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ENVIRONMENTAL LEAD EXPOSURE AND THE KIDNEY

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ABSTRACT

Lead and its components remain widely distributed in the environment and in some workplaces. Lead serves no useful physiological function, yet is potentially toxic to several organ systems. For many years human health effects have been recognized after heavy lead exposure. Recently more subtle human effects have been suggested invoking nervous system, reproductive and kidney function. Assessing lead body burden and dose-response relationships of this metal by blood lead determination, porphyrin assessments, chelation testing or bone lead studies may be difficult. Quantitative assessment of subtle changes in kidney function by routine BUN, creatinine, or urinalysis also poses problems. There is now mounting evidence that chronic low level environmental lead exposure may subtly effect kidney function. This paper first examines the history of lead and kidney function and then examines critically the evidence associating low-level environmental lead exposure and effects on renal function.

ENVIRONMENTAL LEAD EXPOSURE AND THE KIDNEY

Lead serves no useful purpose in the human body [1]. Recent evidence suggests that occupational and environmental exposure to lead may contribute to a significant portion

of chronic renal disease [2]. Despite the dramatic declines in occupational and atmospheric levels of lead, environmental lead exposure is considered by some to be a serious health hazard. Since traditional diagnostic criteria of renal function and methods of quantifying lead burden may be insensitive and nonspecific, the chronic effects of low levels of lead on the kidney may go unrecognized, until irreversible kidney disease exists [3,4,5,6].

This paper reviews the evidence for renal disease from environmental exposure, and explores the relationship of lead nephropathy with the development of hypertension and gout. We also review the distribution of lead in the body, and its methods of detection by laboratory analysis, and the inadequacies of those methods for diagnosing chronic lead nephropathy. Newer, more sensitive diagnostic tests for renal injury and lead body burden are considered, including urinary enzyme analyses and the oral chelating agent DMSA. Finally, we attempt to determine whether or not, using the newer methods of detection of renal injury, we will be able to detect environmental lead nephropathy at a stage which might will be reversible.

Historical Perspective

The use of lead antedates the bronze and iron ages. Lead's history is well documented, as is its impact on human health. Since ancient times, lead intoxication has been widespread as a result of both food contamination and occupationally related lead exposure. Occupational exposure to lead began in approximately 2500 B.C., when the discovery of silver in lead ores brought forth large mining and smelting operations in Southeast Asia and Europe. Pliny observed that exhausts from the lead smelting (cupellation) ovens were so dangerous that dogs died when exposed. Lead may have contributed to the decline of Roman Civilization (Nriagu 1983 [7]) and the Shang Dynasty in China through its deleterious effects from ingestion of contaminated food, water, and wine.

The first description of the clinical signs and symptoms of lead poisoning was recorded by Nicander of Colon about 2500 B.C.; but it was not until 4000 years later that the link of lead exposure and kidney disease was postulated. Lancereaux [8], in 1862, was the first to attribute lead as a cause of kidney disease. He was also the first to record the histological appearance of lead nephropathy. At autopsy of an artist with known high exposure to lead paints, Lancereaux found grossly shrunken, granular kidneys. Microscopically, the kidneys revealed atrophy of the renal tubules and proliferation of cells between tubules. Lancereaux also noted that lead nephropathy had only minimal

proteinuria, a finding that would later assist in distinguishing lead nephropathy from other forms of chronic renal failure.

Following Lancereaux's work, there was scepticism that lead nephropathy was truly a separate disease entity. Ollivier [9], in 1863, described the renal disease of lead in his publication, "De l'albuminuria saturnine", but felt that it was a variant of Bright's disease. Others accepted chronic lead nephropathy as a definite clinical entity. Sir Thomas Oliver [10], in 1914, wrote that "interstital nephritis...is undoubtedly the lesion of chronic lead poisoning." Allbutt, in his Disease of the Arteries, 1915, responded that "high arterial tension is the rule in chronic lead poisoning" and was "associated with renal involvement".

With the widespread use of lead in industrial processes during the late 19th and early 20th century, lead nephropathy became an accepted diagnosis in occupationally exposed lead workers. The appearance of granular, contracted kidneys was recognized as a feature of chronic lead intoxication, and could be found in standard medical texts, including William Osler's [11] Textbook of Internal Medicine.

With the development of stricter enforcement and controls on industrial lead exposure, largely due to the work of Dr. Alice Hamilton, there was a decline in the incidence of frank lead intoxication accompanied by nephropathy. Diagnosed cases of frank nephropathy attributed to lead exposure became infrequent. By the 1920's, there was controversy whether lead nephropathy could occur in the absence of other overt symptoms of acute lead intoxication such as encephalopathy, colic or palsy. In 1925, S.A. Smith [12], an Australian physician, reported that tissue damage to the arteries and kidneys could not occur with lead exposure levels that did not give concomittant classical signs of lead poisoning. He wrote that "the absorption of lead over long periods of years does not produce necessarily any disease or tissue damage to arteries or kidneys."

Epidemiologic mortality studies of selected lead exposed occupational cohorts revealed increased mortality due to renal disease [13]. The British Register General's Report [14] found the standard mortality rate due to nephritis for printers and those occupationally exposed to lead to be significantly increased. In 1949, Lane [15] reported evidence of chronic interstitial nephritis at autopsy in 9 battery pasters, men who had been exposed for long periods to high concentrations of lead.

Investigations in Queensland, Australia [16,17], at the turn of the century, were the first to explore the relationship of chronic lead exposure and renal disease in an environmental, nonoccupational setting. As early as the 1890's, a high prevalence of lead poisoning in Australian children was observed by Gibson [18], who later traced the source to the paint used on the houses in Queensland. Later observations found an increased

incidence of chronic nephritis in both male and female residents of Queensland as compared to other parts of the country. The kidney disease was thought to have resulted from protracted accidental ingestion of leaded paint debris from the verandas of homes painted with lead carbonate, and from ingestion of rain water collected by runoff from house roofs sheathed with shingles covered with lead paints (Nye, 1929 [19]). Cilento, in 1932, and Nye [19], in 1933, found evidence of past lead intoxication in one third of the Queensland patients examined, and they reported that chronic lead exposure was responsible for the interstitial nephritis in these patients.

Further evidence for lead intoxication as the cause of this kidney disease was found in a retrospective study on the Queensland population by Henderson,in 1954 [20]. After finding excess mortality from chronic nephritis in Queensland as compared to the other Australian states, he concluded that the excess mortality was attributable to a lead, which he felt was known to cause insidious progressive kidney damage.

