

TOXICOLOGY OF LEAD ON KIDNEY AND OTHER ORGANS

Dr. Robert A. Goyer
University of Western Ontario

A B S T R A C T

Renal effects of lead in man are of two types. Children with acute lead poisoning have a proximal renal tubular defect characterized by amino-aciduria, glycosuria, and hyperphosphaturia. Adults with chronic lead poisoning have a toxic or interstitial nephropathy with nonspecific morphological changes. Alcohol and dust, apart from renal function, may influence susceptibility to lead intoxication. A case will be presented in which an asymptomatic, former lead worker developed a reversible neuropathy and biochemical features of lead poisoning during an episode of acute alcoholism and low dietary intake.

In this brief presentation, the pertinent renal effects of lead will be summarized and two topics introduced for discussion which, I believe, should receive more study. The first is a possible decrease in the ability of an individual with chronic lead nephropathy to excrete lead, and the second is the role of alcohol, nutrition, and other metabolic factors in alteration of susceptibility to lead toxicity.

First, the pathological effects of lead on the kidney will be reviewed before introducing these two topics.

Figure 1 summarized the morphologic and functional effects of lead on the kidney. There are at least two stages in the development of lead nephropathy. The first stage is an acute reversible effect usually seen only in children. It consists of morphological and functional changes in proximal renal tubular lining cells. These changes include alterations in mitochondrial structure and function, and the formation of intranuclear inclusion bodies or lead-protein complexes. These changes are accompanied by an increase in urinary excretion of amino acids, glucose, and by an increase in urinary excretion of amino acids, glucose, and phosphate. These changes are reversible with chelation therapy and it has recently been shown that the initial large excretion of lead within twelve hours of a dose of EDTA is associated with mobilization of inclusion bodies from nuclei of renal tubular lining cells.

Stage I	Swollen proximal tubular lining cells Mitochondrial changes Nuclear inclusion bodies Proximal tubular dysfunction
Stage II	Fewer inclusion bodies Interstitial fibrosis Tubular atrophy and dilatation
Stage III (rats only)	Renal tumors

Figure 1 Stages of Lead Nephropathy

Whether acute lead nephropathy, treated or untreated, influences the development of any form of chronic nephropathy without continuous lead exposure is uncertain. Follow-up studies of children in this country with documented acute lead poisoning show no evidence of higher incidence of renal disease as adults, so the evidence is that Stage I lead nephropathy is completely reversible.

Stage II nephropathy can be produced in experimental animals by feeding a high dosage of lead for more than a year. Similar changes are found in workmen with excessive lead exposure for more than two or three years. The interstitial fibrosis becomes progressively more severe with tubular atrophy and eventually reduced glomerular filtration and renal failure. This process may progress for many years without renal failure occurring so there are many little known influencing factors. Of course, the actual level of lead exposure and frequency are more important factors of chelation therapy.

With continued feeding of lead to rats, renal tumors occur, but only in rats, and have not been observed in other species of animals or as a result of chronic lead exposure in man.¹

These illustrations show the renal effects being discussed^{2,3}.

An example of stage I or acute lead nephropathy is shown in Figure 2. It is a biopsy from a young man with only eight-months experience as a ship wrecker in Sweden. In his job he burned off heavy layers of lead paint from old naval vessels with an acetylene torch, an occupation that may result in heavy exposure to lead. The nucleus of the proximal renal tubular lining cell contains a lead-protein complex or inclusion body.

