

Chronic Effects of Lead on the Renin-Angiotensin System

by Arthur J. Vander*

This paper reviews the chronic effects of lead exposure on the renin-angiotensin system in experimental animals and human beings. In rats, when lead exposure is begun several weeks after birth in doses that cause blood lead concentrations (PbB) of 30 to 40 $\mu\text{g}/\text{dL}$, the result is an increase in basal plasma renin activity (PRA) and renal renin concentration, with no change in the metabolic clearance of renin; this is presumptive evidence for increased renin secretion. PRA is also increased in 1-month-old animals whose exposure to lead (in doses that raise PbB to 9 $\mu\text{g}/\text{dL}$) was begun *in utero*. In contrast, older animals whose exposure was begun *in utero* manifest no change or a decrease in their PRA and renal renin concentration. Regardless of when the exposure is begun, lead can decrease the plasma concentration of angiotensin II at any given PRA, but the dose required for this effect is highly variable. The hypertension induced by lead exposure is associated with low PRA and a normal angiotensin II/PRA ratio. Chronic human exposure to lead also is associated with highly variable changes in PRA from study to study; it has been reported to be decreased under both basal and stimulated conditions, unchanged, or increased in a manner exponentially related to PbB. The human data are consistent with the tentative hypothesis that lead-exposed persons may have higher PRA than normal during the early periods of modest exposure but normal or depressed PRA following more chronic severe exposures. In a small preliminary study, blood lead concentration was found to be higher in high-renin hypertensive persons than in normotensive persons.

Introduction

Since the renin-angiotensin system is one of the most potent pressor systems in the body, lead-induced changes in the system might well influence arterial blood pressure. Our laboratory has extensively studied the effects of both acute and chronic lead exposure on this system in experimental animals, but the present review of those experiments will be restricted to the chronic studies, as these are most relevant to the issue of whether lead exerts a chronic influence on human blood pressure. The second part of this paper will review the existing data relating lead exposure and the renin-angiotensin system in humans.

Animal Studies

Renin

Table 1 is a summary (1) of published animal studies performed in our laboratory relating chronic lead exposure to plasma renin activity (PRA) or to plasma renin concentration. Typical results from these experiments are illustrated in Figures 1-8.

Figure 1 is an example of the effects of lead on plasma

renin concentration (PRC) in rats, using the simplest protocol: exposure of the animals to 500 ppm lead in drinking water beginning at 5 weeks of age and continuing for 4 to 5 months. The basic and replicable finding in this type of exposure is a lead-induced increase in PRA or PRC of approximately 50% (2,3). [PRA and PRC may be taken as equivalent measures in all these experiments, because lead exposure does not cause a dissociation between these two methods for evaluating plasma renin (2).]

Figure 2 shows that renal renin concentration is also elevated to the same degree as plasma renin (2,3). This constitutes strong indirect evidence that increased renin secretion is the cause of the increased plasma renin, as renal renin concentration and renin secretion are known to vary in the same direction in a wide variety of situations. This conclusion—that an increase in renin secretion, not a decrease in renin removal from the plasma was the cause of the increased plasma renin—was confirmed by our finding that the metabolic clearance of renin is unchanged during this type of chronic exposure (2). [In contrast, lead-induced changes in metabolic clearance importantly influence plasma renin in acute studies (4).]

Figure 3 presents an experiment similar to that shown in Figure 1; however, in addition to studying basal PRA, renin secretion was experimentally stimu-

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Table 1. Summary of animal studies relating chronic lead exposure and plasma renin activity.^a

