelators to prevent lead induced inhibition of ALA dehydratase, a heme pathway enzyme, as a therapeutic benefit.

What is the evidence that chelation is efficacious in human lead intoxication? Here we have to rely on historical trends, case series and clinical experience. As Dr. Chisolm's work has pointed out, there have been

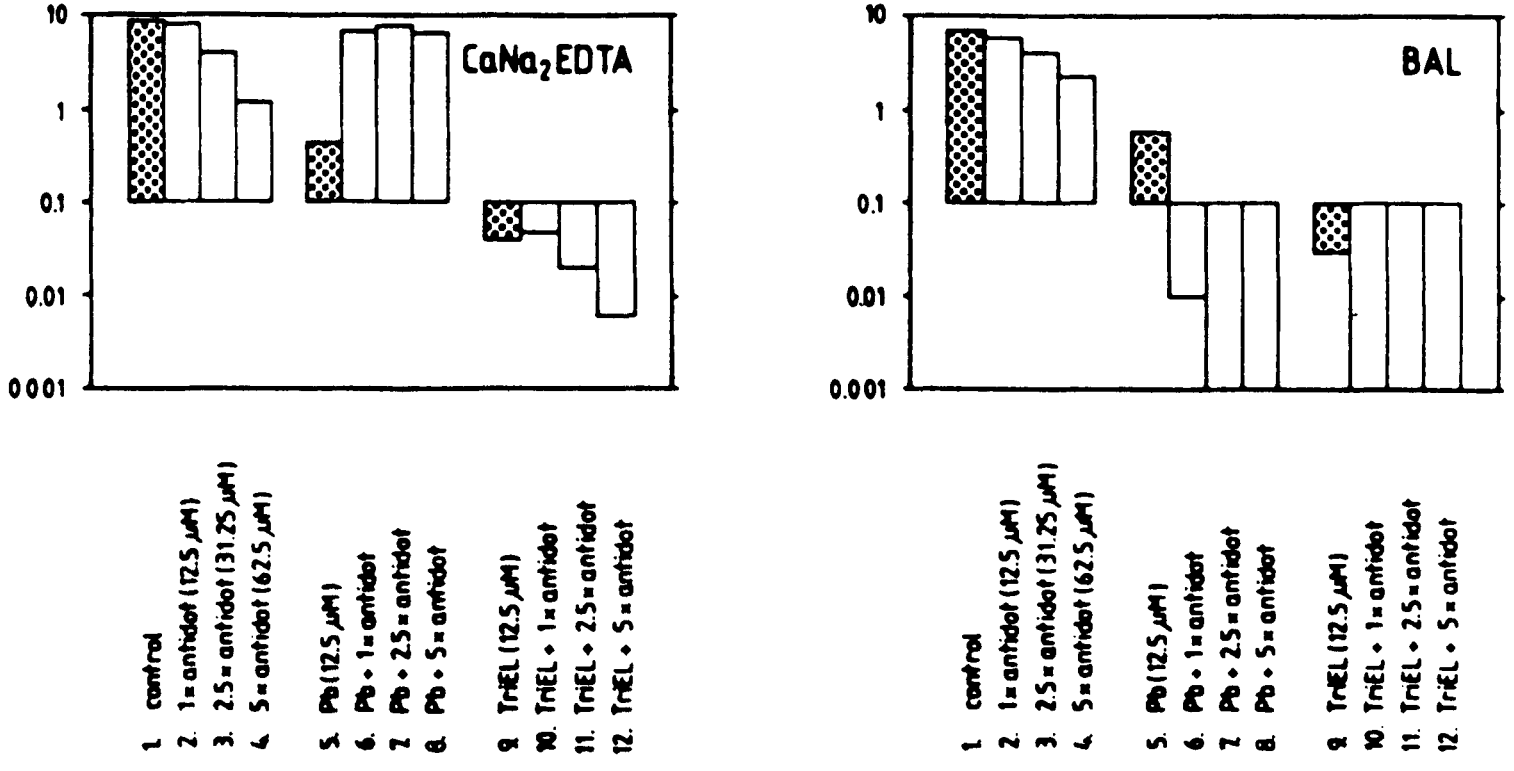

Figure 1. Influence of lead-antidotes and related compounds on toxicity of Pb and TriEL to *P. malhamensis*. Reprinted with permission from *Chem Biol Inter* 1983;**46**:247-254 by copyright permission of Elsevier Science Publishers.