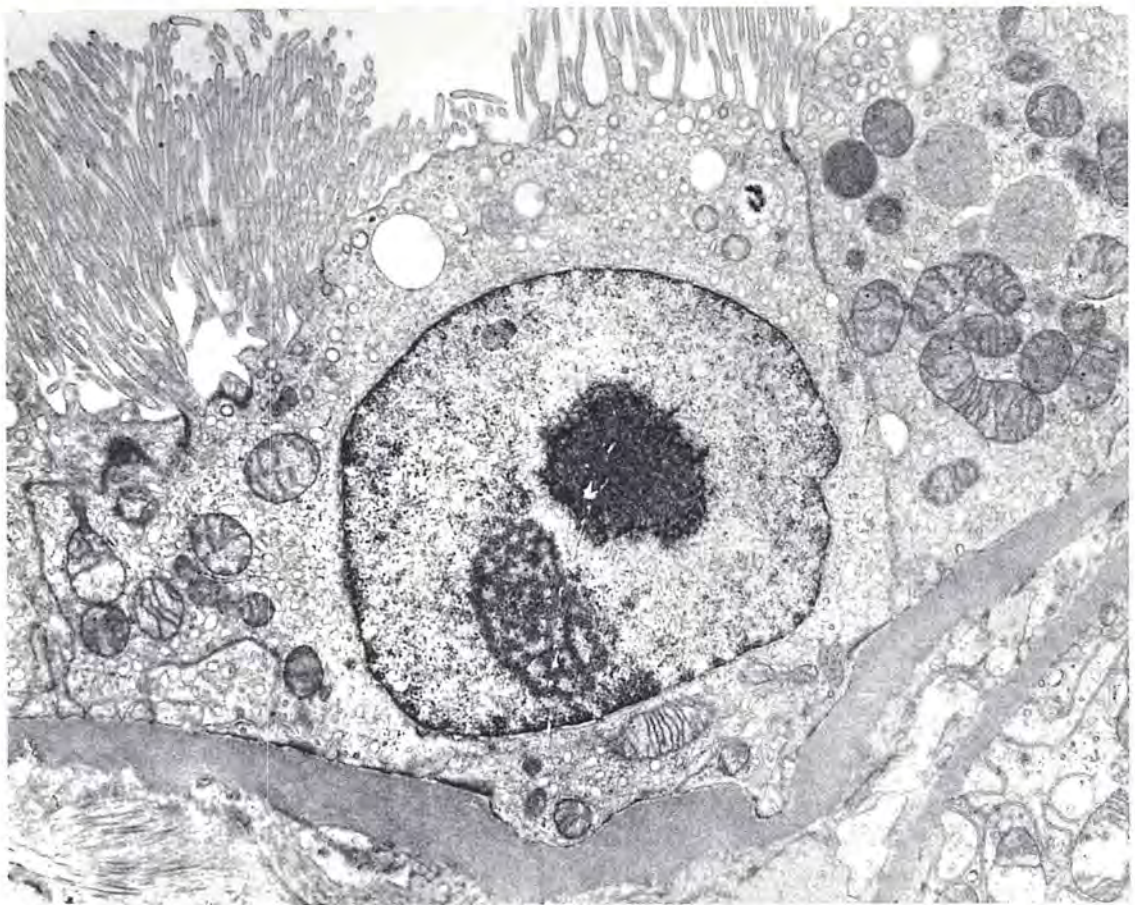


Figure 2 Renal biopsy of a 28 year old shipwrecker shows a dense intranuclear inclusion body characterized by a fibrillary outer margin and independent of the nucleolus. Mitochondria have abnormal arrangement of cristae.

From Cramer, Goyer, et al, *Brit J Indust Med*, 31:113-127, 1974

The abnormal mitochondria are better seen at higher magnification in Figure 3. These mitochondria show swelling, abnormal arrangement of cristae and attempts at cleavage or budding. All of these changes are reversible with EDTA therapy.

