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Cadmium and the Kidney

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The paper is a review of certain aspects of importance of cadmium and the kidney regarding the assessment of risks and understanding of mechanisms of action. The review discusses the following topics: history and etiology of cadmium-induced kidney dysfunction and related disorders; cadmium metabolism, metallothionein and kidney dysfunction; cadmium in urine as indicator of body burden, exposure and kidney dysfunction; cadmium levels in kidney and liver as indicators of kidney dysfunction; characteristics of early kidney dysfunction; the critical concentration concept; critical concentrations of cadmium in kidney cortex; and prognosis.

Introduction

Long-term exposure to cadmium via inhalation or ingestion may give rise to kidney damage, from minor tubular dysfunctions to severe impairment involving tubuli as well as glomeruli. Cadmium induces various other effects; obstructive lung disease, for example, is common after long-term inhalation of cadmium. The kidney is, however, generally believed to be the critical organ (*1*). If early signs of kidney dysfunction are prevented, other toxic effects will be avoided. The question of cadmium and cancer is still controversial, but conclusions have been reached (*2,3*) that certain forms of cadmium exposure may contribute to the development of cancer of the prostate in man. Results from recent animal studies (*4*) have shown a high and dose-related incidence of pulmonary cancer in rats exposed for 18 months to a cadmium chloride aerosol at concentrations between 12 and 50 μg Cd/m^3. That lung cancer in the future may become a critical effect for certain forms of cadmium exposure cannot be excluded.

This presentation is an overview, focusing on aspects of cadmium and the kidney relevant to the assessment of risks and an understanding of the mechanisms of action. Detailed discussions of specific areas will be presented in other papers at this symposium or are summarized in recent reviews on renal effects of cadmium by Nomiyama (*5*) and Piscator (*6*). Tsuchiya has reviewed cadmium studies in Japan (*7*). The monograph "Cadmium in the Environment" from our group in Sweden (*8*) is now extensively rewritten and updated. The manuscript for a new monograph, "Cadmium and Health," will be submitted for publication early 1984 (*9*). Furthermore, WHO has issued an interim report of a criteria document for cadmium (*10,11*) and within the International Programme for Chemical Safety a new criteria document on cadmium is in preparation.

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History and Etiology of Cadmium-Induced Kidney Dysfunction and Related Disorders

At the IXth International Congress on Industrial Medicine in London in 1948, I presented preliminary results from studies on cadmium-exposed battery workers. The major signs were from the kidneys, a tubular and glomerular dysfunction with proteinuria, low concentration capacity, decreased inulin clearance, and from the lungs emphysema. These signs were observed only among workers with several years' employment (*12*). At that time it was not possible to conclude, with certainty, whether cadmium or nickel was the cause of the disease. Exposure to both metals had occurred, and there was a lack of relevant information in the literature. The results were presented in more detail in 1950. In collaboration with Ohlhagen it was shown that the largest component of the urinary proteins had a low molecular weight. Animal data also definitely incriminated cadmium as the etiological agent (*13*). It is of interest to note that there is a

report from 1897 (*14*) describing lead poisoning among employees in zinc works, where 82% of 65 men had proteinuria and 83% emphysema. Already in 1948 I pointed out that it appeared more reasonable to consider cadmium the etiological agent rather than lead. No doubt, there must have been considerable exposure to cadmium in the zinc works.

It was some time before the etiology of the disease was widely recognized. With time, however, more and more evidence appeared showing that long-term exposure to cadmium can give rise to proteinuria and kidney damage in animals as well as in humans. Reports in the fifties and sixties by British investigators, such as Adams, Bonnell, Kazantzis, Potts, and Smith (*8*) were of particular importance. They showed that the cadmium syndrome had occurred in workers in other occupations besides those in battery production. A high prevalence of kidney stones has been reported in Swedish workers (*13,15,16*) as well as those from Britain (*17–19*). There are no reports on kidney stones from Belgium or Japan. Other disorders in mineral metabolism have also been observed. Kazantzis et al. (*20*), for example, reported an increased urinary excretion of calcium in workers with kidney dysfunction. One of the workers later developed osteomalacia (*21*).

Concern about long-term exposure to cadmium became more acute after recognition of the Itai-Itai disease among part of the general population of Japan. The Itai-Itai disease, a multifactorial disease but where cadmium is a necessary agent, is a combination of severe kidney damage and osteomalacia. It has occurred among inhabitants in certain areas of Toyama prefecture, where rice had become heavily contaminated due to irrigation of the soil with water contaminated with cadmium from industrial sources (*7,8,10,11*).

