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Renal Tubular Dysfunction and Abnormalities of Calcium Metabolism in Cadmium Workers

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Tubular proteinuria is generally accepted as the critical effect following long-term, low-level exposure to cadmium as seen in an industrial environment. This effect may not be of immediate importance to the health of the individual, but the significance, in terms of long-term morbidity and mortality, of the renal tubular defect of which it is an indicator is not fully understood, and certain sequelae may have remained unrecognized due to inadequate follow-up.

Follow-up studies have been performed in nine of 12 workers who were initially investigated in 1962. In six of the men exposures ranged from 28 to 45 years to cadmium sulfide dust and for shorter periods in the earlier years to cadmium oxide fume and dust. These six men had tubular proteinuria when first seen, and this has persisted in the five survivors. All six men had hypercalciuria, and two of them became recurrent stone formers. One man whose urinary calcium excretion later fell to a low level more recently developed vitamin D resistant osteomalacia. In addition, each of the six men had exhibited some, but not all, of a variety of biochemical abnormalities related to other proximal renal tubular defects, and the worker who developed osteomalacia had additional evidence of a distal tubular defect. The five survivors also have evidence of slowly progressive deterioration in glomerular function.

Follow-up of this small group has shown that renal tubular dysfunction in cadmium workers may continue symptom-free for long intervals, but in a proportion of cases serious clinical effects may develop after a number of years.

The earliest observed effect following long-term industrial exposure to cadmium is a low grade proteinuria which, once developed, is generally persistent (*1*, *2*). The proteinuria is of the form associated with proximal renal tubular damage and is characterized by the excretion of low molecular weight proteins (*3*). Further examination may reveal a disturbance in the renal handling of other filtered components and of concentration and acidification, so that proteinuria is usually only one aspect of a more generalized renal tubular dysfunction (*4*, *5*). The significance of such dysfunction to the health of the worker has been inadequately determined, as due to the slow progression of the condition these men in the past have had inadequate follow-up, and certain sequelae may have gone unrecognized. The relationship between cadmium-induced renal tubular dysfunction and abnormalities of calcium metabolism with their effects on bone is of particular importance in view of the predominant manifestation of osteomalacia, or itai-itai disease, in persons with renal tubular dysfunction in an area of high environmental cadmium pollution in Japan (*6*). The predominance of osteomalacia in elderly, multiparous women in the endemic area has been contrasted with the scarcity of this condition in cadmium workers. Data are lacking on the effects of cadmium on calcium metabolism, including the role of the parathyroid gland and of vitamin D, both in the endemic area and in cadmium workers.

Osteomalacia in cadmium workers was first noted in cadmium-nickel battery workers with 8 to 16 years exposure. Four of the six cases were in females; all complained of pains in the legs and back and of difficulty in walking, and all had the specific radiological appearances of osteomalacia (*7*). The associated muscle weakness, commented the authors, resembled a myopathy. Investigation of tubular function was not performed, but the urinary calcium excretion given in only one case was high. In eight further cases of radiologically diagnosed

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osteomalacia in cadmium workers (*8*) the concomitant presence of osteoporosis was noted, but the authors could not comment on the significance of this lesion, affecting in particular the lumbar vertebrae, owing to its common occurrence in an older population. The pathogenesis of the disorder was attributed either to a direct action of cadmium on bone or to a disorder of calcium metabolism brought about by cadmium. Three of these cases showed impaired glomerular function, but again tests of tubular function were not performed. In two further cases of histologically confirmed osteomalacia (*5*, *9*), careful tests of tubular function showed the pattern of impairment seen in the acquired Fanconi syndrome and which has come to be associated with excessive cadmium exposure. One of these cases (*5*) occurred in a group of cadmium workers who showed evidence of a multiple tubular reabsorptive defect which varied in individuals from mild to severe. What was of particular interest in this group was that many of the men with tubular proteinuria showed increased urinary excretion of calcium and phosphorus, and some of the nonproteinuric men also had hypercalciuria with low serum calcium levels. Five workers with proteinuria and seven exposed men without proteinuria had developed renal colic or calculi over the course of 10 years, but the number of risk was not given, and the significance of this finding could not be assessed. In the second case (*9*) with histologically proven osteomalacia, hypercalciuria without hypercalcaemia was observed, and both cases had evidence of an additional distal renal tubular defect, an impairment of urinary acidification. This worker also had carcinoma of the lung.

