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Occupational Lead Exposure, Nephropathy, and Renal Cancer

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A 48-year-old lead worker was found to have a cystic renal carcinoma during an evaluation of his occupational lead poisoning. Clinical studies showed elevated blood lead levels, impaired urinary concentrating ability, and reduced creatinine clearance. Histologic and electron microscopic studies showed this cystic tumor to be similar to renal carcinomas observed in animals with prolonged lead exposure. Lead content of the tumor was elevated (2.49 μg/gm) in comparison with adjacent renal tissue and with normal adult levels. In light of previous animal studies, this case adds increased evidence to the concern over the carcinogenic potential of prolonged lead exposure.

Key words: renal carcinoma, lead poisoning, chronic renal failure, environmental carcinogenesis

INTRODUCTION

The induction of renal carcinoma in animals following chronic oral and subcutaneous administration of lead salts is a well-recognized and reproducible phenomenon [Zollinger, 1953; Van Esch et al, 1962; Boyland et al, 1962; Roe et al, 1965; Mao et al, 1967; Zawirska et al, 1968; Van Esch et al, 1960; Oyasu et al, 1970; Ishibe et al, 1970; Ito, 1973; International Agency for Research on Cancers, 1972; Kobayaski et al, 1974; Stoner et al, 1976]. These neoplasms have been associated with administration of various inorganic lead compounds (basic lead acetate, lead carbonate, lead arsenate, lead subacetate, lead acetate, and lead phosphate) for periods of 16 to 29 months in several animal species. Malignant tumors in other sites have also been reported [Zawirska et al, 1968; Oyasu et al, 1970].

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Reports in humans are scanty and less consistent than the animal studies. An astrocytoma of the frontal lobe was reported in a worker with excessive occupational lead exposure over 40 years [Portal, 1961]. Five patients with lung cancer were found to have lead concentrations in lung tissue which were equivalent to those found in controls dying from other causes [Jecklin, 1956].

Two epidemiologic studies have examined the causes of death in lead workers and found little evidence that lead is a carcinogen in humans. The first study [Dingwall-Fordyce, 1963; Lane, 1965], of pensioners from a British accumulator factory, showed that workers with "negligible exposure, with lead-in-urine values within the normal range" had an excess of deaths from malignant neoplasms (10 observed vs 4.7 expected based on UK national rates). However, no excess was seen in workers with more significant exposure to lead (10 observed vs 12.5 expected). Another study [Cooper, 1975] of US lead smelter and battery plant workers showed an excess of cancer when compared with the general US population. The sites responsible for the excess were primarily the lung and digestive system.

The following case study reports the clinical and pathological findings of a worker with prolonged occupational lead exposure who developed a renal carcinoma histologically similar to those seen in animals and also had evidence of chronic lead nephropathy.

CASE HISTORY

The patient, a 48-year-old man, had worked with lead for 22 years in his job as a furnace tender at a smelting company. In 1978, when seen at a local hospital, he had been told that he had lead poisoning. He was not hospitalized or treated at that time, but was told to "avoid lead exposure as much as possible." Since that time he continued working at the smelting company. He had been retested in August 1979 and had been found to have an elevated blood lead level.

He denied any recent history of abdominal cramps, nausea, vomiting, diarrhea, irritability, or mood changes, but did recall having been particularly tired and weak over the previous 2 to 3 weeks, and he felt that he was sleeping somewhat more than usual. He denied having an abnormal taste in his mouth and had not experienced upper extremity weakness or sensory loss.

The patient had taken oral penicillamine 3 to 4 weeks prior to our initial evaluation. These pills had been given to him by a supervisor; the patient had not seen a physician in connection with the dispensing of this medication. One other fellow worker had been seen with lead toxicity during the previous month.

The physical examination showed a blood pressure of 220/120 in the right arm supine, and funduscopic examination revealed tortuosity and narrowing of the vessels as well as some mild AV compression. Neurological examination showed no evidence of wrist extensor weakness. Sensory testing to pin, vibration, light touch, and position was normal, and tendon reflexes were 1–2+ and symmetrical. Heart and lungs were normal. Possible lead lines were noted.

