To: Dr. C. C. Pfeiffer

CCP note:

These papers contain some very supportive statements regarding DuPonts analyses

Donald R. Lynam, Ph.D.

Ethyl

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Blood lead concentration, blood pressure, and renal function

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Abstract

Blood lead concentrations were related to blood pressure and indicators of renal function in a clinical survey of 7735 middle aged men from 24 British towns. There was no overall evidence that blood lead concentrations were associated with systolic or diastolic blood pressure ($r=+0{\cdot}03$ and $+0{\cdot}01$, respectively). In the 74 men with a blood lead concentration of 1·8 μmol/l (37·3 μg/100 ml) or more there was some suggestion of increased hypertension, but this did not reach significance. Blood lead concentration did not have any relation with serum creatinine concentration. Moderate increases in blood lead concentration were associated with small increases in mean serum urate concentration and small decreases in mean serum urea concentration; these associations were both reduced when alcohol consumption was taken into account.

There is no indication that exposure to lead at concentrations commonly encountered in British men is responsible for impaired renal function or increased blood pressure.

Introduction

Considerable public concern has been shown about the effects on health of exposure to lead both in adults and in children. In response to reports that moderate increases in blood lead concentration are associated with hypertension and impaired renal function[1–3] we present findings from a clinical survey of British middle aged men, relating measurements of blood lead concentration to blood pressure and serum creatinine, urate, and urea concentrations.

Patients and methods

The Regional Heart Study recruited 7735 men aged 40 to 59 who were randomly selected from representative general practices in 24 British towns. Details of the selection of towns and general practices and the methods of screening and data collection have been reported.[4] Each man's blood pressure was measured twice in succession with the London School of Hygiene sphygmomanometer, with the subject seated and his arm supported on a cushion. Diastolic blood pressure was recorded at disappearance of sounds (phase V). The mean of two readings of blood pressure was adjusted for observer variation within each town to allow for any inconsistencies among the three observers.

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Blood samples for biochemical analysis and haematological studies were taken into evacuated tubes. All samples reached the Wolfson Research Laboratories, Birmingham, by the next morning, and estimations were completed by noon. Serum concentrations of creatinine, urate, and urea were measured on a Technicon SMA 12/60 analyser. Blood lead concentrations were analysed at the University of Southampton with flame microsampling atomic absorption spectroscopy.[5] A strict quality control protocol was maintained and the performance of the laboratory was continually monitored by participation in national and international quality assessment schemes for analysis of blood lead concentration.

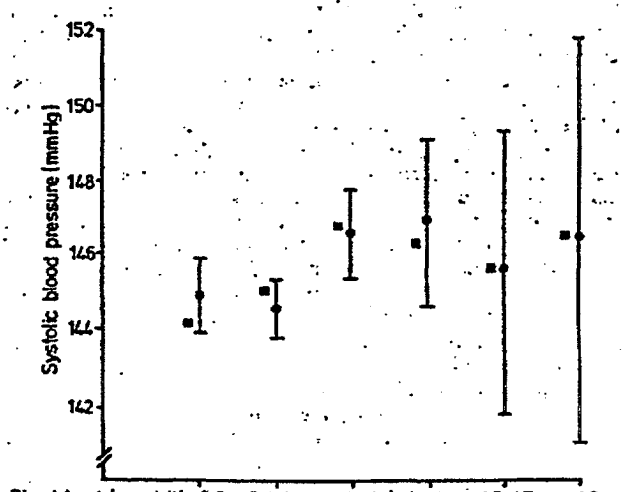
Alcohol consumption was recorded using questions on frequency, quantity, and type similar to those in the General Household Survey.[6] A drink was defined as half a pint of beer, one glass of wine, or a single tot of spirits. For data analysis, eight drinking categories were used: non-drinkers, occasional drinkers, weekend drinkers (one or two, three to six, or more than six drinks a day) and daily drinkers (one or two, three to six, or more than six drinks a day).

Results

BLOOD LEAD CONCENTRATION AND BLOOD PRESSURE

Blood pressure and blood lead concentrations were both measured in 7371 men (95% of men screened). The correlation coefficients of blood lead with systolic and diastolic blood pressure were $r=+0{\cdot}03$ and $r=+0{\cdot}01$ respectively. The association with systolic blood pressure, although close to zero correlation, was significant at the 1% level. In large scale surveys, however, it is the magnitude of an association, not its significance, that is biologically important.

