

OBSERVATIONS ON URINARY CADMIUM AND PROTEIN EXCRETION IN MEN EXPOSED TO CADMIUM OXIDE DUST AND FUME

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Prolonged exposure of workmen in the alkaline accumulator industry to cadmium oxide dust led in many cases to the appearance of protein in the urine (Friberg, 1950). This observation has been confirmed in a preliminary publication (Smith, Kench, and Lane, 1955). Proteinuria has also been observed in men exposed to cadmium fume (Bonnell, 1955). There is reason to believe that this urinary protein is not a normal major serum protein constituent (Friberg, 1950; Kekwick, 1955). This paper presents further data on the incidence and degree of proteinuria in relation to cadmium exposure and excretion.

Materials and Methods

The subjects of this study were men exposed to cadmium oxide dust in an alkaline accumulator factory and to cadmium oxide fume in two foundries concerned with the manufacture of copper-cadmium alloy.

The accumulator factory employs some 500 workers of whom 120 had been exposed to cadmium now or in the past. The products of the factory are exclusively alkaline accumulators of various types. The positive and negative electrodes are manufactured separately, the former from a "positive mass" consisting of 80% by weight of nickel hydrate and 20% graphite. The "negative mass" is composed of 60% cadmium and 25% iron, both largely oxidized, with 3% kerosene as a binding agent. The process of manufacture is such that finely divided dust is liberated and is not entirely removed by the ventilation system.

Both foundries make a copper-cadmium alloy containing 0.5 to 1.0% cadmium for the manufacture of wire. A 50% cadmium master alloy is first prepared by addition of cadmium to molten copper, and the final copper-cadmium alloy is made by fusion of this master alloy in molten copper. The flux is stirred manually and yellow fumes of cadmium oxide are liberated at this stage. In each factory only a small group of men were engaged in the foundry (six in Foundry I and 20 in Foundry II) but a larger group worked near the furnaces.

Wide-necked pyrex bottles of 400 ml. capacity, previously cleaned and sterilized, were provided to collect urinary specimens from the workmen, a small crystal of thymol being placed in each bottle to minimize bacterial growth during transit to the laboratory. Urinary specimens from selected workmen offered the possibility of more detailed study. Spot specimens obtained mid-morning and throughout the shift were transported to the laboratory, with minimal delay, for quantitative evaluation of cadmium and protein. A group of 100 workmen of similar age range without known exposure to cadmium were used as controls.

Each specimen was examined for the presence of protein by the addition of trichloroacetic acid, which was found to be the most sensitive of a number of precipitants employed. To 2 ml. urine, that had first been filtered until clear, 2 ml. 25% (w/v) trichloroacetic acid was added. A just perceptible opalescence was recorded as a trace (\pm), definite opacity as positive (+), and a precipitate as strongly positive (++) .

The urinary cadmium was determined by the dithizone method of Smith *et al.* (1955) and the total urinary protein by the biuret method of Hiller, McIntosh, and Van Slyke (1927), using 40 ml. urine instead of 2 ml. as in the original procedure.

The creatinine concentration of each specimen was determined by the alkaline picrate (Lloyd's reagent method of Owen, Iggo, Scandrett, and Stewart, 1954) and the specific gravity measured by weighing the urine in a calibrated 50 ml. volumetric flask corrected for temperature.

Each specimen was tested for reducing sugar using Benedict's qualitative reagent.

Results

The specific gravity and creatinine concentration were determined for each urinary specimen analysed for cadmium and protein. Typical examples from four workmen excreting various quantities of cadmium are given in Figs. 1 and 2.

Data on the incidence of proteinuria in this study

FIG. 1.—Relationship between urinary cadmium concentration and specific gravity for four workmen excreting cadmium at different rates (spot specimens). Correlation coefficients: A, +0.77; L, +0.80; I:3, +0.61; N, +0.64.

