Urinary cadmium and lead concentrations and their relation to blood pressure in a population with low exposure

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ABSTRACT The 24 hour urinary excretion of cadmium (U-Cd) and lead (U-Pb), and the excretion of beta-2-microglobulins and retinol binding protein concentration in spot urines, were determined in a random 4% sample of the population of a small Belgian town. Blood pressure and body weight were measured on two separate occasions. U-Cd averaged 2.4 nmol/24 h in 46 youths, increased with age, and was significantly higher in 57 adult men as compared with 59 women (9.3 v 7.2 nmol/24 h; $p < 0.01$). U-Pb averaged 28 nmol/24 h in youths and similarly increased with age: adult men excreted more lead than women (64 v 40.0 nmol/24 h; $p < 0.001$). Among men, manual workers excreted more cadmium (12.6 v 7.5 nmol/24 h; $p < 0.05$) but a similar amount of lead (62 v 61 nmol/24 h) compared with office workers. After adjusting for sex and age, U-Cd and U-Pb were not related to body weight and cigarette consumption. In simple regression analysis, U-Cd was positively correlated with both systolic ($r = +0.30$; $p < 0.05$) and diastolic ($r = +0.38$; $p < 0.01$) blood pressure in women. After adjusting for other contributing variables, however, a weak but negative relation became apparent between systolic pressure and U-Cd in women ($t = -2.21$; $p = 0.033$) and between diastolic pressure and U-Cd in men ($t = -2.04$; $p = 0.047$). In women urinary beta-2-microglobulin was related to diastolic pressure ($r = -0.44$; $p < 0.01$) and after adjusting for age to both systolic ($t = -2.75$; $p = 0.009$) and diastolic ($t = -3.07$; $p = 0.004$) pressure. In none of the sex-age groups did U-Pb and retinol binding protein contribute to the blood pressure variability.

Animal experiments have shown that cadmium administration may increase blood pressure (for review see ref 1). Schroeder was among the first to suggest that minimal long term cadmium exposure in man might contribute to the development of arterial hypertension.² Several reports have suggested that chronic or low grade lead exposure may be associated with a rise in blood pressure.³⁻⁶ Nevertheless, the possible role of cadmium and lead in the pathogenesis of hypertension remains controversial, as both affirmative³⁻¹⁵ and negative¹⁶⁻²⁴ studies have been reported. The purpose of the pre-

sent study was to determine the urinary excretion of cadmium and lead in a random sample of the households of a small Belgian town and to investigate whether a significant and independent association could be found between blood pressure and the urinary cadmium and lead output.

Methods

A random sample, consisting of 4% of all households was identified in a Belgian town with a total population of 9000 inhabitants. After excluding subjects who had recently moved or died, 274 people aged 10 years or more were eligible for the study.

Fourteen teams each of two trained volunteers were recruited. After explanation of the rationale

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and methodology of blood pressure measurements, the volunteers were given experience with the use of a regular sphygmomanometer at home for one week. The volunteers were then tested in two phases: firstly, they recorded the "pressures" from the London School of Hygiene sound film, showing a falling mercury column. If all their readings were within 10% of the standard they were finally tested using live subjects and stethoscopes with two pairs of ear pieces.

Each household was visited twice by the same team of volunteers. The first home visit consisted of five consecutive blood pressure readings (phase 5 diastolic pressure) obtained with a standard sphygmomanometer in the sitting position, followed by a pulse rate count and a measurement of body weight. A self administered questionnaire and a wide neck, metal free polyethylene container for a 24 hour urine collection were given to the participants, who were carefully instructed to keep these containers closed except when voiding in order to prevent airborne metal contamination. The questionnaire inquired about the participants' medical history and their current and past occupation, smoking habit, and drug intake. At the second visit two to five weeks later, the questionnaire and a recent 24 hour urine sample were collected and the measurement of blood pressure, pulse rate, and body weight repeated. Each subject was thus characterised by the mean of 10 blood pressure measurements and by both determinations of pulse rate and body weight. At the second visit an aliquot of freshly voided urine was immediately transferred to a small polyethylene bottle (100 ml) containing 100 μ l of a 10% sodium azide solution.