TABLE 3

Effect of Chelation on Survival of Rats Poisoned with Lead Acetate

Chelator (100 μmol/kg ip) 5 d/wk x 5	Pb dose (mg/kg) 5 x 20 % survival	days	5 x 50 % survival	days
Control	18/23 = 78	18.2	1/20 = 5	20.5
CaDTPA	18/24 = 75	25.5	3/20 = 15	21.0
D-Pen	20/24 = 83	20.6	5/20 = 25	18.0
DMPS	18/23 = 78	18.8	1/20 = 5	19.2

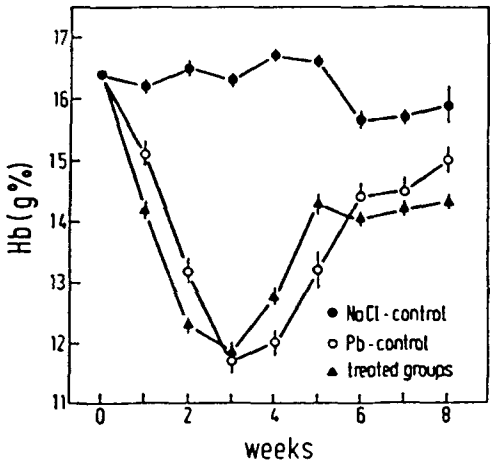

Figure 2. Dependence of hemoglobin on time. Reprinted with permission from *Arch Toxicol* 1975;**34**:213-225 by copyright permission of Springer-Verlag Berling Heidelberg.

tremendous strides in our ability to treat lead encephalopathy. Prior to chelation, lead encephalopathy had a 60% fatality rate. In the 1950s, when BAL or EDTA were used in the treatment of lead encephalopathy, there was approximately a 30% mortality rate. In the 1960s, particularly in Dr. Chisolm's experience in using BAL in conjunction with EDTA, mortality fell to less than 5% (12). However, there were major advances in supportive medical care between the 1940s and 1960s, and the decline in mortality cannot necessarily be attributed to the use of chelation alone. The introduction of intensive care units and critical care innovations such as mannitol for the treatment of elevated intracranial pressure may have substantially contributed to the improved outcome.

If we rely on anecdotal reports to determine whether EDTA is effective in acute human lead intoxication, we see a mixed picture. There are reliable reports that EDTA can rapidly alleviate lead colic in adults (13,14). However, there are also anecdotal reports that EDTA may worsen lead encephalopathy in children (15). Recent data indicating that EDTA might redistribute lead into the central nervous system may account for this adverse outcome (16).

What about other, softer, endpoints? Today, we are not so much interested in severe outcomes such as death and encephalopathy, but we are looking at more chronic, low level effects such as renal insufficiency or subtle neurological deficits. Wedeen generated some enthusiasm in the late 1970s from an uncontrolled case series of EDTA treatment in eight men he diagnosed with preclinical lead nephropathy (17). The men, age 28 -54, had worked in various trades involving exposure to lead. On initial laboratory evaluation, they had a low glomerular filtration rate (GFR), a serum creatinine in the normal range or mildly elevated, and moderately elevated blood lead concentrations, between 20 to 69 μg/dL. All had a positive EDTA provocation test. The intervention consisted of chelating these individuals with calcium EDTA three times a week for periods ranging from six months to four years. The outcome was inconclusive. Four of the patients showed an improvement of GFR greater than 20%, two had a worsened GFR, and two had no change. Subsequently, it was noted that one patient who had improved initially developed hypertension and gout, with a

deterioration in GFR. It's not very convincing evidence to establish a beneficial role for EDTA chelation in reversing lead nephropathy.

What about the effect of lead chelation on neurological endpoints in adults? Here again there are no randomized, placebo controlled, trials of chelation. The importance of a placebo-controlled trial is underscored by the fact that many of the neurological deficits associated with lead will reverse simply by removal from exposure. For example, eight demolition workers were removed from work after five months of exposure to lead. They had mild decrements in their nerve conduction velocity at the time of removal. Fifteen months later, after their mean blood lead concentration had fallen from 80 to 28 μg/dL, their conduction velocity had improved (18). If these individuals had been chelated, it might have been said that the chelation was responsible for the improvement. However, we know that the improvement occurred naturally. Likewise, in one of the few studies that has prospectively studied neuropsychological function in lead-exposed workers, there was a decline in workers' exposure concurrent with the implementation of the OSHA lead standard at a particular foundry. Serial neuropsychological evaluations performed over three years showed an improved mood profile in the workers, such as decreased anger and depression (19). The improvement was associated with a decline in blood lead concentrations. However, there was also a substantial improvement in the work environment, so it may not be surprising that the mood of the workers improved.