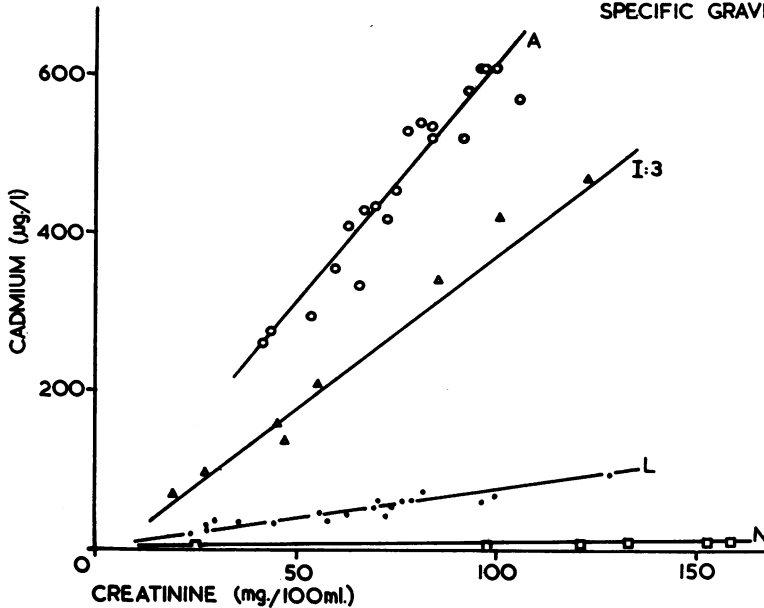
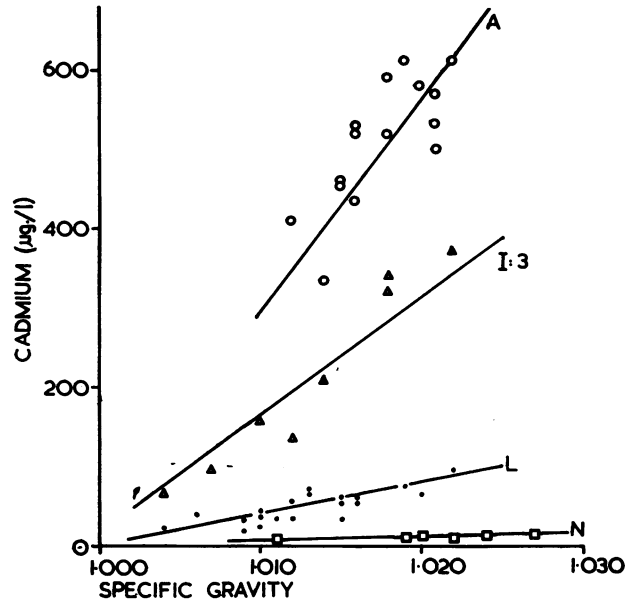


FIG. 2.—Relationship between urinary cadmium and creatinine concentration for four workmen excreting cadmium at different rates (spot specimens). Correlation coefficients: A, +0.93; L, +0.90; I:3, +0.99; N, +0.76.

are presented in Table 1. Proteinuria was observed in 5% of the control group of workers whereas 20% of the workers exposed to cadmium oxide dust and 60% of the workers exposed to cadmium oxide fume showed urinary protein. At this point urinary cadmium concentrations were not measured.

The results of the urinary cadmium and protein determinations are shown in Tables 2 to 10. The urinary cadmium excretion of factory and laboratory

workers with no known exposure to cadmium fell within the range 0-25 µg./l. (Table 2). A group of alkaline accumulator workers not directly exposed to cadmium and with no known past exposure had urinary cadmium concentrations of 10 to 36 µg./l (Table 3). The results for a selected group of the workers in contact with various levels of cadmium in the alkaline accumulator factory are given in Table 4. The processes on which the men were

TABLE 1
INCIDENCE OF PROTEINURIA IN WORKERS EXPOSED TO
CADMIUM AND IN WORKERS WITHOUT KNOWN
EXPOSURE

Degree of Proteinuria	Controls	Number of Workers Exposed to		
		Cadmium Dust	Cadmium Fume I	Cadmium Fume II
+++	1	0	0	0
++	0	1	2	2
+	1	17	1	6
±	3	7	1	5
-	95	95	2	9
Total ..	100	120	6	22
Incidence of Proteinuria (%)	5	20	60	