With regard to renal stone formation, an increased frequency in cadmium workers was first noted by Friberg (*2*), and subsequently Ahlmark et al. (*10*) found that 44% of a group of workers exposed to cadmium dust for more than 15 years gave a history of renal stone, composed mainly of basic calcium phosphate. The point was also made in this group that the higher prevalence of renal stones occurred in the nonproteinuric men. Friberg et al. (*3*) commented on this finding that changes in calcium reasorption in cadmium workers may occur at an early stage in exposure.

The findings given above indicative of tubular dysfunction together with a disturbance of calcium metabolism in cadmium workers have been confirmed and amplified in the small study described here.

A group of mine cadmium workers who formed part of a study initially performed in 1962 (*4*) have been followed for up to 16 years. The total work force exposed to cadmium was seen on the original study (Table 1) with one refusal, but the men followed up included all those with the longest exposure (Table 1, subjects 1–6), now ranging from 28 to 45 years of cadmium sulfide dust and for shorter periods in the earlier years to cadmium oxide fume and dust. The men were engaged on the manufacture of pigments based on cadmium and selenium, but they produced in addition both cadmium oxide powder and some cadmium metal. Exposure to cadmium had been heavy before the initial survey, but in 1962 the manufacture of cadmium oxide powder and of cadmium metal was discontinued, and subsequent regular air sampling ensured that heavy exposure no longer occurred. In addition, three men (subjects 8, 9, and 12) were recently seen again on a single occasion. These men had much less exposure to cadmium, especially under the conditions which had obtained in the past.

On the initial survey in 1962, only one man had symptoms relevant to the renal system. This was subject 2 (Table 1) who previously had two attacks of renal colic with the passage of calculi. This man

Table 1. Cadmium workers: urine examination on original survey, 1962.

Exposure, yr.	Subject number	Protein excretion, mg/24 hr	Urine electrophor pattern[a]	Glycosuria	Amino acid uria	Calcium, mg/24 hr
25-30	1	470	Tubular+++	+	+	301
	2	650	Tubular+++	+	+	325
	3	370	Tubular+++	0	0	672
	4	430	Tubular+++	0	+	383
	5	—	Tubular++	0	0	785
12–14	6	—	Tubular+	0	0	294
	7	—	Tubular+	0	0	224
	8	—	Tubular+	0	0	154
	9	—	Normal	0	0	403
< 2	10	—	Normal	0	0	308
	11	—	Normal	0	0	256
	12	—	Normal	0	0	192

[a] ++, +++ proteinuria detectable on clinical testing.

died of bronchial carcinoma two years later. Examination of the kidneys showed fairly numerous small, subcortical scars, some of which extended through almost the whole thickness of the cortex. The scars were composed of hyalinized glomeruli, round cell infiltration, and atrophied tubules. Some glomeruli at the edge of these areas showed periglomerular fibrosis, while the glomeruli in the nonscarred areas appeared normal. The tubules showed no specific abnormality other than occasional dilation, containing pink hyaline material. The subepithelial tissues showed slight infiltration with chronic inflammatory cells. Small deposits of calcium without an associated inflammatory reaction were scattered throughout the kidney, but more concentrated around and within the tubules. The appearances were similar to those of mild, healed chronic pyelonephritis, together with widespread nephrocalcinosis.

At a later date, subject 3 also developed recurrent renal colic, and he has now passed stones on four occasions. Analysis of one recently passed stone showed this to be composed of hydroxyapatite, together with small amounts of calcium oxalate dihydrate and traces of cadmium. This man now also has marked osteoporosis.