Additional investigations of the Queensland group by Henderson in 1957 [21], confirmed excessive lead absorption and correlated lead content of bone with renal histology in patients expiring with granular contracted kidneys. He found that patients dying with granular contracted kidneys and no recognized cause of death had a significantly greater content of lead in their bones than those patients with a recognized cause of renal disease [22].

ANIMAL STUDIES

Experimental work with laboratory animals has yet to confirm with certainty the existance of a chronic lead nephropathy in animals comparable to that of man (Pejic, 1928 [23]; Tange et al, 1965 [24]; Aviv, 1980 [25]; Goyer 1970 [26]; O'Flaherty 1986 [27]). Confirmation is difficult because, while other heavy metals (e.g. mercury or cadmium) produce toxic damage accompanied by extensive necrosis of tubular epithelial cells, inorganic lead salts produce only subtle changes in epithelial lining cells without extensive visible changes (Chang, Wade, and Lee, 1982 [28]).

The earliest animal studies to examine lead nephropathy exposed guinea pigs to lead (14) and found epithelial cell necrosis, tubular dilatation and obstruction, and interstitial fibrosis. Fairhall and Miller, in 1941 [29], reported studies in which male rats were fed lead arsenate or lead carbonate at 0.01% of their diet. Histologically, enlargement of the kidney cells, vesiculation of the nuclei and accumulation of brown granules were noted in the kidney.

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Shakerin and Paloucek, in 1965 [30], found eosinophilic intranuclear inclusion bodies in the cortical tubular epithelium of the kidneys in rats fed lead subacetate as 1% of their diet. These intranuclear inclusion bodies are thought to be characteristic cellular reaction in the kidney after lead intoxication. They were first described by Blackman, in 1936 [31], in children dying from acute lead encephalopathy, and later in chronically lead treated animals (Stiller 1983 [32]). It has been proposed that these inclusion bodies have a protective effect in sequestering lead and maintaining a relatively low cytoplasmic concentration of lead. Thus, the toxic effects of lead on sensitive cellular functions, such as mitochondria and cytoplasm could be reduced due to the formation of inclusion bodies. Intranuclear inclusion bodies have been found in hamsters, dogs, rats, rabbits, and monkeys exposed to lead by intraperitoneal and oral routes (Van Esch and Krues, 1969 [33]; Stowe et al, 1973 [34]; Hass et al, 1964 [35]; Choie, Richter and Young, 1975 [36]; Fowler et al, 1980 [37]; Goyer, 1971 [38]; Allen et al, 1984 [39]).

Chang, Wade and Lee, in 1981 [28], studied renal pathology in rats injected with 10 mg/kg body weight of lead acetate compared to nonexposed control animals. Light microscopic examination of the lead treated animals showed degenerative and necrotic changes in the proximal tubules. Intranuclear inclusion bodies, edematous dilatation of the intracellular spaces and special microvilli were also noted.

Murakami et al, in 1983 [40], found that once the kidney concentration of lead exceeded 10 ug/g of tissue in rats fed lead, irrespective of increasing dose or duration of exposure, intranuclear inclusion bodies appeared in the renal proximal tubular cells. As exposure to lead continued, the lead became incorporated into the epithelial cells of the proximal tubules and formed an inert chemical form as "concretions". These concretions caused no apparent detrimental effects on kidney function. No human study to date has identified these inert concretions.

Animal studies have shown that renal mitochondria are highly sensitive to lead toxicity in vivo following chronic low level exposure (Fowler, 1980 [37]). Lead may interfere with mitochodrial respiration and damage the organelles. Chronic lead feeding in rats has been shown to cause an increase in mitochondrial membrane permeability and subsequent mitochondrial swelling (Goyer and Rhyne, 1975 [78]). Oskarsson and Fowler, in 1985 [41], examined the effects of lead pretreatment of rats and its effects on the subcellular distribution of lead. They found that the mitochondrial inner membrane showed a preferential affinity for lead following in vivo treatment. The mitochondria were able to alter their affinity for lead after long term exposure.

Prolonged exposure to low levels of lead gives an altered, less intense cellular response than acute exposure in animals. The kidneys of rats and mice exposed to a single high dose of lead are noted to have an increase in proximal renal tubular epithelial cell proliferation (Choie and Richter, 1974 [42]). The mechanism for the stimulation of renal tubular cells is not clear, but an increase in RNA and proteins (m-RNA and enzymes) necessary for DNA replication has been detected. It is thought that lead may affect the cellular control of gene expression by stimulating RNA synthesis. Stimulation of proximal tubular epithelium are also seen after prolonged treatment with lead in rats. However, it was less intense after six months of treatment with lead than after a single dose of lead.

There have been conflicting results detecting a significant relationship between lead induced renal injury and hypertension in animals. Early studies (Griffeth and Lindauer 1944 [43], and Diaz, Rivera and Horn 1945 [44]), showed no relationship between blood pressure and massive lead exposure in animals. Sharp, in 1987 [45], recently reviewed seven animal studies conducted after 1978 which reported statistically significant increases in systolic blood pressures after chronic low-level lead exposure. In these studies, hypertension was not associated with renal disease until the levels of lead exposure exceeded 500 ppm.

Within animal species, the specific toxic effects of lead vary with age, sex and specific organ. Younger animals appear to absorb and retain significantly more lead per dose than older animals (Momcilovic and Kostial, 1974 [46]). This appears to involve changes in renal function, gastrointestinal absorption, and calcium metabolism. There may also be age related differences in excretion of lead by the kidney (Brown 1975 [47]).

Much of the controversy concerning animal studies of lead toxicity centers on the use of the rat as the key animal model. The rat has been thought by some authors to be poorly suited for chronic lead studies (Fairhall and Miller, 1941 [29]; Goyer, 1987). Hirsch, in 1973, concluded that the rat kidney is resistant to the potential toxic effects of lead [48]. Renal studies using rats exposed to lead continue to give conflicting results, some report no renal changes, others with proximal tubular damage, nuclear inclusion bodies, and alterations of the renin-angiotensin systems. The rat has been shown to be resistant to the toxic effects of chronic lead administration. The rat can tolerate 60 mg or more dietary lead per day for more than a year. This dose in man is roughly equivalent to 8 grams of lead per day (Cantarow and Trumper, 1944 [49]). Even under normal

conditions, the rat is prone to chronic glomerular and tubular nephropathy which complicates proper assessment of pathologic changes due to lead.

In contrast, two animal models, the gerbil and the rabbit resemble man more closely in their kidney response to lead (Port and Baxter, 1975 [50]; Hass et al, 1964 [25]). Chronic administration of lead to gerbils has consistantly resulted in a progressive nephropathy with tubular degeneration, interstitial fibrosis and intranuclear inclusion bodies, comparable to those changes observed in man. The renal tubular lesions in the gerbil can be recognized as early as eight weeks and continue to progress during the remainder of the animal's life. Rabbits exposed to lead have renal injury histology patterns more similar to man than to rats, and show a similar sequence of renal pathology after exposure to lead.