The urinary protein was detected using 25% trichloroacetic acid. Approximate quantitative equivalents of degrees of proteinuria employed are as follows:—

+++ > 5 g./l.
++ 2-5 g./l.
+ 0.25-2 g./l.
± 25-250 mg./l.
- < 25 mg./l.

engaged were graded 0-4 on the basis of the aerial cadmium contamination to which they gave rise. An exposure index was computed for each workman by summation of the products of process grading and time of exposure (in years) to give a measure of the atmospheric cadmium in the individual's working life. Tables 5 and 6 show the cadmium excretions

of workers at the two foundries investigated. Further determinations were carried out to discover the degree of variation of urinary cadmium and protein over periods of time. The results over six consecutive weeks for men exposed to cadmium oxide dust have been reported previously (Smith, *et al.*, 1955). A slight net increase in the cadmium excretion of workman A, who was subjected to exceptional exposure and who excreted by far the most urinary cadmium, was found during a period of one year. In other workers with lower urinary cadmium concentrations the rise was less marked but a continuous upward trend was discernible. No major fluctuations were observed over a period of two years.

The day-to-day cadmium and protein excretion of men exposed to cadmium oxide dust and fume are recorded in Tables 7 and 8 respectively. Tables 9 and 10 show the results of spot samples obtained throughout a single shift.

Discussion

The alkaline accumulator workers in this study had been exposed to cadmium oxide dust for periods varying from eight to 30 years, the severity of exposure likewise differing widely throughout the group. There was no clear relationship between their

TABLE 2
URINARY CADMIUM EXCRETION BY FACTORY AND LABORATORY WORKERS WITH NO KNOWN EXPOSURE TO
CADMIUM CALCULATED FROM MORNING SPOT SAMPLES

Factory Workers						Laboratory Workers		
Subject	Cadmium (µg./l.)	Creatinine (mg./100 ml.)	Subject	Cadmium (µg./l.)	Creatinine (mg./100 ml.)	Subject	Cadmium (µg./l.)	Creatinine (mg./100 ml.)
1	6.0	78	11	14.2	82	1	4.2	92
2	2.6	26	12	4.0	52	2	5.0	116
3	21.8	78	13	18.4	102	3	6.6	104
4	5.6	46	14	14.6	72	4	3.6	80
5	6.2	62	15	16.2	90	5	4.2	66
6	6.3	76	16	7.2	60	6	14.0	92
7	20.4	96	17	1.8	26	7	5.6	70
8	18.8	80	18	22.6	84	8	9.2	112
9	19.2	108	19	10.0	94	—	—	—
10	2.0	38	20	10.0	76	—	—	—

TABLE 3
URINARY CADMIUM EXCRETION IN WORKERS NOT DIRECTLY EXPOSED TO CADMIUM BUT WORKING IN AN
ALKALINE ACCUMULATOR FACTORY CALCULATED FROM MORNING SPOT SAMPLES

Specimen	Week 1			Week 2			Week 3		
	Cadmium (µg./l.)	Specific Gravity	Creatinine (mg./100 ml.)	Cadmium (µg./l.)	Specific Gravity	Creatinine (mg./100 ml.)	Cadmium (µg./l.)	Specific Gravity	Creatinine (mg./100 ml.)
N	16	27	160	10	19	99	12	24	154
N	10	22	122	9	11	26	12	10	134
1	20	21	93	36	23	114	—	—	—
2	34	20	86	35	18	90	—	—	—
3	31	28	124	36	20	110	—	—	—
4	31	24	108	28	18	71	—	—	—
5	28	20	—	—	—	—	—	—	—
6	10	18	84	—	—	—	—	—	—
7	33	23	104	—	—	—	—	—	—
8	15	22	92	—	—	—	—	—	—

The last two figures only of the specific gravity measured to four figures (*i.e.*, 27 = 1.027) are given.

