BIOLOGIC CRITERIA FOR EXPOSURES TO LEAD AND CADMIUM

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ABSTRACT

This study aims to establish a dose-response relationship in exposures to lead and cadmium. For lead, lead concentrations in blood and urine were used as indices of dose. Delta-ALA and coproporphyrin in urine were used as responses. Policemen who were exposed to 0.5-1.0 µg/m³ as well as lead workers exposed to about 30 µg/m³ during working hours were subjects for the study. It was concluded that in a work environment in which workers are exposed to about 30 µg/m³ lead, blood lead concentration increased to above normal level without increase of delta amino-levulinic acid (ALA) in urine. Increase of delta-ALA in urine was noted when the blood lead concentration level exceeded 50 µg/100 ml. For cadmium, both blood and urinary concentrations of cadmium and protein in urine were used in order to discuss the dose-response relationship. The relationship between cadmium concentration in blood and in urine was one of logarithmic regression. Among workers exposed to cadmium fume, protein in urine increased when cadmium in urine exceeded 50 µg/l and cadmium in blood exceeded 4-6 µg/100 ml.

INTRODUCTION

Environmental monitoring of a toxic substance in the air of a work place or in ambient air does not necessarily indicate the actual exposure to the substance. The concentration of such a substance in the air may fluctuate greatly depending on the time of measurement, and the rate of absorption may differ depending on the type of chemical compound. In some cases, oral and cutaneous exposures may be more important than that via the respiratory route. For such reasons, biologic monitoring, e.g. blood or urine, etc., in addition to environmental monitoring is necessary for the control of the working environment or of the environment in general, as well as for the prevention of early biologic changes due to a toxic substance.
I. LEAD
MATERIALS AND METHODS

About six hundred policemen in Kanagawa Prefecture, located south of Tokyo, who had been exposed to lead of about 0.5 to 1.0 \( \mu g/m^3 \) on the twenty-four hour average in ambient air were selected as the group with the lowest exposure to lead. For statistical analyses, one hundred pairs were randomly selected for laboratory testing. A second group was composed of 81 electric wire cable workers, including 26 white collar workers as controls from the same company. These lead cable workers had been exposed to lead levels of 12 \( \mu g/m^3 \) average, or 7 \( \mu g/m^3 \) mode value, 6 hours a day, 6 days a week, and monitored by personal samplers. A third group was composed of 43 rubber hose workers engaged in production work similar to that of the electric wire cable workers. The hose is formed inside a lead tube which is later removed. The environmental air of the work place of the rubber hose workers indicated a higher lead concentration of 33 \( \mu g/m^3 \) on the average, 7 hours a day, 6 days a week. A fourth group was composed of 60 storage battery workers who had been exposed to lead of much higher concentrations, the maximum reaching up to a few milligrams per cubic meter in the air of the working environment. However, in those work places of heavy lead exposures, the workers wore respiratory masks. Therefore, the actual exposure of these workers to lead was difficult to estimate. The laboratory tests included lead in blood and urine, quantitative determinations of coproporphyrin\(^1\) and delta-ALA in urine,\(^2\) as well as hematological determinations. Personal interviews were also conducted. Lead concentrations in urine of electric wire workers were not determined due to the existence of the possibility of contamination during transportation. The examination date for each group was different, but all the examinations were performed during the period 1970 to 1971.

RESULTS

In the study on policemen, there was no correlation among levels of blood lead, urinary lead, delta-ALA in urine or coproporphyrin in urine. As seen in Figure 1, blood lead about 7 to 33 \( \mu g/100 \) g with a mean of 17 \( \mu g/100 \) g. Delta-ALA in urine was 2.3 mg/l with a maximum of 4.7 mg/l. Regarding the result of the study on the electric wire workers, a paper was presented in the XVIIth Meeting of the International Congress on Occupational Health in Buenos Aires, 1972, entitled "Biological Responses to Low Level Lead Exposure."\(^3\) In that study it was stated that there were no differences either in blood lead concentration or delta-ALA in urine between the exposed workers and white collar control workers,
Fig. 1 ΔALA and Blood Lead (Policemen, 1971).

