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LEAD EFFECTS ON CARDIOVASCULAR FUNCTION AND STATURE: AN ADDENDUM TO THE U.S. EPA 1986 DOCUMENT, AIR QUALITY CRITERIA FOR LEAD

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PRELIMINARY DRAFT

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INTRODUCTION

The earlier U.S. EPA criteria document, Air Quality Criteria for Lead (EPA-600/8-77-071) has been updated and revised pursuant to section 108 and 109 of the Clean Air Act, as amended, 42 U.S.C. 7408 and 7409, and will be used as a basis for review and, as appropriate, revision of the National Ambient Air Quality Standard (NAAQS) for lead. As part of this process, EPA released two external review drafts of the revised criteria document, Air Quality Criteria for Lead (EPA-600/8-82-028A&B), which were made available both for public comment and peer review by the Clean Air Scientific Advisory Committee (CASAC) of the Agency's Science Advisory Board. A final version of that criteria document incorporating revisions made in response to public comments and CASAC review of earlier drafts is in the final stages of preparation.

Not fully evaluated in the revised Criteria Document, however, are recently published papers concerning: (1) the relationship between blood lead levels and blood pressure; and (2) lead exposure effects on early growth and stature. The present Addendum to the revised document, Air Quality Criteria for Lead, evaluates newly published information on cardiovascular effects of lead, including assessment of both human and animal toxicology studies. The Addendum also discusses newly published data regarding lead effects on growth and stature, as evaluated by epidemiology and animal toxicology studies.

1. Lead Effects on the Cardiovascular System

Lead has long been reported to be associated with cardiovascular effects, in both human adults and children. This section assesses pertinent literature on the subject, including: (1) studies of cardiotoxic effects in overtly lead-intoxicated individuals; (2) epidemiologic studies of associations between lead exposure and increased blood pressure, including observations for non-overtly intoxicated subjects; (3) toxicologic data providing experimental evidence for lead-induced cardiovascular effects in animals and (4) information on possible mechanisms of action underlying cardiovascular effects of lead exposure.

1.1 Cardiotoxic Effects in Overtly Lead-Intoxicated Human Adults and Children.

Structural and functional changes suggestive of lead-induced cardiac abnormalities have been described for both adults and children, always in individuals with clinical signs of overt intoxication. For instance, in reviewing five fatal cases of lead poisoning in young children, Kline (1960) noted that degenerative changes in heart muscle were reported to be the proximate cause of death; it was not possible, however, to establish that the observed changes were directly due to lead intoxication per se. In another study, Kósmider and Petelenz (1962) found that 66 percent of a group of adults over 46 years old with chronic lead poisoning had electrocardiographic abnormalities, a rate four times the adjusted normal rate for that age group. Additional evidence for a possible etiological role of higher level lead exposure in the induction of disturbances in cardiac function derives from observations of the disappearance of electrocardiographic abnormalities following chelation therapy in the treatment of many cases of lead encephalopathy (Myerson and Eisenhauer, 1963; Freeman, 1965; Silver and Rodriguez-Torres, 1968). The latter investigators, for example, noted abnormal electrocardiograms in 21 (20 percent) of 30 overtly lead-intoxicated children prior to chelation therapy, but abnormal electrocardiograms remained for only four (13 percent) after such therapy (Silver and Rodriguez-Torres, 1968). None of the above studies provide definitive evidence that lead induced the observed cardiotoxic effects, although they are highly suggestive of an etiological role of lead in producing such effects. Some recently reported human autopsy study results (Voors et al., 1982) showing associations between heart-disease mortality and elevated aortic lead levels also point toward possible involvement of lead in cardiotoxic disease processes.

1.2 Epidemiologic Studies of Blood-Lead/Blood-Pressure Relationships

Hypertension or, more broadly, increased blood pressure represents the single main type of cardiovascular effect long studied as possibly being associated with excessive lead exposure. As long ago as 1886, Lorimer reported that high blood lead levels increased the risk of hypertension. However, from then until only recently, relatively mixed and often apparently contradictory results have been reported concerning associations between high-level lead exposures and hypertension effects. That is, numerous investigators reported significant associations between hypertension and lead poisoning (Oliver, 1891; Legge, 1901; Vigdortchik, 1935; Emmerson, 1963; Dingwall-Fordyce and Lane,

1963; Richet et al., 1966; Morgan, 1976; Beevers, et al., 1976), whereas other studies failed to find a statistically significant association at $p < 0.05$ (Belknap, 1936; Fouts and Page, 1942; Mayers, 1947; Brieger and Rieders, 1959; Cramer and Dahlberg, 1966; Malcolm, 1971; Ramirez-Cervantes et al., 1978). The potential contribution of lead to hypertension was difficult, if not impossible, to determine based on the results of the above studies, due to many methodological differences and problems (e.g., lack of comparable definitions of lead exposure and prospective control populations, variations in how hypertension was defined or measured as the key health endpoint, etc.).

In contrast to the confusing array of results derived from the above studies, a much more consistent pattern of results has begun to emerge from more recent investigations of relationships between lower-level lead exposures and increases in blood pressure or hypertension. For example, Khera et al (1980) reported a case control study showing higher blood lead levels in hypertensive patients and those with other cardiovascular diseases than for hospital control subjects. Also, Kromhout and Couland (1984) and Kromhout et al (1985) reported associations between hypertension and blood lead among 152 elderly men in the Netherlands; Batuman et al. (1983) reported an association between hypertension and chelatable lead burdens in veterans; and Moreau et al. (1982) reported significant associations ($p < 0.001$) between blood-lead levels and a continuous measure of blood pressure among 431 French policemen (age 24 to 55 years), after controlling for important potential confounding variables such as age, body mass index, smoking, and drinking.

In a larger recent study, Pocock et al. (1984) evaluated relationships between blood lead concentrations, hypertension, and renal function indicators in a clinical survey of 7735 middle-aged men from 24 British towns. Results for the overall group studied indicated correlation coefficients of $r = +0.03$ and $r = +0.01$ for associations between systolic and diastolic blood pressure, respectively, and blood lead levels. The systolic blood pressure correlation, though small in magnitude, was nevertheless statistically significant at $p < 0.01$. However, analyses of data for men categorized according to blood lead concentrations only suggested increases in blood pressure at lower blood lead levels; no further significant increments in blood pressure were observed at higher blood lead levels (either before or after adjustment for factors such as age, body mass index, alcohol consumption, social class, and observer). Evaluation of prevalence of hypertension defined as systolic blood pressure over 160 mm Hg revealed no significant overall trend; but of those men with blood

lead levels over 37 μg/dl, a larger proportion (30 percent) had hypertension when compared with the proportion (21 percent) for all other men combined ($p < 0.08$). Similar results were obtained for diastolic hypertension defined as >100 mmHg, i.e., a greater proportion (15 percent) of men with blood lead levels over 37 μg/dl had diastolic hypertension in comparison with the proportion (9 percent) for all other men ($p < 0.07$). Pocock et al. (1984) interpreted their findings as being suggestive of increased hypertension at blood lead levels over 37 μg/dl, but not at lower concentrations typically found in British men. However, more recent analyses reported by Pocock et al. (1985) for the same data indicate highly statistically significant associations between both systolic ($p < 0.003$) and diastolic ($p < 0.001$) blood pressure and blood lead levels, when adjustments are made for variation due to site (town) in multiple regression analyses. The regression coefficients for log blood lead versus systolic and diastolic pressure were +2.089 and +1.809, respectively, when adjusted for town as well as body mass, age, alcohol, smoking, social class and observer.

