Is a positive association between lead exposure and blood pressure supported by animal experiments?

Jan A. Staessen, MD, PhD,* Robert R. Lauwerys, MD, PhD,† Christopher J. Bulpitt, MD, MSc,‡ Robert Fagard, MD, PhD,* Paul Lijnen, PhD,* Harry Roels, PhD,† Lutgarde Thijs, BSc,* Antoon Amery MD, PhD*

*Katholieke Universiteit Leuven, Leuven, †Université Catholique de Louvain, Bruxelles, Belgium, and ‡Hammersmith Hospital, London, UK

The possible association between low-level lead exposure and blood pressure and the causal nature of any such relationship continue to be debated. A recent meta-analysis of the human model data showed that on average a doubling of blood lead was associated with a rise in blood pressure averaging 1 mm Hg systolic and 0.6 mm Hg diastolic. The older animal studies, however, failed to show a significant pressure increase with massive lead exposure. This review therefore attempts to determine whether the more recent animal studies are supportive of a positive association between lead exposure and blood pressure elevation. Of the 21 animal studies published since 1977, one was carried out in dogs, one in pigeons, and the remainder in various rat strains. In the articles in which all the lead doses had been higher than 1 ppm, the association between blood pressure and exposure was found to be positive in seven, inconsistent in three, absent in four, and negative in one. Of the six animal experiments that employed lead doses not exceeding 1 ppm, five reported a small pressor effect. One of these five positive low-dose studies, however, failed to show a dose-effect relationship when exposure was increased from 0.1 to 1 ppm. In conclusion, most, but not all animal studies published since 1977 found a positive association between blood pressure and lead exposure. However, publication bias may have inflated the number of positive studies appearing in the literature. Whether a lead dose from 0.1 to 1 ppm given to rats, dogs, or pigeons would be equivalent to the human exposure levels, and to what extent one would be able to extrapolate data to human situations from these genetically heterogenous animal models, still needs to be elucidated.

Current Opinion in Nephrology and Hypertension 1994, **3**:257–263

Lead accumulates in the human body during life and has been implicated in the pathogenesis of renal dysfunction [1,2] and hypertension [3–6], particularly in heavily exposed workers [7,8] and in alcoholics drinking moonshine whiskey [9,10]. As a consequence of industrialization and motorized traffic, general populations are still being exposed to lead above the natural background, albeit to much lower concentrations than the industrial workers in the past. It has been suggested that even less-intensive lead exposure, as observed in the general population, may lead to a substantial excess morbidity related to hypertension and its complications [11], although in individual subjects the relative risk may be extremely small and barely detectable.

A recent meta-analysis of 23 studies included 33,141 subjects recruited either from the general population (in 13 surveys) or from occupational groups (in 10 studies). In all but four studies, the results had been adjusted for age, and most studies also considered additional confounding factors [12]. Data from men and women and white and black subjects were analyzed separately, whenever possible. The association between blood pressure and blood lead was similar in

 ISBN 1-85922-614-0 ISSN 1062–4821

both genders and in each race (Figs. 1 and 2). In all 23 studies combined, a twofold increase in the blood lead concentration was associated with a 1.0 mm Hg rise in systolic pressure (CI, 0.4 to 1.6 mm Hg; $P = 0.002$) and with a 0.6 mm Hg increase in diastolic pressure (CI, 0.2 to 1.0 mm Hg; $P = 0.02$). The association with systolic pressure strongly relied on the inclusion of one large study in which women had their blood pressure measured at the end of pregnancy [13]. The association with diastolic pressure was to a large extent due to one single population survey in the United States [11,14]. Across the human studies, the strength of the blood pressure–blood lead relation was not correlated with the average blood lead level. In most of the human studies reviewed, the association between systolic and diastolic blood pressure and the blood lead concentration did not reach a level of statistical significance (Figs. 1 and 2) [12].

Nonassociation in the initial animal experiments

Many of the older animal studies [15–19], some of which did not include a control group [17,19], failed to produce an association of blood pressure elevation with the long-term administration of lead in dogs [16] or in rats [15,17–19]. However, these initial studies [15–19] employed huge lead doses, which had the potential to interfere with a great number of homeostatic mechanisms and enzyme systems. In these heavily intoxicated and severely ill animals, the rise in blood pressure could have been opposed or at least inhibited. Consistent with the latter hypothesis is the observation that the weekly subcutaneous administration of 20 mg lead phosphate did produce hypertension in the rat models, whereas twice this dose did not [20].