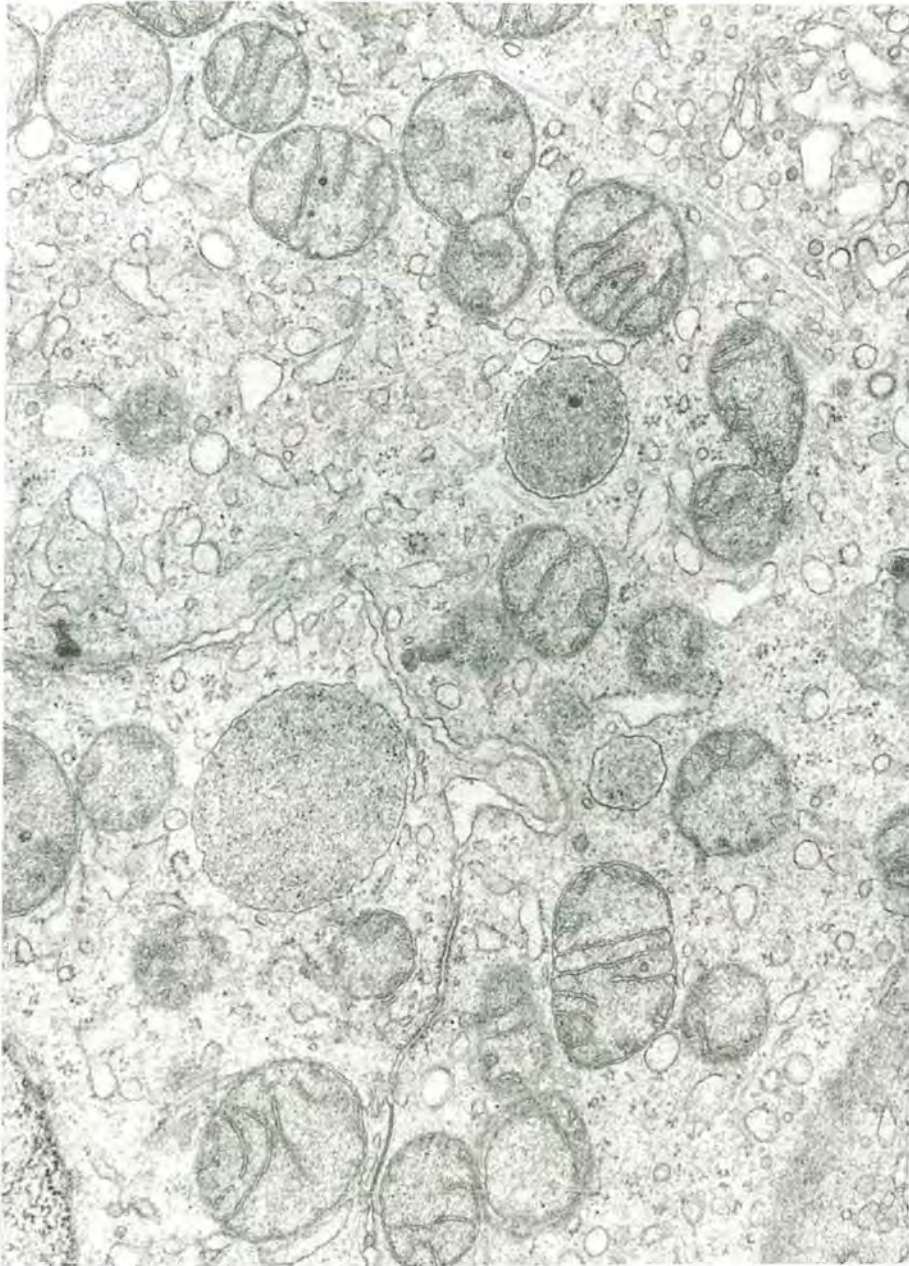


Figure 3 Higher magnification of cells seen in renal biopsy shown in Fig 2. Mitochondria show evidence of cleavage or budding.

From Cramer, Goyer, et al, Brit J Indust Med, 31:113-127, 1974

Figure 4 shows an inclusion body beginning to break up, 24 hours after an injection of EDTA to a lead poisoned rat.