A number of cases with osteomalacia following industrial exposure has also been reported. The first report was by Nicaud et al. (*22*), followed by other reports from France (*23,24*) and Britain (*21,25*).

There are other areas in Japan which have been contaminated with cadmium to a lesser extent. A few cases of a similar bone disease have been reported recently from these areas (*26,27*). The disorder included clinical signs, biochemical findings and cadmium levels almost identical to those found in the recognized cases of Itai-Itai disease. In two of the cases autopsies were performed, and liver cadmium levels were very high (75 and 153 mg Cd/kg) whereas renal cortex cadmium levels were low (53 and 24 mg Cd/kg). These cases have not been acknowledged as Itai-Itai disease by the authorities. It seems almost as if a necessary prerequisite for the acknowledgment of a new case of Itai-Itai disease is that it occurs in an area where Itai-Itai disease previously occurred. However, this will make it impossible to accept cases outside the Toyama prefecture.

The occurrence of Itai-Itai disease in certain areas of Japan constitutes only the top of an iceberg. An increased prevalence of proteinuria, in some areas over 50%, has been observed among the general population in several areas where exposure to cadmium through consumption of rice is high (*7,8*).

Cadmium Metabolism, Metallothionein and Kidney Dysfunction

Cadmium is absorbed both after inhalation and ingestion. Absorption after inhalation depends on particle size and solubility and varies between 20 and 50% of the amount inhaled (*8*). The average absorption after ingestion is approximately 5% but increases considerably in the presence of calcium or iron deficiency and may reach values of up to at least 20% (*28,29*).

After ingestion, cadmium is transported to the liver where it stimulates the synthesis of metallothionein. It was suggested by Piscator as early as 1964 (*30*) that cadmium is bound to metallothionein and transported via blood to the kidneys. Cadmium metallothionein administered parenterally to animals is transported directly to the kidneys and has a different toxicity than that after administration of unbound cadmium (*31–34*). Also, oral feeding of mice with cadmium metallothionein and cadmium chloride, respectively, resulted in a considerably higher cadmium concentration in the kidneys than in the liver, despite similar absorption levels (*35,36*). Recent data (*37*) indicate that humans exposed to very high concentrations of cadmium bound to metallothionein, as is the case for certain oyster eaters in New Zealand, will not acquire as high blood cadmium levels as could be expected from the high daily intake. On the other hand, there are indications that the levels of cadmium in the blood of smokers, who as a result of smoking are exposed to a finely dispersed cadmium aerosol, may be disproportionately high in relation to kidney levels (*38–40*). When assessing available data it seems clear that the chemical form and exposure route of cadmium is of importance not only for absorption, but also for distribution in

the body. This also involves important implications for the interpretation of blood cadmium levels in risk estimations.

Following long-term low-level exposure, approximately one-third of the cadmium in the body will be found in the kidneys, while at higher exposure proportionately more will be in the liver (*8*). The accumulation in the kidneys is explained by the flow of cadmium via blood through the kidney where cadmium bound to metallothionein is filtered with the primary urine and reabsorbed into the tubular cells as are other low molecular weight proteins (*31,41*). The metallothionein cadmium molecule is probably taken up into the tubular cells by pinocytosis (*42–44*). The reabsorption of cadmium metallothionein is almost complete at low levels of cadmium in plasma, whereas the reabsorption may be less effective at high levels of metallothionein in plasma (*45,46*).

A continuous catabolism of the cadmium metallothionein takes place after reabsorption in the tubuli and cadmium is split from the metallothionein and bound to newly formed metallothionein in the tubular cells. It is supposed (*8,47,48*) that kidney damage is prevented until a stage is reached at which the kidneys can no longer produce enough metallothionein. At this stage the non-metallothionein-bound cadmium ions will become very toxic.

Cadmium in Urine as Indicator of Body Burden, Exposure and Kidney Dysfunction

Some of the cadmium filtered through the glomeruli and some of the stored cadmium in the kidneys is excreted via the urine. With time the urinary cadmium will be primarily related to cell cadmium concentration and thus an indicator of kidney burden. Nordberg (*49*) found in a chronic injection exposure experiment on mice that before tubular proteinuria appeared cadmium excretion in urine on a group basis was correlated to body burden, while a large proportion of the gastrointestinal excretion is directly related to the daily dose. The increase of cadmium excretion in urine with age is obvious in human studies also (*50–53*).