Relationships between blood lead and blood pressure among American adults have also been recently evaluated, as reported by Harlan et al. (1985) and Pirkle et al. (1985). These analyses were based on evaluation of NHANES II data, which provide careful blood lead and blood pressure measurements on a large-scale sample representative of the U.S. population and considerable information on a wide variety of potentially confounding variables as well. As such, these analyses avoided the problem of selection bias, the healthy-worker effect, workplace exposures to other toxic agents, and problems with appropriate choice of control groups that often confounded or complicated earlier, occupational studies of blood-lead, blood-pressure relationships. The analyses reported by Harlan et al. (1985) demonstrated statistically significant linear associations ($p < 0.001$) between blood lead concentrations and blood pressure (both systolic and diastolic) among males and females, aged 12 to 74 years. However, using a model controlling for a number of other potentially confounding factors, blood lead was not independently related to blood pressure in women after adjusting for the effects of other variables in the model.

Further analyses reported by Pirkle et al. (1985) focussed on white males (aged 40 to 59 years) in order to avoid the effects of collinearity between blood pressure and blood lead concentrations evident at earlier ages and because of less extensive NHANES II data being available for non-whites. In the subgroup studied, Pirkle et al. (1985) found significant associations

between blood lead and blood pressure even after including in multiple regression analyses all known factors previously established as being correlated with blood pressure. The relationship also held when tested against every dietary and serologic variable measured in the NHANES II study. Inclusion of both curvilinear transformations and interaction terms altered little the coefficients for blood pressure associations with lead (the strongest relationship was observed between the natural log of blood lead and the blood pressure measures). The regression coefficients for log blood lead versus systolic and diastolic blood pressure were 8.436 and 3.954, respectively. No evident threshold was found below which blood lead level was not significantly related to blood pressure across a range of 7 to 34 μg/dl. In fact, the dose-response relationships characterized by Pirkle et al. (1985) are indicative of large initial increments in blood pressure at relatively low blood lead levels, followed by leveling off of blood pressure increments at higher blood lead levels. This pattern is consistent with biphasic blood pressure increases observed in response to blood lead increases in the rat (Victery et al., 1982a,b) and may also account for the failure of other studies to find consistent relationships between blood pressure and blood lead in study groups with mild to moderate elevations of blood lead concentrations. Pirkle et al. (1985) also found lead to be a significant predictor of diastolic blood pressure greater than or equal to 90 mmHg, the criterion blood pressure level now standardly employed in the United States to define hypertension.

Additional analyses were performed by Pirkle et al. (1985) to estimate the likely public health implications of their findings concerning blood-lead, blood-pressure relationships. Changes in blood pressure that might result from a specified change in blood lead levels were first estimated. Then coefficients from the Pooling Project and Framingham studies (Pooling Project Research Group, 1978 and McGee and Gordon, 1976, respectively) of cardiovascular disease were used as bases: (1) to estimate the risk for incidence of serious cardiovascular events (myocardial infarction, stroke, or death) as a consequence of lead-induced blood pressure increases and (2) to predict the change in the number of serious outcomes as the result of a 37 percent decrease in blood lead levels for adult white males (aged 40-59 years) observed during the course of the NHANES II survey (1976-1980). The following declines in serious outcomes were thusly estimated: (1) a 4.7 percent decrease (77,300 fewer events) for fatal and non-fatal myocardial infarctions; (2) a 6.7 percent

decrease (27,500 fewer events) for fatal and non-fatal strokes; and (3) a 5.5 percent decrease (73,900 fewer events) for death from all causes.

Unpublished reanalyses of the NHANES II data have been provided by Schwartz (1985a,b) which confirm that the regression coefficients remain significant for both systolic and diastolic blood pressure when site is included as a variable in multiple regression analyses. Schwartz (1985a,b) reported coefficients of 1.41 ($p < 0.05$) and 3.30 ($p < 0.01$) for blood lead relationships versus systolic and diastolic blood pressure, respectively, for all men over 20 years old and 3.12 ($p < 0.05$) for diastolic pressure for men aged 40 to 59, after controlling for 64 sites included in the NHANES II study. No coefficient was reported for systolic pressure for the latter age group after controlling for site, but it would be expected to be significant since the systolic results are consistently higher than for the diastolic in all other analyses.

Overall, the analyses reported by Harlan et al. (1985), Pirkle et al. (1985), and Schwartz (1985a,b) provide convincing evidence for strong associations between blood pressure increases and blood lead levels, even at blood lead concentrations below 30 μg/dl and, possibly, down to as low as 7 μg/dl. Furthermore, their results are consistent with similar findings of statistically significant associations between blood lead levels and blood pressure increases as derived from other recent epidemiologic studies, such as those of Moreau et al. (1982), Kromhout and coworkers (1984, 1985) and Pocock et al. (1984, 1985). Whether the blood-lead blood-pressure associations observed in these studies are causal or not remain to be more definitively established and the quantification of likely consequent risks for serious cardiovascular outcomes estimated by Pirkle et al. (1985) more precisely characterized.

The specific magnitudes of risk obtained for serious cardiovascular outcomes in relation to lead exposure, estimated on the basis of lead-induced blood-pressure increases, depend crucially upon the size of coefficients estimated for blood-lead blood-pressure associations. Some uncertainty exists in regard to the most appropriate blood-lead blood-pressure coefficients to use in attempting to project more serious cardiovascular outcomes. For example, the coefficients obtained in reanalyzing the NHANES II data, adjusting for site, are smaller than those reported based on analyses unadjusted for site and, thus, it might be argued that Pirkle et al (1985) overestimated probable risks of consequent serious cardiovascular outcomes. On the other hand, adjusting for site would be expected to result in loss of sensitivity and increased bias toward lower coefficients for blood-lead blood-pressure associations, which may

underestimate the strength of the underlying biological relationship and thusly lead to underestimates of risk for more serious outcomes. The best estimates of risk for more serious outcomes may, therefore, fall somewhere between those obtained using blood-lead blood-pressure coefficients unadjusted and adjusted for site in the NHANES II data set. Also complicating the situation at present are the weaker associations between blood-lead and blood-pressure reported by Pocock et al.(1984, 1985). Further analyses of additional large scale epidemiologic data sets may be necessary in order to resolve more precisely quantitative relationships between blood-lead and blood-pressure, and more serious cardiovascular outcomes as well.