ENVIRONMENTAL EXPOSURE

The contribution of environmental lead exposure to renal injury and disease has not been well documented [51,52,53]. Existing studies involving environmental exposure to this metal have dealt only with its effects on blood levels, and not total body burden of lead, nor with lead's effect on renal function. It is important in a discussion of environmental lead to review the sources of environmental lead and the modes of absorption which contribute to the overall body burden of lead.

Lead exposure from environmental sources may occur from lead in air, water, food, soil and dust. A large percentage (95%) of lead is found as salts, or inorganic lead. The major sources of lead are from the combustion of leaded gasoline (85%) and from industrial emissions. Natural sources contribute only a small amount of the total lead found in the atmosphere: urban industrialized areas of the world have a 10,000 fold increase in lead levels as compared to remote areas of the world.

Table 1 summarizes the typical levels of lead in various environments to which the general population may be exposed, which includes urban, suburban, and rural adults. At present, the best available estimates are based on limited information, with the state of knowledge more firm for certain pathways than others.

The quantitative fractions of lead absorbed in the human body through the different routes of exposure have recently been estimated (EPA, 1977; Drill 1979 [54]). (SEE Table 1.) These models contain assumptions about the amounts of air inhaled, amounts of food, water, dust/soil, and paint ingested and the degree of absorption from each source. The exposure factors and absorption factors are values selected from a range which are calculated as typical for the general population.

TABLE 1

Sources of Environmental Lead Exposure And Estimates of Total Absorption

Route of Exposure	Conc. of Lead	Amount Ingested	Absorption Factor	Amount of Lead Absorbed
Air	0.75 ug/m3	20 m3	0.4	6 ug/day
Water	10 ug/l	2 l	0.1	2 ug/day
Food	0.15 ug/g	2 g	0.1	30 ug/day
Soil/dust	500 ug/g	0.02 g	0.1	1 ug/day

* In the general U.S. Urban Population

adapted from Drill et al (1979)

Lead in Air

The concentration of lead in the air in both the general environment and in occupational settings vary widely. Current evidence is that the greatest source of atmospheric lead is from automotive vehicle emissions. When the antiknock additives tetramethyl lead and tetraethyl lead undergo engine combustion, they are oxidized and emitted as a mixture of lead salts. Isotope studies have shown that these lead salts contribute a major proportion of the blood lead in the urban population (NHANES II, 1983 [55]). Gasoline lead also accounts for approximately 80% of air lead in urban areas. Lead in blood samples collected from the National Health and Nutrition Survey II declined proportionally to the fall in the quantity of leaded gasoline sold between 1976 and 1980. The EPA (1977) and WHO (1977) concluded that at typical ambient concentrations of lead in air the concentration of lead in blood is elevated by approximately 1 to 2 ug/100ml for each 1 ug/m^3 of lead in air.

Lead in Soil and Dust

Lead in soil and dusts is also derived from deposition of lead particles from airborne lead and some accumulation by plants. Because of industrial and domestic fallout, lead in surface soils is frequently greater near large cities and close to busy roads. The debris from lead based paints also contibutes to the lead soil concentration. The results of the Queensland, Australia studies of young adolescents who developed chronic nephritis was linked to the remote ingestion of leaded paint debris both from the verandas of the homes and to the lead contaminated soil.

Positive correlations between blood lead levels and concentrations of lead in house dust and soil have been observed in children in urban areas, near roadways, and in the houses of smelter workers. Children are considered at greater risk of exposure to dust and soil lead because of their smaller stature and as a result of their exploratory oral behavior (Sayre et al 1974 [56], Charney et al, 1980 [57]). Increased lead levels in the blood have frequently been associated with lead in dust and soil at concentrations above 500-1000 ppm (Baker et al, 1977 [58]; EPA 1977) approximately a 2 mg/dl increase in blood lead for every additional 100 ppm increment in dust or soil lead content.

Lead in Food

The majority of lead in foods and beverages is derived from processing and storage techniques that increase the concentration of lead far above levels found in raw agricultural commodities. It was estimated in 1983 that between 10 and 40% of lead in

foods came from lead soldered cans. Since 1983, many manufacturers have switched to lead free welded cans, reducing the potential for contamination. Estimates of lead intake from food and beverages are poor, due to the large variation in the quantity of food consumed and the variety of foods with different concentrations of lead.

Lead contaminated flour was thought to be the cause of chronic interstitial nephritis in a study of a Serbian village in 1958. Danilovic, (1958) [59], found an unusually high incidence of chronic nephritis among 12 Serbian families, 37 of whose members had died of the disease in a fifteen year period. Analysis of samples of flour used in the making of the village bread found it to be heavily contaminated with lead acquired through the milling process.

Numerous studies that have used either radiolabeled lead tracers or balance methods have concluded that adults absorb 8-10% of lead ingested in the diet (Jaworski, 1979 [60]; Drill et al 1979 [54]). This poor absorption is due to the low solubility of most inorganic lead compounds.

Lead in Water

The contamination of drinking water comes principally from the use of lead pipes and from lead based solder used in the modern systems with copper pipes. The lead content of water supplies rises dramatically when soft acid water passes through lead plumbing systems. Where water has been allowed to stand in the pipes for prolonged periods there will be the greatest water lead concentration. Very few public water supplies contain lead levels which exceed the EPA standard of 50 ug/l, however, this level may contribute 10 to 40 ug per day for normal consumption of water of 2 liters/day. The EPA recently proposed a reduction in the amount of lead it will permit in drinking water, from the current 50 ppb to 20 ppb.

Summary of Environmental Exposures

A well defined integrated model for assessing total lead absorption using the contributions of different sources of lead in the environment is not available. For many sources of lead, only estimates are available concerning the exposure and absorption of lead.

Models rely on estimates of blood lead levels, which are adequate only to measure acute exposures and give only a rough estimation of body burden of lead. Those models derived to estimate the relative fraction of blood lead from each source of exposure ignore the contribution of environmental sources of lead to the tissues and bone lead compartments, which are by far the largest storage components in the body.