Figure 1 shows the mean and 95% confidence limits for systolic blood pressure for men categorised according to blood lead concentrations. There was no indication of higher systolic blood pressure



Blood lead (μmol/l)	<0·6	0·6–0·8	0·9–1·1	1·2–1·4	1·5–1·7	≥1·8
No of men	1984	3381	1420	386	126	74
No (%) with systolic blood pressure >160 mm Hg	418 (21)	675 (20)	349 (25)	95 (25)	22 (17)	22 (30)

FIG 1—Systolic blood pressure for 7371 middle aged men categorised according to blood lead concentration. ● Represents unadjusted mean and 95% confidence limits. ■ Represents mean adjusted for age, town, body mass, alcohol consumption, social class, and observer.
Conversion: SI to traditional units—Lead: 1 μmol/l ≈ 20·7 μg/100 ml.

...th higher blood lead concentrations. Age, town, body mass ...alcohol consumption, social class, and observer have all ...viously been shown to be associated with systolic blood pressure.[4] Figure 1 also shows the mean systolic blood pressure by blood lead concentration, after adjustment for these other factors using analysis of covariance. Again, there was no evidence of any association between blood lead concentration and systolic blood pressure.

To examine the prevalence of hypertension in relation to blood lead concentration figure 1 also shows the proportion of men with systolic blood pressure over 160 mm Hg for each blood lead concentration. There was no significant trend in these proportions, though, of the small group of men with a blood lead concentration of 1·8 μmol/l (37·3 μg/100 ml) or more, 22 (30%) had hypertension compared with 1559 (21%) of all the other men (p=0·08). Findings for diastolic hypertension (>100 mm Hg) followed a similar pattern. There was an increase in diastolic hypertension in the small group of men with a blood lead concentration of 1·8 μmol/l (37·3 μg/100 ml) or more—that is, 11 (15%) had hypertension compared with 648 (9%) of all the other men. This difference, however, was only marginally significant (p=0·07) and there was no evidence of a trend at blood lead concentrations below 1·8 μmol/l (37·3 μg/100 ml).

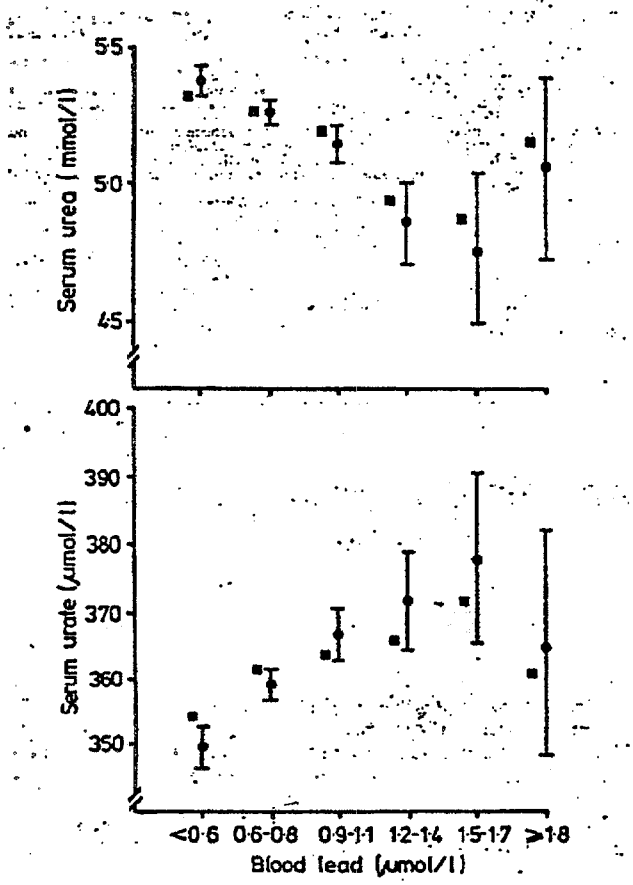


FIG 2—Serum urea and urate concentrations for 7364 men categorised according to blood lead concentration. ● Represents unadjusted mean and 95% confidence limits. ■ Represents mean adjusted for alcohol consumption.

Conversion: SI to traditional units—Lead: 1 μmol/l≈20·7 μg/100 ml. Urea: 1 mmol/l≈6 μg/100 ml. Urate: 1 μmol/l≈16·8 μg/100 ml.

BLOOD LEAD CONCENTRATION AND RENAL FUNCTION

Three indicators of renal function (serum concentrations of creatinine, urate, and urea) were measured in 7364 men for whom data on blood lead concentrations were also available (95% of men screened). As creatinine and urea concentrations both had highly skew distributions log transformations were used in statistical analysis. The correlation coefficients for blood lead concentration with creatinine, urate, and urea concentrations were 0·00, +0·10, and −0·08 respectively, the associations with urate and urea being highly significant (p<0·001). Once again, however, it should be noted that, despite the levels of significance, the magnitude of each correlation was small and unlikely to be of biological importance.