Support for the plausibility of causal relationships between lead exposures and hypertension, as well as consequent more serious cardiovascular effects, is provided by the information discussed below in relation to potential mechanisms underlying lead effects on blood pressure and experimental findings bearing on the subject.

1.3 Mechanisms Potentially Underlying Lead-Induced Hypertension Effects

The underlying causes of increased blood pressure or "hypertension" (diastolic blood pressure above 90 mm Hg), which occurs in as many as 25 percent of Americans, are not yet fully delineated (Frolich, 1983; Kaplan, 1983). Many factors contribute to development of this disease, including hereditary traits, nutritional factors and environmental agents. The relative roles of various dietary and environmental factors in influencing blood pressure and the mechanisms by which they do so is a matter of intense investigative effort and debate (see proceedings of conference "Nutrition and Blood Pressure: Current Status of Dietary Factors and Hypertension," McCarron and Kotchen, 1983). This section discusses plausible biochemical-physiological mechanisms by which lead potentially influences the cardiovascular system to induce increased blood pressure, followed by the evaluation of experimental evidence concerning the contribution of lead exposure to development of hypertension.

Blood pressure is determined by interaction of two factors: cardiac output and total peripheral resistance. An elevation of either or both results in an increase in blood pressure. A subsequent defect in a critical regulatory function (e.g., renal excretory function) may influence central nervous system regulation of blood pressure, leading to a permanent alteration in vascular smooth muscle tone which sustains blood pressure elevation. The primary defect in the pathophysiology of hypertension is thought to be due to alteration in

calcium binding to plasma membranes of cells; this change in calcium handling may in turn be dependent upon an alteration in sodium permeability of the membrane (Blaustein, 1977; Rasmussen, 1983; Postnov and Orlov, 1985). This change affects several pathways capable of elevating pressure: one of which is a direct alteration of the sensitivity of vascular smooth muscle to vasoactive stimuli; and the other of which is indirect, by altering neuroendocrine input to vascular smooth muscle including changes in renin secretion rate.

1.3.1 Role of disturbances in ion transport of plasma membranes

Many stimuli activate target cells in the mammalian body via changes in ion permeabilities of the plasma membrane, primarily for sodium, potassium, and calcium ions (Carafoli and Penniston, 1985); the change in calcium ion concentration is the primary intracellular signal controlling muscle contractions, hormone secretion, and other diverse activities. Extracellular fluid contains high concentrations of sodium and calcium, while intracellular potassium is high. Intracellular calcium is present in two forms, bound and free ion, with the concentration of the free ion normally about 0.1 μM. These concentration gradients across cell membranes are maintained via the action of membrane-bound energy-requiring or voltage-dependent exchange pumps. For sodium and potassium, the regulatory pump is a sodium/potassium-dependent ATPase which extrudes sodium in exchange for potassium ions and in the process is important in maintaining the cell membrane potential. For calcium, there is a membrane potential-dependent sodium/calcium exchange pump which extrudes one calcium ion in exchange for three sodium ions. In addition, there are calcium ATPase pumps located at cell membranes and at intracellular membrane storage sites (endoplasmic reticulum and mitochondria). As calcium ions move in and out of the cell and in and out of intracellular storage sites, the intracellular free calcium ion ($[Ca^{2+}]$) changes from its resting value to something higher or lower. The ion interacts with several calcium-binding proteins which in turn activate cell contractile or secretory processes.

It has been postulated (Blaustein and Hamlyn, 1983) that sodium pump inhibition by some endogenous factor (thought to be a hormone) could be ultimately causatory for development of both essential and volume-expanded hypertension by affecting vascular tone or resistance. As explained above, the sodium pump maintains and restores the membrane potential subsequent to depolarization events. Decreased sodium pump activity may directly increase membrane permeability to calcium and increase reactivity to calcium-dependent stimuli. Small

changes in the distribution of intracellular and extracellular sodium ions affect the membrane potential and cause a much larger decrease in activity of the sodium/calcium exchange pump, resulting in a proportionately much greater elevation in intracellular free calcium ion which in turn increases reactivity to calcium-activated stimuli. Some of the newest antihypertensive therapeutic agents (calcium channel blockers) act to lower intracellular [Ca^{2+}] by reducing movement of extracellular calcium into cells, thereby reducing activation of processes requiring such movement. Diuretic drugs may reduce the postulated rise in intracellular sodium concentration related to the decreased Na/K ATPase activity and thereby reduce elevated intracellular calcium by stimulation of the Na/Ca exchange pump.

If lead exposure could be shown to affect sodium transport (which then indirectly alters vascular resistance) or to directly affect vascular resistance (by changing calcium ion permeability or transport), it could contribute to the development of hypertension. Highlighted concisely below is evidence that lead acts to alter sodium balance and calcium-activated cell activities of vascular smooth muscle. Changes in either or both of these could be expected to produce changes in blood pressure regulation.

1.3.2 Role of renin-angiotensin in control of blood pressure and fluid balance

One major endogenous factor regulating total peripheral resistance of the vascular smooth muscle is angiotensin II (AII), a small peptide generated in plasma via the action of a renal hormone, renin. Renin is synthesized and stored in juxtaglomerular (JG) cells of the kidney and is released when JG cells receive stimuli indicating a decrease in arterial pressure, as sensed by cardiovascular baroreceptors and transmitted to the central nervous system (CNS) with subsequent activation of efferent β-adrenergic signals to the kidney. Changes in the intracellular calcium ion concentration of the JG cell are thought to be involved in renin release (Churchill, 1985), with an increase in intracellular [Ca^{2+}] producing a decrease in renin secretion, while a decrease in intracellular [Ca^{2+}] produces an increase in renin release.

Renin is the first enzyme in a series which splits a small peptide, angiotensin I (AI) from angiotensinogen, or renin substrate, a large protein synthesized by liver and found in circulation. AI is converted to AII by angiotensin converting enzyme (ACE), an enzyme found in plasma and lung tissue. AII is degraded to AIII and other breakdown products by various proteolytic enzymes. Renin is cleared from plasma by the liver.

