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CRITICAL CONCENTRATIONS OF CADMIUM IN HUMAN LIVER AND KIDNEY MEASURED BY PROMPT-GAMMA NEUTRON ACTIVATION

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ABSTRACT

While the effects of cadmium (Cd) have been studied in animals, few data exist on Cd metabolism in human beings. It is essential to develop a more accurate dose-effect relationship. In particular, data are needed on the role of parameters such as age, sex, weight, diet, smoking habits and state of health. More complete data will make possible a more accurate prediction of the pathophysiological consequences of Cd pollution. For example, at present there are only rough estimates of the critical renal Cd threshold concentrations associated with irreversible nephron damage.

Prompt-gamma neutron activation analysis (PGNAA) provides the only currently available means for measuring in vivo levels of liver and kidney Cd. Recently Vartsky et al. (1977) constructed a facility at Brookhaven National Laboratory for in vivo measurements of human kidney and liver Cd by neutron capture prompt-gamma ray analysis. The method employs an 85 Ci, ^{235}Pu,Be neutron source and a gamma ray detection system consisting of two Ge(Li) detector. The dose delivered to the liver and left kidney is 666 mrem (detection limit is 1.4 μg/g Cd in the liver and 2.0 mg Cd for one kidney).

Absolute levels of Cd in the kidney and concentrations of Cd in the liver were measured in vivo in twenty healthy adult males. The Cd contents of their liver and kidney were measured by PGNAA using ^{238}Pu,Be neutron sources. Organ Cd levels of smokers were significantly elevated above those of nonsmokers. Av-

erage total body burden of Cd in men at age 50 was estimated to be 19.3 mg for nonsmokers and 35.5 mg for smokers (38.7 pack-yr smoking index). Biological half-time for Cd in the body was estimated to be 15.7 yr (10-33 yr). Cigarette smoking was estimated to result in the absorption of 1.9 μg of Cd per pack. No relationship was found between body stores of Cd (liver and kidney) and Cd or β-microglobulin levels in urine and blood.

Currently the above neutron activation facility is being mounted on a 34-ft mobile trailer unit. With the support of ILZRO, this unit will be used to monitor levels of Cd in industrial workers. The relative expense and the sophisticated expertise required to mount such a program may limit the availability of the technique to a small scale research oriented need, for the future at least. Nevertheless, it is anticipated that critically important data, particularly on industrially exposed workers, will provide a better basis for determining critical concentrations and for the setting or revision of standards for industrial and environmental Cd pollution.

INTRODUCTION

The medical application of *in vivo* neutron activation analysis has contributed unique information related to body composition in normal subjects and in populations with various metabolic disorders. The neutron sources in use range from major accelerators and research reactors to small compact radioactive neutron sources. Not only are large, non-mobile sources of neutrons employed, but the detection system is usually a permanently installed, heavily shielded facility. Hence, due to technical constraints and clinical priorities, the major emphasis of *in vivo* activation analysis to date has been directed toward the delayed component of the induced activity.

However over a decade ago, Rundo and Bunce (1) proposed a method for the measurement of whole-body nitrogen based on the prompt-gamma component. Comar et al. (2) utilized capture gamma-rays for the partial body measurement of calcium, while Biggin et al. (3,4) measured total-body nitrogen. Vartsky (5) subsequently performed a comparative study between the $^{14}N(n,2n)^{13}N$ and $^{14}N(n,\gamma)^{15}N$ reactions for the absolute measurement of total-body nitrogen. The prompt-gamma studies performed by the Birmingham group were accomplished using a pulsed neutron beam from a cyclotron. Carlmark et al. (6) were the first to use (α,n) sources, in a technique for the measurement of total-body hydrogen. More recently Mernagh et al. (7) employed ^{238}PuBe neutron sources for the measurement of partial-body nitrogen.

A significant environmental-medical problem is the internal deposition of cadmium (Cd) in man. Fortuitously, Cd is particularly suited to detection by prompt gamma-ray analysis. McLellan et al. (8), employing a pulsed neutron beam, developed a facility for the *in vivo* measurement of hepatic concentrations of Cd. The continued development of ^{238}Pu,Be sources has made it possible to de-

sign facilities that are significantly reduced in size and hence portable. Vartsky et al. (9) have designed a facility using ^{238}Pu,Be for the absolute measurement of kidney Cd and liver concentrations. This report describes a self-contained "neutron capture" facility in a mobile trailer which is readily transportable.