Figure 1, from Elinder et al. (*52*), compares the variations with age of urinary cadmium, cadmium in the kidneys, and daily intake among nonsmokers. There is a close correlation between total cadmium (mg) in kidneys and cadmium in urine (μg/24 hr) but no correlation with daily fecal cadmium amount as an indication of daily

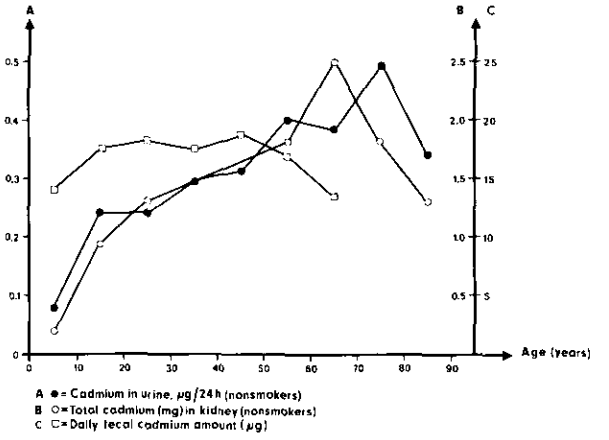

FIGURE 1. Comparison between the variations with age of (●) urinary cadmium, (○) total amount of cadmium in the kidney and daily fecal cadmium (*52*).

intake. If the data are recalculated to μg Cd/g kidney cortex and mg Cd/g creatinine in urine (which were analyzed in the study) and if the correlation between cadmium in urine and kidney is assumed to hold true up to 200 μg Cd/g kidney cortex, this concentration will correspond to roughly 10 μg Cd/g creatinine.

A number of metabolic models have been proposed for cadmium beginning with those of Tsuchiya and Sugita (*54*) and Kjellström (*55*), both of whom used a one-compartment model to more sophisticated models by Kjellström and Nordberg (*56*) and Travis and Haddock (*57*). The biological half-time for cadmium is very long—10–30 years—decreasing with increasing age. A half-time of 26 years has been estimated based on a 2-yr observation period of a human subject given a single dose of radioactive cadmium (*58*). The models developed so far do not take into consideration situations where exposure is not to long-term low levels, but instead to heavy exposure which occurs in certain industries. Under heavy exposure conditions, the excretion of cadmium in urine may be higher and does not follow the general model, as reported by Piscator (*59*) and Lauwerys et al. (*60*). Furthermore, excretion of cadmium in urine increases dramatically when kidney damage occurs. This was shown in rabbits as early as 1952 (*61*) and has since been confirmed in many species, including man (*8,9*). Thus, if the excretion of cadmium in urine is higher than would correspond to an estimated kidney burden, it should always be suspected that the high urinary excretion is due to kidney dysfunction.

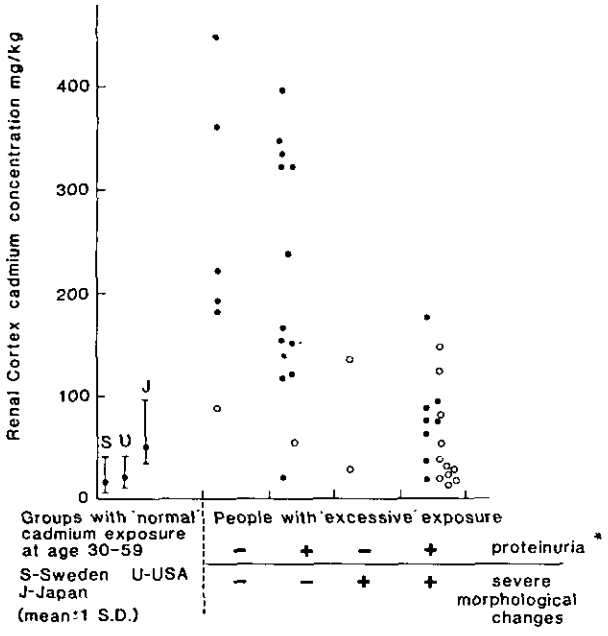

FIGURE 2. Renal cortex cadmium concentrations as a function of renal effects observed (*62*): (●) industrial exposure; (○) general environmental exposure. *For cases with general environmental exposure, a minus in most cases indicates that data on proteinuria were not available.