Inconsistent results in more recent animal experiments

Genetic heterogeneity of the animals

For many reasons, the results of the animal studies performed over the past 2 decades are not easier to interpret than the initial studies previously summarized [21–41]. With the exception of one study in pigeons [31] and another in dogs [27], the more recent animal experiments have been conducted in various rat strains. Both normotensive and genetically hypertensive rats have been studied, but the source of the animals was not always specifically mentioned. Both male and female rats have been employed. Even inbred rats of the same gender [42] may have a different genetic makeup, depending on the commercial sources from which they were bought. Genetic polymorphism between species and even within the same rat strain may lead to major biochemical and physiological differences in blood pressure–regulating mechanisms. Genetic polymorphism has been recognized as one of

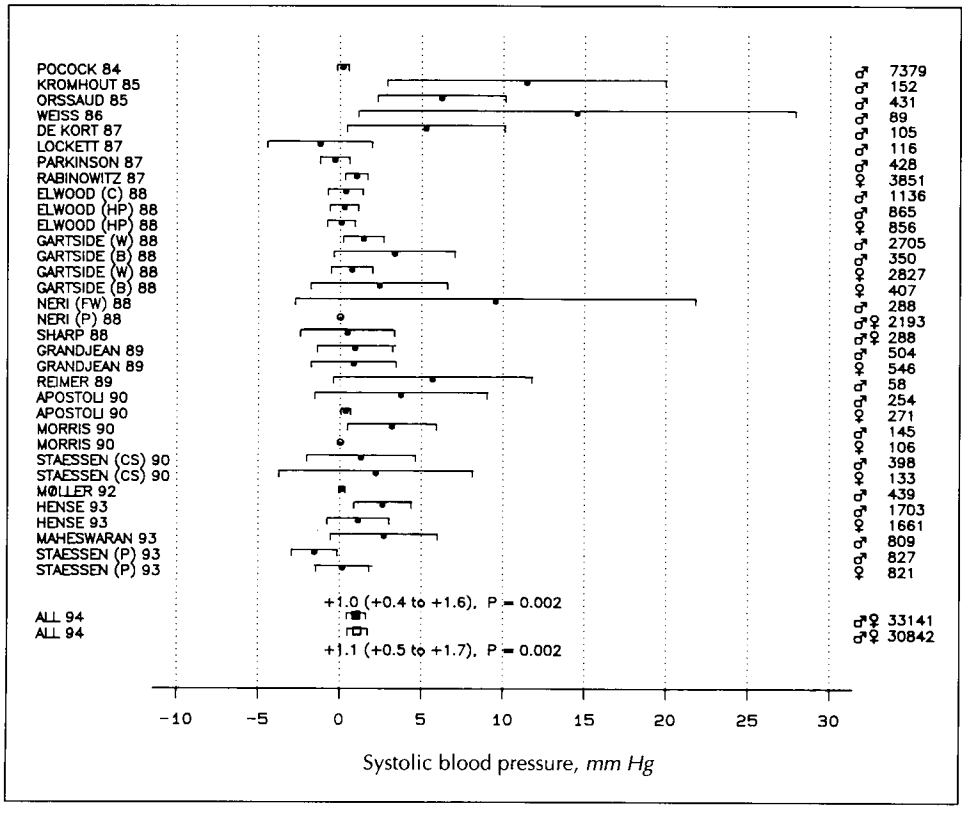

Fig. 1. Differences in the systolic pressure (point estimate with 95% CI) associated with a doubling of the blood lead concentration. *Circles* represent individual groups and *squares* represent the pooled association sizes. For each group, details are given for gender, first author and year of publication, and certain additional characteristics. *Open circles* denote groups for whom a nonsignificant association size was assumed to be zero. The *open square* is the overall association size after removal of the latter subgroups. B—black patients; C—Caerphilly study; CS—civil servants; FW—foundry workers; HP—Welsh Heart Program; P—population; W—white patients. (*From* Staessen *et al.* [12]; with permission.)