Can we consider a more controlled model in which there are fewer variables to consider? Cory-Slechta and Weiss recently published an interesting paper in which they described the effect of chelation in a well-designed rat model of low level lead neurotoxicity (20). The study consisted of exposing young rats to 50 ppm lead acetate or 50 ppm sodium acetate in drinking water for 34 d. The animals were then placed in a cage where they received a food pellet after pressing a lever. Pellet release is limited to one pellet/min. After a while, normal rats learn to space their lever pushing to about one minute intervals because they learn that even if they push more frequently, they are only going to get a pellet at one minute intervals. In this model, the lead-exposed animals pushed the lever excessively at short time intervals. They did not learn to wait the full minute. Some of the lead

exposed animals were more affected than others. The investigators matched the animals by their performance and then randomized them to receive either EDTA or placebo. The result was that EDTA failed to reverse the lead-induced behavioral deficits and, in fact, may have exacerbated them.

Are there any human trials in which someone has randomized children with low level lead exposure to either EDTA or penicillamine versus. placebo? I located one brief report of a case series from Mexico (21). The authors identified 15 children, ages 4-10 y, with a diagnosis of hyperactivity and attention deficit disorder. Six of the children had elevated blood lead concentrations of 21-33 μg/dL and nine of the children had normal lead concentrations of 6-16 μg/dL. The children with elevated lead concentrations were treated with D-penicillamine at a dose of 25 mg/kg twice a day for 10 d. The other children received placebo. Blood lead measurements and psychiatric assessments were conducted before treatment and two weeks post-treatment. A psychiatrist blinded to the treatment performed all the psychiatric assessments. D-penicillamine induced a decline in the blood lead concentration from 26 to 12 μg/dL. Five of the six children in the D-penicillamine group were found to have behavioral improvement, compared to only 1 of 9 children in the placebo group. The limitations of this study are its small numbers and the fact that the criteria used in defining improvement were not disclosed. We really cannot conclude much from this study except to note that a suggestion of benefit exists. As you have heard, there has been talk of potentially treating thousands of children for low-level lead toxicity because of impairment in central nervous system function. However, we still lack data to show that lead-induced impairment responds to treatment.

Lead chelation has existed for forty years, yet we have a dearth of good clinical data to indicate efficacy. We are now on the verge of having available an oral drug, DMSA, for childhood lead poisoning. Once licensed for one use, it will be available for any use. The release of DMSA comes at a time when there is increasing national attention on the hazards of lead. Questions will flow into Poison Centers asking who should be treated with what and for how long.

How should we respond when asked if there is any therapeutic benefit to lead chelation? We really cannot say, but if we assume that removal of lead by chelation is beneficial, what is a rational approach to selection of the

appropriate patient? The first patients we think of are those with high blood lead concentrations. The blood lead concentration reflects the lead burden in two main body compartments. There is a soft tissue compartment which comprises 5-10% of the total body lead in adults, and perhaps up to 30% in children. This so-called fast compartment has a half-life of approximately 40 d. The skeleton contains 90-95% of the body lead burden in adults. It is a slow compartment, with a half-life of 1 to 5 or more years depending on whether you are looking at trabecular bone or cortical bone.

Figure 3 depicts the blood lead concentration against time after removal from exposure. There is a relatively rapid decline in blood lead initially, followed by a slow decline over the course of several years. This reflects a rapid elimination of lead from the soft tissue compartments, and then a much slower elimination of lead from the deeper compartments in bone. We can see that not all high blood lead concentrations are created equal. The decline in lead concentration with time can be vastly different depending on the amount of lead in these different compartments. For instance, consider two individuals with an equally high blood lead concentration, say 60-80 μg/dL. The individual who had brief, heavy exposure to lead will undergo a rather rapid decline in his or her blood lead concentration, and then appear to level off at a low value, perhaps 10-20 μg/dL. The individual with chronic exposure will also show a rapid initial decline, but will then plateau at a much higher level, perhaps 40-60 μg/dL (Figure 3). The work of Schutz's group suggests that approximately two-thirds of the blood lead concentration in individuals with chronic occupational exposure reflects lead in slow bone compartments (22). So, the simple notion that blood lead reflects recent exposure and always declines with a half-life of 40 days is not really borne out by these studies.