I. Prompt-Gamma Activation Technique

When a nucleus Z^A absorbs a neutron, the resulting compound nucleas Z^{A+1} is in a highly excited state, as the neutron adds both its binding energy and its kinetic energy. The compound nucleus may decay either by the emission of nucleons (n,p), (n,α), (n,2n) or by emission of a gamma ray radiative capture (n,γ). While radiative capture can occur at all neutron energies, it is more probable at low energies and, in particular, at those energies (resonances) that produce long lived states of the compound nucleus. The long life of the compound state reflects the fact that the emission of gamma radiation is a lengthy process on a nuclear time scale, approximately 10^{-14}s. If nucleon emission is delayed by more than 10^{-14}s, the compound nucleus may decay by emitting a gamma ray. Since the transition from the excited compound state to the ground state often does not take place directly, but rather proceeds through intermediate states, the emitted gamma ray spectrum is usually complex.

In vivo measurement of small quantities of Cd by neutron activation analysis is possible due to the high radiative neutron capture cross-section of ^{113}Cd (12.3% isotopic abundance, 20000 barn). The effective Cd cross-section for thermal neutrons is about 2450 barn; the first resonance ($\sim$ 7500 barn) occurring at only 0.178 eV. Slow neutron capture by the nucleus of ^{113}Cd is followed by emission of a cascade of gamma rays. The most intense is the 559 keV

transition from the first excited state of ^{114}Cd to the ground state. The yield of this gamma ray is about 80 per 100 neutron captures in natural Cd.

The diagram of the irradiation facility is shown in Fig. 1. The collimator is designed to provide a rectangular beam 13 cm x 20 cm at the level of the bed (Fig. 1). The center of the neutron beam is offset 8 cm from the midline of the bed. The fast neutron flux at the level of the bed was calculated to be 7.5 x 10^3 n cm^{-2} s.

The gamma-ray detection system consists of two Ge(Li) detectors each having approximately 140 cm^3 volume (> 25% efficiency). The detectors are positioned in offset dewars to minimize the detector-skin distance. Each detector is shielded from direct view byof the neutron facility by a 5.5 cm layer of bismuth (BI) and a 20 cm layer of polyehtylene doped with 1% B and 80% Pb. A large number of neutrons are also scattered by the body toward the detectors. To reduce the neutron capture and inelastic scattering in the detectors, a 1.5 cm cup made of paraffin heavily doped with ^6LiF surrounds each detector.

With the development of high yield (α,n) sources, a sufficiently high neutron flux can be obtained for <u>in vivo</u> activation analysis. Coupled with a judicious choice of shielding materials for source and detectors, a reduction in interfering background gamma-rays and neutrons can be achieved. The subsequent compactness of the facility, the constant neutron output for the ^{238}Pu,Be source, and minimal power requirements for the detectors, make the previously described system readily transportable.

The mobile unit is shown in Fig. 2. The trailer is approximately 9.75 m in length and towable by a regular 1-ton pick-up truck. The trailer is a self-contained unit with air conditioning/heating for year-round use. Electrical

trailer. A removable interior partition subdivides the floor area into two compartments. The rear area contains the neutron source, shielding, detector system, and sufficient room for the scanning mode. The forward compartment provides a location for the real-time ultrasonic scanner used to localize the liver and kidney for Cd measurements. This room also serves as a mini-clinic for brief examinations of the patients by the attending physician.

RESULTS

The composite sensitivity for the measurement of Cd needs to be independent of the Cd distribution in the organ. Fig. 3 shows the composite sensitivity as measured by the prompt-gamma detection of the 559 keV gamma-rays from a thin Cd foil positioned at different places in the phantom. The normal anatomical size of the kidney and liver for an adult are represented by the organ limits. Since the sensitivity is non-uniform within the limits of the liver, only the liver concentration (μg/g) is obtained by comparison with an Alderson man-like phantom. The absolute Cd content of the kidney is measured since the composite sensitivity is nearly constant within the volume of the kidney (9).

The beam size allows for repositioning variations of ± 3 cm for the liver and ± 4 cm for the kidney along the Y-axis without a significant change in the measured values. Movement along the x-axis (detector axis), however, can significantly alter the liver Cd value, but does not alter the kidney Cd value. In order to minimize these variations, the detector-organ distance is kept constant for each patient. This is accomplished by locating the organ and outlining its contour by ultrasonic imaging.