In 1973, subject 1, then aged 61, developed severe pain and weakness in the right leg which let him down on several occasions. He found it difficult to rise from a chair, walking was severely restricted, and he used to cry out with pain turning over in his sleep. He also complained of polyuria, which he found particularly troublesome at night. Investigations revealed osteomalacia further considered below. The remaining subjects continued free of symptoms referable to the renal system.

Four men have had persistent clinically detectable proteinuria throughout the period of investigation, which was shown to be tubular by two-dimensional starch gel electrophoresis, and by a high excretion of β_2-microglobulin. In addition, subject 6, who in 1962 showed a tubular pattern on concentration and electrophoresis, developed clinically detectable proteinuria in 1971, and this has persisted. Two men had intermittent renal glycosuria and three had abnormal amino aciduria when first seen. Seven men exceeded a urinary calcium excretion of 300 mg/24 hr, and in addition subject 6 was first noted to have a high calcium excretion in 1973. Taking the stricter criteria for hypercalciuria proposed by Nordin (*11*) of a 90th percentile of 380 mg/24 hr, subjects 3, 4, 5, 6, and 9, i.e., five men, now have persistent hypercalciuria; but only subject 3 is a recurrent stone former.

Additional evidence of renal tubular dysfunction now present in all the men being followed up is summarized in Table 2. All except the three men with the lowest exposure have a low plasma phosphate level, and all except one has an abnormally high uric acid clearance. Intermittent renal glycosuria has been recorded in five men and abnormal aminoaciduria in five. In addition the five survivors with the longest exposure have evidence of impairment of glomerular function with decreased creatinine clearance and mild to moderate increase in blood urea. Plasma calcium levels were

Table 2. Summary of principal renal findings in six cadmium workers with long-term exposure (1978).

Subject number	Age	Date ceased exposure	Clinical	Tubular proteinuria	Amino aciduria	Renal glycosuria	Hyper Calcuria	Hypo-phosphatemia	Uric acid clearance	Blood urea
1	63	1973 (ret.)	Osteomalacia Neph-calc. Osteoporosis	+	+	+	+	+	+	±
2	57	1964(d)	Calculi Ca bronchus Neph-calc.	+	+	+	+	+	ND	−
3	69	1971(ret.)	Calculi Osteoporosis	+	±	±	++	+	+	±
4	60	Still employed	Osteoporosis	+	±	±	++	+	±	±
5	67	1973(ret.)	—	+	−	−	++	±	±	±
6	63	1975(ret.)	Osteoporosis Hypertension	+	−	±	++	+	±	±
8	52	Still employed	—	(+)	±	−	−	−	±	−
9	60	Still employed	Hypertension	(±)	−	−	++	−	±	−
12	56	Still employed	—	(±)	−	−	−	−	−	−

[a] Symbols: +, present or abnormally raised (hypercalciuria: + = > 300; + + = > 380 mg/24 hr; Hypophosphatemia: + = < 2.5 mg/100 ml, uric acid clearance + = > 10 ml/min, urea + = > 45 mg/100 ml); ±, normal in 1962; −, absent or within limits of normal; ND, not determined.

