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CLINICAL AND BIOCHEMICAL OBSERVATIONS IN MEN WITH CADMIUM NEPHROPATHY. A TWENTY-YEARS STUDY

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ABSTRACT

Over twenty years observations on the clinical state, biochemical changes and causes of death in 39 men with proteinuria, employed in an alkaline accumulator factory, have been made by the company doctor.

An attempt is made to form patterns of morbidity, whilst the relative absence of serious disability likely to have resulted from nephropathy is noted.

One new (mild) case of osteomalacia is reported, but its cause is likely to have been due to previous gastrectomy.

After Friberg's original paper and monograph on cadmium workers in 1948 and 1950[5] and the subsequent reports of osteomalacia and "Itai-Itai" disease, the follow-up of exposed workers and those who had developed proteinuria became an essential policy in industry. This has been effected in an alkaline accumulator industry plant by annual examinations since 1956. A policy of re-employing individuals with proteinuria in non-exposed jobs was put into practice in 1968, when additional investigations were also undertaken. This paper presents the facts from such observations; and attempts to show the presence or absence of patterns of morbidity, and the practical considerations that apply in the health care of such workers.

SUBJECTS AND METHODS

All persons exposed to cadmium at work, about 130–150 in any one year, are subjected to annual examinations which include:

- occupational and general medical histories,
- brief respiratory questionnaire, including smoking habits, the presence of cough and sputum, and evidence of breathlessness (MRC questionnaire),
- blood pressure recording (whilst lying in semi-prone position and after resting for 5–10 minutes),

- olfactory assessment,
- urine-testing for protein, by means of sulpho-salicylic and trichloracetic acids (semi-quantitative measurements made with the Gallenkampf proteinometer),
- urine testing for glucose, with Clinistix and Clinitest,
- cadmium-in-urine estimations on spot morning samples (since 1968 only),
- respiratory spirometry, with a Vitallograph (since 1968 only),
- sporadic haematological values for calcium, phosphate, uric acid, alkaline phosphatase, urea and creatinine (since 1967 and for proteinurics only).

As a result of these regular urine tests during examinations, 41 men have been personally known to have proteinuria, but details on two are extremely scarce. The confirmation of the tubular nature of proteinuria on the remaining 39 was assumed in earlier years by, (1) the insidious mode of development, (2) the history of cadmium exposure, and (3) the lack of other renal symptoms. More recently, and certainly since 1967, the tubular nature of proteinuria has been confirmed by electrophoresis or increased lysozyme excretion[7] and other indices of tubular dysfunction.

RESULTS

Proteinuria

In a previous publication[1] the concentration of protein did not usually exceed 100 mg per 100 ml of urine. The Gallenkampf proteinometer only records up to 100 mg, and by 1977, 18 of the 39 proteinurics excreted protein in concentrations at or above this level. This general increase occurred after the men's removal from exposure; and this removal from exposure was not followed by the complete loss of proteinuria in any, even mild, cases. In the previously mentioned and reported case of osteomalacia the patient excreted about 1.0 g protein in 24 hours on initial admission to hospital[3]. Nineteen patients first showed evidence of proteinuria in or before 1956, the remainder being detected in the ensuing years up to 1974 (usually about one per year).

The total length of exposure varied from 10 to over 40 years. Among 41 patients with proteinuria up to 1978 eight were at work, nine were retired, 23 had died and the fate of the remaining one was unknown. None of them, with the exception of the case of osteomalacia, retired prematurely through ill-health. Figure 1 shows their ages in 1978, or at previous death. Of the seven who died before the age of retirement three had coronary thrombosis, two had carcinoma, one acute or chronic bronchitis and one broncho-pneumonia and congestive cardiac failure.

Table 1 shows the causes of death according to the death certificate issued by private doctor, coroner or pathologist. No further cases of renal failure are apparent, and there does not seem to be any obvious pattern. The previously noted significant incidence of cancer of the prostate in all exposed men, not just proteinurics[11], is no longer significant in those employed since 1948[16].