The sensitivity of the system is 187 counts $mg^{-1}.rem^{-1}$ for the Cd in the kidney. For a 30-min exposure (partial-body dose of 666 mrem) the detection limit for the kidney is 2.0 mg Cd. For the same dose delivered to the liver, the detection limit is 1.4 μg/g corresponding to a sensitivity of 235 counts $(\mu g/g)^{-1}.rem^{-1}$. The reproducibility of the measurements was tested by sequential irradiations of the Alderson phantom. The phantom was repositioned on the bed before each irradiation. After correcting for the error due to the counting statistics, the reproducibility was ± 3% for the liver and ± 2.5% for the kidney. Possible interference from Cd in other organs was also investigated. No cross contribution from the Cd in the kidneys could be observed in the measurement of the liver or vice versa.

A representative spectrum for the left kidney of a normal subject is shown in Fig. 4. The spectrum obtained is that of a 52-year-old male with a moderate smoking history. The Cd peak which is clearly evident represents approximately 4.1 ± 2.5 mg Cd.

To date measurements have been made in 20 normal male volunteers. The group consisted of 12 cigarette smokers and 9 nonsmokers with a mean age of 50 years (range: 31 to 62). The data summarized in Table I reveal values comparable to those obtained by other investigators from tissue samples at autopsy. The urine and plasma Cd levels were determined by atomic absorption. Summary data are shown in Table II. The urine and plasma Cd in smokers were slightly, but not significantly, greater than that observed in nonsmokers. As expected, β_2-microglobulins were within normal limits for both groups. Further details of this study have been described by Ellis (11).

CONCLUSION

The measurement of prompt-gamma rays under the conditions of continuous neutron irradiation is complicated by a significant background of scattered neutrons and gamma-rays. This background is due mainly to neutron capture in the shielding materials and in the detectors. An appropriate choice and location of shielding materials for the neutron source and detectors significantly reduces unwanted capture gamma-rays so that the peak of interest is clearly separated from the background. The present system reduces this interference so that kidney and liver Cd levels within the normal range can be measured.

The neutron dose to the subject (666 mrem for kidney and liver Cd measurements) is well below the maximum permissible per quarter as set by the ICRP (10). The compact shielding and detection system allows for the facility to be completely mobile. Thus it can be easily employed in a more isolated geographical location (Cd levels in industrial workers).

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REFERENCES

1. Rundo, J., Bunce, L.J., Estimation of total hydrogen content of the human body. Nature 210:1023, 1966.
2. Comar, D., Riviere, R., Maziere, B., Kellershohn, C. Proc. 9th Int. Symp. Radioactive Isotopes in Clinical Medicine and Research (Urban and Schwarzenberg), Munich, Berlin, Vienna (1970) 431.
3. Biggin, H.C., Chen, N.S., Ettinger, K.V., Fremlin, J.H., Morgan, W.D., Nowotny, R., Chamberlain, M.J., Measurement of of Whole-Body Nitrogen by Neutron Activation Analysis (Proc. Symp. Bled. 1972), Nuclear Activation Techniques in the Life Sciences, IAEA, Vienna (1972) 639.
4. Biggin, H.C., Chen, C.S., Ettinger, K.V., Fremlin, J.H., Morgan, W.D., Nowotny, R., Chamberlain, M.J., Determination of nitrogen in living patients. Nature 236:187, 1972.
5. Vartsky, D. Absolute measurement of whole body nitrogen by in-vivo neutron activation analysis. Ph.D. Thesis, University of Birmingham, England (1976).
6. Carlmark, B., Reizenstein, P. Human body composition studies. I. Neutron activation of total-body hydrogen and whole-body counting. IAEA Panel on In-Vivo Activation Analysis, IAEA-PL-493/10, Vienna (1973) 113.
7. Mernagh, J.R., Harrison, J.E., Mc Neill, K.G., In-vivo determination of nitrogen using Pu-Be sources, Phys. Med. Biol. 22:836, 1977.
8. McLellan, J.S., Thomas, B.J., Fremlin, J.H., Harvey, T.C., Cadmium - its in-vivo detection in man. Phys. Med. Biol. 20:88, 1975.
9. Vartsky, D., Ellis, K.J., Chen, N.S., Cohn, S.H. A facility for in-vivo measurement of kidney and liver cadmium by neutron capture prompt gamma analysis. Phys. Med. Biol. 22:1085, 1977.