LEAD IN THE BODY

Once absorbed, lead does not become homogeneously distributed throughout the human body, but is transported to one of the three physiologically distinct compartments. Based on radio-labelled isotopes and metabolic balance studies, Rabinowitz et al (1973, 74, 76, 77) [61] proposed a model which would fit the data. That model had divided these compartments into three groups: 1) a "rapid" exchange pool, consisting of blood, tissue fluids, and soft tissue which rapidly exchange with blood, and 2) an "intermediate" exchange pool, consisting of soft tissues and actively exchanging parts of the skeleton, and a "slow" exchange pool, which is thought to consist primarily of bone.

The "rapid" exchange pool contains approximately 4 % of the body burden of lead. Lead is added to the rapid exchange pool by inhalation, by ingestion, or by movement from the deeper compartments. The blood lead measurement generally reflects the lead in the rapid exchange pool, and is a sensitve indicator of recent lead exposure. However, blood lead levels correlate poorly with long term exposure, or past exposure to lead (Baker et al) [58]. The overall half-life of lead in compartment one is about 36 days. Most of this lead is bound to circulating red blood cells, although a small amount is found in the plasma. Plasma lead has a short half-life (minutes to hours) due to its small size and rapid exchange with the larger pool of RBCs and tissue lead. Lead excretion in compartment one is achieved through the kidneys. Glomerular filtration will remove lead from the plasma but not the lead bound to RBCs, so that the urine lead content will fluctuate as rapidly as the plasma level.

Compartment two, the "intermediate" change pool, includes soft tissue and actively exchanging parts of the skeleton. Two percent of the lead body burden is found here, with a half life of about 30-40 days. Excretion occurs through the bile, sweat, hair and nails.

The third compartment, the "slow" exchange pool consists primarily of bone and comprises 94% of the body burden of lead. Lead in compartment 3 has a half life of 10,000 days. This long turnover time makes the amount of lead in bone a reasonable indicator of the cumulative exposure to lead over a lifetime. Lead in bone is felt to be relatively inactive physiologically. However, there are certain factors which may mobilize deep compartmental stores of lead, such as dietary deficiencies, metabolic imbalances or illnesses which involve resorption of bone, and cause amounts of lead to be released which may be hazardous. This mobilization of lead may give rise to untoward effect on the kidneys, and contribute to the development of a lead nephropathy.

BIOLOGICAL INDICES OF LEAD EXPOSURE

The lead concentration in whole blood has traditionally been the principal biologic index of dose for epidemiologic and experimental studies [62]. It provides the most accessible route and has been considered the best estimate of the biologically active lead.

However, there has been considerable debate whether an elevated blood lead concentration is useful for the diagnosis of lead nephropathy [63]. The level of lead in the blood is neither an exact measure of exposure to lead (because of the intervening processes of transfer, mobilization, and storage among the different compartments in the body), nor a direct indicator of concentration in other body compartments nor the amount of lead in the body as a whole (body burden). Blood lead determinations are primarily a measure of absorption when sampled close to the time of exposure. The distribution of lead out of the central compartment is slow as shown by Rabinowitz [61]. A normal blood lead level does not exclude lead nephropathy from diagnosis, as lead nephropathy usually has a remote exposure to lead with an increased body burden. Wedeen et al, (1975 [64] and 1983 [65]), demonstrated reduced renal function in 21 of 57 asymptomatic lead exposed patients, 15 of whom were identified as having subclinical lead nephropathy with blood lead concentrations considered in the normal range.

Other hematologic tests, including hemoglobin concentration, and erythrocyte protoporphyrin, (EP), are not sufficiently sensitive to detect cumulative toxicity from chronic low dose exposure. These hematological tests may be complicated by other factors, e.g., iron deficiency may elevate FEP levels; thus its usefulness may be compromised in obtaining accurate measurements. The results of these tests do not accurately reflect cumulative lead stores and normal values may be observed even when an excessive amount of lead is present in the body.

The EDTA lead mobilization test has been shown to be the most reliable for determining lead burden, and the best test for diagnosing persons at risk of chronic lead nephropathy. Disodium EDTA is a chelating agent that combines with lead and clears it from the blood and some peripheral compartments through renal excretion of the EDTA-lead complex. This chelatable pool of lead is only a fraction of the total body burden (Araki and Ushio, 1982 [66]). To carry out the EDTA test, 1 to 2 grams of Ca Na_2EDTA is administered to adults by IM or IV infusion, then the urine is collected for 24 hours (72 hours for renal failure patients); if greater than 600 ug lead is found in the urine, then there is suggestive evidence of increased body burden of lead (Hammond 1973 [67]; Chisolm et al 1975 [68]; Wedeen, 1984 [14]).

Vitale et al (1975) [69] illustrated the usefulness of EDTA through the results of their study of a group of workers exposed to lead. Through a series of tests, including blood lead, EP, ALA-D, urine lead, and urine lead excretion following EDTA mobilization. They found that whole blood lead did not provide an accurate measure of exposure; 23 out of 26 workers showed lead excretion after chelation indicating excessive body burdens of lead. Wadeen, in 1981 [70] and in 1984 [14], and Batumen, in 1983 [65], have also used EDTA mobilization test to predict unsuspected lead renal effects among patients whose normal lead levels were inadequate as predictors of renal involvement.

In the near future, oral chelating agents are expected to surpass EDTA as the method of confirmation of body burden of lead. Studied extensively in the People's Republic of China and the USSR since the late 1950's, oral chelating agents have received very little attention in the United States until recently. Dimercaptosuccinic acid (DMSA) [71,72], a water soluble chemical analogue of BAL (Dimercapatol), has less toxicity, greater water solubility, and can be given orally for treatment of lead toxicity. DMSA was originally introduced to increase the uptake of antimony for schistosomiasis therapy. DMSA has demonstrated effectiveness as an antidote for heavy metal poisoning [71]. Since that study, DMSA has been reported to be used extensively in the Soviet Union for metal chelation and achieved excellent results. It is given in doses varying from 10 to 30 mg/kg/day, and has been shown to decrease blood lead concentrations by up to 72.5%. DMSA was shown to be as effective as EDTA in the treatment of lead toxicity as judged by the increases in the urinary excretion of lead. In animal studies, when compared to EDTA and penicillamine, DMSA has been found to be the most effective in decreasing tissue lead [71,72]. In human studies, DMSA has been shown to be a safe and effective treatment for lead toxicity, both in acute and chronic lead poisoning. It is expected that the use of DMSA for the detection of chronic lead intoxication and increased body burden will increase because of the advantage of oral dosage.