AII acts to increase total peripheral resistance by: (1) direct action on vascular smooth muscle to increase vasoconstriction (it is 10 to 40 times more potent than norepinephrine and acts to elevate cytosolic calcium of vascular smooth muscle to activate the contraction of actin and myosin); and (2) indirectly, by acting on the area postrema of the medulla oblongata to increase the discharge rate of sympathetic neurons (which increases norepinephrine release, decreases its reuptake, and increases vascular sensitivity to norepinephrine).

AII also influences renal function and overall salt and fluid balance in several ways: (1) Renal hemodynamics: glomerular filtration rate is altered by AII-related changes in renal blood flow or indirectly by increased noradrenergic transmission to the kidney resulting from CNS action of AII. (2) Salt and water metabolism: AII-induced changes in renal sympathetic tone alter reabsorption of sodium and potassium; AII stimulates aldosterone secretion which affects sodium and potassium balance; AII may have direct action on the renal tubules to increase electrolyte and water reabsorption. In addition, AII appears to act directly on the CNS to increase thirst.

The renin-angiotensin system thus has a major influence on regulation of blood pressure; for this reason, investigators interested in hypertension have studied the system in detail. Because renal disease may be an important initiating event in subsequent development of hypertension and because lead is an important renal toxicant, some investigative reports of patients with lead intoxication have evaluated blood pressure changes and changes in the renin-angiotensin system. For example, Sandstead et al. (1970) found that dietary sodium restriction produced smaller increases in plasma renin activity and aldosterone secretion rates in lead-poisoned men than expected. The mechanism of action on the renin-aldosterone system was not known. Gonzalez et al. (1979) studied renin activity, aldosterone, and plasma potassium levels in a group of lead-toxic patients. The patients had low plasma renin activity in response to a furosemide challenge (a volume-depleting stimulus) and were hyperkalemic (evidence that aldosterone levels were low). Bertel et al., (1978) presented a clinical case report of reduced beta-adrenoceptor-mediated function in a lead-toxic man (blood lead >250 μg/dl) with hypertension (160-170/100-105 mm Hg). Prior to administration of the test dose of isoprenaline, the patient had high plasma norepinephrine levels and low PRA activity. The dose of isoprenaline required to increase heart rate 25 beats/min was 15-fold greater than that required in control subjects. The raised plasma norepinephrine level suggests that reactive sympathoneural activity could cause

alpha-adrenoceptor-mediated vasoconstriction which contributes to elevated blood pressure. Lead interference with the receptor-adenylate cyclase system could reduce beta-adrenoceptor-mediated vasodilatation as well as tachycardia and renin release. Recently, Campbell et al. (1985) found Pb-related increases in the concentrations of PRA and angiotensin I in lead-exposed normotensive men. These changes may be precedent to development of hypertension.

The paucity of experimental data linking lead and changes in the renin-angiotensin system stimulated most of the following experimental studies, although many questions remain unanswered.

1.4 Experimental Studies of Lead Effects on Blood Pressure and the Renin-Angiotensin System.

Several questions can be posed regarding how lead might affect the renin-angiotensin system, such as:

(1) Does lead affect sodium handling by the renal tubule?
(2) Does lead directly affect renin release? If so, is AII elevated to an appropriate level? Do normal homeostatic mechanisms function to adjust renin levels under conditions of fluid and electrolyte loss?
(3) Does lead alter renin synthesis (as measured by renal renin content)?
(4) Does lead affect rate of production of AII by altering angiotensin converting enzyme activity?
(5) Does lead alter AII catabolism?
(6) Does lead affect renin substrate production?
(7) Does lead affect renin clearance by the liver?
(8) Does lead affect vascular reactivity directly?
(9) Does lead directly affect aldosterone release?

Many of these questions have been addressed by studies discussed below.

1.4.1 Acute In-Vivo Lead Exposure

Lead injected iv in dogs and rats, at doses as low as 0.1 mg/kg (whole blood lead < 5 μg/dl and renal lead of 1.2 μg/g) produced over the next several hours significant increases in plasma renin activity (PRA) and in excretion of sodium, other cations, and water (Mouw et al., 1978). There was no change in glomerular filtration rate; therefore, the increased sodium excretion could be attributed to decreased sodium reabsorption. The mechanism of lead's action on

tubular reabsorption was not determined but it was suggested that lead could affect mitochondrial ATP production necessary for active transport processes or action directly on carrier molecules or enzymes, e.g., Na/K ATPase, specifically involved in tubular transport. In this report, the mechanism by which lead increased renin secretion was not determined.

In a subsequent report, Goldman et al. (1981) found that the rise in PRA after acute lead injection was not due to increased renin secretion in six of nine dogs; rather, there was elimination of hepatic renin clearance, without evidence for other interference in liver function. In the remaining three dogs, renin secretion increased; this was thought to be due to lead activation of normal mechanisms for renin secretion, although none of the classic pathways for influencing renin secretion were altered. The authors postulated that lead might produce alterations in cytosolic calcium concentration in renin-secreting cells. (Further evidence that cytosolic calcium concentration is indeed important in renin release has been reviewed in detail by Churchill, 1985.) In addition, although angiotensin II (AII) levels in lead-exposed animals were elevated because of increased PRA, the AII levels were not increased proportionately as much as the PRA, leading to a further suggestion that angiotensin-converting enzyme (which converts AI to AII) was suppressed or that AII-degrading enzyme was enhanced. The authors noted that multiple actions of lead on the renin-angiotensin system may help explain confusion about the ability of lead to cause hypertension. At certain exposure conditions, there could be elevated PRA without simultaneous inhibition of angiotensin-converting enzyme, thereby contributing to hypertension, while higher doses or longer exposure might inhibit converting enzyme and thereby cause loss of hypertension.

1.4.2 Chronic Lead Exposure

The literature of experimental findings of lead-induced changes in the renin-angiotensin system and blood pressure in animals is complicated by apparently inconsistent results when comparing one study to another. All studies report changes in the renin-angiotensin system, yet some studies fail to find an effect on blood pressure and others do report hypertension. Doses and exposure periods employed vary widely, but in general, hypertension is observed most consistently with relatively low doses over relatively long exposure periods. The papers reviewed here make specific mention of lead dose employed and blood lead concentration achieved (if measured). For comparison

with human exposure findings, it is helpful to recognize that blood lead concentrations seldom exceed 40 μg/dl in the general population.