10. ICRP, 1959. Permissible Dose for Internal Radiation. Report No. 2 (Oxford: Pergamon Press).

11. Ellis, K.J., Vartsky, D., Zanzi, I. and Cohn, S.H. Cadmium: In vivo measurement in smokers and nonsmokers. Science (in press).

Table I

IN-VIVO MEASUREMENT OF CADMIUM

Subjects	N	Liver* (µg/g)	Kidney* (mg)	Renal / Hepatic Cd
Smokers	12	4.1(1.6)	5.8(1.7)	10.6
Nonsmokers	8	2.3(1.6)	3.1(2.0)	11.3
Smokers / Nonsmokers Ratio		1.78	1.87	----
P		0.05	0.02	N.S.

*Geometric mean (Standard Deviation)

Table II

PLASMA AND URINE CADMIUM (Cd) AND B-2-MICROGLOBULIN LEVELS

Subjects	N	Plasma Cd µG/L	P	Urine Cd µG/L	P
Smokers	12	2.26(1.67)	0.07	2.42(1.68)	0.06
Nonsmokers	8	1.49(1.55)		1.44(1.77)	

Subjects	N	Plasma B-2 MG/L	P	Urine B-2 µG/L	P
Smokers	12	1.52(1.39)	N.S.	46.2(6.0)	N.S.
Nonsmokers	6	1.74(1.10)		28.1(4.7)	

All values expressed as geometric mean (Standard Deviation)