TABLE 4
URINARY CADMIUM EXCRETION OF FACTORY WORKERS EXPOSED TO CADMIUM OXIDE DUST CALCULATED FROM MORNING SPOT SPECIMENS

Specimen	Current Exposure Rating	Exposure Time (years)	Exposure Index	Proteinuria	Week 1			Week 2		
					Cadmium (µg./l.)	Specific Gravity	Creatinine (mg./100ml.)	Cadmium (µg./l.)	Specific Gravity	Creatinine (mg./100ml.)
A	4	14	49	++	420	21	97	436	20	90
D	2	30	84	±	78	21	84	81	22	98
B	2	26	72	+	81	16	60	62	17	62
E	2	17	44	-	88	30	174	68	18	77
F	2	15	38	±	73	28	162	64	22	102
G	2	16	30	-	119	23	114	132	23	125
H	2	15	30	-	118	14	66	115	18	72
C	2	11	26	-	107	20	82	79	16	62
I	2	13	24	+	170	24	154	138	16	60
R	2	10	16	±	28	23	125	37	25	129
K	1	30	53	+	56	15	68	76	18	74
J*	1	25	43	+	53	31	126	49	25	89
L	1	25	43	+	72	13	59	98	22	124
W	1	19	32	-	64	20	101	53	19	78
P	1	30	30	-	84	23	124	48	20	80
S	1	14	24	±	46	20	96	60	23	148
T	1	10	16	±	39	22	92	41	20	87
U	1	8	8	±	41	17	76	47	20	104
V	1	8	8	±	81	15	60	59	16	48
M	0	22	66	+	32	28	160	32	19	96
Z	0	20	60	+	141	17	88	60	05	20
Z ¹	0	9	27	-	163	27	-	56	06	28
O	0	14	22	-	30	21	101	20	20	90
Y ¹	0	12	20	±	73	15	52	90	21	90
Y ¹	0	8	16	±	53	18	62	45	13	46
Q	0	8	16	-	15	19	92	12	17	91

*Workman J reacted as a diabetic to the glucose tolerance test. The last two figures only of the specific gravity measured to four figures are given.

TABLE 5
URINARY CADMIUM EXCRETION OF MEN EXPOSED TO CADMIUM OXIDE FUME CALCULATED FROM MORNING SPOT SAMPLES IN FOUNDRY I

Sample	Time of Exposure (years)	Protein	Cadmium (µg./l.)	Specific Gravity	Creatinine (mg./100 ml.)
1	8	±	410	10	51
2	14	-	40	13	58
3	32	++	425	13	36
4	8	+	121	19	80
5	37	++	47	18	93
6	20	+	190	15	55

TABLE 6*
URINARY CADMIUM EXCRETION OF MEN EXPOSED TO CADMIUM OXIDE FUME CALCULATED FROM MORNING SPOT SAMPLES IN FOUNDRY II

Specimen	Time of Exposure (years)	Protein	Cadmium (µg./l.)	Specific Gravity	Creatinine (mg./100ml.)	Specimen	Time of Exposure (years)	Protein	Cadmium (µg./l.)	Specific Gravity	Creatinine (mg./100ml.)
1	29	+(1000)	26	09	36	12	6	±	17	09	32
2	5	-	54	18	96	13	16	±	72	18	71
3	8	±	68	16	73	14	29	+(1750)	82	19	85
4	7	-	72	21	90	15	10	+(1250)	270	15	51
5	9	-	16	-	62	16	16	+(1600)	91	21	97
6	6	-	92	24	128	17	6NC	-	72	20	98
7	10NC	-	32	10	46	18	6	-	52	24	123
8	22	++(2300)	114	24	115	19	9	±	220	14	48
9	29NC	+(900)	57	13	45	20	14NC	+	46	-	57
10	7NC	-	59	14	65	21	14	-	49	-	97
11	6	±	89	20	90	-	-	-	-	-	-

N.C. not currently exposed. The concentration of urinary protein (mg./l.) is given for the samples graded + and ++.

*During the period which elapsed between the observations in Table 6 and those in Table 1, the number of men involved in Foundry II increased from 21 to 22 (one man left the job and two others joined, all protein negative). In addition the proteinuria of the men had become more severe.

urinary cadmium excretion and the grading of exposure. Likewise in the men exposed to the hazard of cadmium oxide fume in the two foundries surveyed there was no correlation between time of exposure and urinary cadmium excretion.