Perry and Erlanger (1978) found that chronically feeding rats either cadmium or lead at doses of 0.1, 1.0, or 0.5 ppm produces statistically significant increases in systolic blood pressure. The mechanisms for this finding were not discussed but the implications for human populations exposed to very low doses of these metals were pointed out. Victery et al. (1982a) reinvestigated the question, using lead doses of 100 and 500 ppm administered in the drinking water to rats beginning while animals were in utero and continuing through six months of age. At 3½ mo of age, the male rats drinking 100 ppm lead first demonstrated a statistically significant increase in systolic blood pressure (152 ± 3.7 vs. 135 ± 5.6 mm Hg); this difference persisted for the remainder of the experiment. Animals drinking 500 ppm had lower pressures which were not significantly different from controls. Female rats drinking 100 ppm did not demonstrate pressure changes. At termination of the experiment PRA was significantly decreased by 100 ppm lead exposure, but not at 500 ppm. AII values tended to be lower (controls: 22 ± 8 pg/ml, 100 ppm: 13 ± 7, 500 ppm: 10 ± 2). There was a dose-dependent decrease in AII/PRA ratio for lead-exposed rats. Renal renin was depressed in lead-exposed animals. The hypertension observed in these animals was not secondary to overt renal disease (as opposed to an effect on renal cell metabolism), as evidenced by lack of changes in renal histology and plasma creatinine.

With regard to possible mechanisms of the lead-induced hypertension, the animals had low-renin hypertension (which is characteristic of 30 percent of people with hypertension). Thus elevated renin was not responsible for maintenance of the hypertension. Volume expansion may be a factor, as suggested by slight increases in body weight and decreased hematocrit (also possibly related to lead effects on heme synthesis). There was no change in plasma sodium and potassium, although more sensitive determinations of fluid balance and exchangeable sodium were not done. A second potential hypertensive mechanism, increased vascular responsiveness to catecholamines, was examined and is discussed below.

Victery et al. (1983) examined changes in the renin-angiotensin system of rats exposed to lead doses of 5, 25, 100, or 500 ppm during gestation until 1 month of age. All had elevated plasma renin activity, while those at 100 and 500 ppm also had increased renal renin concentration. Lead-exposed animals anesthetized to obtain the blood sample secreted less renin than control animals. It appears that lead has two chronic effects on renin secretion, one

inhibitory and one stimulatory; the magnitude of effect on PRA reflects the dose and timing of the lead exposure as well as the physiological state of the animal.

In another study, Victery et al. (1982b) reported that rats fed 5 or 25 ppm lead for 5 months (blood lead of 5.6 and 18.2 µg/dl respectively) did not develop hypertension but at 25 ppm had significantly decreased PRA. Both groups of animals had a decrease in the AII to PRA ratio. Thus, lead exposure at levels generally present in human population caused observable effects in renin synthesis, and were consistent with either inhibition of conversion of AI to AII or enhanced AII catabolism. No measurements of ACE activity were made. The failure to observe hypertension in these animals may have been due to a number of factors, but additional studies may be required to verify this finding.

Iannaccone et al. (1981) administered 50 ppm lead to male rats for 160 days (average blood lead of 38.4 µg/dl) and found a marked increase in arterial pressure of lead-exposed animals (systolic/diastolic 182 ± 6/138 ± 7 mm Hg) versus pressures in controls of 128 ± 5/98 ± 3. No measurements of hormone levels were performed; determination of vascular reactivity in these animals is discussed below.

Male pigeons fed a diet containing added calcium (100 ppm), magnesium (30 ppm), lead (0.8 ppm), or cadmium (0.6 ppm) in a 2x4 factorial design for a six-month period were observed for alterations in aortic blood pressure and atherosclerotic changes (Revis et al., 1981). Diastolic pressures were 25 mm Hg higher in pigeons exposed to Mg, Pb, or Cd than in Ca-exposed pigeons. Systolic pressure was greatest in Cd-exposed birds. Calcium in the diet resulted in lowered systolic pressures in animals exposed to combinations of other metals (presumably by decreasing their gastrointestinal absorption). Similarly, there was a decrease in number and size of aortic plaques in presence of calcium and an increase with lead exposure.

Keiser et al. (1983b) tested lead-exposed rats (500 or 1000 ppm for 3-4 mo, blood leads of 41 and 55 µg/dl) for the ability of the liver to clear exogenous renin and a test substance (sulfobromophthalein) following nephrectomy and found no difference from control clearance times. Thus, elevations in plasma renin observed in chronically exposed animals must be the result of increased renin secretion. However, the finding of decreased renin activity after some long-term exposure periods (see above) illustrates that lead must also act in an inhibitory way to decrease renin secretion and the finding of

decreased, increased, or no change in renin activity depends on the balance of the stimulatory and inhibitory input to the juxtaglomerular cells. Angiotensin-converting enzyme, which was postulated to be low in lead-exposed animals (see above), was found to be normal in both plasma and lungs.

1.4.3 Renin Secretion by Kidney Slices In-Vitro

The effects of renin-secretion stimuli on the ability of kidney slices to secrete renin *in vitro* either after chronic *in vivo* exposure or *in vitro* exposure to lead have been studied by several investigators. Keiser et al. (1983a) reported that rabbit kidney cortex slices exposed to 10^{-5} or 10^{-6} M lead secreted significantly less renin than controls. Slices obtained from lead-exposed rabbits (500 or 1000 ppm for 7 wk, with blood lead levels of 66 and 109 µg/dl respectively) secreted significantly more renin *in vitro* than controls. They postulated that lead could compete with Ca^{2+} for influx into juxtaglomerular cells and thereby stimulate renin release. Responsiveness to a beta-adrenergic stimulus was less in the higher-dose slices. Since β-adrenergic stimuli are thought to act via reduction of intracellular $[Ca^{2+}]$ (by increased Ca efflux or intracellular sequestration), it was proposed that lead may interfere with these calcium fluxes and interfere with the response to β agonists.

Meredith et al. (1985) found somewhat contradictory results, with lead able to provoke renin secretion from rabbit kidneys both *in vivo* and *in vitro* (at comparable dose levels to that used by Keiser). Calcium channel blockers attenuated this response. These authors propose that lead is able to act at the cellular level to stimulate renin secretion. Since most experimental evidence suggests that increased intracellular calcium decreases renin release, whereas calcium efflux stimulates renin secretion, the authors further postulate that lead uptake by the juxtaglomerular cells promotes calcium efflux which then leads to an increase in renin secretion.

1.4.4 Effects of Lead on Vascular Reactivity

Piccinini et al. (1977) and Favalli et al. (1977) studied the effects of lead on calcium exchanges in the isolated rat tail artery; lead in concentrations of up to 15 µmol *in vitro* produced contractions which required the presence of calcium in the perfusion solution. Therefore, calcium influx was not affected by lead. The fact that tissue calcium content was increased is compatible with the sites of lead action at the cell membrane; lead inhibits calcium extrusion, and at intracellular stores, lead decreases calcium-binding

capacity. Both processes produce an increase in intracellular exchangeable calcium.