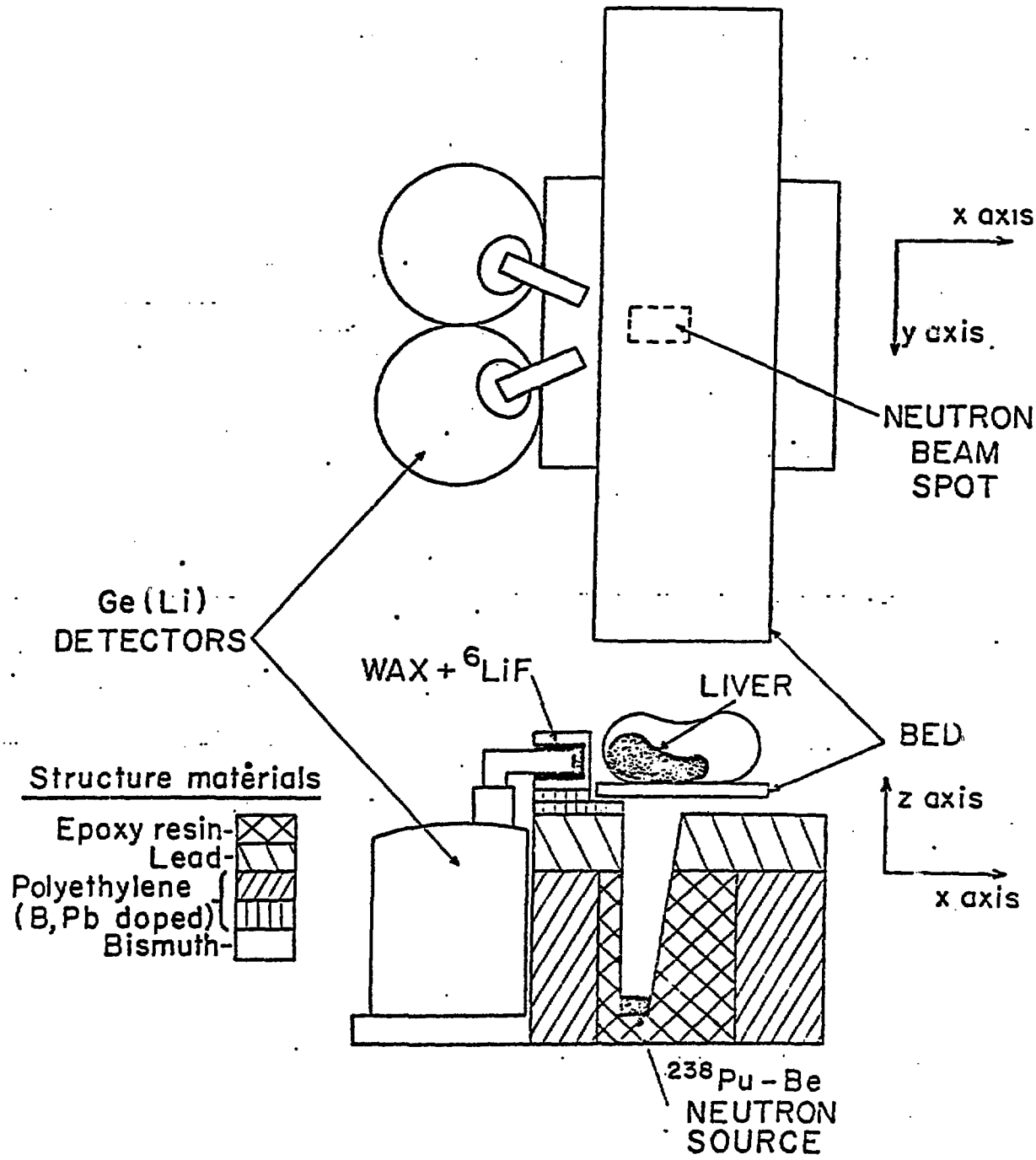

Fig. 1:

Irradiation and detection facility for kidney and liver cadmium.

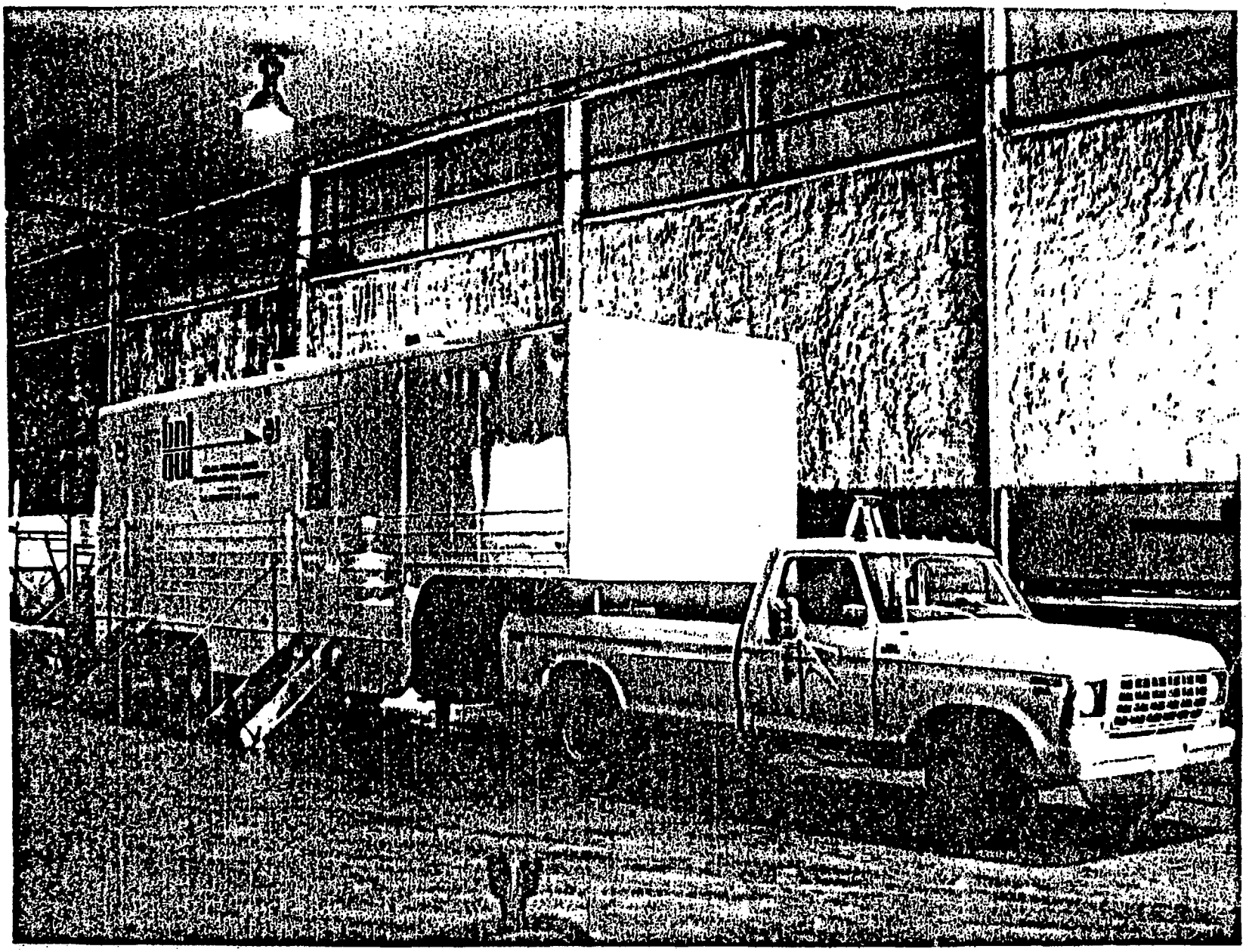

Fig. 2: Brookhaven mobile neutron activation facility.

