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Human Tissue Trace-Element Detection by Neutron Activation Without Chemical Separation.

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ABSTRACT

A method for analysis of 40 trace elements in human tissues without chemical separation involves 8 hours' activation at 10^{13} neutrons cm^{-2} sec^{-1} and 10 to 20 days' decay before counting on Ge(Li) detectors. Five human tissues were examined to determine the feasibility of analysis of necropsy and biopsy tissues on a routine basis. The technique has many advantages if tissues are lypholized and pressed into tablets before activation.

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INTRODUCTION

Many pathological conditions in man have been associated with an excess or deficiency of some trace elements. The effects of lead, mercury, tellurium, radium, etc., are well known. Less well known toxic or pathological conditions include possible lithium deficiency in psychotic depression (1); arsenic excess in lung cancer (2); cadmium etiology of hypertension (3); vanadium inhibition of cholesterol metabolism (4); chromium deficiency in adult diabetes (5); copper, magnesium, and manganese concentrations in neurological diseases (6-8); and cadmium, cobalt, and nickel induction of testicular injury and rhabdomyosarcoma tumors (9). In myocardial infarction there is, relative to normal myocardium, an increase in serum copper (10), and a decrease in myocardial copper and molybdenum with an increase of tissue arsenic and cerium (11).

In many situations trace-element accumulation in a diseased organ might be an effect of the disorder and have no bearing on the disease etiology; thus, the cause-effect relationship is speculative. However,

the correlation of increased kidney cadmium concentration and essential hypertension in man seems more than an associative phenomenon in that hypertension can be easily induced in animals by small doses of cadmium (12,13), and there is a strong correlation between cadmium levels and cardiac deaths in man (14).

Vanadium has been shown to affect cholesterol metabolism, probably through inhibition of cholesterol biosynthesis at vanadium concentrations as low as 50 μM (4). Curran, Azarnoff, and Bolinger have shown a lowering of serum total and free cholesterol levels after oral vanadium salt ingestion in normocholesteremic young men (15). Chromium appears to be an essential trace element involved in glucose metabolism in animals and man. In contrast to other elements, chromium concentration diminishes with increasing age (16). Because chromium dietary supplements shift the glucose-tolerance curve toward normal in adult diabetics, a deficiency in this element has been implicated as a contributing cause of adult-onset diabetes (17). A relation has been suggested between chromium and insulin action at the cellular level (18). Other

relationships between disease and trace elements have been reviewed by Schroeder (19), and the role of metals in cancer has been surveyed by Furst and Haro (20).

Appearance in the tissues of metals not normally seen there which have no known or suspected biological role suggests environmental contamination. Included in this category are gold, silver, and mercury from dental work.

Methods of analysis applicable to trace elements in the ppm concentration range include atomic absorption, fluorescence, neutron activation, and electrochemical techniques (21-26). No single approach is applicable to all elements of interest. Each technique requires special sample preparation and methods to compensate for interference from other elements in the biological system being studied.

Neutron-activation analysis of human tissues suffers from the interference of Na, K, and Cl. The activated 15-hour ^{24}Na, 12.4-hour ^{42}K, and 37-minute ^{38}Cl have gamma-ray spectra which obscure most of the interesting short-lived nuclides. Because it is

desirable to analyze many samples of human tissue without extensive pre- or postirradiation chemical separation techniques, we conducted a feasibility study to ascertain how many elements might be detected. One criterion was that the method should not be overly complicated for analysis of five tissue samples taken from each of 200 cadavers.