Tail arteries obtained from the hypertensive rats in the study performed by Victery et al. showed an increased maximal contractile force when tested in vitro with the alpha-adrenergic agents norepinephrine and methoxamine (Webb et al., 1981). This finding is apparently related to an increase in the intracellular pool of activator calcium in the smooth muscle cells in the artery. This change may also be responsible for decreased relaxation of the muscle after induced contractions.

In vivo tests of cardiovascular reactivity in rats exposed to 50 ppm lead (blood lead 38.4 ± 3.6 μg/dl) for 160 days were performed by Iannaccone et al. (1981). Systolic and diastolic blood pressure readings obtained under anesthesia were 182 ± 6/138 ± 7 mm Hg for lead-exposed rats versus 128 ± 5/98 ± 3 for controls. Humoral agents, norepinephrine and angiotensin II (but not bradykinin and angiotensin I), produced significant increases in systolic and diastolic pressure. This suggests there is decreased conversion of AI to AII. At high doses, epinephrine produced an equal increase in pressure in lead-exposed and control animals; at lower doses, only slight increases in mean arterial pressure were observed. Bilateral carotid artery occlusion under conditions of autonomic blockade produced a two fold greater decrease in blood pressure and heart rate in lead-exposed rats. The data suggest that the lead-related increase in arterial pressure is due at least in part to greater sympathetic tone, with the metal affecting neural control of blood pressure.

1.4.5 Lead Effects on Cardiac Muscle

Lead has been hypothesized to contribute to cardiomyopathy (Asokan, 1974) and to have cardiotoxic properties. Rats fed 1 percent lead acetate for 6 weeks (with blood lead of 112 ± 5 μg/dl) had structural changes in the myocardium. These included myofibrillar fragmentation and separation with edema fluid, dilation of the sarcoplasmic reticulum, and mitochondrial swelling. These changes were observed before any measured changes in myocardial electrolyte concentrations.

Williams et al. (1977a,b) exposed young rats to lead (2000 ppm; blood lead at 21 days of age was 43 μg/dl but was not different from controls at 170-200 days) via maternal milk, from birth to 21 days of age. Animals were studied for cardiovascular response to norepinephrine at 170-200 days of age. There were no differences in the blood pressure increase to norepinephrine but there

was a five- to ten-fold increase in cardiac arrhythymias in lead-exposed animals. There were no differences in the basal or norepinephrine-stimulated cyclic AMP levels in cardiac tissue.

In a subsequent study (Hejtmancik and Williams, 1979), it was reported that only part of the arrhythmogenic activity of norepinephrine in lead-exposed rats was due to reflex vagal stimulation; there was also a direct cardiac effect, probably at the alpha receptor level. Lead appeared to have no effect on beta receptors.

Kopp et al. (1978) worked out an in vitro system for monitoring the cardiac electrical conduction system, electrocardiogram, and systolic tension, and were able to demonstrate that in vitro lead (3×10^{-2} mM) or cadmium (3×10^{-2} mM) depressed systolic tension and prolonged the PR interval of the ECG. Both ions increased conduction times in the His bundle electrograms but conduction blocks occurred at different sites (atrioventricular node for cadmium and distal to the His-Purkinje cell junction for lead).

In a subsequent paper, Kopp and Barany (1980) found that cadmium or lead added to heart tissue perfused in vitro (3×10^{-3} mM and 3×10^{-4} mM, respectively) inhibited the positive inotropic activation of the heart by calcium and isoproterenol, and the concomitant increase in phosphorylation of cardioregulatory proteins. There was no effect of lead or cadmium on the positive chronotropic effects of the beta-adrenergic agonist.

Hearts obtained from rats exposed to low levels of cadmium and/or lead (5 ppm) for 20 months were found to have similar changes in the heart's electrical conduction system (Kopp et al., 1980) with significant prolongation of the P-R interval. In lead-fed animals, this was due to increased conduction time through the His-Purkinje cell system.

Williams et al. (1983) suggested that much of the negative inotropic effect of lead on cardiac tissue and ECG abnormalities can be related to lead's interference with calcium ion availability and/or membrane translocation. In addition, even those lead exposure-related effects that appear to occur through autonomic nerves may be understood in terms of effects on calcium ion which is required for neurotransmitter release.

Evis et al. (1985) studied the effects of chronic low lead treatment (5 and 25 ppm, with blood leads < 10 µg/dl) and hypertension (spontaneously hypertensive rats) on blood pressure and the severity of cardiac arrhythmias in rats. The animals were studied up to 16 months of age and the authors reported

that there were no consistent lead-related effects on ischemia-induced cardiac arrhythmias, blood pressure or P-R interval in the electrocardiogram.

1.5 Summary of Lead-related Effects on the Cardiovascular System

To briefly summarize, lead can directly inhibit renal tubule reabsorption of sodium, probably via action on the sodium/potassium ATPase. Na/K ATPase inhibition may occur in other cell types as well. Some volume depletion may occur which could contribute to elevation in plasma renin activity. The lead effect on PRA can be stimulatory, inhibitory, or without effect, depending on the length of exposure and the exposure level. Lead exposure reduces the increase in PRA which occurs with noradrenergic stimulation. It is not likely that the chronic increase in PRA is due to decreased hepatic clearance of renin. Depending on the length and dose of lead exposure, renal renin concentration is elevated followed by decreased concentrations. In response to elevations in PRA, there are increased levels of AII, but the levels are inappropriately low; this does not appear to be due to a lead-related decrease in ACE, but rather to increased AII catabolism. Aldosterone levels are also inappropriately low, possibly due to a lead-related defect on calcium ion-dependent release of aldosterone. Vascular smooth muscle isolated from lead-exposed animals has increased reactivity to noradrenergic stimuli, probably due to an increase in intracellular calcium ions. There appears to be increased sympathetic activity in lead-exposed animals. Cardiac arrhythmias are usually observed to be more frequent in lead-exposed animals.