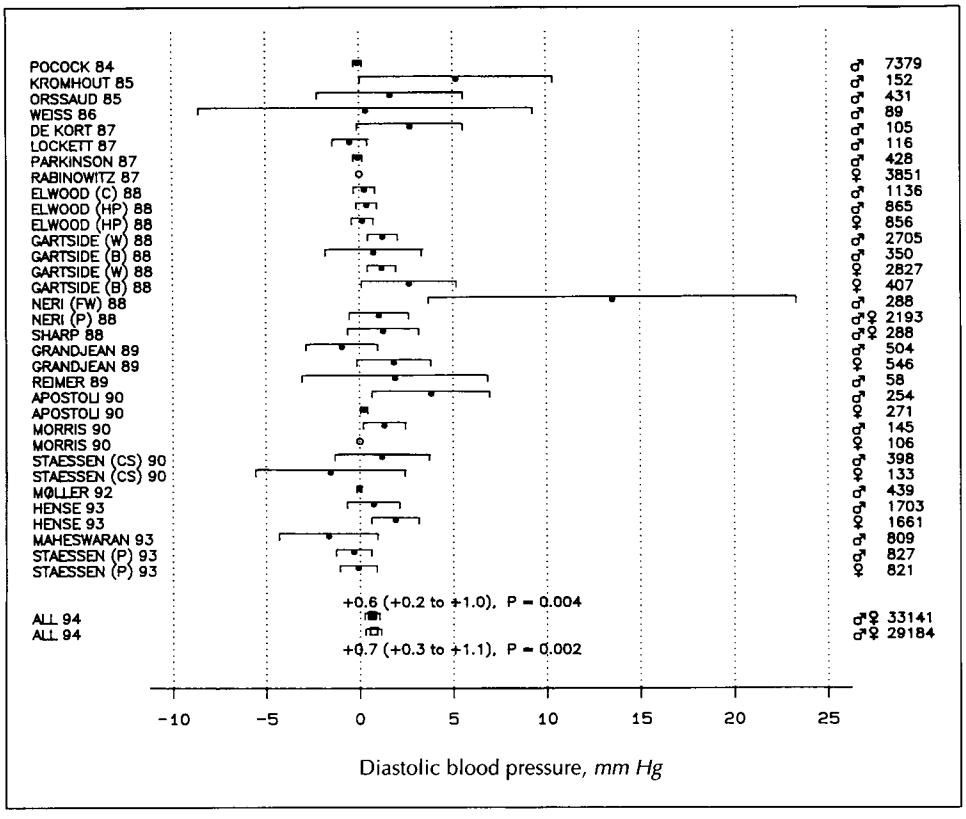

Fig. 2. Differences in the diastolic pressure (point estimate with 95% CI) associated with a doubling of the blood lead concentration. *Circles* represent individual groups and *squares* represent the pooled association size. For each group, details are given for gender, first author and year of publication, and certain additional characteristics. *Open circles* denote groups for whom a nonsignificant association size was assumed to be zero. The *open square* is the overall association size after removal of the latter subgroups. B—black patients; C—Caerphilly study; CS—civil servants; FW—foundry workers; HP—Welsh Heart Program; P—population; W—white patients. (*From* Staessen *et al.* [12]; with permission.)

the major problems hindering the study of the pathophysiology of hypertension [43–45]. Obviously, this limitation must also apply to animal experiments focusing on environmental factors, such as lead, which according to the genetic background of the experimental animals, may or may not cause hypertension. Whether or not a single genetic locus, or a gene or genes associated with the sex chromosome [39,46] play a predominant role in determining the blood pressure response to lead exposure has not yet been elucidated. Thus, for now, it remains at least questionable whether the numerous animal experiments performed in different species and even within the same rat strain can be extrapolated to the human situation.

The dose of lead

In many of the more recent animal experiments, doses of lead have been employed that by far exceeded the past and current exposure levels of the general population. In two reports [27,47] lead was administered via food consumption, but in 19 other experiments lead was added to the drinking water. In 14 of these 19 studies, the lead concentrations in the drinking water always exceeded 1 ppm [21,22,25,26,29,30,32–39]. In some reports, the investigators suggested that the animals had been exposed at an intensity encountered at the population level because at the completion of follow-up the animals had blood lead concentrations comparable with those observed in people. However, the toxicokinetics of blood lead not only show a big interindividual variability [48], but they are to a large extent also species specific [49,50]. Thus, a similar blood lead level in rats and humans does not necessarily translate into a comparable or equivalent internal lead burden or into similar toxic effects.

In all but two studies [27,47], the lead dose was expressed as a concentration in the drinking water, which may have led to quite different absolute amounts of lead actually having been administered to the animals. Indeed, the volume of the drinking water is age dependent [40] and may also be considerably influenced by various other factors, such as the salt content of the diet. The volume of the drinking water was in most experiments either not reported or not measured. In addition, neither the duration of the lead administration nor the dietary content of ions and nutrients, such as the calcium ion and iron [51], which may potentially affect the gastrointestinal absorption of lead and its sequestration into the mineralizing tissues, have been standardized across experiments [49,50]. It is therefore not surprising that apparently similar doses of lead have resulted in quite different blood lead concentrations not only between [21,26,28,32,34,37] but even within [28,34] studies. For instance, a lead dose of 100 ppm in the drinking water has been associated with blood lead concentrations ranging from 5.3 [37] to 55.8 [34] μg/dL, whereas the duration of exposure and follow-up has ranged from 8 [37] to 52 [21] weeks.

In most experiments the internal lead burden was monitored and lead was measured either in the blood or in various tissues. Of the reports in which lead was measured in the blood, two [32,39] did not provide a description of the analytic technique, 11 [21,22,25–27,29,30,34,36–38] provided a description, but only two [28,33] also organized a quality control of the blood lead determinations. Similarly, one [39] study did not describe the technique of the tissue lead measurements, five articles [26,29,30,36,38] reported the analytic method, and only two [28,33] also mentioned quality control. In six reports the internal lead burden was apparently not monitored because the authors did not include any lead measurement in blood or tissues [24,31,35,40,41,47].