Reference	Sex, species	n	Pb exposure, ppm	PbB, µg/dL	Age exposure begun	Duration of exposure	Effect on basal PRA ^b relative to control	Effect on provoked PRA relative to control	AI/PRA
(3)	M rat	6	0		—				
	M rat	6	500	30.0	5 weeks	5 months	Increased	Blunted	—
(6)	M rat	10	0	1.4					
	M rat	10	5	5.6	<i>In utero</i>	5 months	NS ^c	NS	NS
	M rat	5	25	18.2	<i>In utero</i>	5 months	Decreased	Increased	Decreased
(7)	M rat	13	0	2.2					
	M rat	16	100	40.4	<i>In utero</i>	6 months	Decreased	NS	NS
	M rat	10	500	70.8	<i>In utero</i>	6 months	NS	NS	Decreased
(5)	F rat	22	0	2.8					
	F rat	23	5	9.0	<i>In utero</i>	1 month	Increased	—	—
	F rat	20	25	18.6	<i>In utero</i>	1 month	Increased	—	—
	M rat	12	0		—				
	M rat	13	100	32.6	<i>In utero</i>	1 month	Increased	—	—
	M rat	13	500	65.8	<i>In utero</i>	1 month	Increased	—	—
	F rat	6	0		—				
	F rat	19	100	30.0	<i>In utero</i>	1 month	NS	Blunted	NS
	F rat	13	500	78.2	<i>In utero</i>	1 month	Increased	NS	Decreased
	(2)	M rat	30	0	2.2				
M rat		18	500	41.3	5 weeks	4 months	Increased	—	NS
M rat		12	1000	54.9	5 weeks	4 months	Increased	—	Decreased
(8)	M rabbit	5	0	7	2 months	7 weeks			
	M rabbit	7	500	66	2 months	7 weeks	NS	—	—
	M rabbit	5	1000	109	2 months	7 weeks	NS	—	—

^aAdapted from Sharp et al. (1).

^bPRA, plasma renin activity.

^cNS, not significant.

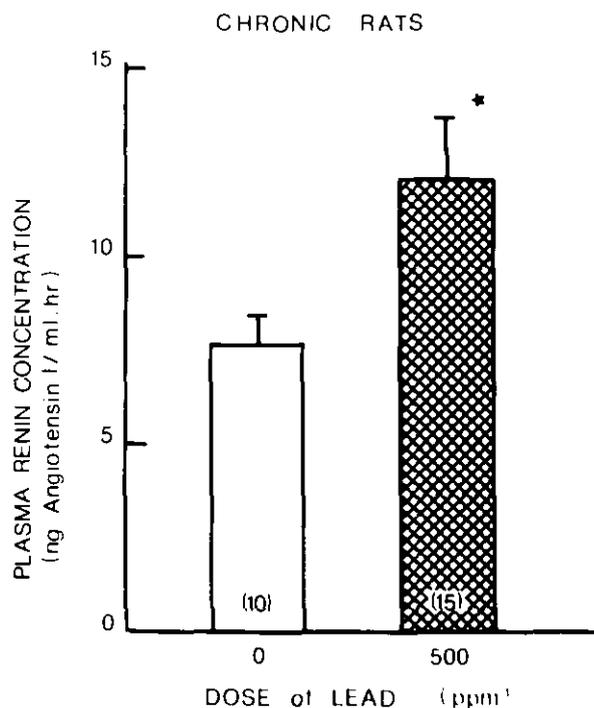


FIGURE 1. Effect of chronic lead exposure (500 ppm in the drinking water) on basal plasma renin concentration in rats. Exposure was begun when the rats were 5 weeks old, and blood samples were obtained by decapitation 4 months later. Asterisk denotes p value of < 0.05 . The PbB in the lead-exposed animals averaged 41.3 µg/dL. Figure originally published in Keiser et al. (2).