What happens when we chelate an individual? Where are we taking the lead from? Several studies indicate that chelatable lead comes predominantly from the soft tissues, with a smaller, but significant contribution from trabecular bone, and compact bone (23). In the body, 80% of the bone is cortical bone, and only 20% is trabecular bone. However, the blood supply of trabecular bone and cortical bone is approximately equal. How is this reflected when we look at the decline in blood lead concentration

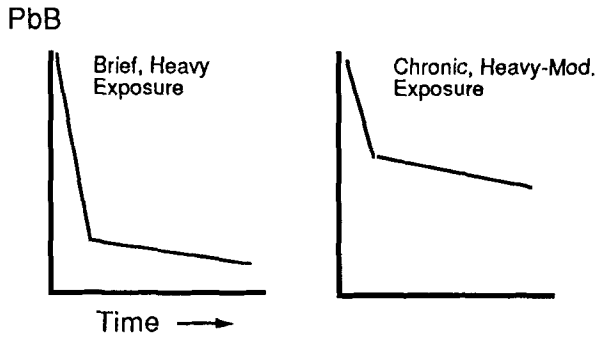

Figure 3.

from chelation? Individuals who undergo repeated courses of chelation over long periods will show a rapid decline in blood lead during the initial course of chelation, but will experience less of an impact on their blood lead from subsequent courses of chelation (24).

Why does the blood lead concentration fall less dramatically during the later courses of chelation? Re-equilibration of lead from bone stores into the blood results in a rebound effect. Consider this data from work by Graziano, in which he used DMSA and EDTA to chelate adult men with chronic lead exposure (Figure 4) (25). There was an initial decline in blood lead during the treatment period. When treatment was stopped, there was a rebound upward. Blood lead measurements were not reported beyond 20 days, but it is possible that further rebound may have occurred. The amount of lead typically excreted during a five day treatment may be on the order of 5-10 mg, which is minimal compared to a body burden in the skeleton that may be 500 to 1000 mg.

In fact, you can have normalization of urinary lead excretion after repeated courses of chelation, despite the fact that the patient may still have a significant amount of lead in the body. For instance, Germain described an individual with renal insufficiency who underwent 12 consecutive weeks of chelation (26) Before chelation, a positive EDTA challenge test resulted in 1157 μg of urinary lead per 72 h. After 12 wk of repeated chelation, a follow-up EDTA challenge test produced 196 μg of lead in 72 h. This latter

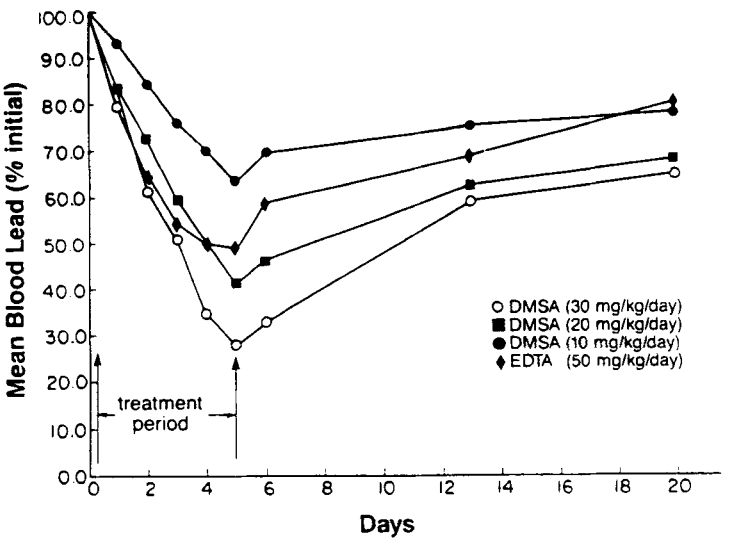

Figure 4. Reprinted with permission from *Med Toxicol* 1986;1:155-162 by copyright permission of ADIS Press Limited.

value would be considered a negative test. Nevertheless, when this patient expired ten weeks later, an autopsy specimen showed a markedly elevated amount of lead in the bone.

Can we use what we know about rebound as a guide to the duration of chelation? Some data suggest that if a significant post-chelation rebound occurs after a five-day treatment period, the patient has a preponderance of lead in the slow pools, and chelation will have a minimal impact on the total body lead stores or the blood lead half-life. This is characteristic of chronic, heavy exposure. We might look for this pattern of rebound as an indication that we are not going to accomplish much by chelating these individuals.

On the other hand, in the absence of rebound, repeated courses of chelation may be useful to clear the fast compartment and significantly reduce the body lead burden. These individuals most likely had brief, intense exposure and do not have much lead in their skeleton. Who else, besides individuals with acute exposure, may not have a lot of lead in their skeleton? The answer is young children, in whom the skeleton is incompletely mineralized. It is possible that intense chelation in children may reduce their

body burden. But the prospects would appear less promising in children who demonstrate pronounced rebound over several chelation courses.