(Lead in Air 0.5 - 1.0 μg/m³)
(in Kanagawa Prefecture)

Fig. 2 ΔALA and Blood Lead.
(Pb in Working Environment: Arithmetic Average = 33 μg/m³)

\( r = 0.05 \)
\( (N = 43) \)
except for hemoglobin level. The blood lead concentration was 15 μg/100 g in the exposed workers, 17 μg/100 g in the controls, and 1.5 mg/l delta-ALA in both groups. In the third group of the rubber hose workers who had been exposed to lead levels of 33 gμ/m³ during working hours, again, no correlation between delta-ALA and blood lead was observed. This is shown in Figure 2, in which one person with exceptionally high delta-ALA concentration was seen. However, this person showed a low blood lead concentration of 15.5 μ/100 g, and the high delta-ALA value was probably not due to lead absorption, but most likely to an underdetermined condition of porphyrin metabolism or technical error. Nevertheless, this group showed a higher mean blood lead concentration of 32 μg/100 g with a higher mean urinary lead concentration of 38 μ/l as well, compared to those value from the other three groups. The highest blood lead in this group was 50 gμ/100 g, and one sample which showed 80 μg/100 g may have been contaminated. This result implies that if the blood lead level of a group of people who are exposed to lead does not exceed 50 μg/100 g, early biochemical changes due to lead absorption, for instance, the increase of delta-ALA excretion in urine, does not develop. In Figure 3, the association between blood lead and urinary lead is shown. Although the correlation was not very high as is usually seen in higher exposures, some association existed. Since a close association was not observed in the lower
exposures in this study, it may be stated that the absorption and accumulation of lead in rubber hose workers are significant although health effects were not seen.

The above-mentioned observations on the associations between lead concentrations in the air and blood lead levels are summarized in Figure 4. Lead concentrations in the air on the abscissa of Figure 4 were estimated from the concentrations of both the working environment and of the ambient air. It can be seen in Figure 4 that the blood lead level remained constant up to a lead concentration in the air of about 3 μg/m³.

In the storage battery worker group, some health effects, including the development of lead anemia, due to lead absorption were observed in some workers. Figure 5 shows the association between blood lead and delta-ALA in urine. Delta-ALA in urine remained almost constant until blood lead rose up to a level of about 45 μg/100 g. In other words, although there was a significant association between blood lead and delta-ALA in urine, the regression does not necessarily show a straight linear association. From the scatter diagram in Figure 5, it can be seen that the blood lead level at which delta-ALA in urine increases is located between 40 to 50 μg/100 g.
DISCUSSION FOR LEAD

In this study, the dose-response relationship of lead concentrations in the air with early biologic responses was observed. Some data concerning this subject have been presented by early investigators. Selander and Cramér showed results similar to those obtained in this study. However, in low lead exposure, such as seen in the rubber hose workers, some workers reached a blood lead concentration of 50 μg/100 g, but none of them excreted abnormally high levels of delta-ALA in urine. The reason why workers with 50 μg/100 g blood lead in low lead exposure did not show any increase of delta-ALA may be due to the fact that the probability of reaching a blood lead level of 50 μg/100 g at low exposures is much less in comparison to that in heavy lead exposures. In the latter group there were many who had blood lead concentrations higher than 50 μg/100 g, and the probability of the elevation of delta-ALA among those people is likely to be higher.

Reviewing the data obtained in this study as well as in other reports, it may be concluded that the blood lead value of 50 μg/100 g corresponds with elevated delta-ALA values.
II. CADMIUM

MATERIAL AND METHODS

Reports in the past have not demonstrated a significant association between blood cadmium and urinary cadmium concentrations. One of the purposes of this study was to find out whether or not this was valid. Furthermore, the correlation between urinary protein, one of the earliest signs of abnormally high cadmium absorption, and cadmium in urine has not been well documented.