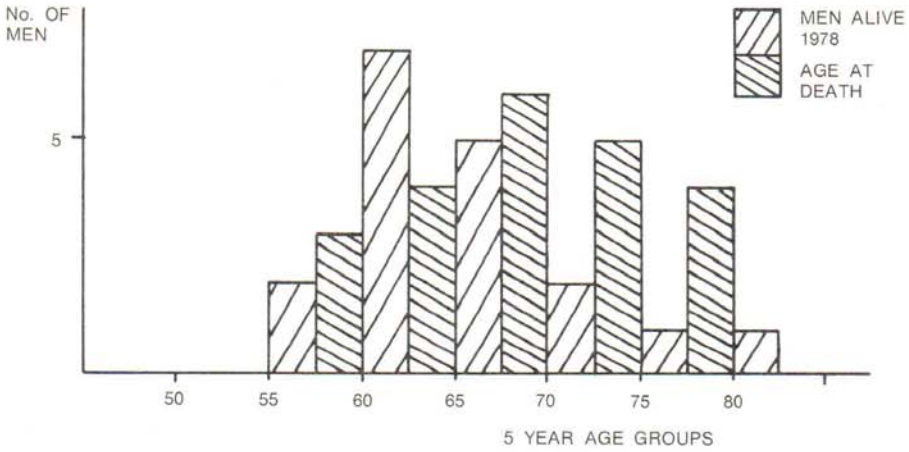

FIG. 1 – Ages of men with proteinuria (40–1 unknown).

TABLE 1
Causes of death in 23 patients with proteinuria.

Renal failure (uraemia)	1		1
Cerebro-vascular disease	2		2
Cardio-pulmonary disease	11	Coronary occlusion	7
		Acute or chronic bronchitis	1
		Broncho-pneumonia or chronic bronchitis	1
		Mixed cardio-pulmonary	2
Carcinoma	7	Lung	2
		Prostate	2
		Pancreas	1
		Gall-bladder	1
		Unknown primary	1
Others	2	R.T.A.	1
		Unknown	1

Table 2 is included to show the frequency of possible morbid effects associated with nephropathy.

Renal impairment

As regards overt renal morbidity, one man developed renal failure after lobectomy (for "sequestration of the lung"), but recovered to his pre-operative state after his blood urea had risen to 180 mg/100 ml; and one, as previously reported[1] experienced a mild nephrotic-like illness shortly before tubular proteinuria developed.

TABLE 2
Associated morbidity in 29 workers with proteinuria.

Overt renal disease	4	Acute nephrosis	1
		Renal failure (uraemia) post-op	1
		Cystic kidney	1
		Phenacetin	1
Diabetes	7		7
Bone disease	4	Osteomalacia	2
		Pagets	2
Urinary tract calcification	6	Calculi	3
		Renal colic	2
		Post-mortem calcification	1
Duodenal ulceration	8	No operation	3
		Operative treatment	5
Liver disease	0		0

TABLE 3
Total dust measurements of cadmium in air (in mg/m³) from dust samples collected by static samplers. Both means and range are approximate, and unless stated otherwise are taken from many recordings.

			Department 1		Department 2	
Factory B	Phase (1)	1926–1947	No sampling			
Factory A	Phase (2)	1947–1956	Single group of samples in 1949 Range 0.16–0.24			
		1957–1967	Process I	Range 0.12–1.5 Mean 0.4	Process I	Range 0.02–0.2 Mean 0.1
			Process II		Process II	Range 0.02–0.6 Mean 0.25
			Process III	Range 0.07–1.6 Mean 0.25		
	Phase (3)	1969–1974	Process I	Range 0.01–1.3 Mean 0.2		
			Process II	Range 0.01–0.5		
			Process III	Range 0.01–1.1 Mean 0.2		

Calcification in the urinary tract and calculi have not been a marked clinical feature, particularly in recent years, and because of the frequent occurrence of glycosuria, diabetes may have been over-diagnosed. (Most of these diagnoses have been made by family doctors or hospital specialists.)