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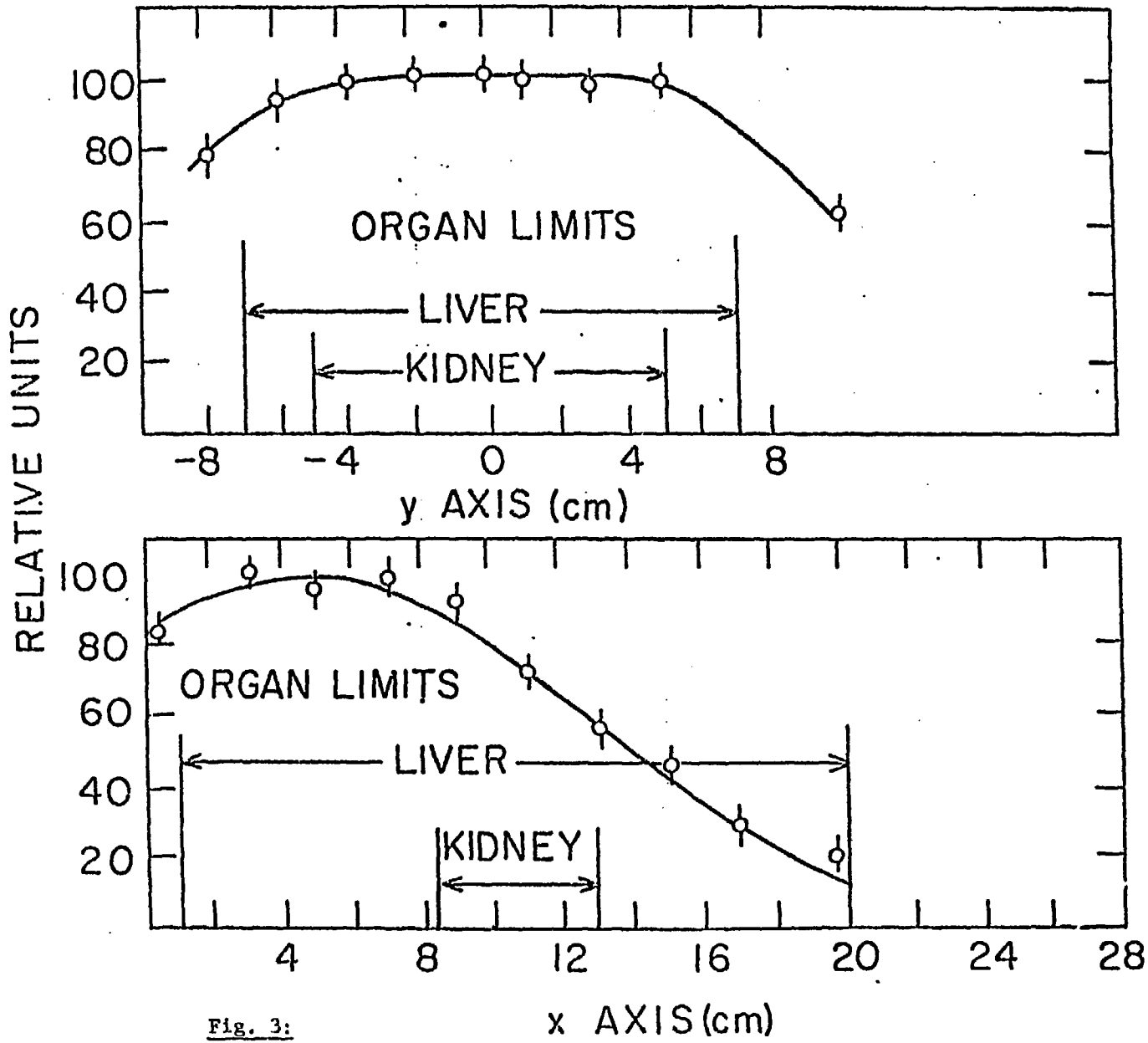

Fig. 3:

Composite sensitivity for cadmium along the Y-axis and X-axis. The organ limits for the liver and left kidney are also shown.