The blood lead level was 64 μg/100 ml of whole blood and the erythrocyte protoporphyrin level was 290 μg/100 ml. The BUN was 26 mg/100 ml, creatinine was 2.6 mg/100 ml, uric acid was 8.0 mg/100 ml, calcium was 9.3 mg/100 ml, sodium was 134 mEq/liter, potassium was 3.9 mEq/liter CO_2 was 28 mm/liter, and chloride

was 100 mEq/liter. The hemoglobin was 13.4 gm/100 ml with normal red cell indices. The sedimentation rate was 50 mm/hr.

Routine urinalysis showed specific gravity of 1.008 with 2+ protein, a pH of 5.0, and no sugar. The sediment showed 0 to 2 red blood cells and occasional hyaline casts per high power field. No cellular casts were present. The electrocardiogram showed abnormal ST origins and T waves consistent with subendocardial ischemia. The chest x-ray showed borderline cardiomegaly and an enlarged left ventricle.

EMG and nerve conduction studies showed a slightly reduced right ulnar sensory action potential and a slightly slowed right ulnar velocity. Motor and sensory studies of the median, peroneal, and sural nerves were entirely normal.

Neuropsychological evaluation revealed impaired visual-motor coordination, difficulties in concentration, difficulties in learning new material, and deficits in visual memory.

A 24-hour urine contained 1,528 mg of creatinine in a volume of 1,400 ml. The calculated creatinine clearance was 41 ml/min. A standard one-day test of renal function was performed [Edwards et al, 1964]: urinary acidification was normal. Following water deprivation and the administration of vasopressin, the urine osmolality reached only 474 mOsm/kg, normal being approximately 900 mOsm.

An intravenous pyelogram revealed the presence of a mass in the upper pole of the right kidney. Echo studies of the kidney showed this mass to be cystic in nature. Cytologic studies of aspirated cells were felt to be consistent with renal cell carcinoma, and a right nephrectomy was performed Nov 28, 1979. No evidence of tumor spread was noted at the time of surgery, and no additional foci of metastasis were noted on preoperative scans of the liver and bones. Preoperatively, the serum creatinine concentration was 2.6 mg/100 ml and the BUN was 44 mg/100 ml. Following surgery, the patient's serum creatinine concentration rose to 5.1 mg/100 ml and the BUN to 54 mg/100 ml. He has since stabilized to a creatinine of 4.0.

PATHOLOGICAL STUDIES

The right kidney was received in the fresh state in the pathology department, within minites of its removal. Representative samples of the cortex, the medulla, and the tumor were taken immediately for electron microscopy and tissue lead analysis. The remainder was processed for routine histology.

Gross Pathological Examination

The 280 gm kidney (11.0 × 7.5 × 3.5 cm) had a 5.5 × 4.0 × 3.5 cm soft, tense, partly cystic mass projecting from its lateral surface. A similar but smaller (0.7 cm) nodule was present 0.3 cm from the main mass. The cut surface of the mass was somewhat papillary, soft, mushy, and yellow brown (Fig. 1). Renal vessels were not involved by the tumor. The renal parenchyma contained a few subcapsular cysts containing clear fluid.

Light Microscopy

Sections of cortex contained numerous glomeruli, a few of which had some degree of sclerosis; many others were normal. Tubules were not remarkable, but the lumen of many tubules contained protein casts. The proximal tubular lining cells showed varying degrees of swelling. The characteristic lead-induced intranuclear

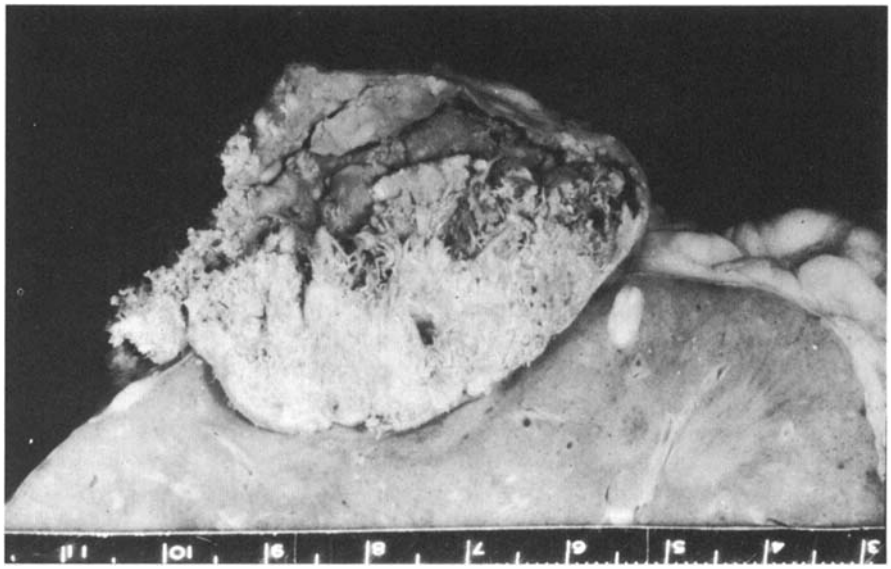

Fig. 1. The kidney tumor with partly solid and partly cystic cut surface. Papillary fronds of the tumor are easily discernible.