Bone disease

Duodenal ulceration appears to have been in vogue, and may be significant more from the possible metabolic hazards of gastric surgery, than its incidence per se. Certainly the only other case of osteomalacia, one which was mild, occurred in a man who had had a gastrectomy some years before. It was the gastrectomy, rather than mild nephropathy (protein 10–30 mg/100 ml) that was deemed to be more responsible[8]. The diagnosis of osteomalacia was made on symptoms of pain, waddling gait, hesitancy on rising, rib fractures, a serum alkaline phosphatase of 41 K.A. units, and a histology report quoting "most of the bony trabeculae were lined with osteoid seams, some of which showed five or four lamellae". The patient showed symptomatic and biochemical response to treatment with Vitamin D, but has since died of carcinoma of the gall-bladder. Two other patients have been shown to have Paget's disease of bone, with slightly elevated serum alkaline phosphatase.

Blood pressure

Figure 2 shows the means of the last three recorded systolic and diastolic blood pressures in 36 men (three having been excluded because they had not had three measurements). The figure has been arranged so that if a hypertensive effect was present, it would appear as an increasing slope from left to right. The diastolic pressures in particular show no such effect, and seem normal, particularly for older men.

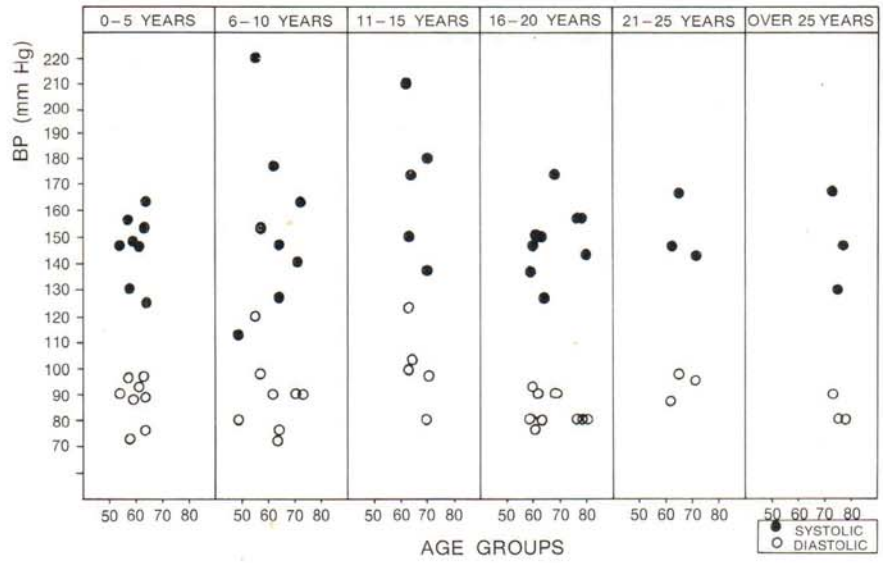

FIG. 2 – Systolic and diastolic blood pressure in men with proteinuria related to age and duration of proteinuria. Blood pressure measurements shown are the means of the last three recordings. Each column includes results from individuals for the appropriate length of time.

Respiratory disease

Respiratory disease has not been a cause of disablement, but 14 of 37 patients with proteinuria questioned (two could not reply) claimed mild dyspnoea on exertion. The latest spirometry recordings in 26 patients tested since 1968 are included in Figure 3. Among them five show a reduced $FEV_{1.0}/FVC\%$, as judged by Berglund and co-workers[2]. In Figure 4, seven of them show a reduced $FEV_{1.0}$, as judged by Kory and co-workers[12]. There is therefore some evidence of obstructive airways disease, but I am unable to comment on whether its incidence is higher than might be expected in such a working population. The investigation of such a risk is beyond the scope of this presentation; and a sound interpretation of the incidence of such a common English complaint as obstructive airways disease, including emphysema, in such a small population at risk seems most unlikely.