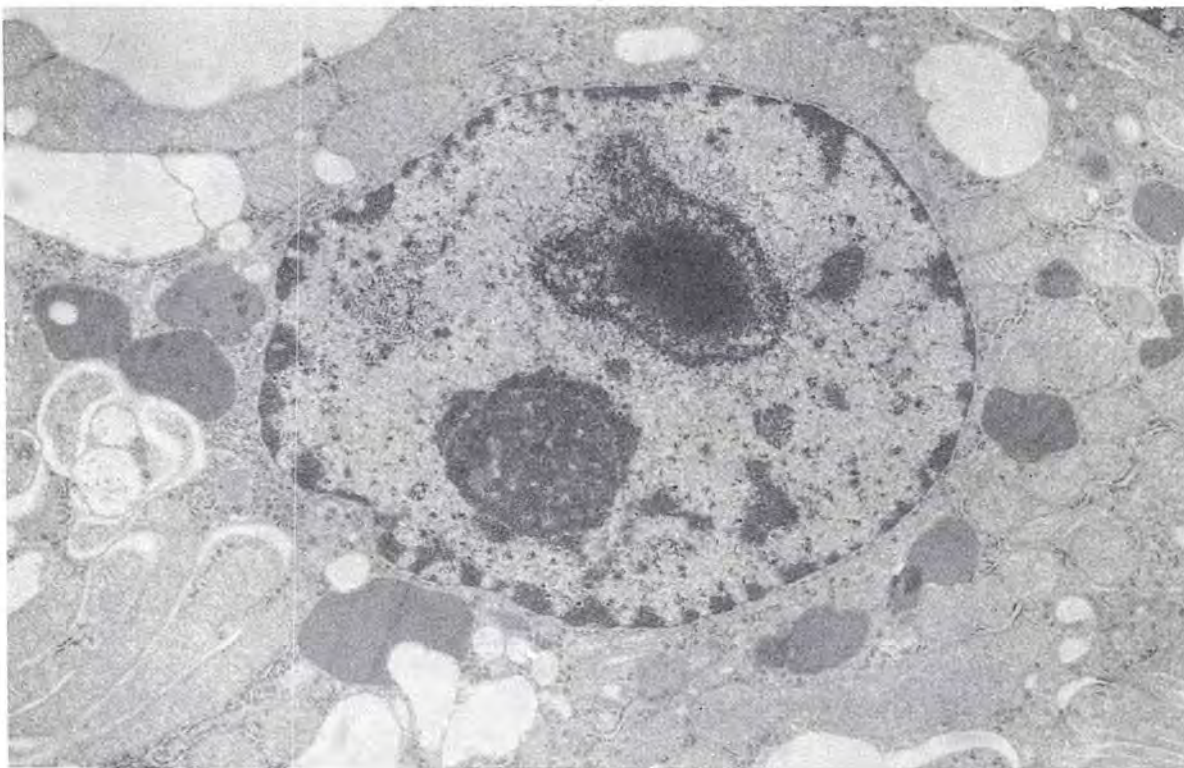


Figure 4 Lead induced inclusion body in the nucleus of a proximal renal tubular lining cell of a lead poisoned rat 24 hours after a single injection of EDTA. There is slight disruption of the periphery of the inclusion, and the fibrillary margin is loosened.

From Goyer and Wilson, Lab Invest, 1975

In Figure 5 there is formation of nucleo-cytoplasmic channel for passage of the inclusion body into the cytoplasm.



Figure 5 Migration of nuclear inclusion body through channel in nuclear membrane of renal tubular lining cell, 24 hours after a single injection of EDTA

From Goyer and Wilson, Lab Invest, 1975

Finally, Figure 6 shows a cytoplasmic vacuole containing a body which looks like a nuclear lead-protein complex.