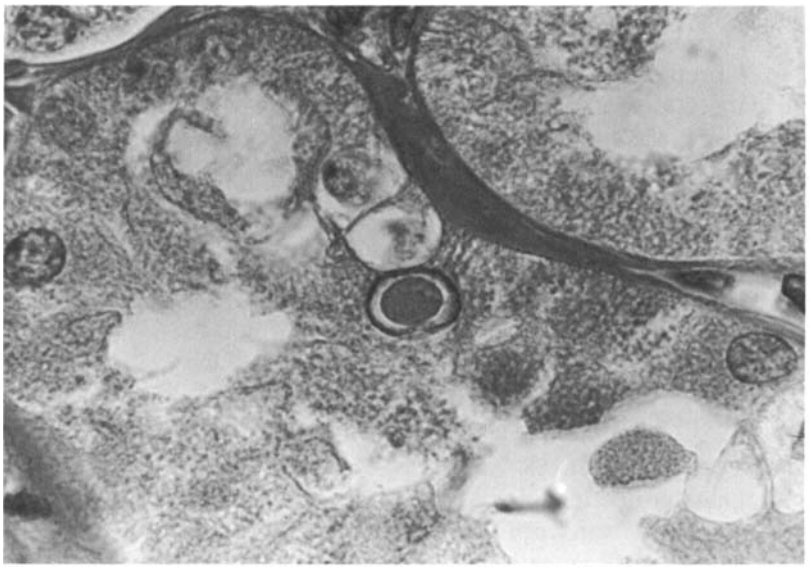

Fig. 2. Proximal convoluted tubule with an amphophilic intranuclear inclusion in one epithelial cell (magnification, 100 ×).

inclusion bodies were sparse but present (Fig. 2). There were focal areas of interstitial fibrosis containing some atrophic tubules. The interstitial tissue also contained foci of inflammatory cells, mostly mononuclear cells.

The renal parenchyma contained an adenocarcinoma with a predominantly tubular pattern (Fig. 3). The tumor contained extensive areas of necrosis.

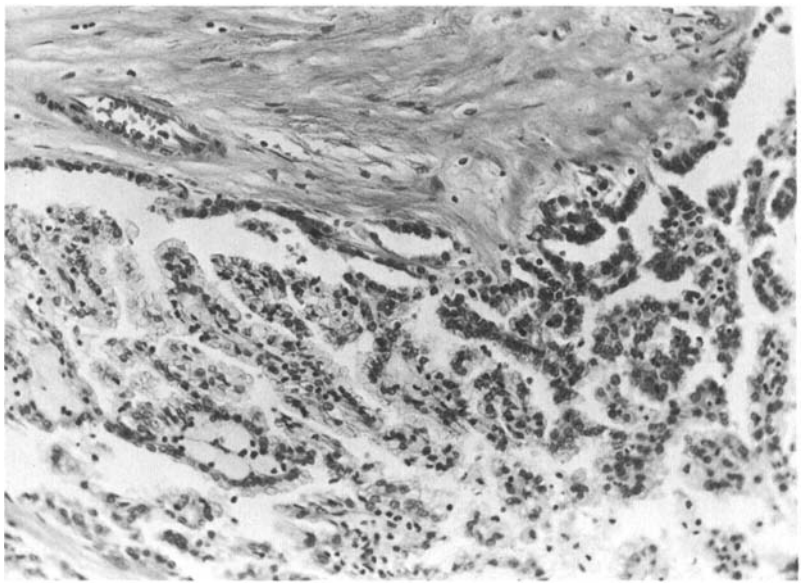

Fig. 3. Tumor composed of clear cells arranged in a papillary configuration with delicate fibrovascular cores (magnification, 40 ×).