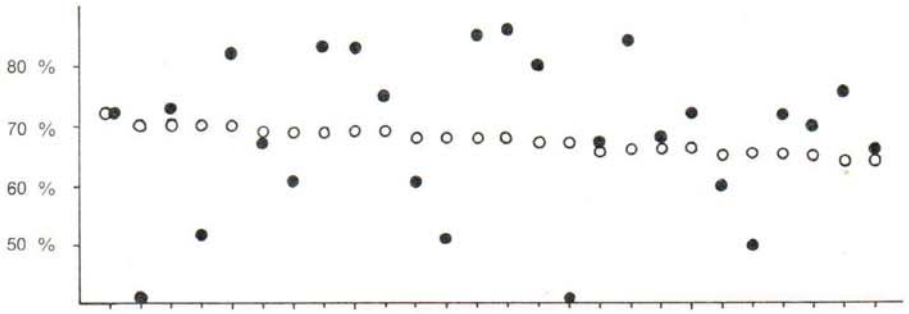

FIG. 3 – $FEV_{1.0}/FVC\%$ in men with proteinuria (26 tested). Open circles: predicted, solid circles: recorded. Standard deviation 7.2%.

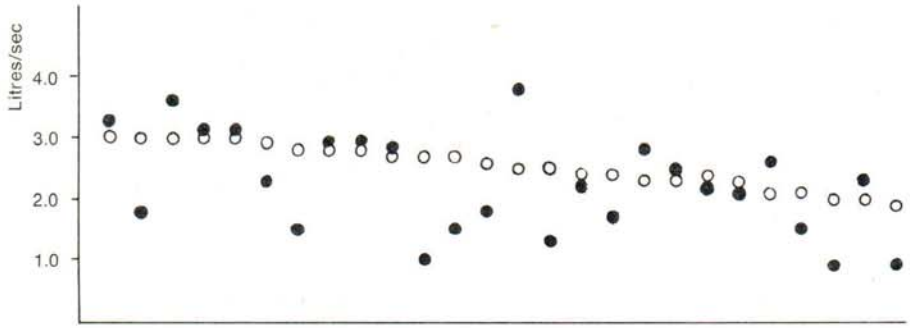

FIG. 4– $FEV_{1.0}$ in men with proteinuria (26 tested). Open circles: predicted, solid circles: recorded. Standard deviation 0.5 litres. Predicted values from Kory and co-workers[12].

Biochemistry

Figures 5–10 show the pattern of results from compiled sporadic blood estimations for phosphate (low), calcium (normal), uric acid (low normal), alkaline phosphatase (high normal), urea (high normal to slightly elevated) and creatinine (raised), in 23 patients with proteinuria followed-up since 1967.

There is therefore evidence of serum phosphate disturbance and some reduction of whole nephron performance.

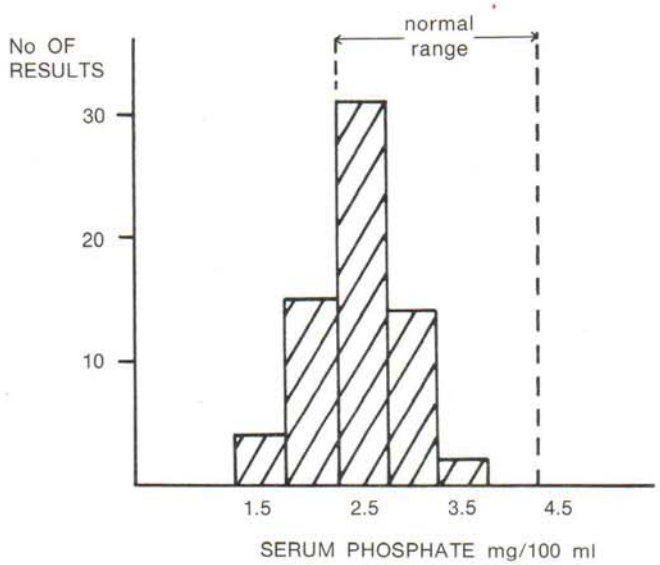

FIG. 5 – Serum phosphatase in men with proteinuria.