TESTS OF KIDNEY FUNCTION - OLD AND NEW

An accurate diagnosis of lead induced alteration of kidney function has been impeded by the standard laboratory methods traditionally used for the detection of renal abnormalities [73,74]. Unlike the hematopoietic system, the means available to diagnose the early onset of renal disease is far more limited, thereby making prevention much more difficult. Most studies of kidney function involving lead have used levels of blood urea nitrogen (BUN), serum creatinine or urinary protein as measurements of renal function. However, because the kidney has a great reserve capacity, these measures of

excretory function can be normal or in the "normal range" despite major unrecognized impairment of renal function. BUN and creatinine will be increased only when approximately two thirds of kidney funtion is lost. These tests are therefore unlikely to detect early or moderate loss of renal function due to lead injury and are unlikely to discover a lead nephropathy. They will only be able to detect acute or chronic renal disease, without allowing for specific diagnoses.

Multiple enzyme analyses has been shown to be a sensitive indicator of renal injury (Meyer, 1984 [75]; Thun, 1986 [76]), especially for the detection of proximal tubular damage, where lead injury is thought to take place. N-acetyl-beta-D-glucosamidase, (NAG), a lysosomal enzyme, and gamma glutamyl transpeptidase (GGT), found in the brush borders of the proximal tubular cells, have been shown to be elevated in the urine at early stages of renal injury, before abnormalities in excretory function takes place. GGT has a higher activity in renal than in other tissue, showing a four-fold higher activity in the urine than in the serum, which suggests that the enzyme leaks from the kidney into the urine.

Meyer, 1984 [75], used urinary enzyme analysis to demonstrate that renal effects occur in many persons exposed to lead with blood lead concentrations well below the level currently presumed to be the threshold for nephrotoxic effects. They also found at high lead levels above 70 ug/dl, workers had normal urinary NAG levels. They speculated that long term high exposure to lead may deplete the kidney of NAG or render it insensitive to lead exposure.

Low molecular weight protein detection in the urine may be another sensitive indicator of early renal injury [76]. Both beta-2 microglobulin and retinol binding protein are freely filtered from the plasma by the renal glomerulus and are taken up by the proximal tubular cells where they are catabolized. The reabsorption of these proteins by the normal kidneys is nearly complete (99.97% of the filtered load), so that their concentration in urine is a sensitive index of altered proximal tubular function. Although beta 2 microglobulin has been found to be unstable in acid urine, retinol binding protein, the major alpha 1 microglobulin, does not hydrolyze in the usual range of pH of urine, and thus shows more promise as a screening tool for lead effect. The few lead studies that have examined low molecular weight proteinuria have used populations with remote histories of acute high exposure to lead (Sachs, 1986 [77]), with negative results. However, no study to date has looked at specific populations thought to be at risk from chronic environmental lead exposure.

The mechanisms of indicators of early renal injury is not known. It is unclear whether the appearance of increased urinary excretion of these enzymes and low molecular weight proteins represents direct cytotoxic effects on the renal tubular cells, interference with renal cell catabolism of circulatory proteins, increased production of these substances, or a combination.

LEAD NEPHROPATHY

Renal Effects of Lead

Goyer and Rhyne in 1970 [78] and Cramer, 1974 [79] defined two principal stages of lead effects on the kidneys. Stage one involves acute reversible stages, with intranuclear inclusion bodies and alteration of mitochondrial morphology. Intranuclear inclusion bodies have been extensively studied in experimental animals and from renal biopsy material from occupationally exposed workers and children with acute lead poisoning.

The renal proximal tubules are rich in mitochondria, and much of lead's damage can be found here. In experimental animals, swelling of mitochondria can be observed at relatively low levels of exposure to lead. Lead workers need only be exposed a few months before distortion of the proximal tubules occurs.

The intranuclear inclusion bodies are reported to be the most characteristic feature of stage one nephropathy. These occur in the lining cells of the proximal tubules and are composed of sulfhydryl-rich lead-protein complex (Goyer et al 1971 [38]). They are thought to serve as protective temporary storage mechanisms by which soft tissue lead is complexed in a non-diffusable form, thereby reducing the concentration of lead available to disrupt essential cell function (Goyer 1971 [38]). The lead inclusion bodies disappear with appropriate chelation and are shed into the urine upon the death of the tubular cell (Landing and Nakai, 1959 [80]).

Stage II is defined as a chronic condition, characterized by interstitial fibrosis, tubular atrophy and dilatation and arteriosclerotic changes (Lilis et al, 1968 [81], Goyer 1971 [38], Wedeen 1978, 1982 [70]). Goyer found Stage II changes in lead workers with excessive lead exposure for more than two years, but these workers did not have to exhibit renal failure until many years later. Lilis et al (1969) [81] found nephropathy more common in workers exposed over ten years. In those subsets suspected of chronic lead nephropathy, e.g. those men with hypertension or gout and renal failure it is not possible to state whether the changes found on renal biopsy are a result of lead exposure. Although the changes are similar (interstitial fibrosis, tubular atrophy, and atherosclerotic changes),

TABLE 2A
Studies Relating Lead Exposure and Kidney Disease

STUDY	SUBJECTS	EXPOSURE	OUTCOME
Dickinson 1881	42 men	occupational	26 with chronic interstitial nephritis
Purdy, 1886.	42 men	occupational	2/3 with granular kidneys
Nye 1929	34 m & f	severe childhood poisoning	29 with chronic nephritis
Blackman 1936		ingestion, childhood exposure, few months to years	renal changes: inclusions bodies in proximal renal tubules
Henderson 1954	401 children	ingestion	108 deaths from hypertension or nephritis
Danilovic 1958	12 families	lead contaminated flour	37 deaths from chronic nephritis, 23/44 living with renal disease
Emmerson 1960	23 adolescents	ingestion	4 patients with increased lead excretion after chelation
Radosevic 1961	53 subjects	occupational or environmental	2/53 with chronic nephropathy, 23/53 with functional renal impairment
Emmerson 1963	32 children	ingestion	32 patients with increased lead excretion after chelation
Emmerson 1963	19 controls 22 cases 23 renal pts	none, ingestion	controls with normal lead excretion, lead intoxicated pts with increased excretion, renal pts with normal excretion

these are also the kidney's nonspecific response in chronic renal disease from many causes.