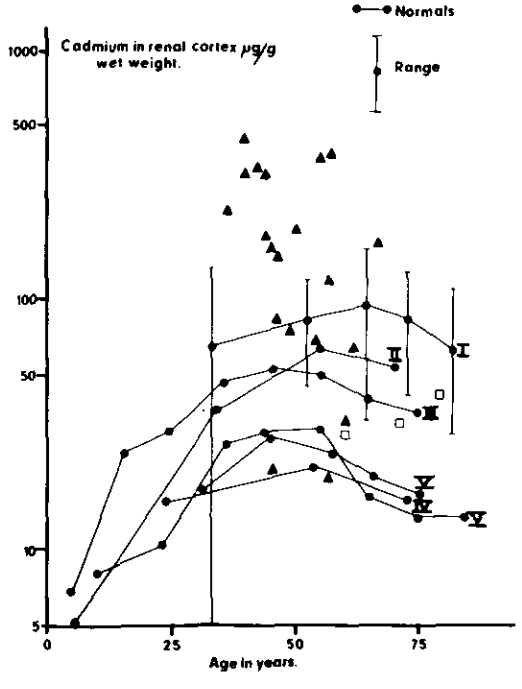

FIGURE 3. Cadmium concentrations in renal cortex from (●) normal human beings in different age groups (mean values), (▲) exposed workers (single values) and (□) Itai-Itai patients (single values). Logarithmic scale (*8*). (I) Kanazawa, Japan; (II) Kobe, Japan; (III) U.S.A.; (IV) U.K.; (V) Sweden (2 areas).

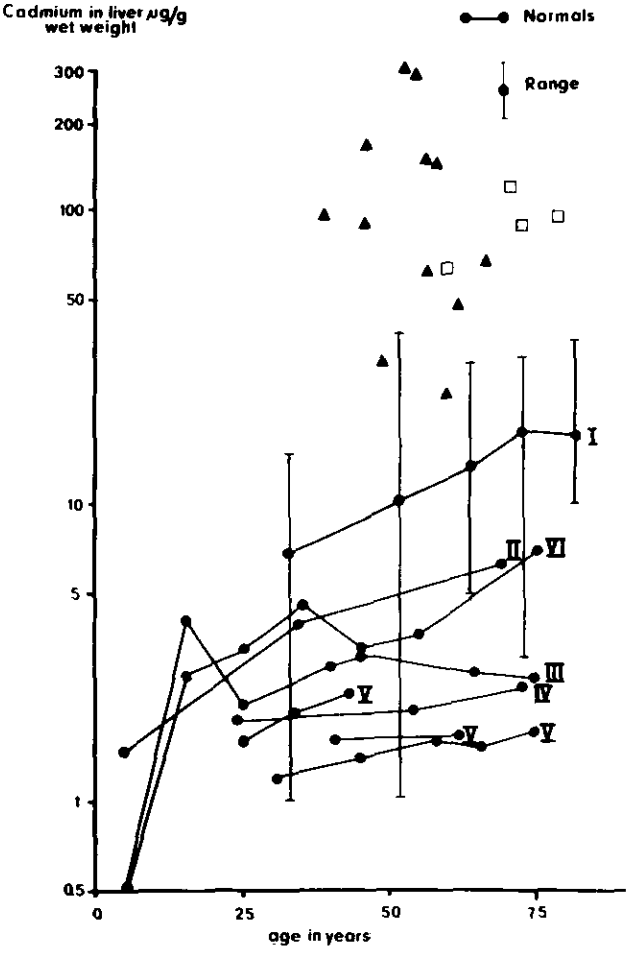

FIGURE 4. Cadmium concentrations in liver from (●) normal human beings in different age groups (mean values), (▲) exposed workers (single values) and (□) Itai-Itai patients (single values). Logarithmic scale (*8*). (I) Kanazawa, Japan; (II) Kobe, Japan; (III) U.S.A.; (IV) U.K.; (V) Sweden (3 areas); (VI) Tokyo, Japan.

Cadmium Levels in Kidney and Liver as Indicators of Kidney Dysfunction

After some time the increased cadmium excretion due to kidney damage gives rise to a typical distribution pattern of cadmium in the body. In advanced cases of cadmium intoxication one will find high liver values in combination with low kidney values. The kidney values, in fact, may well be comparable with values found in persons in the general population without known excessive exposure to cadmium. In Figure 2, Kjellström (*62*) has compiled renal cortex concentrations as a function of renal effects in 42 cases, industrially exposed and subjects from the gen-