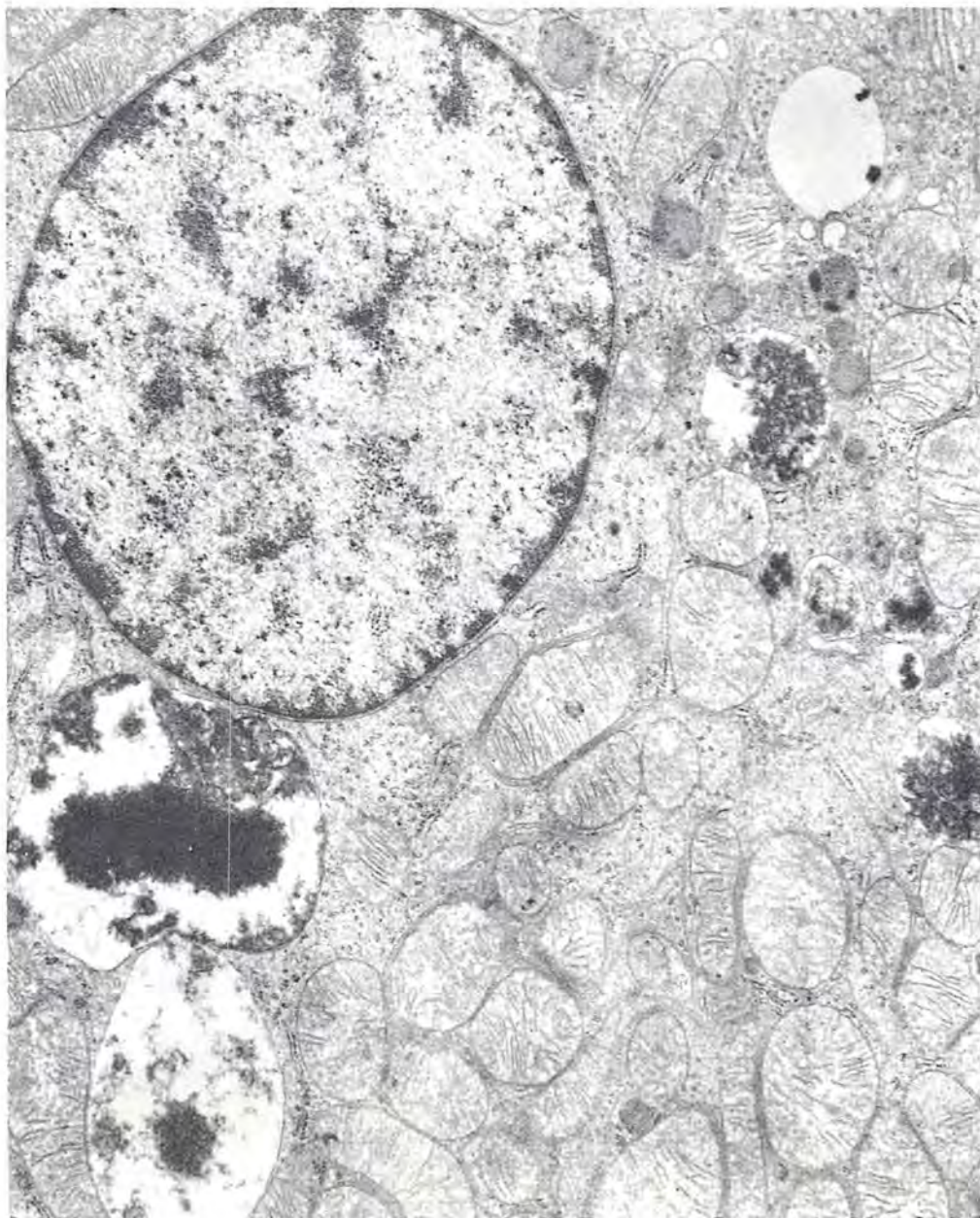


Figure 6 Vacuoles in cytoplasm of proximal renal tubular lining cell, 24 hours after three daily injections of EDTA. The nucleus does not contain an inclusion body. A cytoplasmic vacuole contains a dense body which is probably the remaining portions of a lead-inclusion body following disruption and migration from nucleus.

From Goyer and Wilson, Lab Invest, 1975

There are no inclusion bodies remaining in tubular lining cells after a 72-hour course of EDTA therapy. Also, the mitochondria appear normal and renal tubular function is normal, indicating that acute lead nephropathy is reversible by EDTA. Versenate is a form of EDTA and in view of some comments made this morning, I do not want to imply that it is a completely innocuous substance. Long term or repeated exposure to EDTA does have pathological effects on renal tubular lining cells.

A biopsy from an older workman with chronic lead nephropathy is shown in Figure 7. It shows interstitial fibrosis, tubular atrophy and dilatation, some hyperplasia of cells in functioning tubules and no inclusion bodies. These changes are non-specific.