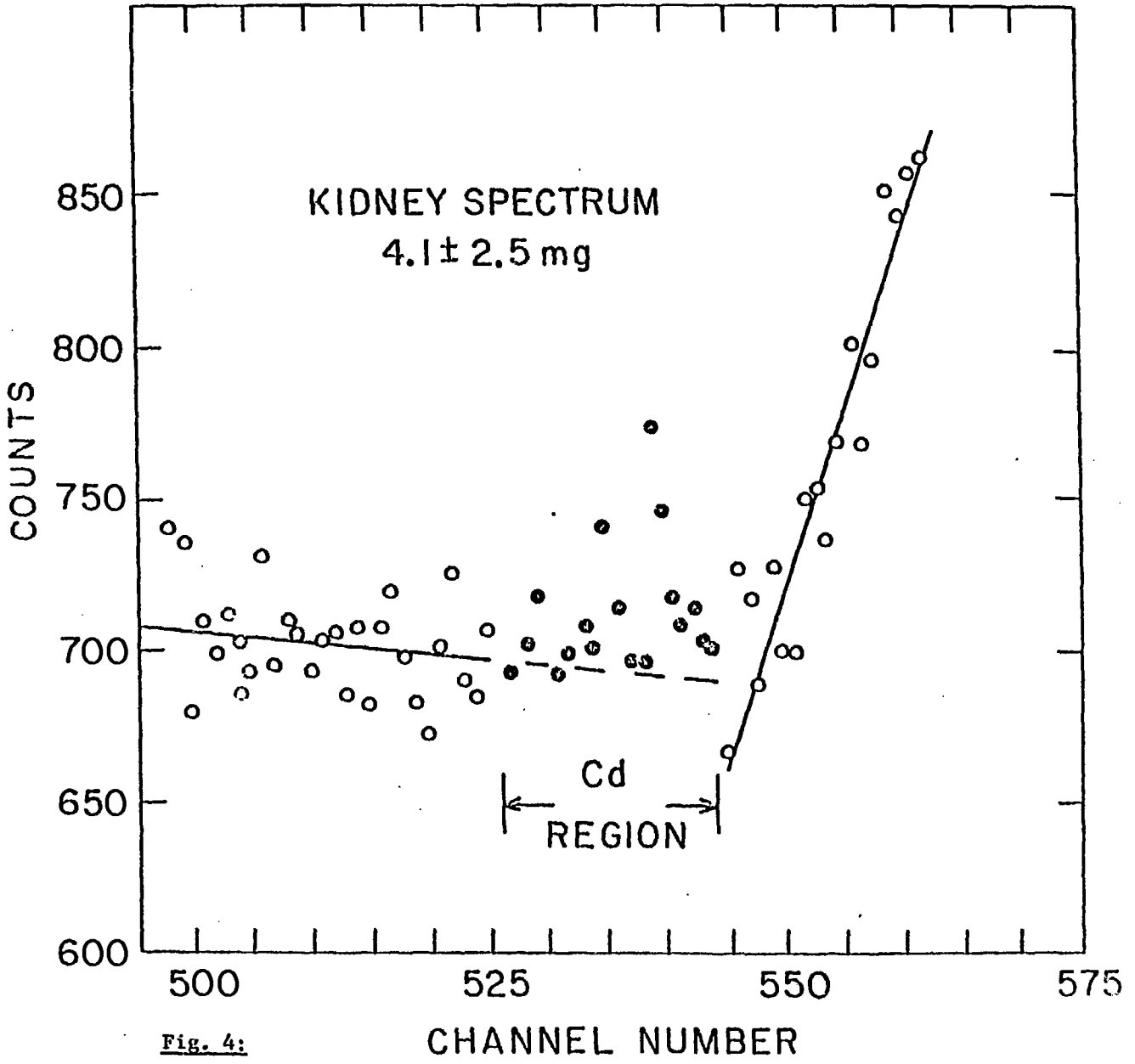

Fig. 4:

Gamma-ray spectrum of Cd in the left kidney of a 52y male. Counts are from a single detector (19% efficiency) for a kidney dose of 666 mrem.