No significant difference in urinary excretion of cadmium was apparent between the group exposed to dust and that exposed to fume. Both groups of men exhibited a urinary cadmium excretion (10 to 610 µg./l.) which extended considerably above the

TABLE 7

URINARY PROTEIN AND CADMIUM EXCRETION OF TWO MEN, A AND L, EXPOSED TO CADMIUM OXIDE DUST CALCULATED FROM MORNING SPOT SPECIMENS OBTAINED DAILY DURING TWO WORKING WEEKS

Day of Specimen	Week 1							
	A				L			
	Urinary Protein (mg./l.)	Urinary Cadmium (μ g./l.)	Creatinine (mg./100ml.)	Specific Gravity	Urinary Protein (mg./l.)	Urinary Cadmium (μ g./l.)	Creatinine (mg./100ml.)	Specific Gravity
1	2,820	570	106	21	1,230	66	97	19
2	2,360	520	92	18	700	34	73	15
3	2,790	610	100	22	640	33	45	12
4	1,790	530	78	16	380	34	58	13
5	1,660	460	60	15	350	33	36	09
Day of Specimen	Week 2							
	A				L			
	Urinary Protein (mg./l.)	Urinary Cadmium (μ g./l.)	Creatinine (mg./100 ml.)	Specific Gravity	Urinary Protein (mg./l.)	Urinary Cadmium (μ g./l.)	Creatinine (mg./100 ml.)	Specific Gravity
1	4,120	610	96	19	530	56	74	15
2	2,500	520	84	16	110	23	28	04
3	2,320	430	67	16	780	49	56	12
4	2,040	410	63	12	620	62	71	15
5	2,000	455	75	15	300	—	56	14

TABLE 8

URINARY PROTEIN AND CADMIUM EXCRETION OF TWO MEN EXPOSED TO CADMIUM OXIDE FUME CALCULATED FROM MORNING SPOT SPECIMENS OBTAINED DAILY DURING A WORKING WEEK AT FOUNDRY I

Day of Specimen	I : 3				I : 5			
	Urinary Protein (mg./l.)	Urinary Cadmium (μ g./l.)	Creatinine (mg./100 ml.)	Specific Gravity	Urinary Protein (mg./l.)	Urinary Cadmium (μ g./l.)	Creatinine (mg./100 ml.)	Specific Gravity
1	1,250	158	46	10	1,325	56	81	18
2	2,740	68	20	04	975	50	114	22
3	2,430	207	56	14	1,700	34	82	17
4	3,480	136	48	12	1,380	43	131	24
5	2,850	340	86	18	2,030	53	158	27
6	2,680	96	28	07	1,930	37	137	27

TABLE 9

URINARY PROTEIN AND CADMIUM EXCRETION OF THREE MEN EXPOSED TO CADMIUM OXIDE DUST CALCULATED FROM SPECIMENS OBTAINED THROUGHOUT SHIFT

Specimen	A				D				M			
	Urinary Protein (mg./l.)	Urinary Cadmium (μ g./l.)	Creatinine (mg./100ml.)	Specific Gravity	Urinary Protein (mg./l.)	Urinary Cadmium (μ g./l.)	Creatinine (mg./100ml.)	Specific Gravity	Urinary Protein (mg./l.)	Urinary Cadmium (μ g./l.)	Creatinine (mg./100 ml.)	Specific Gravity
1	2,850	540	81	18	100	106	110	20	980	60	100	18
2	2,650	580	93	19	60	94	80	18	860	32	34	11
3	3,200	610	97	20	30	58	56	15	380	26	20	08
4	—	—	—	—	20	54	40	13	—	—	—	—

TABLE 10

URINARY PROTEIN AND CADMIUM EXCRETION OF MEN EXPOSED TO CADMIUM OXIDE FUME CALCULATED FROM SPOT SPECIMENS OBTAINED THROUGHOUT SHIFT AT FOUNDRY I