Figure 2 shows means and 95% confidence intervals for serum urate and urea concentrations for men categorised according to blood lead concentration. Except for the small groups of men with a blood lead concentration of 1·8 μmol/l (37·3 μg/100 ml) or more there were consistent trends with blood lead concentration, decreasing for urea and increasing for urate concentrations. Alcohol consumption has previously been shown to be associated with increasing serum urate concentration and decreasing serum urea concentration.[7] In this previous report, heavy drinkers—for example, those drinking more than three pints of beer daily—had a 13% increase in mean serum urate concentration and a 9% decrease in mean serum urea concentration compared with occasional drinkers. Also, as previously reported, heavy drinkers had a 30% increase in mean blood lead concentration.[8] Thus alcohol consumption must be taken into account when associations between urea, urate, and blood lead concentrations are studied. Accordingly, figure 2 also shows the means for serum urate and urea concentrations adjusted for alcohol consumption using analysis of covariance. The trends with blood lead concentration are weakened but not eliminated after allowance for alcohol consumption. The partial correlation of blood lead concentration with serum urate concentration was reduced from +0·10 to +0·06. For serum urea concentration the correlation changed from −0·08 to −0·05 after allowing for alcohol consumption.

Discussion

BLOOD LEAD CONCENTRATION AND BLOOD PRESSURE

In this large representative sample of British middle aged men there was no overall evidence that moderate increases in blood lead concentration were associated with increased blood pressure. This finding contradicts a previous case-control study done in Glasgow.[1] In that study 135 subjects with hypertension were each paired with a normotensive subject matched for age and sex. In a paired analysis of blood lead concentrations significantly more of the men with hypertension had increased blood lead concentrations than did the men with normal blood pressure and there was a similar but non-significant trend in women with hypertension. These findings were the basis for a conclusion that high blood pressure is associated with high blood concentrations of lead and that this might explain the high prevalence of cardiovascular disease in the west of Scotland. The possible bias in such case-control studies must, however, be considered. For instance, the important influences of alcohol consumption and cigarette smoking on blood lead concentration were not known at the time of the Glasgow study and thus were not taken into account. The higher blood lead concentrations in some patients with hypertension may therefore have been due to their high intake of alcohol rather than any causal influence of lead on blood pressure. Another possible explanation is that blood lead concentrations were higher in the Glasgow study largely because of plumbosolvent water supplies, and any potential effect of raised blood lead concentration on blood pressure may have been present only above certain critical limits such as 1·8 μmol/l (37·3 μg/100 ml). This would be consistent with no association being found in a similar case-control study in Birmingham, in which blood lead concentrations tended to be lower.[3] There is a weak suggestion from the data of the Regional Heart Study that subjects with blood lead concentrations of 1·8 μmol/l (37·3 μg/100 ml) or more may suffer more often from hypertension. As only 74 men (1%) had blood lead concentrations of 1·8 μmol/l (37·3 μg/100 ml) or more it seems reasonable to conclude that exposure to lead makes a negligible contribution to high blood pressure in the general male population of Great Britain.

BLOOD LEAD CONCENTRATION AND RENAL FUNCTION

The association between blood lead concentration and three indicators of renal function (serum concentrations of creatinine,

...ce, and urea) was examined in 7364 middle aged British men. After allowing for the influence of alcohol consumption on serum biochemistry there was no substantial association of increased blood lead concentration with renal function. There was a weak positive trend towards increased serum urate concentration at high blood lead concentration and a reverse trend for serum urea concentration. These findings differ from those of a previous study carried out in Scotland on people selected because their homes were thought to have lead pipes or storage tanks.[2] In that study raised blood lead concentration was associated with raised serum urea and urate concentrations and excessive lead in domestic water supplies was considered to have a harmful effect on the community's health. A review paper then questioned their use of arbitrary cut off points for serum urate and urea concentrations, particularly in an elderly population.[9] In addition this case-control study took no account of alcohol consumption, which is now known to have a considerable effect on both blood lead concentration and indicators of renal function.

Several studies have reported that occupational lead poisoning can result in severe renal impairment. For instance, an investigation of renal function was carried out in 102 Rumanian patients with lead poisoning attributed to occupational exposure who had a mean blood lead concentration of 4 μmol/l (83 μg/100 ml).[10] Seventeen patients had chronic nephropathy, mostly after more than 10 years of exposure to lead. Thirteen of these patients had also developed hypertension. Studies such as this have stimulated inquiry into whether more moderate exposure to lead in the general population could affect renal function or blood pressure.