Although the exact mechanisms involved in lead-induced changes in renin secretion rate have not been examined, it is likely that lead could be affecting the cytosolic free calcium ion of the juxtaglomerular cells. When there is a stimulation of renin release, there is presumably a decrease in intracellular $[Ca^{2+}]$ due to lead blockage of calcium entry through voltage-sensitive calcium channels. After lead enters the juxtaglomerular cells, lead could enhance or block calcium exit via Na/Ca exchange pumps or increase or decrease the intracellular sequestration of calcium in storage compartments. It is not yet clear whether lead stimulates or antagonizes calcium fluxes that occur in the JG cells; therefore it is not possible to state definitely which of these possibilities is more correct. Renin release in response to adrenergic stimuli binding to receptor-operated calcium channels appears to be inhibited. The reasons for this are not known, but lead may decrease the number of receptor sites or change the intracellular calcium response which is normally elicited

when these channels are stimulated. For example, if intracellular free calcium ion levels are already elevated and there were to be a smaller decrease in $[Ca^{2+}]$ than normal due to blocking of calcium efflux via the Na/Ca exchange pumps or lowered pumping into intracellular stores, renin secretion would be less under conditions of adrenergic stimulation.

The changes in vascular reactivity which have been reported in animals chronically exposed to lead are probably the key finding which can lead to an understanding of how lead can contribute to development of hypertension. The vascular smooth muscle changes are necessary and sufficient in themselves to account for the increase in blood pressure and the fact that these changes are observed in animals exposed to relatively low lead levels makes it increasingly important to evaluate these findings in additional experimental studies. There may be additional changes (not yet evaluated) in the entire sympathetic neural control of vascular tone which acts to amplify the contractile response to any endogenous vasoconstrictor substance.

Two authors (Audesirk, 1985, and Pounds, 1984) have recently reviewed experimental evidence on the influence of lead on calcium movements at the subcellular level in a variety of cell types including neurons, neuromuscular synapses, and hepatocytes. The reader should consult these reviews for experimental documentation of the postulated changes in calcium-activated systems. Lead may interact with any process normally influenced by calcium ions and, depending on the system, lead may act as a calcium antagonist or as an agonist. In addition, lead interferes with the function of many proteins, especially enzymes such as Na/K ATPase and the mitochondrial respiratory enzymes. These interactions may influence calcium ion concentrations and movements. If lead interferes with calcium ion movement through calcium channels, either by blocking entry or blocking efflux, there will be a decrease or an increase in cytosolic free calcium ion. Lead may alter the distribution and uptake rates of calcium ion in cell storage sites with the result that mitochondrial and endoplasmic reticulum levels can be increased or decreased; this in turn would affect cytosolic free calcium levels. Lead binds to calcium-binding sites on calcium regulatory proteins (calmodulin, in particular [Cheung, 1984]) and thereby can alter enzyme systems such as Ca-specific ATPase, which would then alter calcium efflux from the cytosol.

This review has discussed some of the major experimental data concerning lead-related changes in blood-pressure regulatory systems. Further research efforts are necessary to evaluate more fully cellular mechanisms by which lead

exposure produces its effects. Most data, however, are consistent with an effect of lead (even at very low levels) on the renin-angiotensin system and on vascular reactivity. Both of these effects are probably related to lead-induced changes in intracellular free calcium ion concentration, in juxta-glomerular cells of the kidney, in neural centers controlling blood pressure, and in cardiac and vascular smooth muscle. The result is altered renin and AII levels, and increased responsiveness of the vascular smooth muscle to vaso-constricting stimuli. As long as these factors are stimulated by lead exposure, it would be logical to expect that increased blood pressure would result. However, there appear to be other effects of lead, particularly at higher doses for longer exposure periods, at which blood pressure is no longer elevated. This may reflect more extensive deterioration of the hemeostatic controls of blood pressure so that further increases in pressure do not occur. Additional experimental studies will be necessary to explain the so-called biphasic dose-response curve for the lead-related changes in blood pressure, which appear to parallel those observed in humans as delineated by epidemiologic studies of blood-lead blood-pressure relationships discussed earlier.

2.0 Lead Effects on Growth and Stature

The effects of lead exposure early in development on physical growth and stature have recently become a matter of increasing interest and potential concern, in light of certain newly published epidemiologic observations. The new epidemiologic results, coupled with earlier reports of findings from human and experimental animal studies, point toward retardation or "stunting" of physical growth or stature due to lead exposure during early prenatal or post-natal development, including at relatively low lead exposure levels encountered in the general population.

2.1 Epidemiologic Observations

Among the earliest indications of lead effects on stature are observations reported by Nye (1929) regarding "runting," along with squint and foot drop, as physical signs characteristic of overtly lead-poisoned Australian children seen in the 1920's. Remarkably, since then very few systematic evaluations of possible stunting of physical growth have been included among the health end-points examined in the numerous epidemiologic studies of lead effects on early human development.

In one such study, Mooty et al. (1975) obtained physical measurements (weight, height) for children (2-4 years old) chosen according to low ($\bar{x}$ ± S.D.= 20.4 ± 4.3 µg/dl) and high (56.9 ± 8.3 µg/dl) blood lead levels. The 21 high-lead children, with blood lead levels in the range 50-80 µg/dl, were both shorter ($\bar{x}$ = 32.1 percentile on Stuart's Boston Growth Charts) and weighed less ($\bar{x}$ = 43.8 percentile) than the 26 low-lead children with blood leads of 10-25 µg/dl (height = 41.1 percentile, weight = 48.7 percentile). The average age for the control subjects was 34 months and was comprised of 12 Puerto Rican, 8 Black and 5 Caucasian children, whereas the high-lead group's mean age was 33 mos. and was comprised of 4 Puerto Rican, 17 Black and no Caucasian children. Because of the slightly younger age and lack of Caucasian children in the high-lead group (as well as other differences, e.g., dietary intakes), it is not possible to clearly determine the relative contribution of lead to the observed smaller stature of the high lead subjects versus other factors.

In a later study, Johnson and Tenuta (1979) studied the growth and diets of 43 low-income Milwaukee children (aged 1 to 6 yrs) in relation to their blood lead levels. Children with low (12-29 µg/dl; N = 15), moderate (30-49 µg/dl; N = 16) and high (50-67 µg/dl; N = 12) blood lead levels had average daily calcium intakes of 615, 593, and 463 mg, respectively. Also, there was a relative decrease ($p < 0.075$) in individual height percentile with increasing blood lead level (the high blood lead children had means of 25.7 percentile for height and 42.2 percentile for weight; no specific data for other lead groups reported), and higher incidence of pica (eating of plaster and paint) on the part of the children with blood leads ranging from 30 to 67 µg/dl. Unfortunately, the specific racial composition and age of the different blood lead groups were not reported, making it impossible to determine the relative contribution of such factors (or the differences in calcium intake or other dietary factors) versus lead to the observed smaller stature among the high lead children.