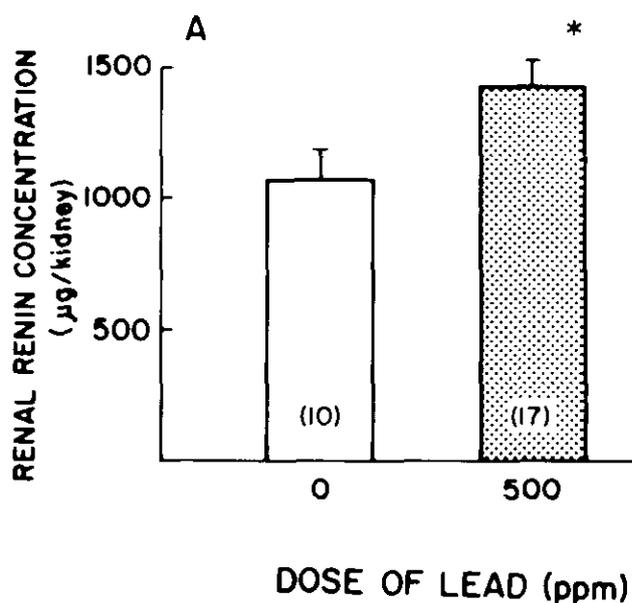


FIGURE 2. Effect of chronic lead exposure (500 ppm in the drinking water) on renal renin concentration in rats. These measurements are from the same animals whose PRA values are shown in Fig. 1. Asterisk denotes p value of < 0.05 . Figure originally published in Keiser et al. (2).

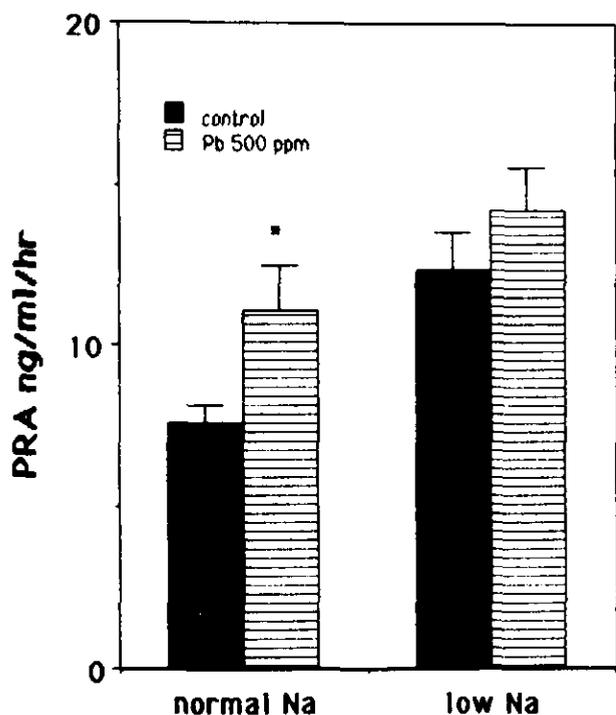


FIGURE 3. Effects of chronic lead exposure (500 ppm in the drinking water) on plasma renin activity (PRA) in rats on standard low sodium rat chows. Exposure was begun when the rats were 5 weeks old and blood samples were obtained 5 months later. Asterisk denotes p value of < 0.02 . The PbB in the lead-exposed animals averaged $30.0 \mu\text{g/dL}$. Data are from Fleischer et al. (3).

lated in two groups of animals by placing them on a low sodium diet (3). Under such conditions, although basal PRA (i.e., PRA in the animals on the usual rat diet) was elevated in the lead-exposed animals, there was no significant difference in PRA between the unexposed and exposed animals on the low sodium diet. Thus, lead exposure appeared to blunt the renin response to the stimulus of a low sodium diet.

The next sets of experiments involved exposure of the animals to lead *in utero*, followed by continued exposure after birth for the remainder of the experiment. We used this model to mimic more closely human exposures to lead. Figures 4 and 5 illustrate the effects of this type of exposure on PRA at 1 month after birth (5). As expected from the studies previously described, the lead-exposed animals showed a significant elevation of PRA; indeed, as shown in Figure 5, a significant increase in PRA was seen with an exposure of only 5 ppm. (Also consistent with the studies described above, the increase in PRA in response to the stimulus of anesthesia and laparotomy was significantly less than that of the control animals.)