It has been suggested that, in areas where occupational lead nephropathy is common, patients seen at the stage of hypertension or chronic renal impairment typically have normal blood lead concentrations; their lead overload is shown only by bone biopsy or an edetic acid excretion test. Thus the possibility that exposure to lead earlier in life might account for subsequent hypertension or renal disease cannot be excluded. Our cross sectional study, however, using current blood lead concentrations, has not shown any evidence that recent exposure to lead at concentrations commonly experienced by British men is responsible for increases in blood pressure or impaired renal function.

The British Regional Heart Study is supported by a programme grant from the Medical Research Council. Biochemical estimations were carried out at the Wolfson Research Laboratories under a programme supported by the Department of Health and Social Security. Blood lead concentrations were estimated in the department of chemical pathology and human metabolism, University of Southampton (Professor B Clayton), supported by the DHSS.

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Cardiac arrhythmias during rewarming of patients with accidental hypothermia

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Abstract

Accidental hypothermia has a high mortality and is associated with cardiac arrhythmias. To determine the incidence of arrhythmias and their importance 22 patients with accidental hypothermia (core temperature <35°C) were studied by 12 lead electrocardiography and continuous recording of cardiac rhythm. Although 14 of the patients died (64%), only six died while hypothermic. Prolongation of the Q-T interval and the presence of J waves were related to the severity of the hypothermia. Supraventricular arrhythmias, including atrial fibrillation, were common (nine cases) and benign. Ventricular extrasystoles were also common (10 cases), but ventricular tachycardia or fibrillation did not occur during rewarming. In eight patients who died while being monitored the terminal rhythm was asystole. There was no correlation between the severity of hypothermia or the rate of rewarming and the clinical outcome.

In the absence of malignant arrhythmias there is no indication for using prophylactic antiarrhythmic treatment in patients with accidental hypothermia. The presence or absence of severe underlying disease is the main determinant of prognosis.

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Introduction

Accidental hypothermia is a common reason for admission to hospital during the winter[1 2] and has a high mortality, especially in the elderly.[3 4] The condition is associated with life threatening arrhythmias, in particular ventricular fibrillation, and there have been several reports of prolonged but successful resuscitation in such patients.[5-8] Our aim was therefore to record continuously the cardiac rhythm of hypothermic patients during rewarming in order to discover the incidence of arrhythmias and whether they contribute to the mortality.

BLOOD LEAD AND BLOOD PRESSURE IN MIDDLE-AGED MEN

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ABSTRACT

The British Regional Heart Study is a large prospective investigation into the risk factors for ischaemic heart disease based on a cohort of men aged 40 - 59 recruited from general practice registers in 24 British towns. Blood lead concentrations and measurements of blood pressure were recorded for 7371 men at initial screening in 1978 - 80. This paper uses these data to explore the hypothesis that an elevated body lead burden may be affecting blood pressure in adults.

Univariate analysis showed no association between blood lead and blood pressure, r= +.03 and +.01 for systolic and diastolic respectively. Multiple regressions of blood pressure on log (blood lead) were carried out adjusting for the following confounders: age, body mass, alcohol, smoking, observer, social class and town of residence. These estimated that doubling of blood lead is associated with an estimated increase of 1.45 mm Hg for systolic and 1.25 mm Hg for diastolic BP. The association is very weak, the study is observational and it is difficult to adjust for all relevant confounders. Therefore, it is premature to conclude that an elevated body lead burden has a causal influence on blood pressure.

INTRODUCTION

Considerable public concern has been shown about the effects on health of exposure to lead in adults and in children. In response to reports that moderate increases in blood lead concentration are associated with hypertension we present findings from a clinical survey of British middle aged men, relating measurements of blood lead concentrations to blood pressure.

The Regional Heart Study recruited 7735 men aged 40 - 59 who were randomly slected from representative general practices in 24 British towns. Details of the selection of towns and general practices and the methods of screening and data collection have been reported (ref 1).

BETWEEN TOWN COMPARISON

The mean systolic and diastolic blood pressure were computed for men in in each town (around 300 men per town). There was a marked geographic variation in blood pressure. For instance, mean systolic BP ranged from 153 mm Hg in Dunferline to 136 mm Hg in Guildford. The mean blood

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lead in each town (around 300 men per town) showed a marked geogra variation, ranging from 0.99 μmol/l in Ayr and Harrogate to 0.55 μmo in Ipswich. It was noted that six towns with the highest mean blood lead were in soft water areas and that three of these had evidence elevated levels of lead in drinking water. Thus, it seems likely geographic variation in body lead burden is substantially affected the nature of water supplies. There was no association between th 24 towns' mean blood lead and mean blood pressure, either systolic o diastolic.