Electron Microscopy

The tissue blocks, fixed in combined formaldehyde-glutaraldehyde fixative [McDowel et al, 1976] and transported in buffer, were post-fixed in osmium tetroxide [Millonig, 1962], dehydrated in a graded series of alcohols, and embedded in Epon described elsewhere [Fowler et al, 1975]. Thin sections 600–900 Å thick were cut with a diamond knife in a Porter-Blum MT-1 ultramicrotome and mounted on Formvar-coated copper-alloy 200-mesh grids. The sections were examined in a Philips EM 300 electron microscope operated at 80 keV. Photographs were taken at an initial magnification of 3,735 × and a final print magnification of 11,205 ×. In addition, adjacent sections of tissue from the same blocks were cut 2,500 Å thick and processed for electron microscopy as previously described [Fowler et al, 1973]. These sections were analyzed in a Philips EM 300 electron microscope fitted with an EDAX energy dispersive x-ray analysis unit. Analyses were conducted using a 1 μm diameter spot, 80 keV accelerating voltage, and 100-second counting times.

Cortex. The most marked ultrastructural changes were observed in proximal tubule lining cells. These cells contained swollen mitochondria with distorted cristae, electron-dense lysosomes, and thickened basal lamina with interstitial fibrosis (Fig. 4). No intranuclear inclusion bodies could be found in the samples examined.

Medulla. Interstitial fibrosis was the most marked morphological change observed.

Tumor. The tumor cells were characterized by the absence of microvilli, numerous vacuoles which contained flocculent material of myelin figures, and occasional dense lysosomes (Fig. 5). Numerous leucocytes were also present.