However, as illustrated in Figures 6 and 7, a reversal of this pattern was seen when animals subjected to this exposure protocol were studied at 5 to 6 months of age, the exposure having been continued throughout (6,7). Instead of a significant increase in PRA, animals exposed to the middle range of lead doses (25 ppm and

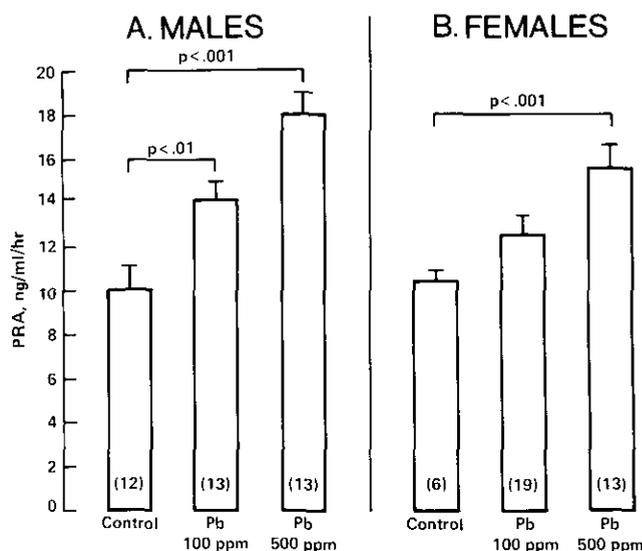


FIGURE 4. Effects of lead exposure, begun *in utero*, on plasma renin activity in rats at 1 month of age. The pregnant mothers were given 100 or 500 ppm lead in the drinking water throughout pregnancy and lactation, and the offspring were given the same dose following weaning and continuing for 1 month. The PbB in the lead-exposed animals averaged $32.6 \mu\text{g/dL}$ in the 100-ppm group and $65.8 \mu\text{g/dL}$ in the 500-ppm group. Figure originally published in Victory et al. (5).

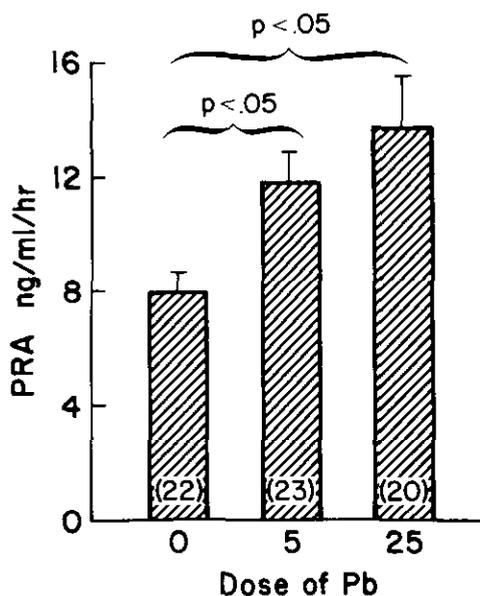


FIGURE 5. Effects of lead exposure, begun *in utero*, on plasma renin activity in rats at 1 month of age. The pregnant mothers were given 5 or 25 ppm lead in the drinking water throughout pregnancy and lactation, and the offspring were given the same dose following weaning and continuing for 1 month. The PbB in the lead-exposed animals averaged $9.0 \mu\text{g/dL}$ in the 5-ppm group and $18.6 \mu\text{g/dL}$ in the 25-ppm group. Figure originally published in Victory et al. (5).

100 ppm) showed significant reductions in PRA. Doses of 5 ppm and 500 ppm had no effect on PRA. Renal renin concentrations paralleled the changes in PRA, indicating that the decreases in PRA were due to decreases in renin secretion.