Before use the containers for the 24 hour urine collections were thoroughly cleansed by bristle and detergent. Thereafter, they were filled with 200 ml of 65% nitric acid and deionised water up to their total volume of two litres and left for 24 hours. They were then rinsed five times consecutively, again using deionised water, and dried in an oven. Finally, 10 ml acetic acid (99–100%) and 200 mg thymol were added to the containers which were tightly closed before storage. Before use in the study, a random sample of the prepared containers was checked for cadmium and lead contamination and none was found to be positive. When 24 hour urine samples were returned to the laboratory, an aliquot of 50 ml was transferred to a small container and kept frozen at -20°C until analysed.

The 24 hour urine samples were analysed for cadmium, lead, sodium, potassium, and creatinine. The cadmium and lead concentration in urine were measured as described previously,²⁵ using a Perkin-Elmer, Model 305 atomic absorption spec-

trophotometer equipped with a deuterium background correction system and a Perkin-Elmer HGA-74 atomiser unit. From the spot urine samples, β_2 -microglobulin²⁶ and retinol binding protein²⁷ were determined, since these light molecular weight proteins are often used to monitor cadmium toxicity^{28,29}: pH and creatinine concentration were also measured in spot urines.

The response rate was 68% and table 1 shows the

Table 1 Age and sex distribution of responders and non-responders

Age (years)	Responders*		Non-responders*	
	Men	Women	Men	Women
10–19	27	24	8	6
20–29	11	19	12	9
30–39	19	18	8	5
40–49	19	16	5	6
≥ 50	17	15	14	16
Total	93	92	47	42

*Number of subjects in each age and sex group are given. (Chi-square = 18.86; p = NS).

age and sex distribution of responders and non-responders. Results of blood pressure, anthropometric measurements, and urine analyses were available from 185 subjects. Thirteen of them were taking drugs known to reduce blood pressure and were excluded from further analysis. Their mean age was 54.3 ± 3.4 years (mean $\pm$ standard deviation) and their blood pressure $143 \pm 5/82 \pm 3$ mm Hg. Their urinary excretion of cadmium and lead averaged 10.0 ± 1.8 nmol/24 h and 59.1 ± 10.0 nmol/24 h, respectively. Twenty four hour urine collections are sometimes incorrect (incomplete or collected for more than 24 hours). The urinary creatinine excretion was therefore plotted against body weight in both sexes separately and subjects who fell outside the 2 standard deviation range of the regression lines were excluded. Altogether 162 24 hour urine collections were considered for analysis. Spot urine samples with pH equal to or higher than 5.5 were available for 143 of these 162 subjects, the other 19 being excluded since β_2 -microglobulin undergoes proteolytic degradation when pH falls below 5.5.²⁹

Student's t test for unpaired data was used to compare group means. Blood pressure and other items were correlated with each other, using Pearson's correlation coefficients and significance levels, derived from two-tailed tests. To determine the independent effects of the anthropometric and urine measurements on blood pressure multiple regression equations were calculated, using a stepwise (stepup) procedure terminating when all regression

coefficients were significant at the 5% level. Comparison of group means and regression analysis were performed after normalising the distributions of 24 hour urinary cadmium and lead and those of urinary β_2 -microglobulin and retinol binding protein by a logarithmic transformation.

Results

GENERAL CHARACTERISTICS OF THE PARTICIPANTS

Table 2 shows the average age, blood pressure, and body weight, separately in youths (10–19 years) and adults (≥ 20 years) of both sexes. The pulse rate was similar in the four age-sex groups and averaged 75 ± 10.3 beats/min (range 51–110).

RESULTS OBTAINED FROM 24 HOUR URINE SAMPLES

Table 3 shows the mean 24 hour excretion of the urinary constituents, together with their standard deviation and ranges. The figure illustrates the aver-

age urinary cadmium and lead excretion for both sexes and five age groups. Over the age of 20, the urinary cadmium and lead output was higher ($p < 0.01$) in male than female subjects (Table 3) and increased with age until age 50. The excretion of urinary cadmium and lead increased also with body weight, but this effect disappeared after adjusting for sex and age.