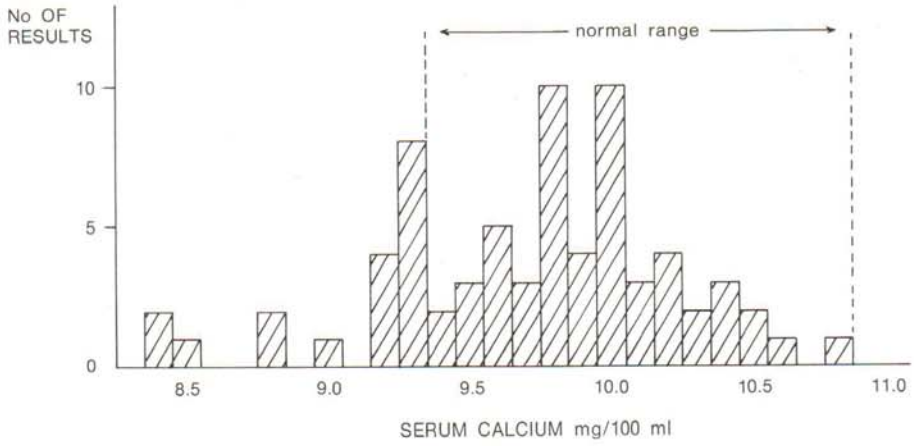

FIG. 6 – Serum calcium in men with proteinuria.

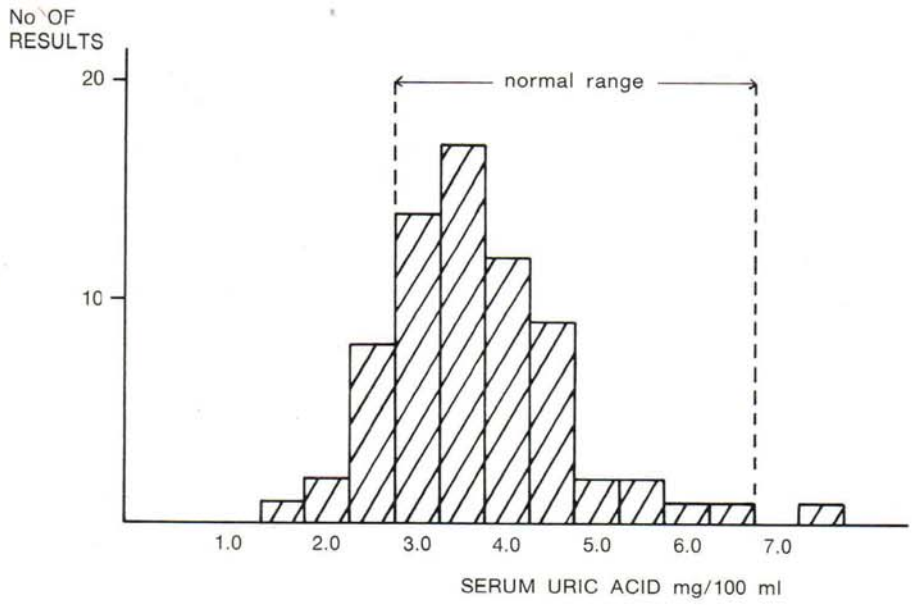

FIG. 7 – Serum uric acid in men with proteinuria.