COMPARISON OF INDIVIDUALS - UNIVARIATE ANALYSIS

Blood pressure and blood lead concentrations were both measured in 73 men (95% of men screened). The correlation coefficients of blood le with systolic and diastolic blood pressure were r=+0.03 and r=+0.01 respectively. The association with systolic blood pressure, although close to zero correlation, was significant at the 1% level. In larg scale surveys, however, it is the magnitude of an association, not it significance, that is biologically important. In this same sample of men, it was noted that blood pressure was markedly related to age and body mass. Also alcohol intake, observer, social class, smoking and town of residence seemed important factors to take into account (ref1) Alcohol intake was of particular interest since it has been shown that blood lead levels show a marked dose response relationship with alcohol consumption (ref 2).

ALLOWANCE FOR CONFOUNDERS

Multiple regression techniques have been used to relate blood pressure (systolic or diastolic) to the natural logarithm of blood lead and also to the potential confounders mentioned above. The results are shown in the following table:

REGRESSIONS OF BLOOD PRESSURE ON LOG (BLOOD LEAD)

Systolic BP	Regression coefficient for log (blood lead)	P-value
Unadjusted	+ 1.684	.009
adjusted for body mass, age alcohol, smoking, social class and observer	+ 0.675	.28
adjusted also for town	+ 2.089	.003
(Pirkle et al - NHANES II	+ 8.436)	
Diastolic BP		
Unadjusted	+ 0.302	.46
adjusted for body mass, age alcohol, smoking, social class and observer	- 0.063	.87
adjusted also for town	+ 1.809	.001
(Pirkle et al - NHANES II	+3.954)	

It can be seen that adjustment for other personal factors (notably age, body mass and alcohol) makes the association of blood lead and blood pressure non-significant, even though this is a very large sample of middle-aged men.

However, when one also adjusts for town of residence the regression coefficient for log (blood lead) becomes statistically significant both for systolic and diastolic blood pressure.

The magnitude of these associations can best be expressed as follows: a doubling of blood lead is associated with an estimated increase of 1.45mm Hg for systolic BP (with 95% confidence limits 0.48, 2.42 mm Hg) and 1.25 mm Hg for diastolic BP (95% confidence limits 0.65, 1.85mm Hg).

DISCUSSION

The observed associations above are much weaker than those reported by Pirkle and colleagues (ref 3). They studied blood lead and blood pressure in 564 men aged between 40 - 59 from the American National Health and Nutrition Examination Survey (NHANES II). For systolic blood pressure they found much larger regression coefficients for log (blood lead) after adjusting for age, body mass and many nutritional and biochemical variables, as indicated in the table above. However, their sample is much smaller and hence their estimation is subject to a larger random error. Also their findings relate to a selected sub-group of a much larger sample of over 5,000 adults and analyses of the full information indicate a somewhat weaker association (ref 4)

Adjustment for town of residence made a notable difference to our findings. Since NHANES II was conducted in 64 locations over a period of several years it would seem important to take account of place of residence and hence time in their analyses. Since blood lead levels and the incidence of hypertension have both been falling over time it could be that their observed association is not present once these time trends are accounted for. Other demographic and lifestyle factors (eg: alcohol intake) would also merit further exploration.

In the Regional Heart Study we have found a weak but statistically significant positive association between blood lead and blood pressure after allowance for relevant confounding variables. Since it is difficult to take account of all relevant confounders and the association is so weak we would consider it premature to assume that the relationship is causal and of any significance to public health.

Further exploration of these findings has been reported (ref 5) and a further description will be undertaken shortly.

ACKNOWLEDGEMENT

The British Regional Heart Study is supported by a programme grant from the Medical Research Council.

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quinine, severe hypoglycaemia was not detected (p 1169) (Hall and Bhattacharya, unpublished).