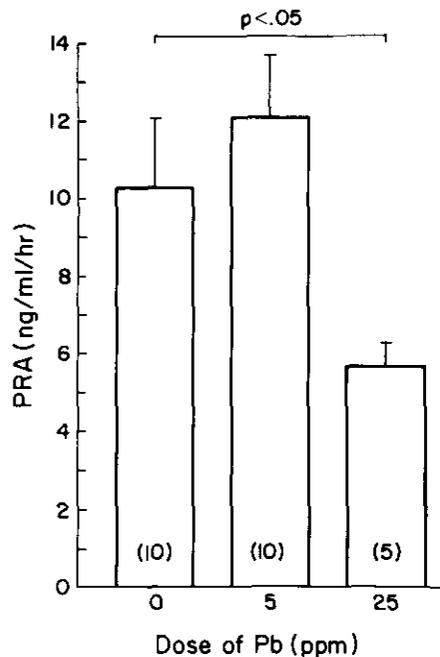


FIGURE 6. Effects of lead exposure, begun *in utero*, on plasma renin activity in rats at 5 months of age. The pregnant mothers were given 5 or 25 ppm lead in the drinking water throughout the pregnancy and lactation, and the offspring were given the same dose following weaning and continuing for 1 month. The PbB in the lead-exposed animals averaged 5.6 $\mu\text{g}/\text{dL}$ in the 5-ppm group and 18.2 $\mu\text{g}/\text{dL}$ in the 25-ppm group. Figure originally published in Vickey et al. (6).

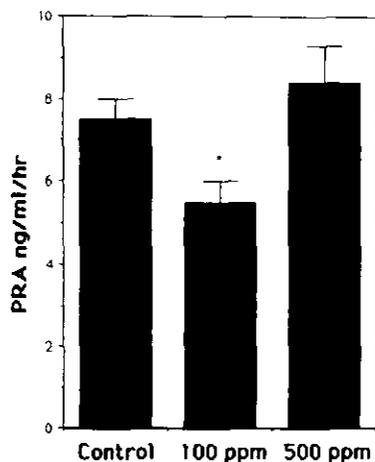


FIGURE 7. Effects of lead exposure, begun *in utero*, on plasma renin activity in rats at 6 months of age. The pregnant mothers were given 100 or 500 ppm lead in the drinking water throughout pregnancy and lactation, and the offspring were given the same dose following weaning and continuing for 1 month. The PbB in the lead-exposed animals averaged 40.4 $\mu\text{g}/\text{dL}$ in the 100-ppm group and 70.8 $\mu\text{g}/\text{dL}$ in the 500-ppm group. Asterisk denotes p value of < 0.01 . Data from Vickey et al. (7).

The final animal experiment was performed in rabbits rather than in rats (8). Exposure to lead (500 and 1000 ppm) was begun at 2 months of age and continued for 7 weeks. PRA was not different in the exposed rabbits, but kidney slices from exposed groups secreted significantly more renin *in vitro* compared to controls; interestingly, the responsiveness of the slices to a β -adrenergic stimulus was significantly lower in the 1000 ppm group.

The generalization that emerges from these animal studies is that the chronic effects of lead on renin secretion vary over the entire spectrum from stimulation to inhibition, depending not only on dose, but on the time the exposure is begun, the length of exposure, and the physiological state of the animal (for example, whether sodium depleted). The ability of lead either to increase or decrease renin secretion is not surprising in light of the present knowledge of cellular mechanisms controlling renin secretion (9). It is thought that renin secretion is inversely related to the cytosolic calcium concentration of the renin-secreting cells (the granular cells of the juxtaglomerular apparatus). By influencing different pathways of calcium metabolism in the granular cell under different experimental conditions, lead could either increase cytosolic calcium (thereby decreasing renin secretion) or decrease it (thereby increasing renin secretion).

Angiotensin II

This review has dealt thus far only with renin, but it is angiotensin II (AII), not renin, that is the vasoconstrictor agent in the renin-angiotensin system (acting both directly on vascular smooth muscle and indirectly by facilitating the activity of the sympathetic nervous system). Normally, since renin is rate-limiting for the generation of AII, there is a linear relationship between plasma renin concentration and AII, as shown in Figure 8 (5). This figure also shows that the relationship is not altered by chronic exposure to 100 ppm lead, but that the slope is decreased in animals exposed to 500 ppm, i.e., at any given PRA, plasma AII is lower than normal.