Twenty two male manual workers, aged 20 and over, had higher ($p < 0.05$) average cadmium excretions than 35 male office workers of similar age (12.6 nmol/24 h v 7.5 nmol/24 h). This difference was not apparent for their urinary lead excretion (62 nmol/24 h and 61 nmol/24 h respectively). Though at least four and possibly more of the manual workers were occupationally exposed to cadmium, the highest cadmium excretion encountered in this group was only 36.5 nmol per 24 hours, which is far less than the average in male workers with heavy cadmium exposure.²⁸ Among men, the average 24 hour urinary excretion of cadmium and lead was not statistically different between 11 non-smokers and

Table 2 General characteristics of the male and female subjects

	Adolescents (10–19 years)		Adults (≥ 20 years)	
	Boys	Girls	Men	Women
No	24	22	57	59
Age (years)	14.6 ± 2.86 10–19	13.5 ± 2.94 10–19	41.0 ± 13.50 20–75	38.7 ± 13.80 20–80
Systolic pressure (mm Hg)	122 ± 14.6 99–149	115 ± 12.7 95–138	131 ± 10.9 111–167	128 ± 15.6 98–178
Diastolic pressure (mm Hg)	61 ± 8.6 48–81	62 ± 6.1 49–78	76 ± 9.5 45–94	76 ± 8.5 55–94
Body weight (kg)	55.1 ± 15.80 33.0–84.8	47.0 ± 9.56 30.8–65.0	78.2 ± 12.54 51.5–107.3	62.8 ± 10.25 44.0–91.0

Values are arithmetic means $\pm$ standard deviation; the range is also given.

Table 3 Results of the urine analyses in male and female subjects

	Adolescents (10–19 years)		Adults (≥ 20 years)	
	Boys	Girls	Men	Women
No	24	22	57	59
Volume (l/24 h)	1.06 ± 0.452 0.39–1.98	0.82 ± 0.298 0.38–1.78	1.55 ± 0.506 0.68–2.90	1.33 ± 0.506 0.38–2.65
Creatinine (mmol/24 h)	12.5 ± 4.85 5.4–27.1	10.8 ± 2.54 7.0–17.2	17.9 ± 4.57 6.4–28.6	12.3 ± 3.27 5.1–20.2
Sodium (mmol/24 h)	141 ± 63.2 47–292	121 ± 40.8 44–215	187 ± 57.9 84–325	133 ± 48.9 40–285
Potassium (mmol/24 h)	64 ± 24.9 20–128	63 ± 22.3 35–139	70 ± 22.3 25–164	61 ± 18.8 20–117
Cadmium (nmol/24 h)	2.1 ± 1.27 0.4–5.4	2.7 ± 2.20 0.9–11.3	9.3 ± 6.82 2.0–36.5	7.2 ± 5.00 0.6–19.3
$\log_{10}$ distribution*	0.23 ± 0.300	0.34 ± 0.270	0.88 ± 0.284	0.73 ± 0.359
Lead (nmol/24 h)	32 ± 21.2 2–86	23 ± 11.2 10–59	64 ± 31.4 21–158	40 ± 22.1 7–99
$\log_{10}$ distribution*	1.40 ± 0.347	1.33 ± 0.180	1.75 ± 0.215	1.52 ± 0.256

Values are arithmetic means $\pm$ standard deviation; the range is also given.

*For non-normal distributions the arithmetic mean and standard deviation obtained after logarithmical transformation are shown in addition.

Twenty four hour urinary excretion of cadmium and lead, expressed in nanomoles (mean $\pm$ standard error), according to age in male (Δ) and female ($\circ$) subjects. Number of subjects in each age group is given for both sexes.

