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IN VIVO MONITORING OF HEAVY METALS IN MAN: CADMIUM AND MERCURY

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INTRODUCTION

Direct in vivo measurements of selected heavy metals is possible by nuclear analytical techniques. In particular, cadmium and mercury are retained in the body in sufficient quantities for their detection by neutron activation analysis. Autopsy data on cadmium of adult male non-smokers living in the U. S. indicates an average body burden of 30 mg by age 50. The distribution of cadmium in the body, however, is nonuniform, approximately 50% being located in the kidneys and liver. The increased concentration of cadmium within these organs has made possible the direct in vivo measurements of this metal by prompt-gamma neutron activation analysis (PGNAA). At present, in vivo determinations of mercury have been performed on phantoms only. These in vivo techniques provide a unique method of obtaining accurate organ burden data in humans that can be related to the toxicological effects of these metals.

PROMPT-GAMMA NEUTRON ACTIVATION ANALYSIS

In vivo neutron activation analysis has become an established method in clinical studies of body composition measurements (1). The PGNAA technique was initially developed for the measurement of total body nitrogen (10). Body nitrogen is measureable because it is a major element in the body (2 kg in 70 kg male) and has a neutron capture cross-section of a few mb. The trace elements of Cd and Hg are detectable by PGNAA (9) because their neutron capture cross-sections are considerably larger than those for the bulk elements in the body. The PGNAA cross-sections for Cd and Hg in the body are approximately 2540 barns and 375 barns, respectively. Although the nuclear process in PGNAA involves thermal neutrons, higher energy neutrons are needed in order to reach the target organs within the body. For

this purpose, ^{252}Cf and $^{238}PuBe$ neutron sources have been used at Brookhaven.

In the capture process, an excited nucleus is produced which promptly returns to the ground state. A cascade of gamma-rays is emitted in this process, which are detected externally to the body. For cadmium, the most prominent gamma-ray energy is 559 keV; for mercury, the gamma-ray energy is 368 keV. As these gamma-rays are emitted promptly from the body, the subject must be irradiated and counted simultaneously.

DESCRIPTION OF MEASUREMENT FACILITY

The first mobile Brookhaven system (2) used a $^{238}Pu,Be$ neutron source placed in a shield consisting of polyethylene bricks doped with boron and lead. This facility was modified in 1980 to that shown in Fig. 1. A 100 μg ^{252}Cf source replaced the $^{238}Pu,Be$ source and a certified transportation container serves as the bulk shielding. The 15 cm diameter steel insert with a tapered opening gives a collimated beam area of approximately 126 cm^2 at the level of the bed. Additional shielding using Pb bricks and polyethylene bricks (Pb,B doped) are placed around the two Ge(Li) detectors (25% efficiency, 2.1 keV resolution). The signals from these detectors are amplified, and processed using a computer-based multi-channel analyzer. Figure 1 also provides a cross-sectional view of the position of the body for in vivo measurements of the kidney. An ultrasonic scan of the body is used to accurately locate the kidney within the body and to assist in positioning the patient properly in the neutron beam.

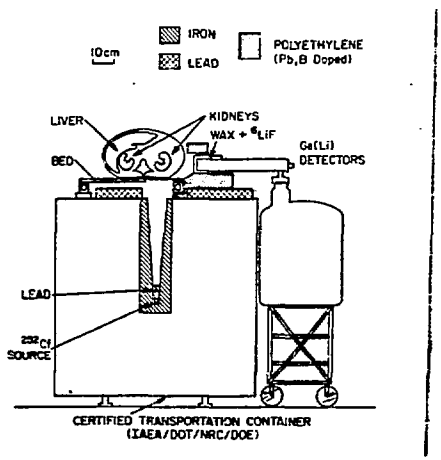

Figure 1: Cross-Sectional View of PGNAA Facility.

At present, the facility has been calibrated for the in vivo measurements of cadmium and mercury in the kidney and liver. The levels in the liver are expressed in parts per million (μg/g) because the cross-section of the neutron beam is less than the cross-sectional area of the liver. As the kidney fits within the dimensions of the beam, the total amount of the metal (in mg) in the kidney can be obtained. Further studies are currently in progress to establish calibration standards for the in vivo measurement of mercury in the brain. For the kidney and liver, the in vivo detection limits are 2.2 mg and 1.5 μg/g for cadmium, and 13 mg and 11 μg/g for mercury. These values are for a measurement time of 2000 sec with a localized skin dose of 2 mSv (200 mrem). For industrially related exposures where the signal to background ratio increases significantly, the actual dose required for the in vivo measurement may be reduced to as low as 20% of the above value.