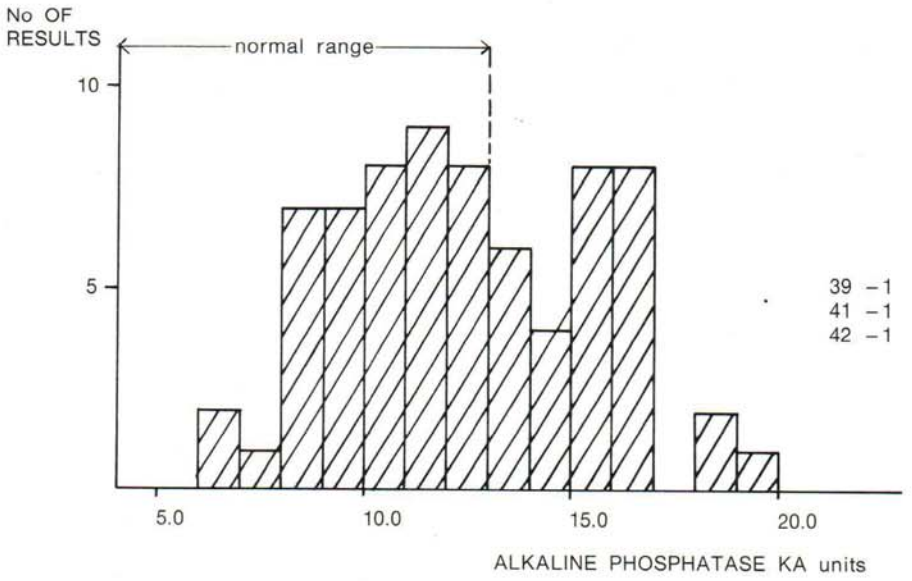

FIG. 8 – Serum alkaline phosphatase in men with proteinuria.

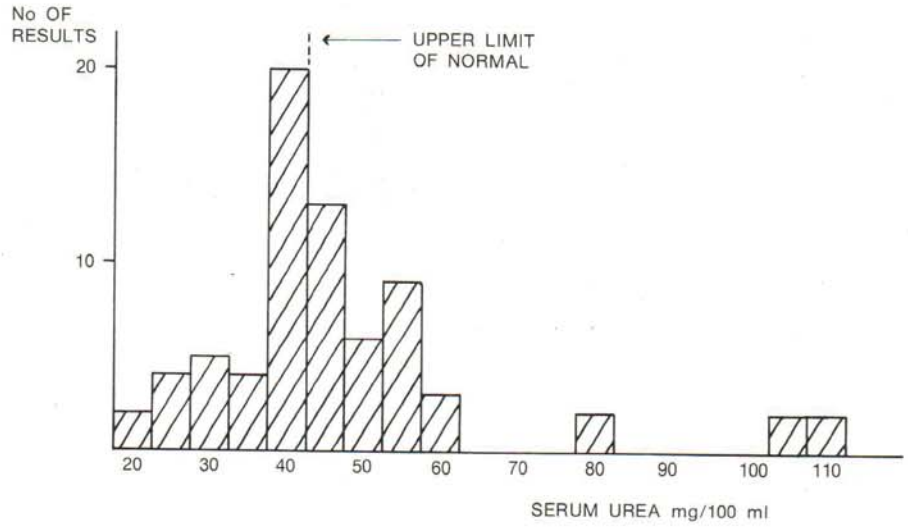

FIG. 9 – Blood urea in men with proteinuria.

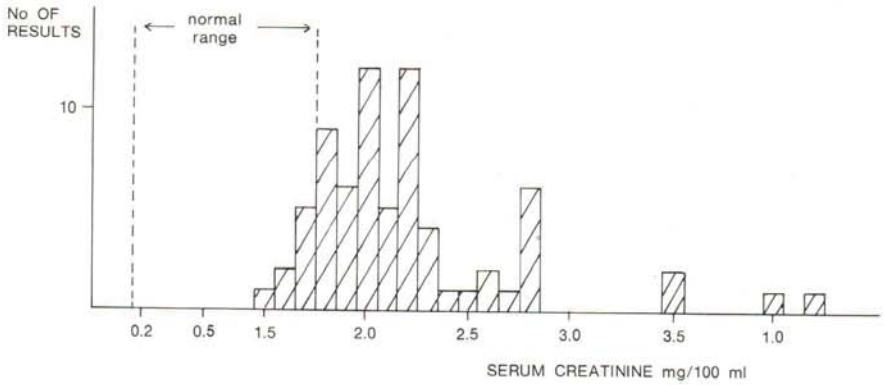

FIG. 10 – Serum creatinine in men with proteinuria.

Cadmium excretion

Cadmium-in-urine estimations are unreliable as an index of an individual's exposure and absorption, and wide variations in one person can be recorded. Nephropathy itself may increase excretion. Nevertheless the estimations are used on a group basis as a guide to trends. Figure 11 shows these estimations in some of the subjects both before and after removal from exposure, and suggests that a definite reduction occurs in the first three years and that excretion levels out at about 20–25 μg/l thereafter.