46 smokers (8.7 ± 9.6 nmol/24 h cadmium and 61 ± 65 nmol/24 h lead, respectively); also among women, 31 non-smokers and 28 smokers excreted similar amounts of cadmium and lead (7.8 ± 6.5 nmol/24 h cadmium and 37 ± 41 nmol/24 h lead, respectively). Furthermore, the output of urinary cadmium was similar in present (35 men and 24 women) and past (11 men and 4 women) smokers, and remained independent of smoking habits when, in addition to sex, age and body weight were also taken into account.

RESULTS OBTAINED FROM SPOT URINE SAMPLES
Table 4 gives the average concentration of urinary

β_2 -microglobulin and retinol binding protein for youths and adults of both sexes. Both the concentration of these light molecular weight proteins and the amount excreted per gram creatinine were independent of age and sex.

CORRELATION BETWEEN BLOOD PRESSURE AND URINARY CONSTITUENTS

Table 5 gives first order correlations between blood pressure and various other items. Systolic pressure in youths, diastolic in men, and both systolic and diastolic pressure in women were positively and significantly correlated with age and body weight. In women systolic and diastolic pressure were

Table 4 Results obtained from spot urine samples in male and female subjects

	Adolescents (10-19 years)		Adults (≥ 20 years)	
	Boys	Girls	Men	Women
No	24	21	52	46
pH	6.7 ± 0.58 5.8-8.0	6.5 ± 0.67 5.5-7.8	6.3 ± 0.62 5.5-7.6	6.5 ± 0.75 5.5-9.4
Creatinine (mmol/l)	11.2 ± 5.49 1.6-20.2	10.9 ± 3.82 4.0-17.9	12.6 ± 5.53 2.0-26.8	11.4 ± 5.7 1.8-27.9
β_2 -microglobulin concentration ($\mu\text{g/l}$)	110 ± 77.5 7-323	75 ± 36.2 4-126	90 ± 72.5 6-353	84 ± 53.9 14-240
$\log_{10}$ distribution*	1.91 ± 0.390	1.79 ± 0.347	1.80 ± 0.414	1.83 ± 0.312
β_2 -microglobulin (μg) per gram creatinine	88 ± 57.9 9-253	65 ± 27.9 3-107	67 ± 49.1 4-263	72 ± 36.6 8-170
$\log_{10}$ distribution*	1.88 ± 0.389	1.73 ± 0.361	1.70 ± 0.373	1.79 ± 0.285
Retinol binding protein concentration ($\mu\text{g/l}$)	56 ± 40.9 13-202	51 ± 53.6 5-240	59 ± 34.5 10-164	61 ± 50.4 11-253
$\log_{10}$ distribution*	1.66 ± 0.281	1.55 ± 0.393	1.69 ± 0.304	1.65 ± 0.341
Retinol binding protein (μg) per gram creatinine	50 ± 33.5 19-160	39 ± 32.2 5-157	45 ± 22.0 7-118	51 ± 32.0 11-169
$\log_{10}$ distribution*	1.64 ± 0.236	1.49 ± 0.300	1.59 ± 0.257	1.62 ± 0.275

Values are arithmetic means $\pm$ standard deviation; the range is also given.

*For non-normal distributions the arithmetic mean and standard deviation obtained after logarithmical transformation are also shown.

significantly and positively related to the 24 hour urinary cadmium excretion and diastolic pressure significantly but negatively to the urinary β_2 -microglobulin concentration.

The results of stepwise (stepup) multiple regression of blood pressure on different variables are summarised in table 6. The explanatory variables included: age, square of age, body weight, pulse rate, smoking habit, the 24 hour urinary constituents, and urinary β_2 -microglobulin and retinol binding protein (expressed in $\mu\text{g/l}$ and in $\mu\text{g/g}$ creatinine). In youths there was a positive association only between blood pressure and body weight. In men multivariate analysis confirmed a significant and negative relation between systolic pressure and 24 hour urinary potassium as previously reported in this population.^{30,31} After adjusting for age, diastolic pressure was significantly and negatively related to 24 hour urinary cadmium in men. The t -value for the partial regression coefficient was -2.04 ($p = 0.047$), whereas the corresponding t -value for entering potassium instead of cadmium just failed to