A cadmium alloy factory where approximately 15 to 17 workers had been exposed to cadmium fumes has been under observation for health care supervised by the present authors and their associates for about ten years. After one of the authors presented a paper at a conference in Japan, the working environment of the factory has been greatly improved. Seventeen cadmium workers and 8 workers who had had a history of cadmium exposure in the past, or intermittent exposure, as well as 10 control workers, were subjected to the present study. Cadmium in urine and blood as well as protein in urine were examined. Cadmium was calibrated by atomic absorption spectrometry after wet ashing and dithizone extraction. Protein in urine was quantitatively determined by the method reported by Kuno and Kihara. The urine samples were collected over an 8-hour period, starting at 8:00 AM and ending at 4:00 PM. For blood cadmium analysis, a sample of 20 ml was drawn from each subject.

RESULTS

The correlation between the blood cadmium concentration and the urinary cadmium concentration is demonstrated in Figure 6. The figure was expressed in logarithmic scale and showed a fairly good straight linear relationship between cadmium in urine and cadmium in blood. According to this relationship, 50 µg/l cadmium in urine corresponds with roughly 4 µg/100 g cadmium in blood. Figure 7 shows the correlation between protein in urine and cadmium in urine. The relationship did not show a straight linear regression, but protein in urine did not rise until cadmium in urine reached 1.7 (logarithmic) or 50 µg/l. As 100 mg/l urinary protein is considered to be the upper level for normal people, 50 µg/l cadmium is the critical point at which urinary protein starts to increase above 100 mg/l. In Figure 8, a relationship between protein in urine and cadmium concentration in blood is indicated on a group basis. As shown in the figure, urinary protein started to increase as the cadmium concentration in blood rose above 4–6 µg/100 g, or above 50 µg/l in urine.
Fig. 6 Correlation between Blood and Urinary Cadmium Concentrations.

Fig. 7 Correlation between Cadmium and Protein in Urine.
DISCUSSION FOR CADMIUM

Up to the present time, the relationship between the cadmium concentration in urine and the urinary protein level, and that between cadmium concentration in blood and urine have been uncertain. The present paper, however, demonstrates a close association among those components on a group basis. Tsuchiya reported elsewhere that cadmium workers who had been exposed to cadmium excrete elevated cadmium in urine for many years even after the cessation of cadmium exposure, whereas blood cadmium decreases within a fairly short period of time (approximately one year) after the cessation. In this study some workers who had been removed from exposure for a period of over one year showed high cadmium concentrations in urine with low blood cadmium, as shown in Figure 6. However, this was seen even in some workers who were presently exposed to cadmium. This kind of contradiction is frequently observed in biological phenomena, particularly on an individual basis. Many samples are required in order to establish a general rule concerning associations among biologic responses to toxic substances, particularly at relatively low levels of exposure. Well designed and technically reliable epidemiologic studies as well as follow-up studies on newly exposed workers are required.
CONCLUSION

The following conclusions have been drawn, based on epidemiologic field studies on biological responses to various levels of exposure to lead and cadmium.

1. In an average lead exposure in air of 33 μg/m³ in the working environment, 7 hours/day, 6 days/week, both blood and urinary lead concentrations increased to some extent, but in such an environment, delta-ALA in urine did not rise above the normal level.

2. The critical point at which delta-ALA in urine starts to increase corresponds to a blood lead concentration of 50 μg/100 g.

3. Cadmium concentrations in blood and urine showed fairly close relationships, and 50 μg/l urinary cadmium corresponded with about 4–6 μg/100 g blood cadmium.

4. The critical level at which urinary protein increased corresponded to about 50 μg/l urinary cadmium and 4–6 μg/100 g blood cadmium.

REFERENCES

Note: Since this study was presented at the XVIIth International Congress on Occupational Health in Buenos Aires, September 17–23, 1972, reports which have appeared since that time have not been included in the references.