The protocol involves long irradiation at high flux and 7 to 15 days of decay time to allow ^{24}Na and ^{42}K activity to diminish. High resolution was obtained by using a Ge(Li) detector and 400- to 1000-minute counts. The amount of isotope produced is based on the amount of parent element present, flux of neutrons, and half-life of the isotope. The amount detected is dependent on the amount produced in the reactor and the time delay between irradiation and counting. These relationships are shown in Fig. 1, where the relative amount of an isotope that can be detected is shown as a function of the number of half-lives for irradiation and for delay between irradiation and detection. Thus long-half-life isotopes are detected after the shorter-half-life isotopes have decayed, and we take advantage

of this fact to obviate the need for chemical separation of Na and K. For human tissues studied our results compare favorably with the much more tedious Na, K postirradiation separation techniques. If our high-flux long-duration irradiation is supplemented by a low-flux short-duration procedure with immediate counting as developed for archaeology samples (27), all elements detected by the Na, K separation techniques can be detected.

The following is a description of our procedure and qualitative results on human bone, blood, plasma, liver, lung, and kidney.

METHOD

Sample Preparation

Blood samples were drawn by venipuncture from healthy subjects, and lung, bone, liver, and kidney samples were from recently deceased hospital patients. Plasma was separated by centrifugation at 40,000 rpm for 5 minutes. Sample sizes (before freeze-drying) were: whole blood and plasma, approximately 2 cm^3; lung, liver, and kidney, approximately 1 g wet weight; bone, about 150 mg. All samples were placed in Petri

dishes, frozen in liquid nitrogen, and lyophilized overnight. Samples were transferred to either 50 X 12.5-mm quartz vials or 23.5 X 11.5-mm polyethylene vials. Polyethylene vials were found to be cheaper and more convenient than quartz sealed ampules. Commercially available polyethylene vials maintain integrity during 1 megawatt TRIGA reactor exposure for 8 hours. An alternative method of sample preparation consists of compressing tissue in a standard mechanical press to pill sizes, wrapping in aluminum foil, and activating these small tablets together with comparison standards. To minimize contamination of samples, all vials, Petri dishes, centrifuge tubes, syringes, and needles, as well as scalpels and spatulas used in cutting and transferring samples, were washed in alcohol, then acetone, then triple-distilled water.

Neutron Irradiation and Counting

Samples were irradiated in their respective vials for 8 hours in the TRIGA reactor of the Department of Nuclear Engineering, University of California, Berkeley, at a flux of 2 to 3 X 10^{13} thermal neutrons per second

per cm^2. They were removed from the reactor and allowed to decay in their vials for various times, usually several weeks, to allow ^{24}Na activity to diminish.

After being transferred to nonirradiated vials, samples were counted by a high-resolution lithium-drifted germanium gamma spectrometer. The samples were placed 5 cm from the planar detector, which is 3.6 cm in diameter and 1 cm in active depth with a cooled-FET input stage and a low-noise preamplifier (Lawrence Radiation Laboratory design). Spectra were accumulated by using a 1600-channel pulse-height analyzer, calibrated at approximately 1 keV energy per channel. Assignment of photon energies and intensities to peaks in these spectra was performed by computer code SAMPO (28). Isotopes were then identified by comparison of these energy and intensity values with published decay-scheme data (29,30).

RESULTS

Results of qualitative analysis from various tissues are shown in Table I, with the spectra illustrated in Figs. 2 through 4. After long activation

and approximately 2 weeks' decay time, 24 elements were detected. As expected, Cd, Hg, Br, Cs, Fe, Co, and Sb show up consistently in liver and kidney, where the concentration is 30 to 100 times that normally found in either whole blood or plasma. Some elements rare in nature or in man's experience, e.g., hafnium and tantalum, have not to our knowledge been reported in tissue. These spectra, resulting from long activation periods and long decay time, make up part of a library that will facilitate further qualitative and quantitative analysis of the occurrence in human tissue of these and other activated isotopes with long half-lives.