reach statistical significance ($t = -1.80$; $p = 0.077$). After adjusting for age, present smoking habit, and urinary β_2 -microglobulin a weak ($t = -2.21$; $p = 0.033$) but negative correlation became apparent between systolic pressure and urinary cadmium in women. In women the urinary β_2 -microglobulin concentration was also negatively and independently related to both systolic ($t = -2.75$; $p = 0.009$) and diastolic ($t = -3.07$; $p = 0.004$) pressure, whereas in men there was no such relation with systolic (t to enter β_2 -microglobulin concentration = 0.31 ; $p = 0.758$) nor with diastolic ($t = -0.55$; $p = 0.588$) pressure.

There was no significant and independent contribution of 24 hour urinary lead to blood pressure in any of the age-sex groups and the same was true for urinary retinol binding protein.

Discussion

The present study aimed to determine the excretion of urinary cadmium and lead in a random sample of

Table 5 First order correlation coefficients between systolic (SBP) and diastolic (DBP) blood pressure and different variables

	Adolescents		Adult men		Adult women	
	SBP	DBP	SBP	DBP	SBP	DBP
Age	+0.56***	+0.16	+0.15	+0.45***	+0.65***	+0.45***
Body weight	+0.78***	+0.37*	-0.10	+0.38**	+0.40***	+0.39**
$\log_{10}$ 24-h cadmium	+0.11	+0.03	-0.02	+0.18	+0.30*	+0.38**
$\log_{10}$ 24-h lead	+0.01	+0.03	-0.19	+0.07	+0.06	+0.08
24-h potassium	+0.11	-0.02	-0.27*	-0.18	-0.08	+0.04
$\log_{10}$ β_2 -m concentration ($\mu\text{g/l}$)	-0.07	-0.16	-0.01	+0.01	-0.28	-0.44**
$\log_{10}$ β_2 -m (μg) per gram creatinine	-0.01	-0.21	-0.04	+0.05	-0.15	-0.17
$\log_{10}$ RBP concentration ($\mu\text{g/l}$)	+0.11	+0.07	+0.03	-0.05	-0.05	-0.15
$\log_{10}$ RBP (μg) per gram creatinine	+0.18	-0.04	+0.05	-0.02	+0.14	+0.12

Significance of the correlation coefficients: * $p < 0.05$; ** $p < 0.01$ and *** $p < 0.001$. β_2 -m = β_2 -microglobulin. RBP = Retinol binding protein.

Table 6 Results of multiple regression of systolic (SBP) and diastolic (DBP) blood pressure and different variables

			Regression coefficients					Constant	Correlation§ coefficients
	Age	(Age) ²	Weight	Tobacco†	Potassium	log ₁₀ cadmium	log ₁₀ β ₂ -microglobulin concentration (μg/l)		
Adolescents (10–19 years):									
SBP	NS	NS	+0.786***	NS	NS	NS‡	NS‡	+78.22	r = +0.81***
DBP	NS	NS	+0.201*	NS	NS	NS‡	NS‡	+51.23	r = +0.37*
Adults (≥20 years):									
SBP men	NS	NS	NS	NS	−0.131*	NS‡	NS‡	+139.86	r = −0.27*
DBP men	+2.505***	−0.024***	NS	NS	NS	−8.517‡	NS‡	+24.75	R = 0.66***
SBP women	+0.981***	NS	NS	−4.218*	NS	−13.77*	−16.11**	+129.1	R = 0.77***
DBP women	+0.295***	NS	NS	NS	NS	NS‡	−10.74**	+83.52	R = 0.63***

§ Simple (r) or multiple (R) correlation coefficients obtained as a result of stepwise (stepup) regression analysis.

† Coded as follows: +1 present-smokers; -1 past-smokers and non-smokers.

* $p < 0.05$; ** $p < 0.01$; and *** $p < 0.001$; NS = Not significant and therefore not included in the multiple regression equation.