Different experimental protocols cause difficult generalizations

Blood pressure is highly variable and is heavily influenced by various environmental factors [52]. For instance, the blood pressure of rats is higher if they are housed in stainless steel rather than in plastic cages [40]. In addition, blood pressure measurements are subject to observer bias. Anesthesia may profoundly interfere with both the level and the regulation of blood pressure, depending on the nature, the doses, and the method of administration of the anesthetic drugs. Ideally, the blood pressure should have been repeatedly measured in conscious animals over a long period of time. Moreover, the observer measuring the blood pressure or reading the intra-arterial pressure from an oscilloscope or polygraphic recording should have been kept blinded with respect to the exposure level to which the animals had been randomized. Few experiments comply with all these requirements. In most experiments, all or at least some [24,39] of the animals were anesthetized when their blood pressure was taken [22,23,25,26,29,30,33,34,36,38,40,41]; in some studies [35,47] no details were provided on the anesthesia at the time of blood pressure measurement. In only one report was blinding of the observer explicitly mentioned as a part of the experimental protocol [27].

Blood pressure is influenced by many organ systems and is subject to manifold regulating mechanisms, which are considerably altered by environmental and dietary factors. For instance, inbred rodents with genetic hypertension, such as the spontaneously hypertensive rat, may be particularly sensitive to salt. Not only the toxicokinetics of lead, but its toxicity as well, may be directly or indirectly modified by the presence of other cations, such as cadmium, calcium, and iron. Yet, few experiments presented details on the amount of sodium chloride in the animals' diet or drinking water or on the coadministration of other cations. Moreover, in most species blood pressure increases with advancing age and the blood pressure–regulating mechanisms evolve with development from weanling to adult animals. In the more recent animal experiments, exposure was variously started in utero [25,26,32,53], in weanling [24,28,29,33,35,36,38,40,41], young [27,34,39], or adolescent animals [21,37,47], or during adult life [22,23,30,31,39]. The duration of exposure has ranged from 3 [37] to as long as 72 weeks [24]. These extra sources of variability must have contributed to some of the inconsistencies among the animal studies.

The groups of experimental animals comprised from 12 [27] to 163 [24] animals. In a few studies, the number of animals was not clearly stated [21,33]. In most [23,24,27–30,34–36,38,39], but not all reports [21,25,26,31–33,37,40,41,47], random allocation of the animals to different levels of exposure to lead was explicitly mentioned as an intricate part of the experimental procedures.

Animal studies with high lead doses

In the articles in which all lead concentrations in the drinking water were higher than 1 ppm, the association between blood pressure and exposure was found to be positive in seven [22,30,32,34,36–38], inconsistent in three [21,26,29], absent in four [25,33,35,47], and mainly negative in one (as determined in six of seven experimental series) [39]. The results were considered to be inconsistent if an association was not demonstrated for both systolic and diastolic pressure [29], if in the same study a pressor effect was not observed in all rat strains [39] or under all experimental conditions [29], or if there was no dose-effect relationship with blood pressure across the employed lead doses [21].

Animal studies with lead doses not exceeding 1 ppm

Higher doses of lead are likely to result in renal dysfunction and in overt histopathological kidney lesions [2,54–59]. They do produce many aspecific toxic effects that render observed blood pressure changes difficult to interpret.

Of the reviewed animal experiments, five employed lead doses of 1 ppm or lower in the drinking water [24,28,31,40,41] and one [27] employed a lead dose of 1 mg per kg of body weight (Table 1). In one study weanling male Wistar rats were randomized, their awake blood pressure was measured, and the sodium and calcium content of their diet was measured and reported [28]. At a lead exposure level of 1 ppm, their intra-arterially measured mean blood pressure was not significantly raised. In a second study [27], female dogs were randomized, their awake blood pressure was measured by a blinded observer, and the sodium content of their diet was 0.3% [27]. In this study there was a slight (12 mm Hg) but significant rise in the

mean pressure, noninvasively measured by a Doppler ultrasound technique.

The studies by Perry *et al.* [24,40,41] are somewhat more difficult to interpret because in most instances the blood pressure was measured in anesthetized animals and because it remains unclear whether the animals were randomly allocated to the various exposure levels. The cadmium [40,41] or calcium [24], but not the sodium content of their diet was documented. In one experimental group [24], in which blood pressure was measured by the tail-cuff method in Long-Evans rats, a dose-response relationship could not be established because the increase in the systolic pressure was the same at a lead dose of 0.1 ppm (15 mm Hg; $P<0.001$) as it was for 1 ppm (14 mm Hg; $P<0.001$). Finally, the experiments by Revis *et al.* [31] in conscious pigeons also demonstrated a slight but significant increase in the intra-arterially measured systolic (13 mm Hg) and diastolic (9 mm Hg) pressure, which was potentiated by the simultaneous administration of cadmium, but which was not reduced by augmenting the calcium content of the diet.