Quinidine has long been recognised to be at least as good a blood schizonticide as quinine. Recent studies in Thailand have shown both that this drug (the D-enantiomer of quinine) is severalfold more active than quinine against *P falciparum* in vitro and that it may replace it for the treatment of uncomplicated infections (P Suntharasamai, S Vanijanond, T Harinasuta, *et al*, paper presented at 11th international congress of tropical medicine and malaria, Calgary, Canada, 1984).[10] The theoretical objection to quinidine is that it causes a greater prolongation of the Q-T interval than quinine,[11] but it may be used to treat severe falciparum malaria.[12,13] Again in Thailand, White and his team recommended a loading dose of quinidine of 15 mg base/kg followed by 7·5 mg base/kg every eight hours.[13] They have not, however, done a controlled study of intravenous quinine and intravenous quinidine. Quinine in the non-toxic doses used should normally be given for severe falciparum infections from areas other than Thailand (p 1169)[2] (Hall and Bhattacharya, unpublished). Quinidine in equivalent doses should be used if quinine is not available in the hospital pharmacy. Preliminary reports suggest that an even more rapid schizonticidal response may follow the infusion of artesunate, a soluble derivative of the Chinese compound artemisinin.[14] There were 960 patients with falciparum malaria from Africa treated in Britain between 1983 and 1984 but only one patient from Thailand (Malaria Reference Laboratory reports).

Supportive management of the life threatening complications of severe falciparum malaria include the reduction of hyperpyrexia, control of convulsions if present, exchange blood transfusion mentioned above, haemodialysis for anuric renal failure, and endotracheal intubation with intermittent positive pressure respiration for acute pulmonary oedema or severe coma (A P Hall, unpublished). Corticosteroids are now agreed to be contraindicated in the management of falciparum malaria.[5] The careful maintenance of fluid balance is of vital importance, since fluid overload may precipitate acute pulmonary oedema with its serious prognosis.[2]

Malaria caused by some strains of *P falciparum* acquired in areas where chloroquine resistance is prevalent, and especially in South East Asia,[3] may recrudesce after initial response to quinine or, less often, to quinidine.[10] This problem may be avoided by concluding treatment with either a single dose of the pyrimethamine-sulfadoxine combination Fansidar in countries where this remains effective[15] (Hall and Bhattacharya, unpublished) or a five to seven day course of tetracycline if resistance to this combination is present.[16]

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Blood lead and blood pressure

Exposure to lead and its possible effect on health has long been a topic of public and scientific concern. Much of this concern has focused on the contribution of leaded petrol to the total body content of lead and the possibility that moderate rises in body lead may affect the mental development of children.[1,2] Concern has also been expressed about the link between exposure to lead and hypertension, even though no consistent relation has been shown in those who have been exposed to high concentrations of lead in an industrial setting.[3] The hypothesis that hypertension may be causally related to raised blood lead concentrations has been supported by the fact that the solubility of lead is increased in soft, acidic water, that in areas where the water supply is soft the mortality rate from cardiovascular disease is increased, and that hypertension is a major contributor to cardiovascular mortality.

Glasgow was the centre for much of the early work on this subject, for the drinking water is extremely soft, lead plumbing systems are common, and there is a high prevalence of hypertension and a very high cardiovascular mortality rate. In 1972, in the suburb of Renfrew, 3001 men and women residents aged 45-64 were screened for hypertension (diastolic blood pressure greater than 100 mm Hg).[4] Hypertension was present in 468 and the first 135 who attended a follow up clinic were matched for age and sex with 135 normotensive people randomly selected from the same population. Mean blood lead concentrations were higher in the hypertensive group, in whom concentrations greater than 2 μmol/l (41 μg/100 ml) occurred more frequently. In a paired analysis of hypertensive and normotensive men (n=74), using three categories of blood lead concentration, there were more pairs in which the hypertensive man had a higher blood lead concentration. A similar analysis for women gave results that were not statistically significant. The authors concluded that high blood pressure in the west of Scotland "is associated with high blood lead levels, which might explain the high prevalence of cardiovascular disease in the area." When this study was carried out the important influences of alcohol and smoking on blood lead were not known,[5] nor was there an awareness of the effects of alcohol on blood pressure.[6] Thus it is possible that the higher blood lead concentrations in the hypertensive subjects were due to

higher intakes of alcohol and to the smoking that commonly accompanies drinking. Furthermore, the control group might have differed in some other way—for example, in social class or area of Renfrew—and that may have influenced blood lead concentrations. But despite these possible drawbacks the Renfrew study is still quoted widely in support of the positive relation between blood lead concentration and hypertension.