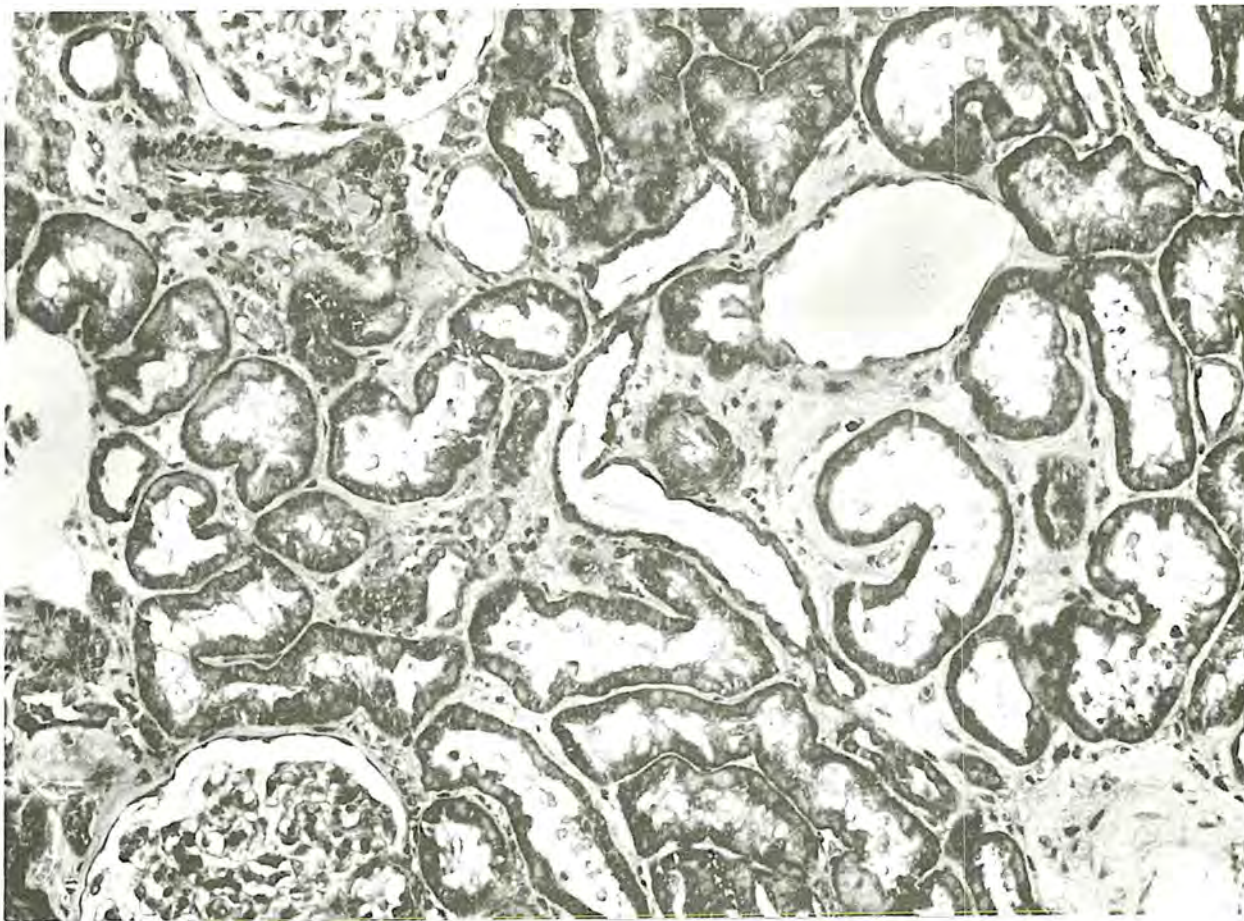


Figure 7 Renal biopsy from a ship-wrecker with many years of excessive exposure to lead. Photomicrograph is from cortex of kidney and shows a diffuse interstitial fibrosis with atrophy of some tubular lining cells.