Conclusions

Most but not all animal studies published since 1977 found a positive association between blood pressure and lead exposure. If only the animal experiments in which the lead dose did not exceed 1 ppm were considered, an increase in the blood pressure was reported in five of six reports [24,27,28,31,40,41] (Table 1). Whether or not a lead dose from 0.1 to 1 ppm given to rats, dogs, or pigeons would be equivalent to

Table 1. Animal experiments relating low-level (< 1 ppm) lead exposure to blood pressure

Study	Species (gender)	Age at initial exposure, *mo*	Follow-up, *wk*	Technique of blood pressure measurement	Animals, *n*	Lead dose, *ppm*	Other ion, *ppm*†	Sodium chloride in chow, %	Lead concentration, *μg/dL*	Blood pressure, *mm Hg*	Change in blood pressure, *mm Hg*¶	*P* value
Bogden	WR (m)	W	31	IA, c	8	0	Ca, 2000	1.2	1.87	Mean, 110	NR	NR
et al. [28]*§					8	1	Ca, 2000	1.2	3.50	Mean, 118	8	NS
					8	0	Ca, 40,000	1.2	2.00	Mean, 122	NR	NR
					8	1	Ca, 40,000	1.2	3.20	Mean, 130	8	NS
Fine	Dogs (f)	3	20	D, c, b	6	0‡	NR	0.3	9.2	Mean, 108	NR	NR
et al. [27]*					6	1‡	NR	0.3	35.8	Mean, 120	12	<0.01**
Perry and	LER (f)	W	24	TC, a	45	0	Cd, 0	NR	NR	Systolic, 99	NR	NR
Erlanger [41]					15	0	Cd, 0.1	NR	NR	Systolic, 112	13	NR
					15	0.1	Cd, 0	NR	NR	Systolic, 109	10	NR
					15	0.1	Cd, 0.1	NR	NR	Systolic, 126	27	<0.05
Perry	LER (f)	W	12	TC, a	15	0	Cd, 0	NR	NR	Systolic, 103	NR	NR
et al. [40]§					15	0	Cd, 1	NR	NR	Systolic, 118	15	<0.01
					15	1	Cd, 0	NR	NR	Systolic, 115	12	<0.01
					15	1	Cd, 1	NR	NR	Systolic, 146	43	<0.001
Perry	LER (f)	W	72	TC, a	89	0	Ca, 39,000	NR	NR	Systolic, 110	NR	NR
et al. [24]*					15	0.1	Ca, 39,000	NR	NR	Systolic, 126	16	<0.001
					30	1	Ca, 39,000	NR	NR	Systolic, 123	13	<0.001
					29	5	Ca, 39,000	NR	NR	Systolic, 122	12	NS
			52	TC, c	69	0	Ca, 39,000	NR	NR	Systolic, 120	NR	NR
					36	0.1	Ca, 39,000	NR	NR	Systolic, 135	15	<0.001
					35	1	Ca, 39,000	NR	NR	Systolic, 134	14	<0.001
Revis	WCP (m)	3	24	IA, c	32	0	NR	NR	NR	S/D, 195/149	NR	NR
et al. [31]					32	0.8	NR	NR	NR	S/D, 208/158	13/9	<0.01/<0.01
					16	0	NR	NR	NR	S/D, 185/144	NR	NR
					16	0	Cd, 0.6	NR	NR	S/D, 206/155	21/11	NR
					16	0.8	NR	NR	NR	S/D, 208/154	23/10	NR
					16	0.8	Cd, 0.6	NR	NR	S/D, 209/163	24/19	<0.05/NS††
					16	0	NR	NR	NR	S/D, 193/153	NR	NR
					16	0	Ca, 100	NR	NR	S/D, 197/146	4/–7	NR
					16	0.8	NR	NR	NR	S/D, 211/160	18/7	NR
					16	0.8	Ca, 100	NR	NR	S/D, 206/157	13/4	NS/NS††

*Indicates report explicitly referring to a randomization procedure to allocate the animals to varying exposure levels.
†Ion other than lead that potentially influenced blood pressure.
‡Lead dose relative to body weight.
¶Indicates the difference in systolic, mean, or diastolic pressure as compared with the control group.
§Indicates that approximate blood pressure results were read from a figure.
**Indicates specific mention of a multiple comparisons test procedure or of an adjustment of the *P* value for multiple comparisons.
††Indicates the significance of the lead-cadmium and lead-calcium interaction.
a—anesthetized; b—blinded observer; c—conscious; D—Doppler ultrasound; f—female; IA—intra-arterial; LER—Long-Evans rats; m—male; NR—not reported; NS—not significant; S/D—systolic/diastolic; TC—tail-cuff method; W—weanling animals; WCP—white Cameau pigeons; WR—Wistar rats.

the exposure levels usually found in human populations and to what extent one is entitled to extrapolate results from genetically heterogenous animal models to human cases remains controversial. Moreover, there are substantial differences in the bioavailability of lead across the animal models [60], and the human exposure levels are generally at least one order of magnitude inferior to the lowest lead doses to which the animals have been exposed [61,62].

Finally, the problem of publication bias should not be dismissed. Research with statistically significant results that confirm a favored line of thinking is much more likely to be submitted and published than work with null or nonsignificant results. Publication bias is more likely to occur for observational than for laboratory-based research [63]. Nevertheless, all overviews of animal experiments, such as this review, must be interpreted with caution before any generalization can be made.