EPIDEMIOLOGY AND OCCUPATIONAL STUDIES (Tables 2A, 2B)

Childhood Environmental Lead intoxication

No study carried out in the United States has been able to identify a nephropathy from chronic lead exposure [82]. Tepper (1966) [83], traced 139 of 165 Massachusetts cases who had evidence of lead absorption and intoxication 20 to 35 years earlier. Screening

TABLE 2B
Studies Relating Lead Exposure and Kidney Disease

STUDY	SUBJECTS	EXPOSURE	OUTCOME
Tepper 1963	139 m & f	ingestion 30-35 years earlier	42/139 screened for renal disease, 6 with mild dysfunction.
Chisolm 1970	62 m & f	ingestion 11-16 years earlier	No increased lead with chelation.
Sachs 1986	74 m & f	ingestion 9-17 years earlier	All renal tests:WNL (serum cr, cr clearance, protein excretion, low urinary osmol., b2 microglobulin).
Morgan 1966	13 men	moonshine or occupational exposure	All abnormal renal biopsies.
Ball & Morgan 1967	98 men V.A.H.	moonshine or occupational exposure	Minimal to moderate renal failure.
Cooper & Gaffey 1975	7000 men	occupational lead workers	Indreased mortality due to renal disease.
Wyngaarden & Kelly 1976	9 men	moonshine whiskey	Moderate renal failure.
Campbell 1977	970 households	drinking water	blood lead associated with increase in BUN.
Wadeen 1979	140 men	lead workers	15 with nephropathy 4 with gout.
Lilis et al 1980	269 males	lead smelter workers	increased prevalence of reduction in GFR* in heavily exposed as compared to low exposed.
Hernmen et al, 1986	71 production workers	occupational	significant decrease in glomerular function, no tubular damage.

renal function tests were carried out on 42 of the follow-up cases, with 6 of the 42 having mild abnormalities in renal function. Tepper concluded that there was no evidence of renal disease from the childhood lead exposure.

Chisolm (1979) [68], also failed to find evidence of a lead nephropathy in 62 American adolescents known to have lead poisoning 11 to 16 years earlier. However, unlike the Queensland group, the subjects in Chisolm's study did not show excessive mobilizable lead when given a Na EDTA challenge. With his results, Chisolm did not dismiss lead as the cause of Queensland nephropathy, but felt that the lead toxicity seen in the Queens-

land group had a more protracted course and thus gave rise to a more chronic form of lead poisoning.

Recently, Sachs et al, in 1986 [77], examined the renal function in 74 Chicago adolescents with a history of lead intoxication (range 100-471 mcg/dl) 9 to 17 years after the event. Results of renal function tests (including creatinine clearance, protein excretion, low urinary osmolality, and Beta-2 microglobulinemia) were compared with 21 age-matched sibling controls. There were no significant differences in the results of the renal function tests in the cases and the controls. However, the lead intoxication studied was from an acute high exposure and not long term exposure as was found in the Queensland study group.

Craswell et al, in 1986 [84], found that Queensland, Australian controls with normal renal function excreted a significantly higher amount of lead than German controls when given an EDTA challenge, suggesting that people living in Queensland have a greater exposure to lead than those in Germany.

Lead in Water Supplies

Campbell et al, in 1977 [85], demonstrated a significant correlation between lead concentrations in household water and both renal insufficiency and hypertension in 283 persons in Scotland. Fifty-seven people (20%) were found to have abnormal renal function as assessed by BUN. The mean duration of lead exposure was 21.5 years, and none of the 283 persons had the diagnosis of lead intoxication. Blood lead levels in these persons were significantly elevated compared to those in sex and age matched control subjects. It was questioned whether the high blood lead levels were secondary to the diminished lead excretion from renal insufficiency. In followup, Campbell in 1977 [85], attempted to answer this question by assessing whether there was evidence of depressed lead excretion in subjects with severe renal dysfunction. In 12 patients with differing levels of renal function assessed by creatinine clearance, blood lead and urinary lead outputs were determined over three 24 hour periods. Using the relationship of blood lead concentration to urinary lead output expressed as a single arithmetic function, they concluded that the variance in lead excretion was in no way related to the severity of renal disease. It is unfortunate that EDTA chelation was not performed on these groups of patients, as it would have allowed comparison of the body burdens of lead in these three groups.

In contrast to Campbell's study, Pocock et al (1984) [86], in their population based study, found no correlation between three indicators of renal function (Creatinine, urate,

and BUN) and blood lead levels in 7,735 middle aged men in 24 British cities. However, these findings are thought to differ from those of Campbell's study carried out in Scotland, primarily because Scottish homes had a higher use of lead pipes and lead storage tanks.

Moonshine

Renal failure associated with ingestion of lead contaminated whiskey was examined in studies by Vaughan, 1922 [87] and by Morgan et al in 1966 [88]. Thirteen adult patients with frequent past or present use of illegal alcohol and a negative history of renal disease underwent kidney biopsy and chelation studies. All 13 had confirmatory excessive lead accumulation, anemia compatible with lead toxicity and impairment of renal function, although none had advanced renal disease. Histologic findings showed interstitial fibrosis with few inflammatory cells, tubular degeneration with intranuclear inclusion bodies and fibrosis of the adventitia and media of the small arteries.

Gout, Lead, and Possible Kidney Disease (Table 3)

A relationship between gout and lead nephropathy has been recognized for more than two centuries (Craswell 1984, Ball 1968, Campbell 1978) [89,90,91]. The English physician Sir Alfred Barring Garrod, in 1854 [92], noted a high incidence of gout among painters and workers in the lead trades, and is credited with the recognition of the relationship between hyperuricemia and lead nephropathy.

Lorimor, 1886 [93], investigated 108 cases of gout and found several clinical features of saturnine gout to distinguish it from ordinary gout: it usually occurs in early adult life, has no familial predisposition, affects the lower limbs, and is more frequently found in women than in idiopathic gout.

Gout occurs more frequently in the presence of chronic lead nephropathy than in any other type of chronic renal disease. Henderson, in 1957 [21], reported 8 out of 41 patients with lead nephropathy to have gout, three of whom were females.

Emmerson and Thiele, in 1960 [94], in their first reports of the Queensland Australian group with chronic lead nephropathy due to accidental ingestion of paint debris, noted two patients with symptomatic gout. Later, Emmerson in 1963, reported 35 cases of saturnine gout found in a group of 62 patients with lead nephropathy, with a similar frequency in males and females.

TABLE 3

Studies Relating Gout, Lead, and Kidney Disease

STUDY	SUBJECTS	EXPOSURE	OUTCOME
Wagner 1882	15 men	occ. lead exposure	6 cases gout 15 with nephropathy.
Morgan 1966	13 men	moonshine whiskey	6 cases gout 13 abnl kidney biopsies
Ball and Morgan 1967	2734 V.A. admissions with gout	unknown	98 chronic lead intox. 37 saturnine gout elevated urinary leads
Emmerson 1979	140 m & f	environmental exposure	23 with gout and nephropathy
Batumen 1981	44 men	unknown	increased lead excretion in those with gout and mild renal failure.
Craswell 1984	42 m & f	environmental	increased lead excretion in 19/23 —— with gout.
Wright 1984	10 men	moonshine or occupational	increased lead excretion in 2/10.
Daelemans ;1985	35 patients	unknown	46% with increased lead excretion after chelation; BPb, FEP were of no value.
Behringer 1986	21 controls, 19 renal patients, 16 gout patients with renal failure	unknown or occupational	controls normal, 7/19 renal pts lead excretion 95th percentile, 9/16 gout pts with increased lead excretion.
Colleoni & D'Amico 1986	12 controls, 12 gout patients with renal failure	unknown or occupational	"greater" lead excretion in gout patients, controls with normal excretion.