DISCUSSION

The successful application of activation analysis for trace-element assay in human tissues has in the past been hindered by the high neutron capture cross sections and the abundance of ^{24}Na and ^{42}K. After the introduction of high-resolution germanium-lithium detectors, it was demonstrated that photopeaks of interesting trace elements could be resolved if samples were irradiated for long periods at high flux (6 to 8 hours

at 10^{13} neutrons per second), and long counting periods were introduced after decay intervals of as much as 2 weeks (31-33). In order to observe the photopeaks of trace elements in germanium-lithium spectra of irradiated tissues, it is not absolutely necessary to reduce the concentration of ^{24}Na and ^{42}K, as was recently suggested by Tang and Meletcoss (34). Without chemical separation, it is possible by using both short and long activation protocols to detect almost all the elements of interest (Tables II, III). The sensitivity of detection is an important factor which distinguishes the radiochemical separation technique (34) from our technique. In cases in which the greater sensitivity is necessary, less tedious methods--e.g., atomic absorption or X-ray fluorescence--might be employed more practically and economically for those elements that decay too fast or have cross sections too low for activation analysis by long irradiation followed by long count after long decay times.

The success of a general program of analysis and correlation of trace-element concentration with disease

for a significant group in a region--e.g., 200 cadavers from the San Francisco Bay Area--is dependent on an optimization between tedium of sample preparation and accuracy of the procedure. The availability of reactors and cost of processing are such that X-ray fluorescence, atomic absorption, electrochemical techniques, and neutron activation are comparable in cost. Sample preparation required for atomic absorption and electrochemical techniques are much more involved than those required for X-ray fluorescence or neutron activation.

Compressing tissue in a standard press to pill sizes, wrapping in aluminum foil, and activating at the same time these arrays of small tablets and appropriate standards is by far the simplest procedure, but was not implemented in these initial results. The analysis of data and total investment of time appear to be less in neutron activation than in other procedures if a large volume is being run. However, if neutron activation is elected as the only procedure, some elements of importance will not be measured.

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Thus, if lead or cadmium is the only tissue element of interest, perhaps atomic absorption is the procedure of choice. Our efforts are continuing in the direction of pill-sample preparation for irradiation of as many as 25 samples at one time (27). With the long irradiation and long wait procedure, we expect to detect any significant quantities of the elements listed in Table II. Isotopes of short half-life (e.g., Al, Cu, Mn, etc.; cf. Table III) can be detected by a separate short activation with no-delay counting. Some elements; e.g., Br, cannot be quantitated because of partial volatilization due to reactor heat.

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TABLE I

Isotopes Found in Six Tissues.

Period	Isotope	Lung	Liver	Kidney	Bone	Whole Blood	Plasma I	Plasma II	Plasma III
3	^{24}Na	*	*	*		*	*		
4	^{47}Ca				*				
	^{46}Sc	*					*		
	^{51}Cr	*	*	*				*	*
	^{54}Mn	*							
	^{59}Fe	*	*	*		*		*	*
	^{60}Co	*	*	*				*	*
	^{65}Zn	*	*	*	*	*	*	*	
	^{75}Se	*	*	*			*	*	
	^{82}Br	*	*	*	*	*		*	*
5	^{86}Rb	*	*	*		*	*	*	
	^{95}Zr	*					*		
	^{110m}Ag					*	*	*	*
	^{115}Cd		*	*					
	^{124}Sb	*	*	*			*		
6	^{134}Cs	*	*	*			*	*	*
	^{131}Ba	*					*	*	*
	^{140}La	*							
	^{181}Hf	*					*		
	^{182}Ta	*							
	^{198}Au		*				*	*	*
	^{203}Hg	*	*	*			*		

Table II (cont.)