‡ t to enter $\log_{10}$ cadmium = -2.04 ($p = 0.047$); t to enter urinary potassium instead = -1.80 ($p = 0.077$).

‡ +0.28 $> t$ to enter > -1.01 ($p > 0.3$).

the population of a Belgian town and to investigate whether the urinary elimination of these metals was in any way related to blood pressure.

URINARY CADMIUM EXCRETION

In accordance with previous reports^{1,32,33} the urinary cadmium excretion increased with advancing age and was higher in men than women. When age and sex were taken into account urinary cadmium was not dependent on body weight. Expressed per gram creatinine, the urinary output of cadmium averaged 0.21 μg in youths, 0.54 in men, and 0.62 μg in women. The small amounts of cadmium and lead excreted in the urine in the present population are compatible with a low average exposure. In middle aged male workers living in Belgium but without professional exposure Bernard *et al* found an average cadmium excretion of 0.82 $\mu\text{g/g}$ creatinine.²⁸ Other investigators estimated the output of urinary cadmium to be 1.25 $\mu\text{g/g}$ creatinine in adults²³ and 2.1 $\mu\text{g/day}$ in hypertensive men and women.²¹

The average urinary cadmium excretion observed in the present study was similar to that found in non-occupationally exposed subjects with a daily dietary cadmium intake of about 15 μg ,^{32,33} which is in agreement with the median value (15 $\mu\text{g}/24$ h) reported in a recent duplicate meal study in the Belgian population.³⁴ It should not be forgotten, however, that since cadmium is a highly cumulative metal, which is preferentially concentrated in the kidney, urinary excretion is more a reflection of an individual's life time exposure and body burden than of day to day variations in intake. This explains why the elimination of urinary cadmium increases with advancing age. In the older age groups (≥ 50 years) the urinary cadmium excretion seems to level off but the reason for this is not clear unless levels of exposure have increased in more recent generations.

In the present study no difference in urinary cadmium output could be shown between non-smokers, present smokers, and past smokers. Though there is general consensus that tissue^{18-20,35} and blood^{6,9,22} concentrations of cadmium are raised in smokers, studies on urinary cadmium have either not taken into account cigarette consumption^{21,23} or have failed to show any significant correlation with smoking.¹⁹ In the postmortem studies of Lewis and co-workers,³⁵ and in a recent WHO survey³⁶ the tissue concentrations of cadmium showed considerable overlap between smokers and non-smokers and, in multiple regression analysis, were related to moderate and heavy but not to light (less than one pack a day) smoking.³⁵ In the present study only 25% of the smokers consumed more than one pack a day, and this may explain the absence of any significant relation between 24 hour urinary cadmium output

and smoking habit. The negative correlation observed in women between systolic pressure and present cigarette consumption is in accordance with previous experience.³⁷

The work environment, if polluted by cadmium, may constitute a major source of body cadmium. Male manual workers had a greater 24 hour cadmium output than men with other occupations. Nevertheless, urinary β_2 -microglobulin and retinol binding protein frequently used for biological monitoring of exposed workers were not significantly related to the urinary elimination of cadmium and lead in the present population, which had a low average exposure.

URINARY LEAD EXCRETION

In the present population with low average exposure, urinary lead excretion increased with age and was higher in men than women. Body weight, occupation, and tobacco consumption did not influence the amount of lead excreted in the urine. Expressing urinary lead output per gram creatinine eliminated the differences between sexes (6.9 μg in men v 6.0 μg in women) but not between the various age groups (4.5 μg in youths v 6.5 μg in adults). In middle aged Belgian workers with no occupational exposure urinary lead excretion is 14 μg lead/g creatinine²⁸; in unexposed Italian workers it is 29 $\mu\text{g}/24$ h,³⁸ whereas in Czechoslovakia an average urinary concentration of 52 $\mu\text{g/l}$ is found.³⁹ The greater urinary lead output in men as compared with women is in accordance with other reports where men have also been shown to have higher blood concentrations.⁴⁰

