

Editorial

Cadmium and the kidney

An important toxicological feature of cadmium (Cd) is its long biological half life in man (10–30 years). In the newborn, Cd is virtually absent but by the age of 50 the body burden of cadmium may have increased up to 20–30 mg and in those with occupational exposure it may reach values as high as 200–300 mg. Furthermore, Cd concentrates in vital organs, particularly in the kidneys, where it is bound mainly to metallothionein, a low molecular weight protein that offers some protection against Cd toxicity. Excessive exposure to Cd has been linked to the occurrence of pulmonary insufficiency, renal disturbances, and osteomalacia. All these effects have been described in Cd workers whereas only the kidney and bone lesions (Itai-Itai disease) have been reported in elderly Japanese women exposed to Cd by the oral route.¹ The question of the carcinogenicity of Cd in man is still unsettled.²

In long term occupational or environmental exposure to Cd the kidney is considered the critical organ—that is, the first to be damaged. Since the first description of the nephrotoxic effects of Cd by Friberg,³ several features of cadmium induced nephropathy have been clarified. The earliest sign is an increased proteinuria that is frequently similar to the proteinuria described by Butler and Flynn⁴ in tubular disorders. The measurement of specific low molecular weight proteins in the urine is now routinely performed to assess the integrity of proximal tubular function in workers exposed to Cd. The analytical difficulties resulting from the instability of β_2 -microglobulin in acid urine may be obviated by measuring urinary retinol binding protein concentrations.^{5,6}

Since inhalation is the major route of exposure to Cd in industry, attempts have been made to assess the relation between the prevalence of renal effects and integrated exposure to airborne Cd. Our proposal that exposure to $20 \mu\text{g Cd/m}^3$ (respirable dust from soluble salts) for 40 hours a week for 20 years is the threshold effect concentration for increased urinary excretion of specific proteins^{7,8} has been corroborated by several studies.^{9–12}

With the development of neutron activation techniques allowing the “in vivo” determination of Cd in tissues, it has been possible to assess directly the critical concentration of Cd in the renal cortex.^{13–15} When the concentration of Cd in the renal cortex

reaches 215 ppm, renal dysfunction is likely to develop in 10% of male workers occupationally exposed to the metal. The occurrence of kidney damage leads to a progressive decrease of Cd concentration in the cortex. The relations between the concentration of Cd in the urine and the renal cortex and the prevalence of increased proteinuria have also allowed a biological threshold for urinary Cd to be proposed. In Cd workers a concentration below $10 \mu\text{g Cd/g creatinine}$ is rarely associated with increased proteinuria.^{16,17}

So far, the concept of the critical concentration of Cd refers to the total amount of metal stored in the kidney cortex. Nevertheless, only a small fraction is not bound to metallothionein and capable of reacting with the critical sites to induce nephrotoxicity. Animal data indicate that the renal concentration of non-metallothionein bound Cd needed to cause an increased β_2 -microglobulinuria is approximately 2 ppm (unpublished observations). This value corresponds to 1% of the critical concentration of total Cd in the kidney of adult male workers. There is now increasing evidence that the critical concentration of non-metallothionein bound Cd may be reached at even lower concentrations of total Cd in the kidney depending on the exposure conditions and exogenous or endogenous factors influencing renal cellular function—for example, the ability to synthesise metallothionein). For instance, the chronic administration of paracetamol in doses resulting in a reversible proximal tubular dysfunction renders rats more sensitive to the tubulotoxic action of Cd. Another factor is aging which may substantially decrease the critical concentration of Cd associated with the development of tubular injury in animals.^{18,19} Preliminary observations among the elderly living in Cd polluted areas indicate that the same phenomenon may occur in people.^{20–22}

Several aspects of Cd nephropathy are still obscure or remain a matter of controversy. Epidemiological studies carried out among Cd workers have shown that an increased urinary excretion of high molecular weight proteins (albumin, for example) may be detected either as an isolated finding or in association with an increased excretion of low molecular weight proteins.^{7,16} Since an increased albuminuria without a concomitant change in the excretion of low molecular weight proteins probably results from an increased

glomerular permeability,²³ these results suggest that even at an early stage of intoxication, Cd, at least in some individuals, interferes with glomerular function. Electronmicroscope and functional studies in animals tend to support this conclusion.¹⁸⁻²⁴ The molecular mechanisms by which Cd interferes with the tubular reabsorption of low molecular weight proteins and with the glomerular filtration of high molecular weight proteins probably differ. The former effect is presumably due to the non-metallothionein bound Cd released intracellularly during the breakdown of the reabsorbed hepatic Cd-thionein or during the normal turnover of the renal Cd-thionein. The mechanism by which Cd can alter glomerular function is unknown. There is some suggestion that Cd may exacerbate the processes involved in the aging of the kidneys.¹⁸⁻¹⁹ Circulating antiglomerular basement membrane antibodies have also been found in animals treated with Cd but their pathological importance is unknown since they were not associated with deposits along the glomerular basement membrane.²⁵ Measuring the reserve glomerular filtration capacity as recently suggested by Rodrigues-Iturbe *et al*²⁶ may be a useful approach by which to solve the controversial issue of the early interference of Cd with glomerular function.

The long term health importance of an increased urinary excretion of low molecular weight proteins is also the subject of much debate. The Cd induced proteinuria seems to progress slowly but once started it is usually irreversible.¹¹⁻²⁷ Because of the lack of progression to renal insufficiency, some authors consider that an isolated increased β_2 -microglobulinuria has no health significance. Since a significant excess of deaths from renal diseases has been reported among workers with more than 15 years exposure to Cd,²⁸ however, it has also been proposed that interference by Cd with the renal handling of proteins should be considered an adverse effect. Follow up studies are needed to assess the predictive value of increased urinary excretion of specific proteins in workers exposed to Cd.

The study of the impact on health of environmental pollution by Cd in certain areas in Europe has provided discordant results. Several studies carried out in Belgium have shown that people who had lived in an industrial area (Liège) polluted by Cd had accumulated more Cd in their renal cortex and liver than residents from other areas of Belgium and that this could be linked with an exacerbation of the age related decline in renal function.²¹⁻²² Studies carried out in an industrial area of Germany (Stolberg)²⁹ and in a rural area in the United Kingdom (Shipham)³⁰ where the soil is contaminated by Cd did not show renal effects that could be attributed to the environmental pollution by Cd. These discrepancies, how-

ever, may be more apparent than real since comparison of the average concentrations of Cd in urine (which reflects the accumulation of Cd in the target organ) indicates that the uptake of Cd by the Liège residents was higher than in the United Kingdom and in Germany.

An increased incidence of urinary tract stones in workers exposed to Cd has been reported in the United Kingdom⁴⁻³¹⁻³⁴ and in Sweden.³⁵ Further investigations are needed to establish the importance of this phenomenon, since there are no reports of kidney stones from other countries. In particular, it is not yet known whether hypercalciuria³⁶ can precede the occurrence of increased specific proteinuria and whether the prevention of the latter is sufficient to prevent the induction of renal stones by Cd.

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