A convenient way of expressing this relationship between renin and AII is as an AII/PRA ratio. The minimal dose of lead required to reduce this ratio significantly varied considerably (from 25 to 1000 ppm) from experiment to experiment (Table 1). Neither angiotensinogen nor the ability of renin to catalyze the generation of angiotensin I (AI) is influenced by lead exposure (3); therefore, a likely cause of the ability of lead to reduce plasma AII at any given PRA is inhibition of angiotensin converting enzyme, the zinc-containing enzyme that converts AI to AII. However, although we have shown (unpublished observations) that acute administration of lead to experimental animals does partially inhibit the pulmonary conversion of AI to AII (as well as increase the metabolic clearance of plasma AII), we have not been able to

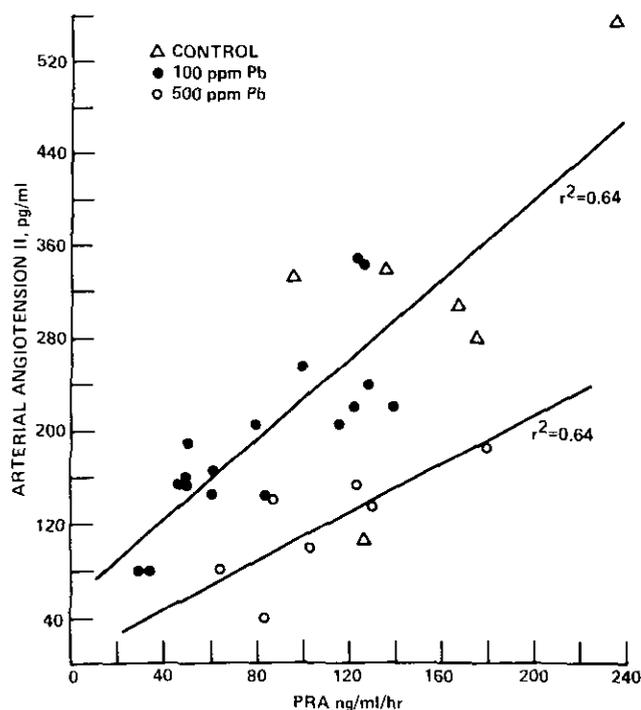


FIGURE 8. Linear regression of AII on PRA for 1-month-old rats subjected to pentobarbital anesthesia and laparotomy to increase plasma AII into the easily measurable range. See legend of Fig. 4 for further details. Figure originally published in Victory et al. (5).

demonstrate directly any inhibition of pulmonary converting enzyme in chronic studies.

Correlation of Changes in the Renin-Angiotensin System with Blood Pressure

In two of the experiments previously described using the *in utero* exposure protocol, systolic arterial blood pressure was also measured in the animals (6,7). These experiments are summarized in the paper by Victory in this volume (10) and are mentioned here because they are the only attempts of which we are aware to correlate lead-induced changes in both the renin-angiotensin system and arterial blood pressure in animals. The important findings were that a dose of 100 ppm induced a modest but stable chronic hypertension, whereas a higher dose (500 ppm) and two lower doses (5 and 25 ppm) failed to do so. As described previously, the 100 ppm dose that produced hypertension produced a decrease in PRA (but caused no change in the AII/PRA ratio). Thus, in our studies, the hypertension induced by lead was low-renin hypertension. This would suggest that the renin-angiotensin system is not the cause of the hypertension; however, recall that these animals (as judged by the results from their litter-mates shown in Fig. 4) probably went through a high-renin phase earlier in life. As in several other models of experimental hypertension, it is possible that the early high-renin phase

was critical for the later development of the hypertension. More longitudinal studies with and without blockers of the renin-angiotensin system are required to test this hypothesis.

The fact that in the same protocol 100 ppm produced hypertension whereas the higher dose of 500 ppm did not suggest, along with other studies (7,10) that there may be a biphasic effect of lead on blood pressure, at least in experimental animals, with hypertension occurring at certain exposure levels but not at higher levels. One speculative explanation of this phenomenon is that the decrease in AII induced by higher exposures (the 500 ppm dose, for example, in the experiment just described) may prevent the development of hypertension, as the presence of normal concentrations of AII is known to be permissive for most types of hypertension.

