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# Absence of Tubular Proteinuria Following Environmental Exposure to Chromium

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**ABSTRACT. Certain chromium compounds are known to be nephrotoxic, but renal damage from long-term environmental or occupational exposure to chromium has not been documented. To detect possible preclinical renal damage, we tested the urine of 55 lifelong residents of an area contaminated with chromium landfill. The levels of four proteins were determined in urine samples: (1) human intestinal alkaline phosphatase, (2) tissue nonspecific alkaline phosphatase, (3) *N*-acetyl-ß-D-glucosaminidase, and (4) microalbumin. No elevated levels of proteins were found, and there were no significant correlations between urine protein and urine chromium concentrations. We concluded that long-term environmental exposure to chromium dust did not lead to tubular proteinuria.**

DURING the past 90 y, chromium slag has been used for landfill in Hudson County, New Jersey. A total of 160 contaminated sites, which are located in Jersey City, Kearney, and Bayonne, contain approximately 2 million tons of chromium slag. Many of these sites are within or adjacent to residential and recreational areas.[1] The dust is mobile in air during dry periods, and during wet periods high concentrations of chromium leach into rain water and local streams.

Since the beginning of this century, it has been recognized that chromium salts are carcinogenic.[2] Hexavalent chromium, when administered parenterally to experimental animals, induces potentially fatal acute tubular necrosis. Low-level occupational exposure to chromium reportedly induces the appearance of minute quantities of specific proteins in the urine.[3] Low-molecular-weight proteins, which are normally filtered at the renal glomerulus, appear in the urine as a result of interference by chromium, with tubular reabsorption and catabolism. In addition, specific tubular proteins and lysosomal enzymes are released into the urine from damaged tubular cells.

In 1994, the Chromium Household Dust Study in Hudson County was undertaken for the New Jersey Department of Health (NJDOH),[4] and significantly higher chromium concentrations in dust (228 µg/g) were found in Jersey City homes than in control homes outside of Hudson County (111 µg/g). A Chromium Medical Surveillance Program was initiated in 1992 by the NJDOH because it was anticipated that potential chromium-related health effects would be identified, and a basis for public health decisions about chromium in Hudson

County would be provided.[1] Fourteen residential areas and 78 workplaces were targeted for screening, and a total of 2 224 individuals participated. Approximately 10% were referred for detailed medical evaluation, including urine examination, because clinical symptoms or elevated urine chromium concentrations warranted it. Children and adults (to age 60 y) had small, but statistically significant, increases in urine chromium, compared with the baseline control group. The geometric mean, unadjusted urine chromium concentration was 0.20 µg/l in 315 baseline subjects (0.53 µg/l 90th percentile) and 0.23 µg/l for 2 213 screened subjects (0.76 µg/l 90th percentile). The findings were interpreted as being indicative of a small excess of current chromium exposure in the surveillance population, but it was impossible to assess exposure that occurred prior to the initiation of chromium remediation activities in Hudson County. No increase was found in the single specific urine-protein marker evaluated ($ß_2$-microglobulin).

The present study was designed to extend the examinations for tubular proteinuria among a convenience samples of the surveillance group referred for urine examinations by the NJDOH.

## Method

Four urinary markers of renal injury were measured: (1) human intestinal alkaline phosphatase (IAP), tissue nonspecific alkaline phosphatase (TNAP), *N*-acetyl-ß-D-glucosaminidase (NAG), and microalbumin (mAlb). Tissue nonspecific alkaline phosphatase, as well as NAG, are increased in urine after injury to any portion of the proximal tubule. Microalbuminuria is usually considered to be an indicator of glomerular injury. All four urinary markers were measured in the laboratory of Marc E. De Broe in Antwerp, Belgium. Creatinine was measured by the Jaffé reaction. Urine concentrations of proteins and chromium were expressed per g urine creatinine to normalize for the renal diluting-concentrating operation. No correction for the urinary concentrating and diluting operations was necessary when proteins were compared with chromium in the same urine specimen.

Informed consent was obtained from all study subjects. Freshly voided urine was transferred into 5-ml collection vials that contained stabilizing buffer for IAP, TNAP, and NAG, and the solution was immediately chilled to 4 °C. Urine samples were stored at this temperature for up to 3 wk, after which they were stored permanently at –80 °C. The buffer contained 1 M imidazole at a pH of 7.0, 2% Triton X-100, 20 mM benzamidine, 2 000 U/ml aprotinine, and 1% Na-azide. Urine for measurement of microalbumin was transferred to 20-ml vials and was immediately frozen and stored at –20 °C. Urine samples were mailed to Antwerp by Air Express and were packed in dry ice.