Emmerson [95,96,97,98,99] found that those patients with lead nephropathy had persistantly higher levels of uric acid than patients with non-lead renal disease. This higher plasma urate level in the presence of existing kidney disease is believed to be the underlying cause of joint disease, and is generally attributed to lower clearance of urate, increased urate reabsorption rather than impaired tubular reabsorption.

Morgan in 1966 [88] reported that 6 out of 13 men with a history of lead contaminated moonshine whiskey ingestion were found to have gout, along with impaired renal function and diminished kidney size. He concluded that there was strong supportive evidence that the gout was lead induced by the temporal sequence and by biopsy findings.

Ball and Sorensen, in 1969 [100], investigated all patients admitted for gout at Birmingham Veterans Administration Hopsital with particular emphasis on those with gouty arthritis and chronic renal disease who were also chronic moonshine abusers. They found elevated urinary lead concentrations and no family history of gout. They hypothesized that impaired renal function due to lead poisoning from the contaminated moonshine was the sole cause of hyperuricemia and gout.

Rapado, in 1969 [101], in his study of 450 cases of gouty arthritis, found 30 of them with nongouty nephropathy, and 10 with a history of lead intoxication. He speculated that 70 or more of them might have had chronic low level exposure to lead though their work as truck drivers, and this lead exposure may have been responsible for the gout.

Batumen et al, in 1981 [102], found excessive body stores of lead by EDTA chelation in 44 patients with clinical gouty arthritis. One half had renal failure manifested by serum creatinine of 1.5 mg/dl or greater. In these patients there was remarkable correlation between the degree of renal failure and the amount of mobilizable lead. Those with renal disease excreted a mean of 806 ug lead during the 3 day EDTA chelation test. Those gout patients without renal disease excreted only 407 ug lead. The gout patients with renal disease did not differ with respect to age, blood pressure, history of lead exposure, serum uric acid, blood lead or tests of porphyrin function.

Craswell et al, in 1984 [103], studied 42 patients with chronic renal failure (Cr > 0.13 mmoles/l), all of them with normal blood lead concentrations. EDTA lead mobilization and Xray fluorescence finger bone lead tests were done in all patients. Nineteen out of 23 patients with gout had positive EDTA lead mobilization (excessive urinary lead output). Seventeen of the gout patients denied any childhood or industrial exposure to lead. They concluded that gout was a useful marker of chronic lead poisoning.

Wright et al, in 1984 [104], suggested that factors other than lead may be the cause of renal failure in most patients with gout and renal disease. EDTA mobilization failed to show excess urinary lead excretion in 8 of 10 patients with gout, hypertension and moderate renal insufficency. They did, however, recommend diagnostic testing of patients who present with gout, unexplained renal insufficiency, history of ingestion of illegal alcohol no matter how recently, and a history of occupational exposure to lead.

Reynolds, in 1983 [105], found that gouty patients whose one day EDTA tests were positive had creatinine clearance of 85/25 ml/min, whereas those with normal results of lead mobilization tests had creatinine clearance of 111/28. However, he concluded that factors other than lead may be responsible for the decreased urate clearance observed in gout patients.

Colleoni and D'Amico, in 1986 [106], conducted a case/control study using EDTA lead mobilization test to determine whether gout patients with nephropathy excreted more lead than patients with nephropathy caused by chronic glomerulonephritis. The urinary excretion of lead after the mobilization test was significantly higher in the gouty patients (505 ug/48 hrs. vs 180 ug/48 hrs).

Behringer et al (1986) [107] examined urinary excretion of lead before and after EDTA chelation in healthy German controls and in patients with chronic renal failure with and without gout. Both basal lead levels and post-EDTA infusion lead levels were considerably lower than most values reported previously in the literature. An elevated lead body burden was found in 7 of 8 patients who developed gout in the course of renal failure, but only in 2 of 8 patients with gout prior to renal failure. In 7 of 19 nongouty patients with impaired renal function secondary to known renal diseases, urinary lead excretion was above 95% of normal. All these patients had occupational exposure to lead. The high prevalence of increased lead body burden in patients with renal failure of known cause may not be coincidental and raises the possibility that lead adversely affects the course of renal disease.

Campbell and associates, in 1977 [85], studied 283 people in Scotland who lived in homes with lead contaminated water. They found an association between elevated blood lead levels, hyperuricemia, and renal insufficiency. It was conceded that the disease states themselves may have been partly responsible for the elevations of blood lead concentration by depressing lead excretion.

HYPERTENSION

Hypertension has long been associated with lead exposure and nephrosclerosis [108]. Until recently, hypertension was considered a secondary event, arising as a result of arteriolar sclerosis and arteriosclerosis, the primary lesions in chronic lead nephropathy [109]. There is now evidence to suggest that lead may play a primary role in hypertension through direct effects on arterioles and through metabolic processes relating to calcium metabolism [110]. These effects may occur directly on the kidney arterioles. Sharp et al, 1987 [45], recently reviewed chronic low-level lead exposure and its role in the pathogenesis of hypertension.

The notion that unrecognized low level lead absorption contributes to renal disease and hypertension has been raised, but not fully explored. In the National Health and Nutrition Examination Survey II (NHANES II) [55], blood lead was measured in a large

sample of subjects (9000) from across the country. The blood lead level was observed to vary geographically with air levels. Black American males had a significantly higher levels of blood lead than white males. Blacks who lived in the area with high environmental lead exposure, also have a disproportionate amount of hypertensive renal disease, including end-stage renal disease. Data from NHANES II also showed an interesting association of whole blood lead level and blood pressure itself, independent of function. Blood pressure was observed to be directly related to the blood level in black and white persons from age 12 to 74. Among both men and women, those with hypertension had significantly higher mean blood levels than normotensive persons of the same age, although still within what is considered the normal range for blood lead. Thus, NHANES II found evidence which involves excess lead exposure in both hypertenisve nephropathy and hypertension itself.