Human Studies

Data from the seven published studies examining the relationship between lead exposure and PRA in humans are summarized in Table 2. (As is the case for the experimental animal work, the results are quite variable. The two earliest studies (11,12), performed in the United States, were of 11 subjects, all with frank lead toxicity (9 from drinking moonshine and 2 from occupational exposure). PRA was found to be low and nonresponsive to stimulation by diuretics and salt deprivation. A third study in the U.S. (13), again of lead-intoxicated moonshine drinkers, showed similar results, i.e., depressed PRA, but only in patients with hyperkalemia; those with normal plasma potassium concentrations had normal PRA. This contrasts with the two earlier studies in which the subjects had depressed PRA despite normokalemia. A fourth study (14) reporting reduced and unresponsive PRA following lead exposure involved a single individual who had suffered marked lead toxicity after cleaning his garage, which had been formerly used as a foundry.

In contrast to these studies is a report (15) from the United Kingdom of normal PRA in 11 subjects exposed occupationally to high levels of lead. In addition, an Italian study (16) of 22 occupationally exposed persons showed considerable variability in PRA; in 14 of the subjects, PRA was normal (both before and/or after assumption of the upright posture), but was reduced in 5 subjects and elevated in 3. Unfortunately, there was no statistical evaluation of the group as a whole.

These six studies were of subjects with marked long-term lead exposure. More recently, a study has been published (17) of 33 workers with "slight to moderate" occupational lead exposure for weeks to months (mean PbB = 35.6 $\mu\text{g}/\text{dL}$). The mean PRA for this group was reported to be "slightly high for a group of normotensive subjects not on sodium restriction," but no statistics were given. However, as shown in Figure 9, there was a striking positive exponential correlation

Table 2. Summary of studies examining relationship between lead exposure and plasma renin activity in humans.^a

Country, reference	n	Symptoms of lead toxicity	Exposure duration/type magnitude ^b	Status of PRA ^b
United States (16)	33	No	Weeks-months Occupational Slight-moderate	Increased with increasing PbB
Italy (15)	8	Yes	Years-decades Occupational High level	Normal, 4 Reduced, 3 Increased, 1
	14	?	Years Occupational (?) High level	Normal, 10 Increased, 2 Reduced, 2
United Kingdom (15)	11	Yes	Weeks-months Occupational High level	Normal
United States (12)	33	Yes	Years Moonshine High level	Normal (normal K ⁺) Reduced (hyperkalemia)
Switzerland (13)	1	Yes	Day(s) Cleaning old foundry High level	Reduced
United States (11)	2	Yes	Years-decades Moonshine, 1 Occupational, 1 High level	Reduced
United States (10)	9	Yes	Years Moonshine, 8 Occupational, 1 High level	Reduced

^aAdapted from Sharp et al. (1).

^bNumbers refer to the number of subjects.

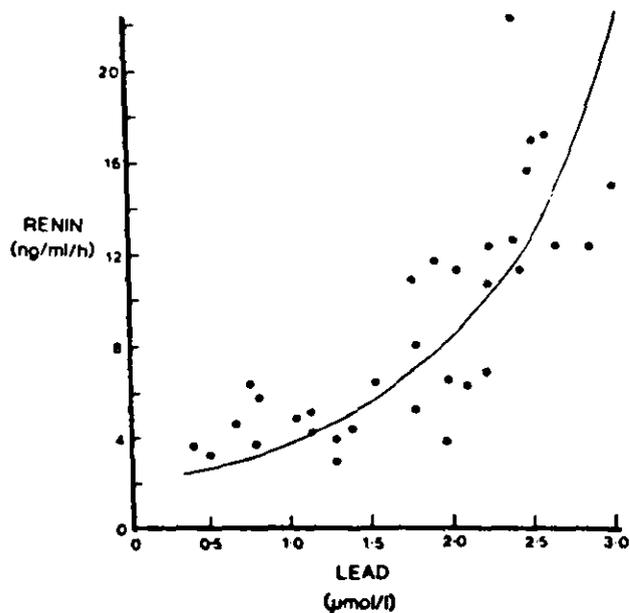


FIGURE 9. The relationship between blood lead concentration and plasma renin activity in men occupationally exposed to lead. From Boscolo et al. (16).

between PbB and PRA ($r^2 = 0.58$). Positive exponential relationships were also found between PbB and plasma AI, plasma angiotensin converting enzyme activity, and plasma aldosterone concentration; these data indicate that the conversion of AI to AII was not altered by lead exposure.