Acknowledgments

The preparation of this review was supported by the Belgian National Fund for Medical Research (Brussels, Belgium), the Belgian Incentive Program 'Health Hazards' (Science Policy Office, Prime Minister's Services, Brussels, Belgium), and the British Council (Brussels, Belgium). Additional financial support was provided by the International Lead Zinc Research Organization (Research Triangle Park, North Carolina, USA). The secretarial assistance of Mrs. K. De Vocht, Miss I. Tassens, Mrs. Y. Toremans, and Mrs. S. Van Hulle is gratefully acknowledged.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • Of special interest
- •• Of outstanding interest

1. Wedeen RP, Mallik DK, Batuman V: **Detection and Treatment of Occupational Lead Nephropathy.** *Arch Intern Med* 1979, **139**:53–57.

2. Staessen JA, Lauwerys RR, Buchet J, Bulpitt CJ, Rondia, D, Vanrenterghem Y, Amery A, The Cadmibel Study Group: **Renal Function Is Inversely Correlated With Lead Exposure.** *N Engl J Med* 1992, **327**:151–156.

3. Sharp DS, Becker CE, Smith AH: **Chronic Low-Level Lead Exposure: Its Role in the Pathogenesis of Hypertension.** *Med Toxicol* 1987, **2**:210–232.

4. Khera AK, Wibberley DG, Edwards KW, Waldron HA: **Cadmium and Lead Levels in Blood and Urine in a Series of Cardiovascular and Normotensive Patients.** *Int J Environ Studies* 1980, **14**:309–312.

5. Schwartz J: **Lead, Blood Pressure, and Cardiovascular Disease in Men and Women.** *Environ Health Perspect* 1991, **91**:71–75.

6. Shaper AG, Pocock SJ: **Blood Lead and Blood Pressure.** *BMJ* 1985, **291**:1147–1149.

7. Cramér K, Dahlberg L: **Incidence of Hypertension Among Lead Workers: A Follow-Up Study Based on Regular Control Over 20 Years.** *Br J Ind Med* 1966, **23**:101–104.

8. Ibels LS, Pollock CA: **Lead Intoxication.** *Med Toxicol* 1986, **1**:387–410.

9. McAllister RG Jr, Michelakis AM, Sandstead HH: **Plasma Renin Activity in Chronic Plumbism: Effect of Treatment.** *Arch Intern Med* 1971, **127**:919–923.

10. Sandstead HH, Michelakis AM, Temple TE: **Lead Intoxication: Its Effect on the Renin-Aldosterone Response to Sodium Deprivation.** *Arch Environ Health* 1970, **20**:356–363.

11. Pirkle JL, Schwartz J, Landis JR, Harlan WR: **The Relationship Between Blood Lead Levels and Blood Pressure and Its Cardiovascular Complications.** *Am J Epidemiol* 1985, **121**:246–258.

12. Staessen JA, Bulpitt CJ, Fagard R, Lauwerys RR, Roels H, Thijs L, Amery A: **Hypertension Caused by Low-Level Lead Exposure: Myth or Fact?** *J Cardiovasc Risk* 1994, in press.

13. Rabinowitz M, Bellinger D, Leviton A, Needleman H, Schoenbaum S: **Pregnancy Hypertension, Blood Pressure During Labor, and Blood Lead Levels.** *Hypertension* 1987, **10**:447–451.

14. Harlan WR, Landis JR, Schmouder RL, Goldstein NG, Harlan LC: **Blood Lead and Blood Pressure: Relationship in the Adolescent and US Population.** *JAMA* 1985, **253**:530–534.

15. Pardoe AU: **Renal Function in Lead Poisoning.** *Br J Pharmacol* 1952, **7**:349–357.

16. Fouts PJ, Page IH: **The Effect of Chronic Lead Poisoning on Arterial Blood Pressure in Dogs.** *Am Heart J* 1942, **24**:329–331.

17. Griffith JQ Jr, Lindauer MA: **The Effect of Chronic Lead Poisoning on Arterial Blood Pressure in Rats.** *Am Heart J* 1944, **28**:295–297.

18. Padilla F, Shapiro AP, Jensen WN: **Effect of Chronic Lead Intoxication on Blood Pressure in the Rat.** *Am J Med Sci* 1969, **258**:359–365.

19. Diaz-Rivera RS, Horn RC: **Postmortem Studies on Hypertensive Rats Chronically Intoxicated With Lead Acetate.** *Proc Soc Exp Biol Med* 1945, **59**:161–163.

20. Von Cottier P, Kunz HA, Zollinger HU: **Experimenteller Beitrag Zur Frage der Bleihypertonie.** *Helv Med Acta* 1953, **20**:443–449.

21. Khalil-Manesh F, Gonick HC, Weiler EWJ, Prins B, Weber MA, Purdy RE: **Lead-Induced Hypertension: Possible Role of Endothelial Factors.** *Am J Hypertens* 1993, **6**:723–729.

