URINARY METALLOTHIONEIN AS A BIOLOGICAL INDICATOR
OF OCCUPATIONAL CADMIUM EXPOSURE

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Renal tubular dysfunction is a common manifestation observed upon excessive exposure to cadmium (Cd) in experimental animals and man. Lack of correlation between blood or urinary Cd concentration and total body burden makes it difficult to determine the extent of exposure (1); therefore it is not possible at present to predict the onset of renal dysfunction. As described in an earlier presentation (2) it is now possible to determine kidney as well as liver Cd by means of in vivo neutron activation analysis. There is, however, still a need to identify a specific biological indicator of occupational exposure to cadmium.

In two recent studies using a newly developed radioimmunoassay the detection of a low molecular weight Cd-binding protein, metallothionein, in urine of Cd-exposed workers (3) and "itai-itai" disease patients and other Japanese women environmentally exposed to Cd (4) has been demonstrated. In the study to be described here, radioimmunoassay has been applied to measure metallothionein in urine of Cd-exposed workers. The dose-effect relationship between Cd in liver and kidney and metallothionein in urine is also examined.

The urine samples used in the present study were collected from the subjects in August 1979 at the time of their tissue Cd analyses (2,5). The samples from 7 out of 10 control subjects and 23 out of 51 active office and smelter workers at a Cd production plant were analyzed for metallothionein. For comparison of their tissue Cd and metallothionein values, the subjects were divided into four groups, as shown in Table 1.

Figures 1 and 2 show the tissue Cd values of the subjects determined by in vivo neutron activation analysis. The tissue Cd levels of Groups I, II,
and III were low: the geometric means were 3.2, 8.6, and 2.9 μg/g liver and 3.1, 4.6, and 6.0 mg in the left kidney, respectively. In contrast, the mean liver Cd concentration (39.7 μg/g) of the smelter workers with a long employment history at the plant (Group IV) was significantly higher than those of the other three groups. The mean kidney Cd content of Group IV (23.6 mg in the left kidney) was also significantly higher than those of the other groups.

The group labeled "Office Workers" included a few supervisory personnel who had either previously worked in the smelter or routinely visited the smelter area. Further, office areas were within the perimeter of the plant, and thus all office workers were likely to be exposed to higher concentrations of Cd in the ambient air than were control subjects. This may explain the fact that the mean liver Cd concentration of this group was significantly higher than that of the control group.

The urinary metallothionein values of the subjects are shown in Figure 3. Urine from only one subject from each of Groups I and II and two subjects from Group III contained detectable amounts of metallothionein (> 125 μg/l). However, 10 out of 12 smelter workers with long work histories (Group IV) had detectable amounts of metallothionein in their urine. For a conservative statistical comparison between the groups, those samples without detectable amounts of metallothionein were assumed to contain 125 μg/l. The geometric mean values of Groups I-IV expressed as μg of metallothionein per g creatinine were 148, 130, 100, and 331, respectively. The mean value of Group IV was significantly higher than the means of the other three groups. Interestingly, although β2-microglobulin was detected in the urine of all subjects, no significant differences between any of the groups were observed (Figure 4).
When kidney Cd values and corresponding liver Cd values of the 12 smelter workers excreting detectable amounts of metallothionein were plotted, a biphasic relationship, as described earlier (2,5), was observed. During the first phase the kidney Cd level increased with the accumulation of Cd in the liver until the Cd levels reached about 30 µg/g of liver and about 35 mg in the left kidney. Seven of the 12 subjects showed this relationship. The data from the remaining subjects formed the second component of the curve, where the kidney Cd decreased with further increase in the liver Cd concentration.

In all 12 Cd-exposed smelter workers excreting detectable amounts of metallothionein in urine, the logarithm of urinary metallothionein concentration showed a significant correlation \((r = 0.75; p < 0.05)\) with the logarithm of the liver Cd concentration. Similarly, in the 7 subjects belonging to the first phase of Cd accumulation the logarithm of the urinary metallothionein concentration showed a significant correlation with the logarithm of the kidney Cd content \((0.82, p < 0.05)\). In contrast, urinary \(\beta_2\)-microglobulin values did not show any relationship with either the liver or the kidney Cd values.

From these results we conclude that the urinary metallothionein concentration is related to the liver Cd concentration in occupational Cd exposure. It is also related to the kidney Cd content—but only before the onset of renal dysfunction. Further epidemiological studies are needed to establish a dose-response relationship, which may be useful in minimizing the hazard of Cd-induced renal dysfunction.

Acknowledgment. This work was supported at Rochester by NIEHS Grants ES 01247 and ES 01248, and at Brookhaven by DOE Contract No. DE-AC02-76CH00016 and by ILZRO.
References


2. Ellis, K. J. Critical concentrations of cadmium in the kidney. In these Proceedings.


<table>
<thead>
<tr>
<th>Group</th>
<th>Subjects</th>
<th>Number of subjects</th>
<th>Age (mean ± S.E.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Controls (Water Co. employees)</td>
<td>7</td>
<td>40.3 ± 3.2</td>
</tr>
<tr>
<td>II</td>
<td>Office Workers (Cd smelter)</td>
<td>7</td>
<td>44.0 ± 4.5</td>
</tr>
<tr>
<td>III</td>
<td>Smelter Workers (employed for &lt;1 year)</td>
<td>4</td>
<td>26.3 ± 1.9*</td>
</tr>
<tr>
<td>IV</td>
<td>Smelter Workers (employed for 8-29 years)</td>
<td>12</td>
<td>50.3 ± 2.5</td>
</tr>
</tbody>
</table>

* Significantly different from other groups (p < 0.05).
LEGENDS FOR FIGURES

Figure 1. Liver cadmium concentration of the subjects. See Table 1 for subject classification. Each point represents a different subject.
* Significantly different (p < 0.05) from other groups. ** Significantly different (p < 0.05) from Group I.

Figure 2. Kidney cadmium content of the subjects. See legend to Figure 1 for details.

Figure 3. Metallothionein concentration in urine.
* Values above the detection limit.
° Values below the detection limit.
The detection limit was 125 µg/l. For statistical comparison the samples below the detection limit were assumed to contain at least this amount of metallothionein. All values were corrected for creatinine excretion.

Figure 4. β2-Microglobulin concentration in urine.
Fig. 1

Cadmium in Liver (µg/g wet weight)

Fig. 2

Cadmium in Kidney (mg)