A larger study of blood lead and blood pressure has been undertaken as part of the British Regional Heart Study. This is a prospective study of cardiovascular disease in Britain that aims to explain the regional variations in cardiovascular mortality and to identify the environmental and personal risk factors responsible for ischaemic heart disease.[7] The study has shown striking differences in mean blood pressure between groups of men in 24 towns in England, Wales, and Scotland. These were due partly to differences in body mass index and alcohol intake, but these two factors explain only a small part of the between town variation in blood pressure. Soft water supplies are related to cardiovascular mortality rates, and towns with soft water have the highest concentrations of lead both in the water supply and in the blood of the inhabitants.[8] So, could the body lead burden (reflected in blood lead concentrations) be contributing to cardiovascular mortality, either by raising blood pressure or by some other effect on ischaemic heart disease?

Blood lead concentration and blood pressure were measured in 95% of 7735 middle aged men drawn at random from general practices in the 24 towns. No positive association between blood lead concentration and blood pressure was found, although among those men with blood concentrations greater than 1·8 μmol/l (37·3 μg/100 ml) there were more hypertensive subjects than in those with lower concentrations.[9] Nevertheless, since this group accounted for less than 1% of the men in the study it seems unlikely that exposure to lead has an appreciable effect on blood pressure in the male population of Great Britain. These findings contrast with those reported by French workers, who studied 431 men aged 24-55 years and found a positive association between blood lead concentration and blood pressure.[10] The association was statistically significant for men aged under 45 but not for those aged 45-55. The authors suggest that "the increase in blood lead concentration parallels the increase in blood pressure until some limit value so that such a trend is apparent only when other factors (such as age) do not competitively increase blood pressure by greater amounts."

More substantial evidence of a positive association between blood lead and blood pressure comes from the United States. The second United States National Health and Nutrition Examination Survey examined 20 322 people aged 6 months to 74 years recruited from 64 different areas across the United States. For both black and white men and women aged 12-74, blood lead concentrations were positively associated with systolic and diastolic blood pressures.[11] In the younger age group (21-55 years) blood lead concentrations were significantly higher in hypertensive than in normotensive subjects but this was not the case in those aged 56-74. Some 34 other variables were also identified as having a statistically significant univariate correlation with blood pressure. Blood lead had a statistically significant relation with systolic and diastolic blood pressure in men, the magnitude of this association being about one sixth of that observed between body mass index and blood pressure. Blood lead was not independently related to blood pressure in women. Surprisingly, no alcohol effect on blood pressure was observed for men in this study, although in women alcohol intake was independently associated with diastolic blood pressure.

The authors state that "no causal inferences should be drawn from this cross sectional survey about the blood pressure effects of lead." Nevertheless, in a second publication, focusing on the results of a subgroup of 564 white men aged 40-59 years, the conclusions were less guarded.[12] The reason for selecting out this subgroup was to enable data from the United States Pooling Project and the Framingham study to be used in estimating the effects of lead on stroke, ischaemic heart disease, and all causes of mortality. Using a complex multiple regression model which included adjustments for age, body mass index, and a large number of biochemical and nutritional measurements, a significant independent relation was shown between blood lead and both systolic and diastolic blood pressure. It needs to be emphasised, however, that values of haemoglobin, serum albumin, dietary vitamin C, potassium, riboflavin, and oleic acid were also all independently related to either systolic or diastolic blood pressure or both, and at a statistical significance equal to or greater than that achieved by blood lead. Clearly this gives cause for thought, for presumably this paper could have been written to focus on any one of these variables.

The authors hypothesised that if lead is causally related to blood pressure, changes in blood lead concentrations will produce substantial changes in blood pressure and affect the incidence of cardiovascular events. Using the data from the pooling project and the Framingham study they calculated the "effects" of lowering blood lead concentrations on fatal and non-fatal myocardial infarction and stroke and on deaths from all causes. As the second United States National Health and Nutrition Examination Survey showed a decrease of 37% in mean blood lead concentrations during 1976-80 (from 0·81 to 0·57 μmol/l; 16·8 to 11·8 μg/100 ml) they estimated that hypertension would decrease by 17·5%, myocardial infarction by 4·7%, stroke by 6·7%, and deaths from all causes by 5·5%.

The implication of their calculations is that a reduction in environmental lead—derived mainly from car exhaust fumes—would save large numbers of lives as well as reducing the number of non-fatal strokes and myocardial infarctions. Such extrapolations, however, seem simplistic. The determinants of hypertension are complex, and the factors concerned in the development of atherosclerosis and ischaemic heart disease equally so. Thus to leap from an inconsistent relation between blood lead and blood pressure to an immediate effect of blood lead on cardiovascular mortality seems precipitate.

Furthermore, a subsequent reanalysis of the same second United States National Health and Nutrition Examination Survey data on white men aged 46-65 by another group of investigators has come to a totally different conclusion (P G Gartside, letter submitted for publication). Their approach was to confine the multiple regression to a more limited set of variables which had already been identified as probable risk factors for hypertension, plus a few others that had previously been found to be useful. The final multiple regression analysis of 621 observations for diastolic blood pressure yielded significant associations for body mass index, coffee consumption, date of examination, and height but not for blood lead concentration ($p=0·27$). Similarly, systolic blood pressure was significantly related to body mass index, age, and coffee consumption but not to blood lead ($p=0·18$). This curious influence of coffee consumption on the relation between lead and blood pressure needs further clarification,

since coffee is not widely regarded to be a risk factor for hypertension. (There is the current interest in the effect of coffee on blood lipids,[13] as well as hypotheses relating lipid metabolism to blood pressure,[14] but it seems premature to attempt a reconciliation of these various themes.)

In conclusion, the main evidence regarding lead and blood pressure comes from two large cross sectional surveys: the second United States National Health and Nutrition Examination Survey and the British Regional Heart Study. Their conflicting findings make it impossible to make a definitive statement about the effect of environmental lead on hypertension. Further analysis of those studies may produce some rationalisation of these puzzling differences in research findings. But whatever the outcome, the issue of blood lead and hypertension is back and may remain prominent for some time.

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Crohn's disease in the elderly

"Your old men shall dream dreams and your young men shall see visions" said the prophet Joel, recognising that age changes us and modifies our response to important events.[1] In a medical context age may affect the incidence and the type of disease and its course, morbidity, and mortality. As the elderly population increases and the incidence of Crohn's disease rises the pattern of the disease in old people warrants examination. The few publications on the topic make a recent study from the gastrointestinal unit at Birmingham General Hospital of particular interest.[2] Previous studies have tended to be selective and restricted either to patients treated surgically or to those with a particular distribution of disease.[3,4]

Crohn's disease in the elderly is rare. The Birmingham group had identified only 47 patients over the past 40 years who were aged over 60 at the time of diagnosis; they accounted for 8% of the total of over 600 patients, a proportion similar to that found by Goligher in his 500 patients.[5] Epidemiological surveys based on defined populations rather than clinical series show that the peak incidence occurs in the third decade, after which there is a sharp fall which then tails off more gradually after 40 years of age to smaller figures in the elderly.[6,9] Some series have reported a second peak in the eighth decade, but with small numbers the finding may be spurious.[9]

Whether the extent and distribution of disease are different in the elderly has been disputed. In the Birmingham series distal ileal disease with or without spread to the right colon was the most common form, accounting for half of the cases; this is true for all age groups. Distal colonic disease, however, was more common than in younger patients and accounted for 40% compared with only 6% in younger patients. Extensive colonic or small bowel disease was uncommon. This relatively high proportion of colonic disease has been recognised in epidemiological surveys,[7] and in Kyle's series from north east Scotland was most prominent in elderly women.[6]

The course of the disease was found to depend largely on the site of the lesion. Most of those with distal ileal disease needed laparotomy for obstruction, peritonitis, or to exclude carcinoma, but thereafter the prognosis was good. Fourteen of 22 patients with this disease distribution remained well. By contrast, patients with colonic disease rarely required surgery and were managed medically; there were only five resections in this group, and 14 of these 22 patients were also fit and well. This compares with the recently reported experience from St Mark's Hospital, where patients with colonic Crohn's disease had an accumulated probability of having bowel surgery of nearly 40% at 10 years.[10] One further difference was that recurrence after the initial resection—a feature of the disease in general and particularly in young patients—occurred rarely in the Birmingham series and none of the patients required a second operation.

The overall standardised mortality ratio in Crohn's disease is usually quoted as twice the expected value for the general population.[8,11-13] The risk of death is, however, much greater for patients who develop the disease early in life, and in one series those diagnosed in the second decade had a mortality ratio 11 times the expected value.[11] Elderly patients, however, have a mortality rate the same or less than the average for all patients with Crohn's disease. This may be due partly to the prominence of colonic disease, which carries a better prognosis.

Diagnosis of Crohn's disease in the elderly may be difficult because of the high prevalence of diverticular disease[14] and carcinoma of the colon or caecum. Diverticular disease was present in more than half of the patients with colonic Crohn's disease, and lack of a confident radiological diagnosis of the caecal abnormality led to laparotomy in more than a quarter of the patients with ileocaecal disease.

Recognition of the generally favourable prognosis for Crohn's disease in elderly patients, particularly those with distal colonic disease, should be of practical value to gastroenterologists, geriatricians, and surgeons. Plainly this variant is a less aggressive form of the disease than that seen in younger patients.

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