What about x-ray fluorescence? Can this be of value in identifying individuals who have a lot of lead in their slow compartments, and might be subject to significant rebound? X-ray fluorescence involves exposing a superficial bone, such as the tibia, to a low energy x-ray beam and then counting the fluorescence photons. The photon counts can be converted to bone lead concentration. This is a non-invasive measurement of the amount of lead present in the body. The radiation exposure is roughly comparable to a single dental x-ray.

There are two kinds of x-ray fluorescence. Some investigators are using L-shell x-ray fluorescence. When applied to cortical bone, it is limited to measuring lead in the outer one to two millimeters of the bone surface The outer surface of cortical bone may be more metabolically active and may contain lead that is more mobilizable than the lead deeper in bone. A recent study compared a group of lead-poisoned children who were chelated at enrollment and again at six weeks to children with lower initial blood lead concentrations who did not receive chelation (27). In the children who were not chelated, there was a slight decline in blood lead concentration over a six month period. We can presume that efforts were made to remove them from exposure. There was not much change in their urinary lead excretion after EDTA, and there was no significant change in their L x-ray fluorescence. However, children who underwent chelation had a decline in blood lead concentration, a decline in their EDTA challenge test, and a decline in their L x-ray fluorescence measurement six months later. We might expect this because of the good correlation in another study between the lead mobilized by EDTA and the lead detected by L x-ray fluorescence (28).

Other investigators favor the K x-ray fluorescence measurement. This test measures lead throughout deeper layers in the bone. It may have certain advantages with respect to technique and precision. Applied to trabecular bone, such as the patella, K x-ray fluorescence may reflect the more mobilizable lead in the trabecular bone pool. Applied to cortical bone, such as the mid-tibia, it reflects a slower pool of bone lead, and may correlate with long-term, chronic lead exposure.

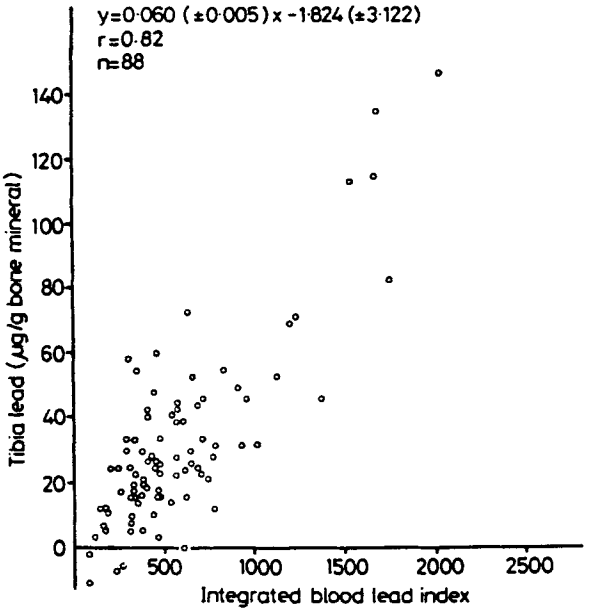

Figure 5. Tibia lead vs time integrated blood lead index for factory B. Reprinted with permission from *Br J Ind Med* 1988;**45**:174-181 by copyright permission of BMJ Publishing Group.

These data were taken from a recent study by Somervaille (Figure 5) (29). K x-ray fluorescence was used to measure tibial bone lead concentration in 88 lead workers. For each worker, a cumulative blood lead index was created by calculating the area under the curve of multiple blood lead measurements obtained over several years. There was good correlation between cumulative lead exposure assessed by the blood lead index, and the tibial lead concentration measured by K x-ray fluorescence. These tools of x-ray fluorescence may give us some insight into what lies behind the blood lead concentration with respect to deeper body compartments.

A significant finding that has emerged from these studies is that chelatable lead is not necessarily an indication of a subject's long-term lead exposure. I particularly direct your attention to a paper by Schutz, who studied active and retired lead workers. Bone lead was measured by K x-ray fluorescence of the phalanx of the finger, and chelatable lead was measured

by urinary excretion after a D-penicillamine challenge (23). He found no correlation between the K x-ray fluorescence bone lead measurement and the lead chelated by D-penicillamine. Active workers, even though they had more chelatable lead, had much lower bone lead. The retired workers had higher bone lead but lower chelatable lead. By combining K x-ray fluorescence with L x-ray fluorescence and blood lead measurement, we may be able to estimate the amount of body lead burden, and predict the response to chelation.

Will individuals with moderate to high blood lead concentrations, but relatively low bone burden by x-ray fluorescence, experience relatively little rebound and be the optimal candidates for chelation? To what extent can high bone lead burdens found by L or K x-ray fluorescence be safely and effectively diminished by long-term chelation? These and many other questions remain to be answered in the future.

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