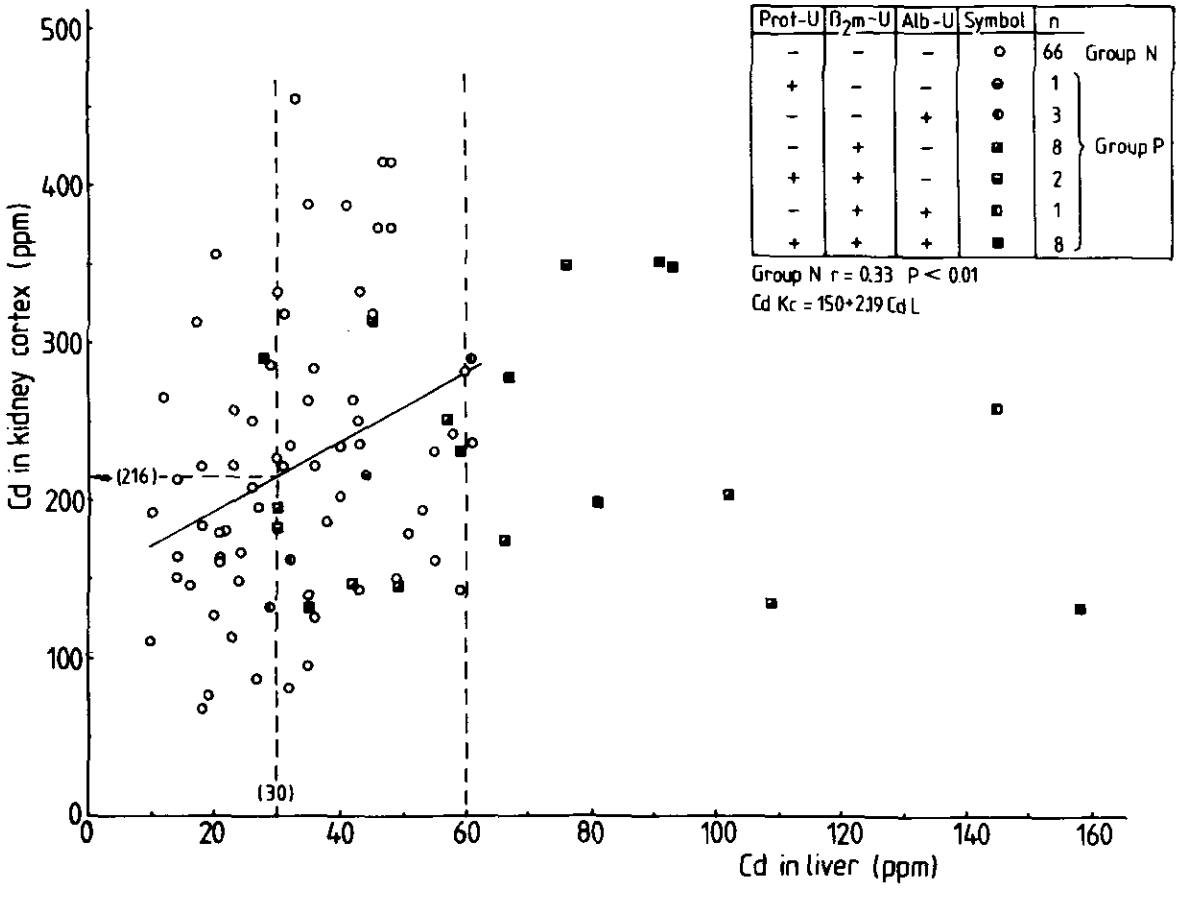

FIGURE 5. Cadmium concentrations in liver and kidney cortex of cadmium workers with and (o) without proteinuria (*67,69*).

eral population. Generally speaking, subjects with both proteinuria and severe morphological changes had on an average considerably lower kidney cortex concentrations than did other subjects. For a number of cases kidney as well as liver concentrations are available; Figures 3 and 4, from Friberg et al. (*8*), show the typical combination of low kidney levels and high liver levels.

Recent studies using *in vivo* neutron activation analysis (*63–65*) have increased the possibilities to study relationships between renal cadmium levels and kidney dysfunction as well as between renal cadmium and liver cadmium levels (*66–69*). Figure 5 shows that in most cases with high liver concentrations the kidney cortex level is disproportionately low. In addition, many of these workers had increased urinary β_2-microglobulin excretion.

In advanced cases, kidney damage involves both the tubular and glomerular function. This has been observed following both occupational exposure and exposure from the general environment in Japan (*8,13*).