From Cramer, Goyer, et al, *Brit J Indust Med*, 31:113-127, 1974

Table I is a summary of renal function in five ship workers with different lengths of exposure to lead.

TABLE I
SUMMARY OF RENAL FUNCTION IN FIVE SHIP WRECKERS
WITH DIFFERENT LENGTHS OF EXPOSURE TO LEAD

Age	Exposure in years	Renal Clearance		Pb-B	Pb-U	U-ALA
		mls/min/1.73 ²		µg/100ml	µg/24 hr	mg/100 ml
		Insulin	PAH			
Normal values		125	600	<60	<150	<4
26	8/12	101	596	103	366	4.7
35	6/52	128	888	129	458	4.7
41	12	65	600	138	259	16.4
47	8	108	710	77	263	7.0
66	10	121	693	109	192	5.7

The top line contains normal values. The first two men have acute lead nephropathy, with inclusion bodies. The first man has an 8-month work history; the second man, 6 weeks. The most interesting point here is that the last three men with chronic lead nephropathy by renal biopsy have lower urinary lead excretion per 24 hours than the two with acute nephropathy. This introduces the first point for discussion.

It is an important consideration in terms of whether workmen with chronic lead nephropathy are, in fact, able to excrete lead as readily as individuals with only acute lead effects, and this observation needs further investigation in larger numbers of workmen, as well as information on lead as determined by bone biopsy or EDTA provocation.

The other topic to be introduced for discussion is the question of whether an asymptomatic workman, even one who is retired from work and no longer has excessive exposure to lead, can, under particular metabolic conditions, mobilize enough lead from storage depots in bone to produce symptoms of lead toxicity.

Studies in experimental animals with various levels of lead intake have shown that both iron deficiency⁴ and low calcium intake⁵ can result in higher absorption of lead as well as mobilization of lead from bone to soft tissues. It is known that symptoms of lead poisoning relate to blood lead levels and soft tissue levels regardless of the body burden in bone.

In a recent study a case of lead poisoning in an older man emphasizes this question. This patient was under the care of Dr. N.M. Jaatoul, Westminster Hospital, London, Ontario. A 60-year old retired male truck driver worked for a period of five years in Trail, British Columbia as a construction worker in the area of lead smelters while they were in operation. This was when he was between the ages of 20 and 25 years. He related no symptoms of lead poisoning at that time but other workers in the area became sick. Because he was not an employee of the smelter, he was never tested for lead poisoning. He later was in army combat in World War II and has worked as a truck driver since then. He had no other known exposure to lead. In the past two years he had repeated, severe episodes of acute alcoholism, and in July of this year was admitted to the Veterans' Administration Hospital (VA) with acute alcoholism, mild diabetes mellitus and polyneuropathy which included ataxia. Because testing did not show motor involvement typical of alcoholism or diabetes and red blood cell smears showed the basophilic stippling typical of lead poisoning, blood lead and ALA analyses were made and elevated blood lead levels were found. He was then treated with EDTA for 3 days and blood lead levels decreased and remained lower; however, he continued to drink and nutrition was generally poor after he was discharged from the hospital. There is no way to ascertain that he did not have recent exposure to lead. It is doubtful that his problem can be attributed to lead contaminated moonshine, since he insisted that he only drinks good clear Canadian whiskey.

On the basis of the known effects of metabolic factors, particularly low dietary calcium as demonstrated in experimental animals, I would like to raise the question of whether bone lead in individuals can be mobilized into diffusible and potentially toxic metabolic compartments such as blood and soft tissues, under the stress of poor nutrition and possible other calcium mobilizing illnesses such as fever, acidosis, or even long term catabolic illness, such as cancer.

A great deal more in-depth study of metabolic influences on blood lead levels in such people will be required before such a relationship can be established. I believe that blood and perhaps urinary lead determination of a few selected individuals could greatly help our understanding of the potential long-term effects of an increased body burden of lead and, at the same time, tell us what factors are important in preventing any potential adverse effects.

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Edited By

Bertram W. Carnow, M.D.

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