Tucker's method was used to measure NAG, Verpooten's method was used to determine TNAP and IAP, and mAlb was measured with a Behring nephelometer.[7] Chromium in urine was measured by electrothermal atomic absorption spectroscopy.[8]

## Results

Thirty men and 25 women residents of Hudson County who had no clinical evidence of renal disease were evaluated. Their mean age was 39.5 y (standard deviation [*SD*] = 19 y). More women (23 of 25) than men (17 of 30) were smokers ($p < .01$).

The mean urine chromium concentration was 0.3 ± 0.2 µg/l (0.3 ± 0.8 µg/g creatinine) for 53 subjects who had provided samples for which TNAP, IAP, NAG, and mAlb were measured. The difference between the mean urine chromium concentration in men (0.3 ± 0.2) and women (0.2 ± 0.1) was not significant statistically.

None of the specific urine protein concentrations exceeded the normal range (DeBroe, ME; personal communication). Pearson's correlation coefficients between urine protein and urine chromium concentrations in the same specimens were not significant statistically (Table 1.)

The urine concentration of NAG was significantly higher ($p < .02$) in women (2.20 ± 1.51 µg/g creatinine [$n = 24$]) than in men (1.40 ± 0.84 µg/g creatinine [$n = 29$]). Significant positive correlations were found between age and TNAP ($p < .05$) and NAG ($p < .01$), corrected for urine creatinine. Urine IAP was correlated significantly with NAG in the same urine specimens ($p < .01$), as well as when correction was made for creatinine ($p < .05$). Creatinine-corrected IAP was correlated significantly with similarly corrected NAG ($p < .05$).

## Discussion

The major finding of this study was that environmental exposure to chromium-containing dust did not result in abnormal proteinuria in lifelong residents of Hudson County, New Jersey. Subjects in this study were self-selected (i.e., voluntarily participated in a state-sponsored surveillance program targeted for residents of Hudson County who were potentially exposed to excessive chromium[1]). Urine chromium concentrations were 5–100 times lower than those encountered in occupational exposure, but levels were comparable with levels encountered in other nonoccupationally exposed groups.[9–13] Excretion of NAG was increased in women, compared with men, and both NAG and TNAP excretion correlated directly with age. Minimum tubular proteinuria did not necessarily indicate the presence of irreversible kidney disease.

These findings are consistent with the absence of $ß_2$-microglobulinuria in 158 Hudson County residents referred for clinical evaluation and from whom our study

**Table 1.—Pearson Correlation Coefficients between Urine Protein and Chromium**

| *Urine proteins* | *r* |
|---|---|
| Microalbumin | .256 |
| Human intestinal alkaline phosphate | –.088 |
| *N*-acetyl-β-D-glucosaminidase | .041 |
| Tissue nonspecific alkaline phosphatase | .003 |

group was gleaned. Twelve of the 178 residents had elevated urine $ß_2$-microglobulin levels, but in each case the examining NJDOH physicians attributed the abnormality to a medical condition that was unrelated to chromium exposure.[1]

Although urine chromium concentration is used often to assess exposure, chromium excretion reflects only recent exposure and, therefore, is not an indicator of cumulative past exposure. On the other hand, the subjects of this study had sustained lifelong exposure to chromium in Hudson County—presumably at approximately the same level as the current exposure.

Chromic acid and hexavalent salts of chromium (e.g., potassium dichromate) induce acute tubular necrosis in experimental animals.[13] In humans, acute tubular necrosis has also been attributed to chromic acid or dichromate. Renal failure is not produced by trivalent chromium. The nephrotoxicity of chromium is derived from specific toxic actions in renal tubular cells. Like other heavy metals, chromium is accumulated selectively in the cells of proximal tubules. In contrast to mercury, which is accumulated maximally in the straight portion of the proximal tubule, chromium is accumulated primarily in the first segment—the convoluted portion of the proximal tubule.

Minimal tubular proteinuria in the absence of reduced glomerular filtration results from occupational exposure to chromium.[14,15] Increased excretion of the proximal renal tubule brush-border antigen BB50, $ß_2$-microglobulin, and retinol-binding protein—but not albumin—was noted. There is little evidence, however, that chronic renal disease results from unusual occupational exposure to chromium.[12,13,17–20] An excessive incidence of kidney disease has not been reported after exposure has occurred in the chrome-plating or welding industries—industries for which the association between chromium exposure and lung cancer has been shown repeatedly. The biological significance of the appearance of tubular proteins in urine is by no means clear. Nevertheless, in conjunction with the findings of an odds ratio of 2.7 (confidence interval = 1.2–6.3) for occupational exposure to chromium in a case-control study of chronic renal failure, these observations warranted further evaluation of the association between environmental exposure to chromium and renal disease.[21] The present study indicated that tubular proteinuria was not observed in individuals who had experienced lifelong exposure to chromium-laden dust from contaminated landfills.

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