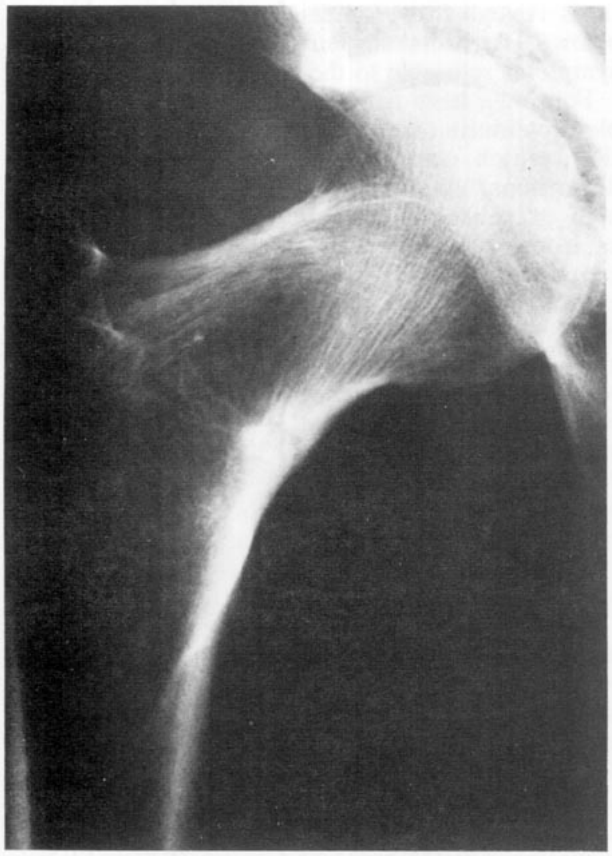

FIGURE 1. Radiograph of neck of right femur showing Looser's zone.

normal in all the men, and serum parathyroid hormone levels were also normal.

In subject 1, the diagnosis of osteomalacia was made following the discovery of Looser's zones in the neck of the right femur (Fig. 1) and shaft of the left fibula. Radiological examination also showed the presence of bilateral renal calcification or nephrocalcinosis and of osteoporosis. An iliac crest biopsy showed the presence of widened osteoid seams confirming the diagnosis. Careful investigation eliminated the possibility of nutritional defect, malabsorption, or other disorders contributing to the development of osteomalacia. Multiple defects of renal tubular function have been demonstrated. In addition to tubular proteinuria, glycosuria, and amino aciduria, plasma phosphate and potassium levels were clustered towards the lower limit of normal with abnormally low levels on some occasions. Plasma bicarbonate was also close to the lower limit and plasma chloride close to the upper limit of normal on repeated occasions, suggesting the presence of a mild hyperchloremic acidosis. An acid loading test confirmed the impaired ability of the tubule to acidify the urine, although hydrogen ion was eliminated by an increased capacity of the tubule to excrete ammonia, and the pH of arterial blood remained normal, indicating the presence of an incomplete renal tubular acidosis. A similar response to ammonium chloride was obtained by Pujol et al. (*9*) in their case of osteomalacia referred to earlier. In addition, a persistent polyuria was exhibited, with an impaired ability of the tubule to achieve a normal osmolar gradient. The osteomalacia responded to treatment with vitamin D_3, 40,000 IU per day, but only when phosphate and bicarbonate supplements had been added, for the bony lesion did not heal with vitamin D_3 alone over a 3-month period.

Subject 1 therefore has evidence of multiple renal tubular defects involving both the proximal and distal tubule (Table 3), the combination of hypophosphatemia with osteomalacia, nephrocalcinosis, and an inability of the tubule to acidify and concentrate the urine indicating the presence of a secondary distal renal tubular acidosis.

In this small group, the acquired Fanconi syndrome first diagnosed in 1962 had progressed in one worker to a serious consequence, osteomalacia, while other workers with similar exposures to cadmium compounds (who also had renal tubular dysfunction) developed hypercalciuria with, in two cases, repeated renal stone formation. The findings on histological examination of the kidney in subject 2 and on renal biopsy in subject 1 which were reported elsewhere (*4*) were predominantly those of an interstitial nephropathy. Similar appearances were reported by Kawai et al. (*12*), who found atrophy of the tubular epithelium with progressive interstitial fibrosis in rabbits and rats dosed orally with cadmium chloride in chronic experiments. However they reported decalcification and cortical atrophy of the femur in the absence of any renal changes in some animals dosed with only 10 ppm cadmium in the diet, which they considered the most sensitive effect. Yoshiki et al. (*13*) noted osteoporosis but no osteomalacia in their rats fed with varying levels of cadmium in the diet for 12 weeks. No histological abnormality was seen in the kidneys, but functional status was not evaluated. While

Table 3. Summary of biochemical abnormalities, subject 1.