In another study, Routh et al. (1979) examined a sample of nonurban children (N = 100; mainly from lower socio-economic families in NC) with developmental and learning disabilities for previously undiagnosed lead intoxication. One child with "moderately" elevated blood lead (according to the then-existing CDC classification, 50-79 µg/dl) and nine with "minimal" elevations (30-49 µg/dl) were identified. Of these 10 children, seven were microencephalic (defined as head circumferences at or below the third percentile for the child's age on standard growth charts). This was a markedly greater proportion

of microencephaly (17 of 62; 25 percent) than that seen among the remaining children with blood leads below 29 μg/dl. Most of the microencephaly syndrome children were Black. Five of the elevated blood-lead children also showed more general growth retardation, in that their height, weight, or both were at or below the third percentile for age and sex. These results, as those from the previously discussed studies, are highly suggestive of possible stunting of growth due to lead exposure early in development resulting in blood lead levels generally above 30 μg/dl. However, again it is not possible to clearly separate the relative contribution of lead from other factors (racial, dietary, etc.) that may have affected growth of the children studied by Routh et al. (1979).

Much stronger evidence for lead exposure producing retardation of growth and decreased stature has more recently emerged in the 1980's from both animal toxicology studies (discussed below) and evaluation of larger scale epidemiologic data sets. In regard to the latter, Schwartz et al. (1986) have reported results of analyses of data from the NHANES II study described earlier in relation to evaluation of blood-lead blood-pressure relationships. More specifically, Schwartz et al. (1986) analyzed results for anthropometric measurements, as well as numerous other factors (age, race, sex, dietary, etc.) likely to affect rates of growth and development, among the NHANES II children.

Linear regressions of adjusted data from 2695 children (aged 7 yrs or younger) indicated that 9 percent of the variance in height, 72 percent of the variance in weight, and 58 percent of the variance in chest circumference were explained by the following five variables: age, race, sex, blood lead, total calories or protein, and hematocrit or transferrin saturation. The step-wise multiple regression analyses further indicated that blood lead levels were a statistically significant predictor of childrens's height ($p < 0.0001$), weight ($p < 0.001$) and chest circumference ($p < 0.026$), after controlling for age in months, race, sex and nutritional covariates. The strongest relationship was found between blood lead and height, with threshold regressions indicating no evident threshold for the relationship down to the lowest observed blood lead level of 4 μg/dl. At their average age (59 mo.), the mean blood lead level of the children appears to be associated with a reduction of about 1.5 percent below the height expected if their blood lead level had been zero. Similarly, the relative impacts on weight and chest circumference were of the same magnitude.

Overall, the above findings of Schwartz et al. (1986) appear to be highly credible, being based on well-conducted statistical analyses of a large-scale national survey data set (which was subjected to rigorous quality assurance procedures) and having taken into account numerous potentially confounding variables. Other recent results, newly emerging from independent, well-conducted prospective studies of prenatal and early postnatal lead exposure effects on human development, also appear to substantiate the likelihood of lead retarding early growth. For example; Dietrich et al. (1986) report that prenatal maternal blood lead levels and early postnatal (10-day) blood lead levels were negatively correlated with birth weight ($p < 0.001$) and gestational age ($p < 0.05$) for 185 infants from low socio-economic inner-city Cincinnati families. The plausibility of reported epidemiologic findings of associations between early lead exposure and retardation of growth reflecting causal relationship is supported by some limited animal toxicology results concisely discussed below.

2.2 Animal Toxicology Studies

Numerous experimental animal studies on the neurobehavioral or other effects of lead exposure early in development have taken into account lead effects on maternal nutrition or postnatal growth of exposed animals as possible confounding factors. Few, however, have systematically evaluated lead effects in growth per se as one of the major health endpoints measured.

One study, by Grant et al. (1980), does provide detailed experimental data relating external lead exposure doses to consequent blood lead levels and growth rate measured in terms of both weight and length. Continuous prenatal and postnatal exposures to lead were accomplished via lead adulteration of the drinking water: (1) of dams prior to conception, throughout pregnancy, and nursing; and (2) of the drinking water consumed post-weaning by their offspring through 180 days (6 mo.). Females from lead exposure groups averaging blood lead levels in the range 18-48 µg/dl were significantly shorter in crown-to-rump length from postnatal days 7 to 180, but lead-exposed males exhibited a transient retardation of growth and were not significantly different in length than control animals by the end of the 180 day observation period. Decreased body weight, (with no decrease in food consumption per unit of body weight) was found in animals with blood leads of 40-60 µg/dl, whereas deficits in rate of neurobehavioral development and indications of specific organic or functional

alterations (Fowler et al., 1980) were observed at blood lead levels in the range of 20-40 μg/dl.

The mechanisms by which lead exposure early in development may affect growth remain to be more fully delineated. One of the more likely possibilities is an effect of lead on neural pathways in the brain regulating neuroendocrine functions mediated by the pituitary gland and/or direct effects of lead on other developing endocrine organs, which may in turn alter feedback mechanisms resulting in disruption of normal CNS neuroendocrine control. In that regard, Petrusz et al., (1979) have reported effects of early postnatal lead exposure on pituitary and serum gonadotropins in neonatal rats - effects which might be part of a complex chain of neuroendocrine alterations that could result in growth disturbances. Similarly, other reports of lead effects on neuroendocrine central mechanisms in animals (e.g., Govani et al., 1980) and man (e.g., Sanstead et al., 1969, 1970) provide additional support for possible involvement of lead effects on endocrine function that could result in growth retardation. Of particular interest are reported observations on somatomedin activity before and after chelation of lead-intoxicated children (Rohn, 1982).

2.3 Summary and Conclusions Regarding Lead Effects on Growth and Stature

The earlier epidemiologic studies discussed above (Mooty et al., 1975; Johnson and Tenuta, 1929; Routh et al., 1979) provided suggestive evidence for lead effects on early growth and stature. However, it is difficult to apportion relative degrees of contribution of lead to observed growth deficits in comparison to other factors due to the manner in which the data from these small scale studies were reported. Much stronger evidence has emerged from the Schwartz et al. (1986) evaluation of the large-scale NHANES II nationwide data set and some additonal data beginning to emerge from prospective studies, such as that of Dietrich et al. (1986).

The plausibility that the observed epidemiologic associations between lead exposure and retarded growth reflect causal relationships is supported by certain limited parallel experimental toxicology observations in the rat by Grant et al. (1980), albeit at blood lead levels distinctly higher than the lower values in the range of blood lead levels of children included in the Schwartz et al. (1986) analysis. Furthermore, the possibility of lead effects on neuroendocrine mechanisms mediating lead-induced retardation of growth is also supported by certain studies, e.g., those of Petrusz et al. (1979) and others, showing effects of lead in neuroendocrine functions in animals and man.

Much remains to be done, however, in regard to more fully characterizing quantitative relationships between lead exposure and growth retardation in children, as well as determining the specific physiological mechanisms underlying such effects.

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