22. Iannaccone A, Carmignani M, Boscolo P: **Neurogenic and Humoral Mechanisms in Arterial Hypertension of Chronically Lead Exposed Rats.** *Med Lav* 1981, **1**:13–21.

23. Iannaccone A, Carmignani M, Boscolo P: **Reattivitá Cardiovasculare Nel Ratto Dopo Cronica Esposizione a Cadmio o Pombio.** *Ann Ist Super Sanita* 1981, **17**:655–660.

24. Perry HM Jr, Erlanger MW, Perry EF: **Increase in the Blood Pressure of Rats Chronically Fed Low Levels of Lead.** *Environ Health Perspect* 1988, **78**:107–111.

25. Victery W, Vander AJ, Markel H, Katzman L, Shulak JM: **Lead Exposure, Begun in Utero, Decreases Renin and Angiotensin II in Adult Rats.** *Proc Soc Exp Biol Med* 1982, **170**:63–67.

26. Victery W, Vander AJ, Shulak JM, Schoeps P, Julius S: **Lead Hypertension, and the Renin-Angiotensin System in Rats.** *J Lab Clin Med* 1982, **99**:354–362.

27. Fine BP, Vetrano T, Skurnick J, Ty A: **Blood Pressure Elevation in Young Dogs During Low-Level Lead Poisoning.** *Toxicol Appl Pharmacol* 1988, **93**:388–393.

28. Bogden JD, Gertner SB, Kemp FW, McLeod R, Bruening KS, Chung HR: **Dietary Lead and Calcium: Effects on Blood Pressure and Renal Neoplasia in Wistar Rats.** *J Nutr* 1991, 121:718–728.

29. Boscolo P, Carmignani M, Carelli G, Finelli VN, Giuliano G: **Zinc and Copper in Tissues of Rats With Blood Hypertension Induced by Long-Term Lead Exposure.** *Toxicol Lett* 1992, 63:135–139.

30. Lal B, Murthy RC, Anand M, Chandra SV, Kumar R, Tripathi O, Srimal RC: **Cardiotoxicity and Hypertension in Rats After Oral Lead Exposure.** *Drug Chem Toxicol* 1991, 14:305–318.

31. Revis NW, Zinsmeister AR, Bull R: **Atherosclerosis and Hypertension Induction by Lead and Cadmium Ions: An Effect Prevented by Calcium Ion.** *Proc Natl Acad Sci U S A* 1981, 78:6494–6498.

32. Webb RC, Winquist RJ, Victery W, Vander AJ: **In Vivo and In Vitro Effects of Lead on Vascular Reactivity in Rats.** *Am J Physiol* 1981, 241:H211–H216.

33. Williams BJ, Griffith WH III, Albrecht CM, Pirch JH, Hejtmancik MR Jr: **Effects of Chronic Lead Treatment on Some Cardiovascular Responses to Norepiniphrine in the Rat.** *Toxicol Appl Pharmacol* 1977, 40:407–413.

34. Aviv A, John E, Bernstein J, Goldsmith DI, Spitzer A: **Lead Intoxication During Development: Its Late Effects on Kidney Function and Blood Pressure.** *Kidney Int* 1980, 17:430–437.

35. Kopp SJ, Bárány M, Erlanger M, Perry EF, Perry HM: **The Influence of Chronic Low-Level Cadmium and/or Lead Feeding on Myocardial Contractility Related to Phosphorylation of Cardiac Myofibrillar Proteins.** *Toxicol Appl Pharmacol* 1980, 54:48–56.

36. Carmignani M, Boscolo P, Ripanti P, Finelli VN: **Effects of Chronic Exposure to Cadmium and/or Lead on Some Neurohumoral Mechanisms Regulating Cardiovascular Function in the Rat.** In *International Conference on Heavy Metals in the Environment,* edn 1. Edited by Müller G. Edinburgh: CEP Consultants; 1983:557–560.

37. Nakhoul F, Kayne LH, Brautbar N, Hu M, McDonough A, Eggena P, Golub MS, Berger M, Chang C, Jamgotchian N, Lee DBN: **Rapid Hypertensiogenic Effect of Lead: Studies in the Spontaneously Hypertensive Rat.** *Toxicol Ind Health* 1992, 8:89–102.

38. Boscolo P, Carmignani M, Sacchettoni-Logroscino G, Rannelletti FO, Artese L, Preziosi P: **Ultrastructure of the Testis in Rats With Blood Hypertension Induced by Long-Term Lead Exposure.** *Toxicol Lett* 1988, 41:129–137.

39. Nowack R, Wiecek A, Exner B, Gretz N, Ritz E: **Chronic Lead Exposure in Rats: Effects on Blood Pressure.** *Eur J Clin Invest* 1993, 23:433–443.

40. Perry HM Jr, Erlanger MW, Perry EF: **Increase in the Systolic Pressure of Rats Chronically Fed Cadmium.** *Environ Health Perspect* 1979, 28:251–260.