Z	Element	Isotope formed	Half-life (days)	Neutron cross section of precursor (barns)	Natural abundance of precursor (%)
48	Cd	Cd-115	2.21	1.1	28.9
50	Sn	Sn-113	115.	1.3	0.95
50	Sn	Sb-125 §	986.	0.1	5.98
51	Sb	Sb-122	2.80	6.1	57.2
51	Sb	Sb-124	60.2	3.3	42.8
55	Cs	Cs-134	767.	31.	100.
56	Ba	Ba-131	12.0	8.8	0.101
57	La	La-140	1.67	8.9	99.9
58	Ce	Ce-141	32.5	0.6	88.5
62	Sm	Sm-153	1.94	210.	26.6
63	Eu	Eu-152	5120.	5900.	47.8
65	Tb	Tb-160	72.1	46.	100.
70	Yb	Yb-175	4.21	54.	31.8
71	Lu	Lu-177	6.63	2100.	2.6
72	Hf	Hf-181	45.0	10.	35.2
73	Ta	Ta-182	115.	21.1	100.
75	Re	Re-186	3.71	110.	37.1
77	Ir	Ir-192	74.0	1000.	38.5
79	Au	Au-198	2.70	98.8	100.
80	Hg	Hg-203	47.0	4.	29.8
90	Th	Pa-233 ‖	27.4	7.4	100.
92	U	Np-239 ¶	2.35	2.73	99.3

§ Daughter of Sn-125. 9.4 day half-life of Sn-125 must be taken into account when this isotope used for Sn-assay.

‖ Daughter of Th-233. ¶ Daughter of U-239.

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TABLE II

Long-Half-Life Elements

Z	Element	Isotope formed	Half-life (days)	Neutron cross section of precursor (barns)	Natural abundance of precursor (%)
11	Na	Na-24	0.625	0.53	100.
20	Ca	Ca-47	4.5	0.3	0.0033
21	Sc	Sc-46	84.0	23.	100.
22	Ti	Sc-47*	3.43		7.32
24	Cr	Cr-51	27.8	17.	4.31
26	Fe	Mn-56*	314.		5.84
26	Fe	Fe-59	45.0	1.1	0.31
27	Co	Co-60	1921.	37.	100.
28	Ni	Co-58*	71.		66.7
30	Zn	Zn-65	245.	0.46	48.9
31	Ga	Ga-72	0.588	5.0	39.8
33	As	As-76	1.10	4.5	100.
34	Se	Se-75	120.	30.	0.87
35	Br	Br-82	1.47	3.2	49.5
37	Rb	Rb-86	18.7	1.	72.2
39	Y	Y-90	2.67	1.3	100.
40	Zr	Ar-95	65.0	0.08	17.4
40	Zr	Nb-95‡	35.0		
42	Mo	Mo-99	2.75	0.51	23.8
47	Ag	Ag-110m	260.	92.	48.7

* Radioisotope produced via (N,P) reaction with neutron energy threshold <1 MeV and strongly energy-dependent cross section.

‡ Daughter of Zr-95.

TABLE III

Short-Half-Life Elements

Z	Element	Isotope formed	Half-life	Neutron cross section of Precursor (barns)	Abundance of precursor (%)
12	Mg	Mg-27	9.50 min	0.027	11.3
13	Al	Al-28	2.30 min	0.235	100.
17	Cl	Cl-38	37.3 min	0.4	24.5
18	Ar	Ar-41	1.83 hr	0.61	99.6
19	K	K-42	12.4 hr	1.2	6.77
25	Mn	Mn-56	2.58 hr	13.3	100.
29	Cu	Cu-64	12.8 hr	4.5	69.1
38	Sr	Sr-87M	2.8 hr	1.3	9.86
39	Y	Y-90M	3.1 hr	0.001	100.
44	Ru	Ru-105	4.43 hr	0.48	18.9
52	Te	Te-127	9.4 hr	0.9	18.7
52	Te	Te-129	68. min	0.14	31.8
52	Te	Te-131	25. min	0.2	34.5
53	I	I-128	25.0 min	6.4	100.
56	Ba	Ba-139	82.9 min	0.4	71.7
63	Eu	Eu-152m_1	9.3 hr	2800.	47.8
66	Dy	Dy-165	139. min	2800.	28.2
73	Ta	Ta-182m	16.5 min	0.07	100.
90	Th	Th-233	22.1 min	7.4	100.
92	U	U-239	23.5 min	2.73	99.3