Many observations have confirmed the high incidence of hypertension in workers exposed to lead. Occupational studies of workers in lead industries in the early part of this century showed an increased incidence in hypertension which appeared to correlate with lead exposure (Canterow and Trumper, 1944) [49]. In contrast, Belknap, (1936) [111], followed 81 smelter workers over a five year period and found no relationship. Dressen, (1943) [112], also found no correlation in his study of occupationally exposed lead workers. A retrospective study carried out by Dingwall-Fordyce and Lane, 1963 [113], on retirees from battery factories in England found an increased mortality due to cerebrovascular disease, but no renal basis for the hypertension was found.

Cooper, in 1981 [114], carried out a mortality study of deaths in 4519 battery plant workers and 2300 lead production or smelter workers during the years 1947-1980. He found a significant excess of deaths from "other hypertensive diseases" and chronic nephritis in both groups. His findings suggested an association between lead exposure, hypertensive heart disease and nephritis.

McMichael and Johnson, in 1982 [115], studied 140 deceased male smelter workers diagnosed as having lead poisoning during 1928 to 1959. A comparison with 695 other male decedents gave a age-standarized proportionate mortality analysis with a substantial excess in the number of deaths from chronic renal disease and hypertensive vascular disease.

Recently, Batumen et al [116] have suggested that a major portion of chronic renal failure associated with essential hypertension may be due to a subtler, but excessive exposure to environmental lead. Using the three-day EDTA lead mobilization test, Batumen noted markedly higher mean urinary lead excretion in patients with

hypertensive renal disease than in patients with a comparable degree of renal failure due to other causes. Fourteen out of 24 patients with hypertensive renal and no known occupational exposure to lead had abnormally high lead excretion levels (above 600 mcg of lead in a three day urine collection). Only five of the 22 control patients had elevated lead excretion levels. A second control group of patients with longstanding hypertension but normal renal function was also examined. This group also had lower mean excretion and only 2 out of 21 subjects had elevated levels.

Pocock et al, in 1984 [86], concluded from his population based study in 24 British towns that there was no overall evidence that blood lead concentrations were correlated with systolic or diastolic blood pressure. However, there was a weak suggestion from the data of 7735 middle aged men in the study that subjects with blood lead concentration of 37 ug/dl may suffer more often from hypertension.

DeKort, in 1987 [117], studied 52 lead and cadmium exposed workers and 53 controls and found an increased prevalence of hypertension in the exposed group but no significant difference in creatinine, BUN, serum uric acid or retinol binding protein between cases or controls. They concluded that if the relationship between lead blood pressure and renal disease is causal in nature, then using these measurements of kidney function would be unable to detect a relationship.

SUMMARY AND SYNTHESIS

The extent to which environmental lead contributes to the cause of renal disease is still uncertain. Published results have been conflicting. However, when critically examining the approaches taken to address the issue of lead nephropathy, several reasons for the conflicting results become clear. Reviewing previous investigations highlights several crucial methodological problems that must be addressed if more firmly based conclusions are to be drawn.

First, there has been a problem of selection bias stemming from the use of study cohorts, the use of volunteer subjects, the differential loss of subjects to follow-up and the failure to obtain systematic data on all individuals in the study. Data from cohorts with long term low level lead exposure is not currently available. Most epidemiological studies of lead exposure have used heavily exposed lead workers, or those with acute toxic ingestion of lead, many of whom had gross evidence of lead intoxication. Those subjects with low-level long term exposure to lead who may have had more subtle changes in kidney function have been considered to be free of lead's effect unless they had evidence of

frank renal failure, and have not been adequately studied. Tepper, in 1963 [83], concluded that there was no lead nephropathy in follow-up of children with remote lead intoxication, yet less than one fourth of the children originally enrolled in the study were examined for renal disease.

Second, almost all the previous studies of lead nephropathy utilized relatively insensitive measures of renal function, relying on BUN and creatinine. Evidence for both animal and human studies reveals that even without changes in routine kidney functions, one can find ulta-structural changes due to chronic lead exposure, without gross changes. Because the early renal effects from environmental lead exposure may be subtle, and not result in alterations of BUN or creatinine, it is imperative to use more sensitive and specific indicators of early tubular damage and renal dysfunction, such as N-acetyl glucosaminidase or retinol binding protein.

Third, because the renal changes may be subtle, it is critical to study large samples. If the effects are small, it follows that large groups will be needed to produce statistically significant results. Large studies using populations with hypertension, gout, and renal dysfunction evaluating body burden of lead, urinary enzyme analyses, and parathyroid hormone need to be carried out to corroborate these entities.

Fourth, there are problems stemming from inadequate markers of exposure to lead. Most early studies relied on single blood lead levels, often with measures obtained several years prior to the renal assessment of the subjects. Because blood lead levels reflect only recent ingestion of lead, they provide a relatively poor guide to the overall lead burden, and they may not reflect the true degree of renal risk. There have been too few studies which use available diagnostic tests which may provide information with respect to cumulative systemic absorption. Chelation studies have been used as a possible gold standard for assessing body lead burden. Chelation tests are still not proven to accurately define total body lead burden. EDTA chelation because of the need to give it parenterally, intravenously or intramuscularly has not been routinely used. However, with extended use of oral chelation with 2,3-DMSA, larger and more extensive studies can be carried out. X-ray fluorescence, bone biopsy and tooth lead have also been utilized but not fully validated.

Fifth, diagnosing lead nephropathy by pathologic means has been limited because presently there is no specific pathological feature of lead nephropathy. Therefore, recognizing lead as the etiological factor in the pathogenesis of chronic nephropathy in particular subjects remains a problem.

Carefully controlled prospective studies to assess the extent of lead mediated renal failure have not been routinely used, and studies have had to rely on blood lead levels, and changes in BUN/Cr which provide little information with respect to systemic absorption and chronic exposure.

Finally, it remains possible that environmental lead effects on renal function are not always direct but may be indirect. Lead is stored in the skeleton. If bone breakdown occurs for any reason e.g. early renal failure from another cause, then lead will be released. The released lead could then indirectly interact with other direct non-environmental nephrotoxins to exacerbate kidney disease.

There are presently many unanswered questions regarding the kidney's response to environmental lead exposure. Major areas of uncertainty generally relate to the relationship between accurate measurements of lead in the body and the parameters of kidney dysfunction and the significance of specific biological lead values with respect to the development of potentially adverse effects. There is no dose-response relationship known that can be applied to lead and the kidney.

With all these concerns in mind, there is obviously a need for the development and validation of suitable biological monitoring techniques which can reliably predict excessive lead absorption and early kidney injury. Further studies to confirm the usefulness of urinary enzyme analysis and diagnostic body burden analysis using oral chelation with DMSA are required. Studies are needed to corroborate these data and to determine dose-response relationships between body lead levels and renal effects in both animals and humans.

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