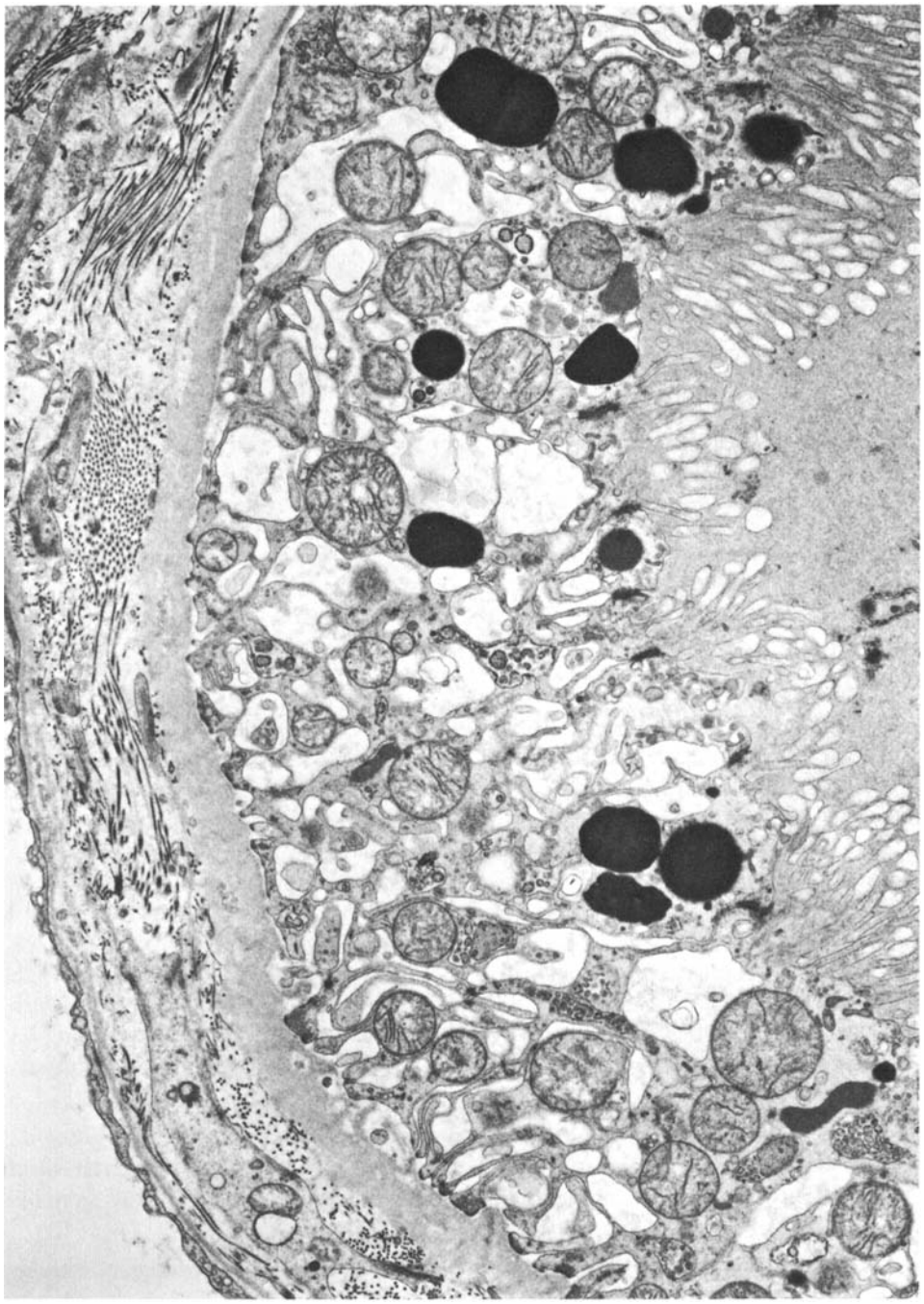

Fig. 4. Electron micrograph of a renal proximal tubule cell from the cortex showing swollen mitochondria, dense lysosomes, and thickened basal lamina (magnification, 10,206 ×).