Exposure

As yet, no satisfactory method for estimating an individual's cadmium absorption has been developed, although neutron activation analysis shows some promising results. Until such a method has been perfected, the measurement of exposure remains one way of assessing the risk, but it is crude and can give wide variations. Sampling processes for dust-in-air have changed, as have analytical methods.

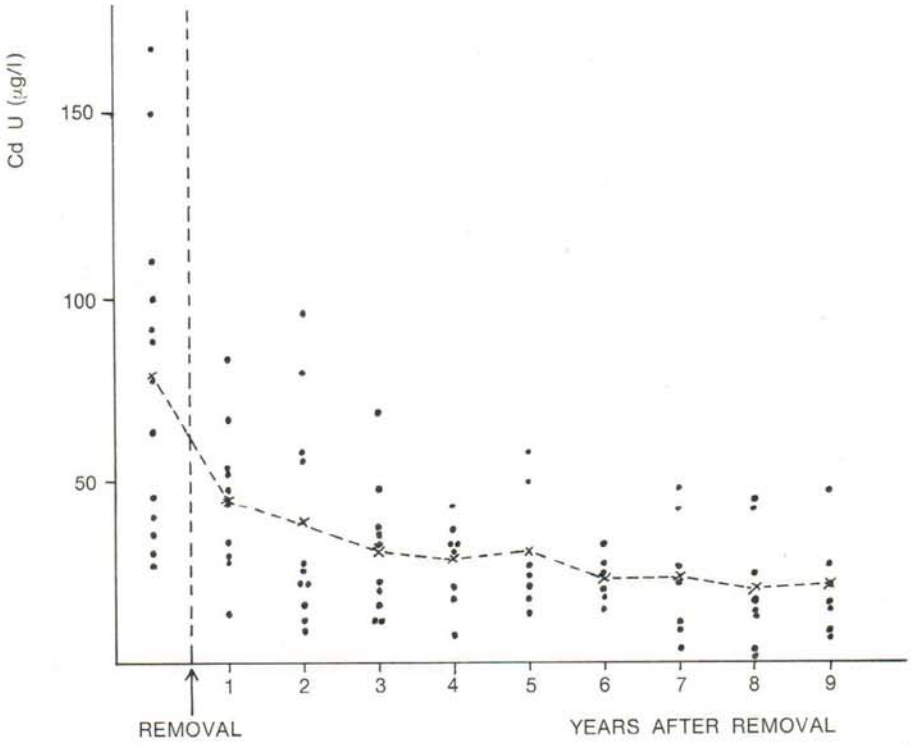

FIG. 11 – Cadmium in urine in men with proteinuria following re-employment in non-exposed jobs.

The chronic effects on the kidney are produced over many years of exposure to cadmium, and it is the total body burden assimilated that produces such effects[6]. It follows that high absorption of cadmium 25 or more years ago, accompanied by lower doses in recent years, may be sufficient to produce the total sum of body cadmium that disturbs the nephron. This must be borne in mind when studying cadmium-in-air figures, and the absence of such figures in previous years (and in older plants) leaves a gap when estimates of total absorption are attempted.

Such a gap is present in this study, for many of the subjects working before 1947 were employed in another plant (Factory B) long since closed. No dust-in-

-air figures were recorded there and the conditions have always been considered to have been much dirtier. Furthermore, the two main manufacturing departments, department 1 (Platemaking) and department 2 (Assembly) were housed in the same workshop in Factory B, but are separate in Factory A. And in Factory A, department 1 (Platemaking) was entirely rehoused in a purpose-built construction in 1968. For many of the workforce, therefore, there have been three phases of exposure – phase (1) in old factory B, phase (2) in department 1 (Platemaking) or department 2 (Assembly) in factory A, and phase (3) in new department 1 (Platemaking) in factory A. The proteinurics, with two exceptions, have come from those employed in phases (1) and (2). None have come from department 2 (Assembly) in phase (2), where the average cadmium-in-air figures were between 0.1 – 0.25 total dust. Nor has proteinuria been diagnosed in any employee employed solely in phase (3), or since 1958 in phase (2).