Characteristics of Early Kidney Dysfunction

In the 1940s and 1950s, no elaborate methods were available to characterize the proteinuria in detail. The proteinuria in the Swedish battery workers, however, was found to differ from common proteinuria in that it displayed different precipitation reactions. Furthermore, it was shown that the main component of the urinary proteins had a considerably lower molecular weight than albumin (*13*). Subsequent studies by Piscator (*70*) and Kazantzis et al. (*20*) showed that an early sign of kidney damage in cadmium intoxication is a tubular dysfunction similar to the one described by Butler and Flynn (*71*). Most researchers in the field now agree that cadmium damage is typically located in the proximal tubuli resulting in decreased reabsorption of proteins. However, there is still not complete agreement. In a number of publications from the Belgian group (*72–75*), high urinary excretion, not only of low molecular weight proteins, but also of larger pro-

teins such as albumin were interpreted as a sign of a primary glomerular damage caused by cadmium. The question of glomerular or tubular etiology of the early cadmium proteinuria will be discussed in detail in other presentations at this meeting. The fact that albumin occurs as part of the proteinuria is not, as such, proof of primary glomerular damage. In normal serum, albumin occurs to a much greater extent than low molecular weight proteins. Despite the fact that only a small proportion of albumin is filtered through the glomeruli (*76*), the absolute amount filtered is still higher than the amount of, e.g., β_2-microglobulin. Due to an efficient reabsorption in the tubuli of all proteins, only a small fraction of the proteins will be excreted in the normal urine. The albumin excretion in urine is, however, still considerably greater than the excretion of low molecular weight protein. Mogensen and Sølling (*77*) have shown in studies on human volunteers that intravenous administration of lysine, which reversibly inhibits the tubular reabsorption, gives rise to a dramatic increase in several proteins in the urine. Albumin increased about 40 times, while β_2-microglobulin increased about 1500 times. Thus, it is to be expected that a tubular dysfunction due to cadmium will give rise to an increase in the excretion of both albumin and low molecular weight proteins. The absolute increase will be highest for albumin, but the relative increase will be highest for low molecular weight proteins (*6,62*). Nowadays quantitative analysis of certain low molecular weight proteins is possible. Most studies have concentrated on the excretion of β_2-microglobulin (*78,79*). Bernard and coworkers have paid particular attention to the determination of retinol-binding proteins and have presented methods for routine analyses of these proteins (*80*). The determination of retinol-binding proteins has certain advantages over β_2-microglobulin analysis, as there is an absence of interference from the pH of the urine.

The Critical Concentration Concept

An issue of particular importance is the dose level at which cadmium gives rise to the first adverse effects in humans. As the kidney is the critical organ, it is of particular interest to estimate the critical concentration in this organ. This concentration is established on an individual basis and varies between individuals. The dose–response relationship which expresses the response of the particular effect as a function of metal concentration in the critical organ displays the frequency distribution of individual critical concentrations.

The concept of critical concentration has been used in risk estimations to establish "acceptable" levels of a metal in the critical organ. Relationships between concentrations in the critical organ, indicator media, such as urine and blood, as well as acceptable concentrations in air and food, may be established by using a metabolic model.

In recent years there has been some confusion over the concept "critical concentration." As a rule, a single number for the critical concentration has been used, thus, omitting consideration of differences in metabolism and sensitivity. In the World Health Organization criteria documents, reference is made to "earliest effect level" for mercury (*81*), "no detected effect level" for lead (*82*), and "critical concentration" for cadmium (*11*). The Commission of the European Communities has used the term "no effect level" in their cadmium document (*83*). As a rule these terms are not well defined and it is not known to what extent they refer to individuals or groups. For cadmium specifically, a WHO Task Group for the preparation of the Environmental Health Criteria for Cadmium (*10,11*) has concluded that the critical concentration is between 100 and 300 μg/g, but that the most likely estimate is about 200 μ/g wet weight. In our 1974 review (*8*) we also considered it justified to start out from a value of 200 μg/g in renal cortex. We pointed out, however, that this did not imply that 200 μg/g would give rise to renal tubular dysfunction in all exposed persons. As always in biological experience, at a certain low concentration only a fraction of an exposed population will show signs of effects. This fraction was, however, not defined and this omission has probably led to misunderstanding. Taking this as a background, "a population critical concentration" (PCC) has been proposed (*84*). A PCC-50 would be the concentration in the critical organ at which 50% of the population exhibits the critical effect; i.e., they have exceeded their individual critical concentrations. In risk evaluations one will have to decide the maximum acceptable response rate based on a risk estimation. If 5% is the maximum, then the PCC-5 has to be established, etc.

Critical Concentrations of Cadmium in Kidney Cortex

The type of data available for estimation of critical concentrations stems partly from animal experiments and partly from experience with humans. The latter data are based on autopsy stud-

ies as well as on *in vivo* measurements of cadmium in human kidney and liver in combination with studies on different effect parameters, such as proteinuria, which have been carried out in recent years.

As discussed above, autopsy and biopsy data have revealed much lower cadmium levels in kidneys among people with severe renal damage (Fig. 2). This evidence was taken as a basis for the evaluation within the WHO Task Group.