These studies indicate that there is as much variability in the effects of chronic lead exposure on renin in human beings as in experimental animals. A tentative hypothesis can be suggested: There may be a tendency for lead-exposed persons to have higher PRA than normal during the early periods of modest exposure and have normal or depressed PRA following more chronic severe exposures. Clearly, longitudinal studies with carefully delineated exposures are needed.

This symposium is concerned with the relationship between lead and blood pressure. In this context, the following hypotheses involving renin can be made: a) If exposure to lead increases plasma renin activity in certain people, this might be reflected in an increase in blood pressure as well; b) In contrast, if lead either lowers plasma renin or does not alter it, then renin should not be involved in any lead-induced elevation of blood pressure in humans. A first approach to this question is to make simultaneous measurements of blood lead concentration, PRA, and blood pressure. However, because PRA is so dependent upon sodium

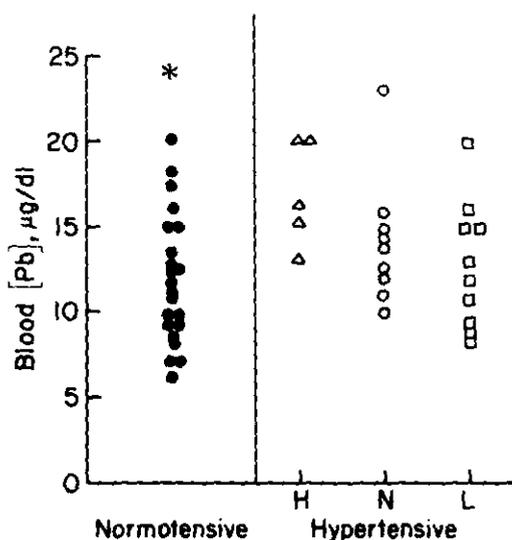


FIGURE 10. Distribution of blood lead concentrations in normotensive persons and hypertensive persons characterized as high-renin (H), normal-renin (N), and low-renin (L). Asterisk denotes a subject who is normotensive but has an elevated renin.

intake, any such study must control for this intake. Accordingly, we performed, in collaboration with Dr. Jean E. Sealey (New York Hospital-Cornell Medical Center), a first preliminary study on a small population of hypertensive persons in whom so-called renin-profiling was done, i.e., PRA was characterized as normal, low, or high on the basis of the expected PRA at any level of sodium excretion (a marker of intake) (18). Another compelling reason for studying this population was that we had just found that the hypertension produced in rats by lead was a low-renin hypertension, and we wished to determine whether patients with low-renin hypertension might have elevated blood lead concentrations compared to other hypertensives.

Figure 10 presents the data from this experiment (unpublished data). Mean blood lead concentrations for the normal subjects and the entire group of hypertensives were 12.4 ± 0.4 and 14.1 ± 0.8 $\mu\text{g}/\text{dL}$, which are not significantly different from each other. However, there was a progression in the blood lead concentrations for the low-, normal-, and high-renin hypertensives, the means being 12.7 ± 1.2 , 14.3 ± 1.3 , and 16.8 ± 1.4 $\mu\text{g}/\text{dL}$; the value for the high-renin group was significantly higher than that for the normal subjects ($p < 0.02$). Another way of looking at the data is that the blood lead concentrations of all 6 persons with high PRA (the 5 persons with high-renin hypertension and the 1 with high-renin normotension) fell in the upper half of the blood lead distribution, in contrast, only 16 of the 41 persons with normal or low PRA fell in this upper half. By chi-square analysis, this difference in ratios is highly

significant ($p < 0.02$). These data are consistent with the hypothesis that lead exposure of modest degree may increase PRA; the data suggest, however, that if lead does play a role in human hypertension, it is with high-renin rather than low-renin hypertension. It must be emphasized that this is only a preliminary study with a very small population size.

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