BLOOD PRESSURE AND URINARY CADMIUM AND LEAD EXCRETION

First order regression analysis showed a positive correlation between blood pressure and urinary cadmium in women. After adjusting for other contributing variables, however, a weak but negative correlation became apparent between systolic pressure and urinary cadmium indicating that a higher cadmium excretion was associated with a lower systolic pressure. In men there was an independent and inverse relation between diastolic pressure and urinary cadmium; taking age into account, a higher urinary cadmium excretion was found to be associated with a lower diastolic pressure. These correlations between blood pressure and urinary cadmium do not necessarily imply a causal relationship, since an unknown third factor might be the common link which produces the association. The association could also be explained by the hypothesis that subjects with a higher blood pressure are less able to eliminate cadmium in their urine. Finally, these cor-

relations could indicate that cadmium, even at its usual environmental concentration, might have some sort of biological action and, for unknown reasons, lower blood pressure. Initially a positive association has been found between the prevalence of high blood pressure and the cadmium content of both drinking water⁶ and ambient air.⁷ The relation between arterial pressure and renal tissue levels of cadmium has been reported to be positive,¹⁰ non-existent,^{16-18 20 35} and negative,¹⁹ whereas the positive correlation observed in some studies^{9 11-14} between arterial pressure and blood concentrations of cadmium could not be confirmed by other investigators.^{6 22} Looking more specifically at urinary cadmium, most researchers^{21 23} were unable to show any significant relationship with blood pressure. Confounding by age, sex distribution, and cigarette consumption may at least account for part of the controversy. Genetic susceptibility and duration of exposure⁴¹ could also be important determinants of the pressure response to cadmium and are likely to differ in the various populations studied. Furthermore, as new techniques became available, more recent studies have used improved methods for measuring trace metals in body fluids and tissues. Finally, the association between cadmium and blood pressure could be more complex than a simple linear relationship, since recent animal experiments have shown a bell shaped dose response curve between blood pressure and exposure to cadmium.⁴²

By contrast with cadmium, urinary lead did not contribute to the blood pressure variability in any of the age-sex groups of the present study. Among subjects with excessive lead exposure the prevalence of hypertension and cerebrovascular disease has been variously reported to be increased³ or not affected,²⁴ whereas Beevers *et al* have shown a positive relation between arterial pressure and blood lead concentrations.^{5 6} Boscolo *et al* looking at urinary lead as an index of long term exposure found a positive association with arterial pressure.¹⁵

A striking but unexplained observation is the negative and independent relation found in women between blood pressure and urinary β_2 -microglobulin. This correlation indicated that higher blood pressure levels were associated with a lower urinary β_2 -microglobulin concentration. Light molecular weight proteins such as β_2 -microglobulin and retinol binding protein pass readily through the glomerular barrier but are subsequently almost totally reabsorbed in the proximal tubule.²⁹ There was, however, no correlation between blood pressure and urinary retinol binding protein. It is unlikely, therefore, that the present relation between arterial pressure and urinary β_2 -microglobulin in women can be explained by a renal mechanism.

On the other hand, it is not clear how a higher blood pressure could be related to decreased endogenous synthesis of β_2 -microglobulin. β_2 -Microglobulin being an integral part of the histocompatibility antigens²⁹ could be considered to be some sort of a genetic marker, but why should it also be related to blood pressure in women?

Appendix

CONVERSION OF UNITS

Cadmium	1 nmol = 112.4 ng.
Lead	1 nmol = 207.1 ng.
Sodium	1 mmol = 23.0 mg.
Potassium	1 mmol = 39.1 mg.
Creatinine	1 mmol = 113.1 mg.

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Twenty four hour urine samples were analysed for electrolytes and creatinine in the Central Laboratory of the University Hospital St Rafaël, Leuven, Belgium, under supervision of Professor J H Claes and Dr W Lissens. Mr Grauwels performed the computer analysis. Expert clerical and technical help was provided by Mrs V Mariën, Mrs M Stinissen, Mrs Y Toremans, and Mrs N Vangeel.

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