Techniques for *in vivo* measurements of cadmium in human kidney and liver are now available (*63–65*). There is still much to be desired from the point of view of quality control of the data generated from such studies. For example, there have been no studies in which concentrations of cadmium have been monitored (e.g., in cadavers) using both neutron activation *in vivo* and conventional analytical techniques. Nevertheless, there is good reason to believe that the data reported in two studies by Roels et al. (*67–69*) and Ellis et al. (*66*) are accurate enough to permit important conclusions to be drawn. Based on cadmium analyses in liver and kidney and data on renal tubular damage, these authors reported on critical concentrations in the kidney. In the report by Ellis et al., the critical concentration based on measurements in whole kidney was estimated to be 319 ± 93 mg Cd/kg kidney cortex. Roels et al. (*69*), correcting their original data (*67*) for an error in the measurement, calculated the mean renal cortex cadmium concentration to be 332 mg Cd/kg. They also reported that a value corresponding to 216 mg Cd/kg or less would show an effect in 10% of the workers. The data of Ellis et al. (*66*) are not presented in a way which makes possible an evaluation of the response rate at different concentrations. The mean value, however, should correspond to a PCC-50. There was also considerable variance in the individual values and according to Ellis (personal communication to Kjellström) the 95% tolerance interval is in the range ±90 mg from the mean.

A recent paper by Kjellström et al. (*85*) on conceptual problems in establishing the critical concentration of cadmium in human kidney cortex reports that there is a possible error in the factor 1.5, commonly used in calculating concentrations in the kidney cortex from levels in the whole kidney. This factor was based on an equal mass of cortex and medulla and concentrations in cortex twice those in medulla. The assumption that, on an average, concentrations of cadmium in cortex are twice those in medulla is still reasonable, although individual variations may be considerable (*86*). There seems to be no support for an equal mass for cortex and medulla, however, and even if there were, the factor would become 1.3 instead of 1.5. A factor of 1.5 has been repeatedly used by several authors, since it was first introduced by Kjellström (*55*) and Friberg et al. (*87*). In a report of the Task Group on Reference Man by ICRP (*88*), the volume of the cortex in one human kidney is given as 70% of the total. In two dogs, corresponding values were 70 and 75%, respectively. If the mass of the cortex is, say 75% of the total mass, this would correspond to a factor of 1.15 when recalculating whole kidney values to cortex values. In order to obtain a factor of 1.5 one would have to assume that the cortex is only about 30% of the total kidney. Preliminary studies (Svartengren et al., unpublished data) carried out at our Institute on seven subjects have given results which support the assumption that the factor of 1.5 should be reduced considerably, possibly to 1.15 on an average. Extended studies are under way. There appears to be considerable individual variation. It certainly seems important to look into this question in more detail both by measuring the mass of the different kidney compartments and by cadmium analysis of whole kidney as well as the different kidney compartments. The use of a factor 1.15 instead of 1.5 in the studies by Roels et al. (*67–69*) and Ellis et al. (*66*) would reduce the PCC-50 to approximately 240 μg Cd/g wet weight and the PCC-10 to approximately 160 μg Cd/g.

Individual critical concentrations have not been calculated in animal studies, and values are often based on small groups of animals. Reports of effects occurring at certain concentrations should usually be interpreted as concentrations at which at least 50% of the animals were affected. When only a small number of animals are tested, the confidence intervals will be very great. Small groups can only be used to measure very high response rates.

A large number of animal studies have been carried out which have resulted in data on both cadmium concentrations in renal cortex and occurrence of tubular damage. These studies are summarized in our new cadmium monograph (*9*). It can be seen that studies have been carried out on several species. With few exceptions, effects have been observed at average renal cortex concentrations of 200–300 mg Cd/kg wet weight, but some effects have also been reported at considerably lower concentrations (*89,90*). Studies on rhesus monkeys by Nomiyama et al. (*91*), on the other hand, are reported to show effects first at higher concentrations. Although the numbers are small and some data due to methodological prob-