The present detection limits for Cd are well within the range of values observed in the general population in the U. S. For mercury the detection limits are in the range observed with industrial exposures. Significant improvements could be achieved, however, by increasing the number of detectors or the detector efficiency. An increase in the dose is an alternative option.

RESULTS AND DISCUSSION

The first mobile activation unit was transported to a cadmium production plant where a comprehensive clinical and in vivo examination of the workforce was undertaken. The study groups consisted of 83 male workers from the plant and 10 control subjects. The kidney and liver cadmium data had log-normal distributions. Differences in the body burden as a function of exposure histories, job classifications, and renal functional status were observed. A biphasic relationship between kidney and liver cadmium values indicates a loss of kidney cadmium when liver cadmium levels exceeded 40 ppm (Fig. 2).

The clinical, biochemical, and in vivo body burden data obtained in this field study have been examined extensively (4-8). The following preliminary studies have been reported:

1. Body burden vs exposure
2. "Critical Concentration" for the kidney
3. Inter-relationships among blood, urine, hair, kidney, and liver cadmium
4. Dose-response relationships.

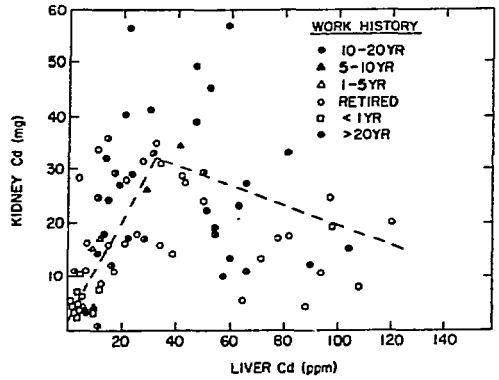

Figure 2: Kidney and Liver Cadmium Burden for Industrial Workers.

The in vivo measurement technique has also been used to obtain estimates of the kinetic behavior of cadmium. The biological parameters of half-time, dietary absorption, and inhalation absorption can be calculated if the exposure history for the individual is known. This approach was used to study the increase in cadmium body burden due to cigarette smoking (3). For example, the body burden of cadmium for a smoker with a 37 pack-yr history of smoking cigarettes is increased by approximately 80%.

As part of a toxicological study, one objective may be to establish dose-response relationships. In the case of cadmium toxicity, it appears that once the kidney burden exceeds a "critical" level, significant renal abnormalities become quite evident. Concurrent with the appearance of these biochemical indices of damage, the kidney loses its cadmium burden. Hence autopsy data obtained from individuals with cadmium-induced renal damage will usually indicate a kidney cortex cadmium value below the threshold or critical concentration for that individual. Therefore, dose-effect or dose-response relationships are extremely difficult to obtain by autopsy studies. The in vivo technique, however, can be used to provide a longitudinal history for the individual worker or a cross-sectional analysis for a particular industrial site. This latter approach was used to develop a dose-reponse relationship for workers employed at the cadmium smelter (Fig. 3). Using a logistic regression model, the probability of having significant kidney dysfunction can be predicted as a function of the individual's body burden.

Direct in vivo monitoring of individuals exposed to toxic metals is now possible. Identification of subjects with an

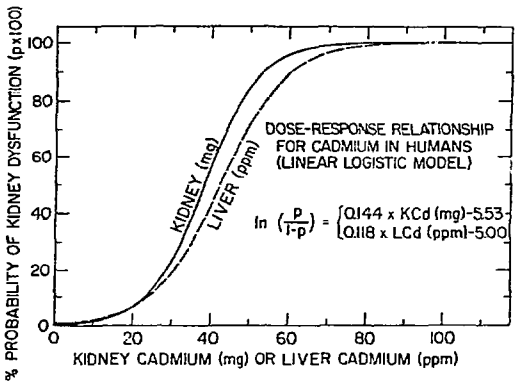

Figure 3: Dose-Response Relationship for Cd.

increased risk of developing kidney dysfunction related to cadmium exposure has been demonstrated. Similar analyses are possible for industry-related mercury exposures. An improvement in the detection limit for mercury, however, must be achieved before non-industrial levels can be examined in vivo. For cadmium, the present facility has sufficient sensitivity for the study of different diseases within the general population associated with cadmium exposure.

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