Specimen	I : 1				I : 2				I : 3			
	Urinary Protein (mg./l.)	Urinary Cadmium (μ g./l.)	Creatinine (mg./100ml.)	Specific Gravity	Urinary Protein (mg./l.)	Urinary Cadmium (μ g./l.)	Creatinine (mg./100ml.)	Specific Gravity	Urinary Protein (mg./l.)	Urinary Cadmium (μ g./l.)	Creatinine (mg./100ml.)	Specific Gravity
1	870	590	87	14	0	40	33	07	2,820	320	101	18
2	1,210	430	67	13	0	37	33	07	3,380	370	123	22
3	850	550	70	15	0	37	39	08	—	—	—	—
4	—	—	—	—	0	39	25	05	—	—	—	—
Specimen	I : 4				I : 5				I : 6			
	Urinary Protein (mg./l.)	Urinary Cadmium (μ g./l.)	Creatinine (mg./100ml.)	Specific Gravity	Urinary Protein (mg./l.)	Urinary Cadmium (μ g./l.)	Creatinine (mg./100ml.)	Specific Gravity	Urinary Protein (mg./l.)	Urinary Cadmium (μ g./l.)	Creatinine (mg./100ml.)	Specific Gravity
1	0	111	86	—	775	35	67	14	1,720	210	69	15
2	0	99	56	12	570	36	66	13	1,640	175	78	16
3	0	177	133	22	1,340	33	74	15	1,020	157	58	13
4	0	142	91	19	1,170	40	95	18	595	93	33	08

normal range (0 to 25 $\mu\text{g./l.}$). The alkaline accumulator workers not exposed to cadmium, whose exposure could therefore be regarded as marginal, had urinary cadmium levels (10 to 36 $\mu\text{g./l.}$) significantly above the normal range.

The values of urinary cadmium were obtained from spot specimens and thus subject to indirect variations due to changes of water excretion throughout the day. To obviate such effects, which may give a misleading value for the cadmium excretion over short periods, it is customary to collect 24-hour specimens. Under industrial conditions such collections present considerable practical difficulties in obtaining all the urine without contamination from the workers' clothing. Spot specimens were therefore obtained from the men on arrival in the morning. Since creatinine excretion was a good measure of the glomerular filtration rate, and its clearance was unaffected by at least one heavy metal, uranium (Wills, 1949), it was hoped that variations in spot specimens could be eliminated by reference to creatinine concentration. In fact, as seen in Fig. 2, a distinct linear relationship was observed between the urinary concentrations of cadmium and creatinine over a considerable range of values. The slopes of the curves vary in accordance with the cadmium clearance rates of the four workmen illustrated. A less close correlation was observed between urinary cadmium and specific gravity (Fig. 1). It would be possible to choose an arbitrary urinary standard of creatinine concentration, say 100 mg./100 ml. urine, to which all spot specimens could be referred, the cadmium concentration being corrected according to the appropriate individual curve. The values of urinary cadmium quoted have, however, not been corrected in this way.

The incidence of proteinuria was greater in workers exposed to fume (60%) and also in those inhaling dust (20%) than in the control group. The quantity of urinary protein from cadmium workers was relatively low (0 to 4 g./l.). No correlation was discovered between urinary cadmium and protein excretion. Whereas the cadmium excretion in a urinary specimen from an individual worker was related linearly to both the specific gravity and

creatinine content, the protein concentration varied independently of these quantities.

The nature of the proteinuria in this intoxication is the subject of continued study and protein from workmen A, L, I : 3, I : 5, and II : 8 is being used for this purpose.

Summary

Information is presented on the urinary cadmium excretion of men exposed to cadmium oxide dust and fume and of men not so exposed.

The incidence of proteinuria in workers exposed to cadmium oxide fume (60%) and to dust (20%) was higher than in controls (5%).

Urinary cadmium excretion in individual workmen is not subject to major fluctuation over periods varying from a few hours to two years.

For individual workmen urinary concentration of cadmium was related linearly to the specific gravity and creatinine of spot specimens, over a wide range of values.

Urinary cadmium and protein excretion appeared to vary independently.

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