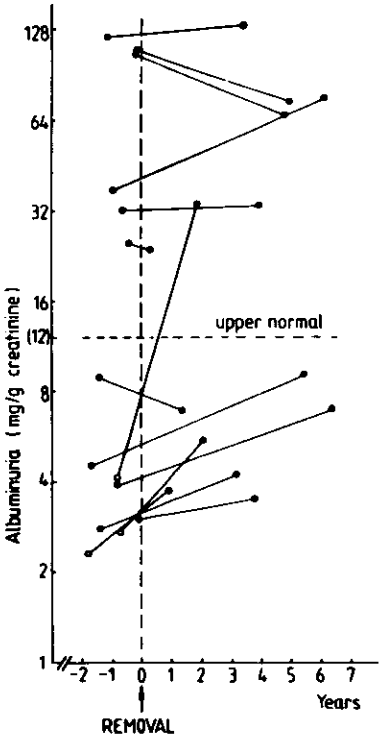

FIGURE 6. Albuminuria before and after removal from cadmium exposure: (○) none of the biological parameters of renal function abnormal; (●) at least one of the renal biological parameters abnormal (*98*).

lems are difficult to interpret, some of the exposed monkeys had extremely high concentrations, i.e., 800–1000 mg Cd/kg, in renal cortex. Similar levels have not been reported in other species. It is possible that the rhesus monkey is not a suitable animal model for studying cadmium nephrotoxic effects. Another monkey, the marmoset monkey, has been shown to differ from all other species studied in relation to arsenic metabolism (*92,93*). Such species on the other hand are of interest as they can be of value in elucidating mechanisms of toxicity.

Prognosis

It is well established that long-term exposure to high concentrations of cadmium may lead not only to slight kidney dysfunction but also to renal disease characterized by severe tubular as well as glomerular disorders. This obviously implies a risk for overt disease, invalidity and even death. A higher than expected mortality rate, including an increased mortality in renal disease, has been observed in Swedish workers exposed to high concentrations of cadmium (*8,94*). In a recent study which examined a large number of British cadmium workers (*95*), only a nonsignificant increase in death due to nephritis or nephrosis was found in a subgroup subject to high exposure. There are no data from studies in which less severe consequences have been examined, e.g., the need for sick leave or hospitalization.

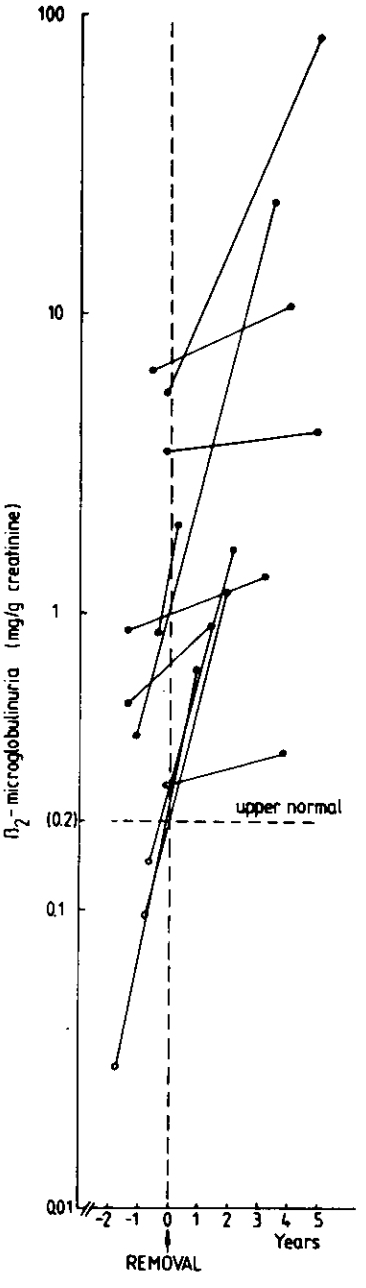

FIGURE 7. β_2-microglobulinuria before and after removal from cadmium exposure: (○) none of the biological parameters of renal function abnormal; (●) at least one of the renal biological parameters abnormal (*98*).

Although the critical concentration in an organ is considered reached even if the changes are reversible (*1*), to what extent the proteinuria may be reversible is a question of importance. Swedish studies (*96,97*) indicate that the proteinuria was persistent for several years after cessation of exposure. In a recent study of Belgian workers by Roels et al. (*98*), neither total proteinuria nor β_2-microglobulin decreased over a 4-yr period after cessation of exposure (Figs. 6 and 7). In fact, three of eleven workers with normal levels of β_2-microglobulin in urine before removal from work developed abnormal levels later. Against these studies there is only one Japanese report (*99*) in which five workers who had shown proteinuria during cadmium exposure 10 yr after cessation showed negative proteinuria on qualitative tests. However, two of the workers still showed a high urinary β_2-microglobulin level. In summary, it seems obvious that cadmium-induced tubular proteinuria is irreversible in most workers, at least for several years. This also agrees with data on the metabolism of cadmium, showing a build-up of high cadmium levels in the kidneys long after cessation of exposure.

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