Urine	Blood
Tubular proteinuria	Low potassium
Renal glycosuria	High normal chloride
Generalized aminoaciduria	Low normal bicarbonate
Polyuria with low osmolality	Low phosphate
Inappropriate pH (High)	Clearances:
High hydroxyproline	Creatinine low
	Uric acid high
	Phosphate high

these experimental observations are difficult to interpret, taken with the clinical findings they do suggest that cadmium may accelerate the appearance of osteoporosis as well as give rise to osteomalacia.

It is difficult to give an adequate explanation for these diverse effects of cadmium on calcium metabolism and on the skeletal system at present. It has been suggested that cadmium may exert a direct toxic action on bone tissue (*13*), but, even if this does occur, a disorder of calcium metabolism must also be present. Hypercalciuria may occur as a result of increased absorption of calcium from the gut or secondarily to defective tubular reabsorption of phosphate. 25-Hydroxy cholecalciferol is hydroxylated in the C-1 position in kidney before it can function as vitamin D on bone and on the intestine (*14*). This 1-hydroxylation reaction by chick kidney mitochondria is inhibited by $0.1mM$ cadmium, but inhibition is prevented when cadmium is bound to metallothionein (*15*). It is therefore possible that in cadmium-induced osteomalacia the unbound metal may interfere with one further tubular cell function, the production of the active form of vitamin D_3. In such a case, hypercalciuria secondary to defective tubular reabsorption of phosphate would not be compensated by increased absorption of calcium, and osteomalacia could be a consequence.

REFERENCES

1. Friberg, L. Proteinuria and kidney injury among workmen exposed to cadmium and nickel dust. J. Ind. Hyg. Toxicol. 30: 32 (1948).
2. Friberg, L. Health hazards in the manufacture of alkaline accumulators with special reference to chronic cadmium poisoning. Acta Med. Scand. 138 (Suppl.): 240 (1950).
3. Friberg, L., et al. Cadmium in the Environment, 2nd ed., CRC Press, Cleveland, 1974.
4. Kazantzis, G., et al. Renal tubular malfunction and pulmonary emphysema in cadmium pigment workers. Quart. J. Med. 32: 165 (1963).
5. Adams, R. G., Harrison, J. F., and Scott, P. The development of cadmium induced proteinuria, impaired renal function and osteomalacia in alkaline battery workers. Quart. J. Med. 38: 425 (1969).
6. Kobayashi, J. Relation between the Itai-Itai disease and the pollution of river water by cadmium from a mine. In: Fifth International Water Pollution Research Conference, San Francisco, July 1970, Pergamon Press, New York, 1971.
7. Nicaud, P., Lafitte, A., and Gros, A. Les troubles de l'intoxication chronique par le cadmium. Arch. Mal. Prof. 4: 192 (1942).
8. Gervais, J., and Delpech, P. L'intoxication cadmique. Arch Mal. Prof. 24: 803 (1963).
9. Pujol, M., et al. Tubulopathie des intoxications chroniques par le cadmium. Arch. Mal. Prof. 31: 637 (1970).
10. Ahlmark, A., et al. Further investigations with kidney function and proteinuria in chronic cadmium poisoning. Int. Cong. Occup. Health 13: 201 (1961).
11. Nordin, B. E. C. Hypercalciuria. Clin. Sci. Molecular Med. 52: 1 (1977).
12. Kawai, K., et al. Morphological alterations in experimental cadmium exposure with special reference to the onset of renal lesion. In Effects and Dose-Response Relationships of Toxic Metals, G. F. Nordberg, Ed., Elsevier, Amsterdam, 1976.
13. Yoshiki, S., et al. Bone and kidney lesions in experimental cadmium intoxication. Arch. Environ. Health 30: 559 (1975).
14. Omdahl, S. L., and De Luca, H. F. Regulation of vitamin D metabolism and function. Physiol. Rev. 53: 327 (1973).
15. Suda, T., et al. Prevention by metallothionein of cadmium induced inhibition of vitamin D activation reaction in kidney. FEBS Letters 42: 23 (1974).