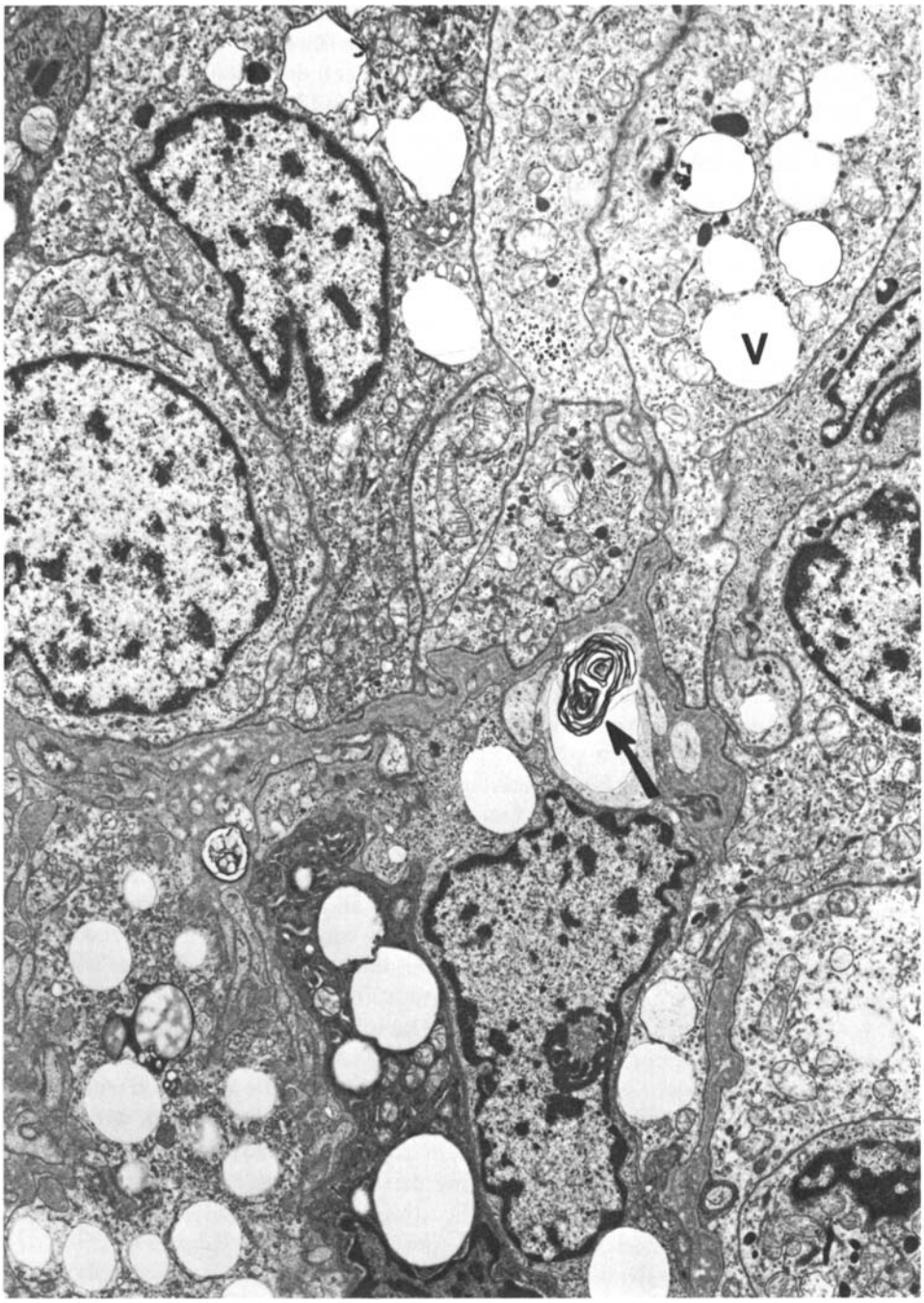

Fig. 5. Electron micrograph of tumor cells showing numerous vacuoles (v) and myelin figure (arrow) (magnification, 8,709 ×).

X-RAY MICROANALYSIS

Results of x-ray microanalysis of microanalytical studies performed on sections of cortex and medulla were negative for lead in the dense proximal tubule cell lysosomes. Analysis of a lysosome within a tumor cell did disclose the presence of iron, but not lead, at concentrations above those found in the adjacent cytoplasm.

TISSUE LEAD ANALYSIS

Samples of the tumor, renal cortex, and medulla were collected from the resected kidney and shipped in lead-free containers to the laboratory* for analysis. The tissue was digested, and lead content was determined using anodic stripping voltametry. The tumor itself contained 2.47 μg of lead/gm (normal adult range: 0.27–1.27). The renal cortex contained 1.07 μg/gm, and the renal medulla contained 0.78 μg/gm.

DISCUSSION

This case report adds to existing evidence [Kang et al, 1980; Choie et al, 1980] which suggests that inorganic lead may be carcinogenic in humans. The histologic similarity of this patient's tumor with those seen in animals experimentally exposed to lead is quite striking. Swollen mitochondria, numerous dense lysosomes, thickening of the proximal tubule cell basal lamina, and extensive vacuolization of the tumor cells were observed in both instances. Furthermore, the presence of increased concentrations of lead in the tumor itself is consistent with animal reports that show elevated lead concentrations in lead-induced renal neoplasms [Mao et al, 1967]. In the animal studies, however, lead concentrations were higher in surrounding non-neoplastic renal tissue than in the tumor itself. The reverse of this relationship was seen in our patient, perhaps as a result of recent penicillamine administration, which may have chelated lead in renal tissue more effectively than in the relatively avascular tumor. Our inability to demonstrate lead in the x-ray microanalysis may well be attributable to this effect as well.

In addition to renal cancer, this patient also demonstrated several manifestations of lead nephropathy. He had hypertension and an elevated serum uric acid; studies showed impaired tubular and glomerular function with a reduced urinary concentrating ability and a diminished glomerular filtration rate, both of which are frequently seen in reports of lead nephropathy [Baker et al, 1979; Weden et al, 1975; Cramer et al, 1974; Lilis et al, 1968]. The interstitial fibrosis seen in the renal medulla is also a frequent finding in lead nephropathy [Goyer, 1971]. A paucity of intranuclear inclusion bodies is to be expected in view of the advanced nature of his disease and also probably as a result of penicillamine administration, which would be expected to mobilize these lead-protein complexes [Goyer et al, 1975].

The inappropriate use of a chelating drug in this case was particularly disturbing. It is clearly stated in the scientific literature, [Lilis et al, 1976] as well as in the recently promulgated OSHA lead standard [Federal Register, 1978], that prophylactic administration of chelating drugs by plant personnel is totally unacceptable. Use by physicians should be restricted to cases where overt symptomatology deserves immediate treatment and where the patient is totally removed from lead exposure.

*Analysis performed by Environmental Sciences Associates, Bedford, Massachusetts.

The relevance of case reports such as this to the determination of the carcinogenic risk of a specific substance in the environment merits brief comment. Such reports serve primarily to point to the potential for an association between exposure and effect but do not demonstrate a casual relationship. Epidemiologic and animal studies provide considerably more insight into chemically induced cancer [International Agency For Research Cancer, 1972]. A case-control study of renal carcinoma is now being planned to evaluate occupational determinants of this type of cancer.

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