41. Perry HM Jr, Erlanger MW: **Hypertensive Effect of Chronically Feeding Very Low Concentrations of Lead and Cadmium Together.** In *Trace Substances in Environmental Health,* vol 12. Edited by Hemphill DD. Columbia, MO: University of Missouri; 1978:268–275.

42. Kurtz TW, Montano M, Chan L, Kabra P: **Molecular Evidence of Genetic Heterogeneity in Wistar-Kyoto Rats: Implications for Research With the Spontaneously Hypertensive Rat.** *Hypertension* 1989, 13:188–192.

43. Saint Lezin E, Simonet L, Pravenec M, Kurtz TW: **Hypertensive Strains and Normotensive 'Control' Strains: How Closely Are They Related?** *Hypertension* 1992, 19:419–424.

44. Johnson ML, Ely DL, Turner ME: **Genetic Divergence Between the Wistar-Kyoto Rat and the Spontaneously Hypertensive Rat.** *Hypertension* 1992, 19:425–427.

45. Lindpainter K, Kreutz R, Ganten D: **Genetic Variation in Hypertensive and 'Control' Strains: What Are We Controlling for Anyway?** *Hypertension* 1992, 19:428–430.

46. Wiecek A, Mann JFE, Nowack R, Ritz E: **Effects of Lead Intoxication on Blood Pressure and Vascular Reactivity in Spontaneously Hypertensive Rats.** *J Hypertens* 1986, 4(suppl):S45–S47.

47. Nomiyama K, Nomiyama H, Liu S, Ishimaru Y, Hirai M: **Trace Elements in Cardiovascular Diseases.** *Ann N Y Acad Sci* 1993, 676:308–326.

48. Schütz A, Skerfving S, Ranstam J, Christoffersson J: **Kinetics of Lead in Blood After the End of Occupational Exposure.** *Scand J Work Environ Health* 1987, 13:221–231.

49. O'Flaherty EJ: **Physiologically Based Models for Bone-Seeking Elements: I. Rat Skeletal and Bone Growth.** *Toxicol Appl Pharmacol* 1991, 111:299–312.

50. O'Flaherty EJ: **Physiologically Based Models for Bone-Seeking Elements: II. Kinetics of Lead Disposition in Rats.** *Toxicol Appl Pharmacol* 1991, 111:313–331.

51. Granick JL, Sassa S, Kappas A: **Some Biochemical and Clinical Aspects of Lead Intoxication.** *Adv Clin Chem* 1978, 20:287–339.

52. Armitage P, Rose GA: **The Variability of Measurement of Casual Blood Pressure: 1. A Laboratory Study.** *Clin Sci* 1966, 30:325–335.

53. Victery W, Vander AJ, Schoeps P, Germain C: **Plasma Renin Is Increased in Young Rats Exposed to Lead In Utero and During Nursing.** *Proc Soc Exp Biol Med* 1983, 172:1–7.

54. Campbell BC, Beattie AD, Moore MR, Goldberg A, Reid AG: **Renal Insufficiency Associated With Excessive Lead Exposure.** *BMJ* 1977, 1:482–485.

55. Cramér K, Goyer RA, Jagenburg R, Wilson MH: **Renal Ultrastructure, Renal Function, and Parameters of Lead Toxicity in Workers With Different Periods of Lead Exposure.** *Br J Ind Med* 1974, 31:113–127.

56. Fowler BA, Kimmel CA, Woods JS, McConnell EE, Grant LD: **Chronic Low-Level Lead Toxicity in the Rat: III. An Integrated Assessment of Long-Term Toxicity With Special Reference to the Kidney.** *Toxicol Appl Pharmacol* 1980, 56:59–77.

57. Goyer RA: **Lead and the Kidney.** *Curr Top Pathol* 1971, 55:147–176.

58. Wedeen RP: **Occupational Renal Disease.** *Am J Kidney Dis* 1984, 3:241–257.

59. Nuyts GD, Daelemans RA, Jorens PG, Elseviers MM, van de Vyver FL, de Broe ME: **Does Lead Play a Role in the Development of Chronic Renal Disease?** *Nephrol Dial Transplant* 1991, 6:307–315.

60. Weis CP, Lavelle JM: **Characteristics to Consider When Choosing an Animal Model for the Study of Lead Bioavailability.** *Chem Specification Bioavailability* 1991, 3:113–119.

61. Galal-Gorchev H: **Global Overview of Dietary Lead Exposure.** *Chem Specification Bioavailability* 1991, 3:5–10.

62. Bolger PM, Carrington CD, Capar SG, Adams MA: **Reductions in Dietary Lead Exposure in the United States.** *Chem Specification Bioavailability* 1992, 3:31–36.

63. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR: **Publication Bias in Clinical Research.** *Lancet* 1991, 337:867–872.

Jan A. Staessen, MD, PhD, Klinisch Laboratorium Hypertensie, Inwendige Geneeskunde-Cardiologie, U.Z. Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium.