EVIDENCE OF CADMIUM TOXICITY IN A POPULATION LIVING IN A ZINC-MINING AREA

Pilot Survey of Shipham Residents

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Summary 22 of 31 residents of a Somerset village where soil levels of cadmium were high had raised blood-cadmium levels, and some had clinical and biochemical findings (including hypertension and biochemical evidence of renal tubular damage) indicating toxic effects which could be attributed to the metal. It is suggested that more detailed studies should be carried out as a matter of urgency and that advice on avoiding local garden produce and not smoking should be emphasised. Probably more serious, however, is the summation effect with industrial exposure.

Introduction

ON Jan. 19, 1979, the residents of Shipham, a Somerset village, received a circular from the Sedgmore District Council informing them that the results of a national survey of heavy metals carried out by geologists from Imperial College, London, had indicated "substantial contamination" of the soil in their area by cadmium. The levels of this toxic metal were especially high in a new estate built over an old zinc mine, as the two metals commonly occur together. The circular said that a full survey for evidence of cadmium toxicity would be carried out and that there was "no cause for great concern".

However, the soil levels quoted ranged from 60 to 998 p.p.m., compared with levels of up to 60 p.p.m. quoted for the region around Toyama City in northern Japan, where a disease associated with painful skeletal collapse, *itai-itai-byo*, had become endemic as a result of zinc mining and smelting. Perhaps more alarmingly, the home-grown vegetables of Shipham were found[1] to contain up to 7·34 p.p.m. dry weight of cadmium, compared with 0·37–3·36 p.p.m. quoted for rice and soya in the Toyama study.[2] Some of the garden produce was discoloured, and some green vegetables from gardens with high cadmium levels had pale translucent leaves, suggesting interference with chlorophyll production. Also a few animals grazing locally had had a variety of mysterious disorders previously attributed to "zinc toxicity". Analyses of offal at the Rowet Institute, Aberdeen, showed high concentrations of cadmium in the kidney and liver even in apparently healthy cattle from the area.

Although *itai-itai-byo* was obviously not endemic in the area there is evidence that cadmium may have other more insidious long-term effects, especially on the cardiovascular system, which could result in an easily missed increased prevalence of a wide range of common disorders. Also, the clinical effects of massive industrial exposure, usually by inhalation,[3] can be totally different from the effects of long-term ingestion. For example, low blood-pressure has been reported in industrial exposure, but hypertension has been found in association with lower levels of toxicity.[4,5]

To try to establish more objectively the level of concern which would be most appropriate to Shipham, and as a pilot study to decide which tests might contribute most to a full-scale study being carried out over the next few months by the Department of the Environment and the Department of Health, a preliminary investigation was undertaken on a number of the residents.

Subjects and Methods

With the permission of the local general practitioners, a house-to-house call for volunteers for the study was made, concentrating on roads where the gardens had been shown to have the highest and lowest cadmium content. Nearly all those who were approached agreed to take part in the study, so that the sample was probably not biased towards the anxious or overtly sick. 14 women and 17 men took part in the study. Each subject was interviewed and asked to complete a questionnaire covering length of residence in the area, occupational exposure, vegetable growing and consumption, smoking habits, general health, and family history.

Resting blood-pressure in the sitting position was measured, under peaceful conditions and with reassurance, with a standard mercury sphygmomanometer. If the blood-pressure was raised the measurement was repeated several times over a 5–10 min period.

Blood-samples were taken for cadmium,[6] zinc, and lead estimations and other biochemical and hæmatological profiles. Random urines were tested with 'Labstix', and samples from each were saved for radioimmunoassay of β_2-microglobulin[7] (with a commercially available kit, 'Phadebas β_2 Microtest'), automated fluorimetric assay of N-acetyl–glucosaminidase (N.A.G.)[8] (as an indicator of renal parenchymal damage), aminoacid chromatography, and creatinine estimation.

Results (Tables I and II)

Clinical Findings

The mean age of the 14 women was 48·9 years, they had lived in Shipham for an average of 15·1 years, and 53·6% of the vegetables they ate were home-grown.

The corresponding mean figures for the 17 men were 50·9 years, 19·4 years, and 52·9%. Allowing for natural anxiety and according to age-related W.H.O. criteria 8 of the women and 10 of the men showed elevations of either systolic or diastolic blood-pressure, or both. 1 further woman was being treated for hypertension. Other clinical disorders are recorded in tables I and II. No significant findings emerged from the family histories, but most of the subjects were first-generation residents in the area and had moved to Shipham with their children.

Biochemical and Hæmatological Findings

Blood-cadmium levels were raised above the normal levels (<9 nmol/l for non-smokers and <18 nmol/l for smokers) given by Prof. Lars Friberg's laboratory in Sweden, where the analyses were done, in 9 of the women and 13 of the men. Blood-zinc (mean 83 μmol/l; range 39–112 μmol/l) and blood-lead (mean 0·85 μmol/l; range 0·45–1·65 μmol/l) were within normal ranges.

Age-related serum-urea was raised in 1 woman and 5 men, serum-creatinine was 105 μmol/l or above in 3 women and 10 men, and serum-urate was raised in none of the women but in 8 of the men. 2 women and 3 men had hypercholesterolæmia. Serum calcium, alkaline phosphatase, and chloride were all normal. Hæmoglobin levels, packed-cell volume, red-cell count, mean cell

hæmoglobin concentration, mean cell volume, white-cell count and blood-film appearances were also normal.

In preference to qualitative measures of proteinuria,[3,9] urinary β_2-microglobulin estimations have been used as a marker of renal tubular damage.[10,11] Long-term exposure to cadmium is associated with such damage, and with increased β_2-microglobulin excretion.[12] Urinary excretion of β_2-microglobulin does not increase with age.[13] In these random urine samples increased excretion is two to four times as common as expected in an unexposed reference population,[12,14] 5 men and 2 women (7 out of 31) having urine levels above 50 μg/mmol of creatinine. Similar β_2-microglobulin results were independently obtained on the same samples in Professor Friberg's laboratory. Urinary N.A.G. was raised in 2 of the women and 1 of the men.

TABLE I—CLINICAL AND BIOCHEMICAL FINDINGS IN 14 SHIPHAM WOMEN

Age (yr)	Residence in Shipham	Vegetables home-grown (%)	Blood-pressure (mm Hg)		Blood-cadmium (nmol/l)	Urinary β_2-microglobulin μg/mmol creatinine)	Urinary N.A.G. (u/mol creatinine)	Serum-urea (mmol/l)	Serum-creatinine (mmol/l)	Other observations
			Systolic	Diastolic						
83	40 yr	75†	220*	95	21*	55*	18·0*	7·6	66	Diabetes, poorly controlled by diet alone
68	11 yr	40†	165*	95	35*	120*	3·2	5·3	74	Carcinoma of colon treated by partial colectomy
66	2 yr	100†	165*	85	<9	29	2·6	5·0	71	Recurrent gastritis, hypercholesterolæmia
64	14 yr	100†	160*	75	<9	14	4·2	5·8	95	Migraine, hypercholesterolæmia
64	13 yr	50†	140	80	18*	3	18·0*	6·5	106*	Renal colic, hæmaturia, heart-failure
50	15 yr	0†	150*	95*	<9	16	6·8	6·0	68	Hysterectomy, breathless on exertion
47	42 yr	70	130	90	21*	8	3·3	4·0	73	Treated hypertensive
41	10 yr	75	150*	85	<9	23	2·9	7·9*	83	
36	36 yr	70†	140	95*	15*	1	4·3	6·4	84	Chest pain
36	2 mo	0	120	70	19*++	10	3·5	7·0	79	Carcinoma of breast treated by radical mastectomy
34	15 yr	50	145*	85	24*+	2	4·2	4·1	109*	
34	7 yr	25†	120	80	23*	1	3·3	5·5	65	
33	5 yr	95†	125	75	<9	6	3·3	5·9	94	
28	1 yr	0†	135	80	19*	5	2·0	5·3	120*	

* Abnormal results.
† High soil-cadmium in gardens.
Cigarette consumption: + (1–10 cigarettes/day), ++ (11–20), +++ (21+).

TABLE II—CLINICAL AND BIOCHEMICAL FINDINGS IN 17 SHIPHAM MEN

Age (yr)	Residence in Shipham	Vegetables home-grown (%)	Blood-pressure (mm Hg)		Blood-cadmium (nmol/l)	Urinary (β_2-microglobulin μg/mmol creatinine)	Urinary N.A.G. (u/mol creatinine)	Serum-urea (mmol/l)	Serum-creatinine (mmol/l)	Other observations
			Systolic	Diastolic						
79	11 yr	40†	190*	110*	10*	10	3·9	8·6	64	Angina, prostatectomy
75	15 yr	100†	145	80	14*	1	6·4	10·3*	116*	Angina, hæmaturia, perforated gastric ulcer, hyperuricæmia.
67	13 yr	50†	230*	120*	13*	58*	29·0*	11·6*	160*	Hypertension, intermittent claudication, under treatment for hypercholesterolæmia
66	66 yr	75	145	90	10*	10	3·9	8·7*	126*	Gout with hyperuricæmia
65	8 yr	75†	170*	120*	<9	70*	6·2	7·3	105*	Gout with hyperuricæmia
62	14 yr	100†	195*	85	31*	52*	5·8	7·2	129*	Hyperuricæmia
58	7 yr	10†	165*	110*	29*+	5	4·3	5·8	45	Hyperuricæmia
54	54 yr	50	145	90	43*+++	52*	8·1	3·3	94	Back pain, heartburn, gastric ulcers, hypercholesterolæmia
49	20 yr	0†	190*	120*	<9	80*	3·8	5·5	150*	Angina
45	10 yr	75†	160*	105*	16*	14	2·1	5·8	78	Back pain treated by laminectomy
44	44 yr	60	140	100*	10*	7	3·3	6·6	110*	
41	30 yr	50	155*	120*	18*	2	5·0	3·0	77	
40	17 yr	70†	160*	100*	59*+++	44	7·0	3·5	86	Hyperuricæmia
38	2 mo	0	110	80	<9	28	4·2	7·9*	101	
36	5 yr	95†	130	90	24*+	15	2·2	5·7	118*	Hyperuricæmia, hypercholesterolæmia
31	1 yr	0†	130	85	133*	14	4·3	8·1*	121*	Industrial exposure to cadmium Bronchitis, gastritis, hyperuricæmia
15	15 yr	50	130	80	<9	9	5·5	3·3	107*	

For explanation of symbols see table I.

No increase in urinary aminoacids or sugars was detected, except for glycosuria in the oldest woman, a known diabetic.

Discussion

A wide range of clinical and biochemical evidence that could be related to cadmium toxicity was found in this small-scale study of the residents of Shipham. Blood-cadmium levels were raised in two-thirds of the residents. This finding is consistent with the estimation of liver-cadmium content carried out by Harvey et al.[15] with in-vivo neutron-activation analysis. In 21 villagers, they found a mean liver-cadmium concentration nearly five times that in controls. Our findings are less reassuring than their references to industrial exposure would suggest.

The serious clinical significance of this high level of exposure to cadmium was shown by the increased prevalence of hypertension and other stigmata of cardiovascular disease, together with evidence of renal tubular damage, of which an increase in β_2-microglobulin excretion appears the most constant. In people with additional occupational exposure, as in the 31-year-old non-smoking man who worked next to a zinc-smelting plant, the clinical and biochemical effects were particularly severe, the blood-cadmium level being fourteen times normal.

Cadmium's nephrotoxicity is generally accepted,[3,9] but there is considerable debate about its cardiotoxicity. Administration of cadmium to laboratory animals will consistently produce hypertension.[16] Hypertension has also been reported in association with industrial exposure[5] and a high water content of the metal.[2,17] Blood-cadmium levels have also been found to be higher in untreated hypertensives than in normotensive subjects.[4] There are several mechanisms by which cadmium could raise blood-pressure and increase the prevalence of cardiovascular disease. First, though the metal predominantly poisons the tubule,[3] most chronic renal disorders can contribute to raising the blood-pressure. Secondly, it has been suggested[4] that cadmium may result in relative sympathetic overactivity by replacing other divalent cations in enzymes which inactivate catecholamines—catechol-*o*-methyl-transferases and monoamine oxidases. In this way, by acting as an inhibitor of these enzymes, cadmium may elevate the blood-pressure and mood simultaneously, acting as a natural antidepressant. In addition cadmium is known to be toxic to the testis.[2] Low testosterone levels have been found in cardiovascular disease,[18] and replacement with the natural hormone can lower blood-pressure and lipid levels, reduce angina, and normalise the ischæmic electrocardiogram.[19]

The clinical picture seen in this study, especially in association with a high prevalence of hypertension, evidence of renal damage, and high blood and liver cadmium values, suggests that more detailed studies of the entire population of the village should be carried out as soon as possible. Meanwhile the advice already given about not eating locally grown vegetables and not smoking needs to be emphasised. Although cadmium causes biochemical abnormalities, long-term ingestion is needed before any of the associated illnesses becomes clinically apparent. Industrial exposure is a more serious and widespread problem. It is hoped that this pilot study will have provided some useful guidelines for larger-scale investigation of cadmium toxicity.

We thank the residents who took part in the study and Linda McDougal, of Thames Television's *TV Eye* programme, who suggested the survey and made it possible. Prof. Lars Friberg of the Karolinska Institute, Fack, Stockholm, kindly arranged blood-cadmium estimations in his laboratory and provided expert advice. We also thank Dr P. O'Gorman, of the Brook Hospital, for zinc and lead analyses, Miss Pat Kind, of St. Thomas' Hospital, for urinary N.A.G. estimations, and Pharmacia Diagnostics Ltd. for β-microglobulin references.

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ANTENATAL DIAGNOSIS OF DUCHENNE MUSCULAR DYSTROPHY

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Summary As a means of assessing the value of fetal serum-creatine-kinase (S.C.K.) levels in the antenatal diagnosis of Duchenne muscular dystrophy (D.M.D.), fetal muscle from control and at-risk fetuses was studied histologically and the findings were related to fetal S.C.K. levels. Of 7 at-risk fetuses 4 were believed to have normal muscle and all these had normal S.C.K. levels. However, of 3 fetuses with abnormal muscle only 1 had a raised S.C.K. level. At present cau-