With such facts in mind, Table 3 is included to give a background of exposure in past years. Individual results for total dust from static samplers show wide variations, and there have been very high levels in occasional instances. The range in the table therefore includes the majority of results, and the mean figures are approximate. They are taken from static samplers at selected sites, personal samplers having been used in the past six years only. (With personal samplers used to estimate total dust, the figures for department 1 (Platemaking) between 1976 and 1978 ranged between 0.005 – 0.45, the mean lying between 0.02 – 0.25. The figures for department 2 (Assembly) between 1976 and 1978 ranged between 0.01 – 0.3, the mean lying between 0.01 – 0.2. These results have been produced after the installation of improved extraction plant.) The samples have been analysed by atomic absorption spectrophotometry since 1967, before which date the polarographic method was used.

DISCUSSION AND CONCLUSIONS

Most of the current interest in cadmium lies in its absorption, metabolism and earliest detectable effects. The dilemma for the company doctor in a cadmium factory is that the complete significance of the various (and sometimes gross) biochemical alterations induced by cadmium over many years is incompletely understood, even by experts. The condition of cadmium nephropathy itself has only been recognized in a few specialised industries in Europe, and in some special communities in Japan, but it is surprising that more information on the follow up of cases has not been forthcoming.

Bonnell and colleagues reported a worsening of respiratory disease and evidence of toxicity developing in copper-cadmium alloy workers after removal from exposure[4]. And Kazantzis, in a follow-up after 15 years on a group of six men in the pigment industry (with previous oxide dust and fume exposure) reported on a case of osteomalacia. Five of these men had mild dyspnoea, and all showed tubular abnormalities additional to those found 15 years previously. The length of exposure varied from 28 – 45 years, but the degree of exposure to cadmium, and its excretion were not recorded[9].

The group of subjects that form this study, all of whom are in the later decades of life, show biochemical changes, with resultant patterns of hypophosphataemia, hypo-uricaemia, hypercreatinaemia and glycosuria. However, morbid clinical patterns from such abnormalities are not apparent and the group shows evidence that, under the conditions prevailing, the renal disorder is compatible with longevity and satisfactory clinical health.

In spite of the controversy over the possible mechanisms behind the development of bone disease, there is no doubt that the serious and crippling disorder of osteomalacia can occur in isolated instances, as a result of tubular nephropathy. The proteinuria which occurs is generally progressive once initiated, even after exposure to cadmium is subsequently stopped, but the severity of the renal lesion, as judged by the level of urinary protein concentration, does not itself seem to determine the development of bone disease. The severe case of osteomalacia reported from this factory in 1969[1], excreted 1.0 g protein/24 hours on initial admission to hospital[3], but no such cases of osteomalacia have been reported from Sweden, where Piscator has quoted similar and even higher concentrations of urinary protein, up to 2.6 g/24 hours[14,15].

Although serum phosphate levels were normal in Friberg's original series[5], hypophosphataemia is present in this study and in others[9,10,13]; and hyperphosphaturia was demonstrated in two English series[1,9]. What distinguishes the Itai-Itai cases from those in this study are the low serum calcium and high alkaline phosphatase readings in the Japanese cases[13]. Some further impetus to increase the bone mineral disturbance is required before osteomalacia supervenes, and it may be that in conditions of relative dietary deficiency of calcium and vitamin D, the requisite amount of vitamin D needed to maintain a steady bone metabolism is still further reduced by inadequate 1 – hydroxylation of 25-hydroxy-cholecalciferol in the renal tubules. Despite the demonstration of reduced glomerular function, renal failure is not a feature of the disorder. The affected kidneys may, however, be more susceptible to the effect of other medical conditions such as operations, hypertension and diabetes. This has only been evident in one 80-year old diabetic, and in the petient who experienced post-operative renal failure.

Hypertension is not concomittant with this nephropathy, but glycosuria is common and may cause confusion in the diagnosis of diabetes.

There is some evidence of obstructive airways disease, but its incidence cannot be compared to that in the general population, where it is a common condition.

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