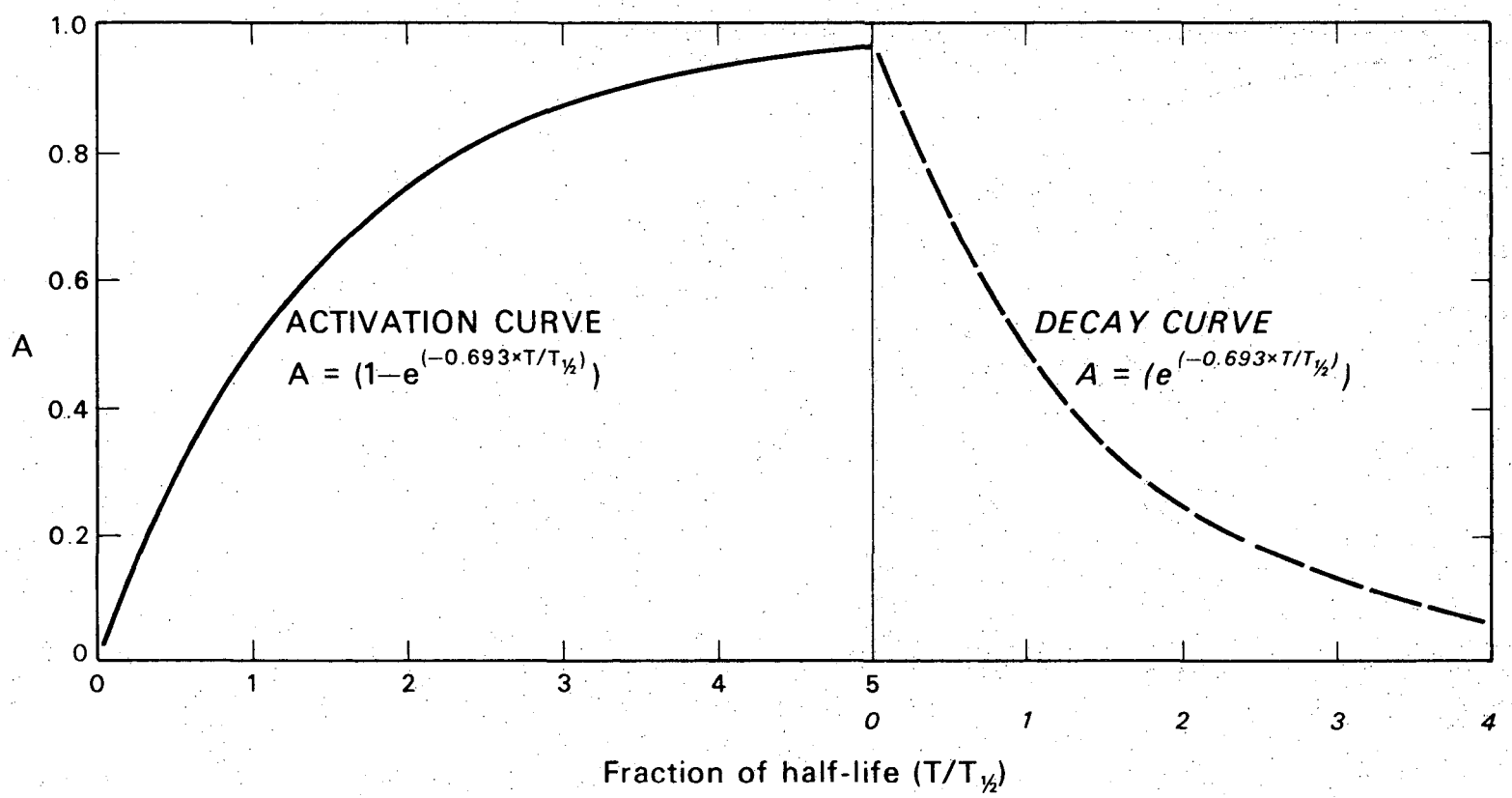
FIGURE LEGENDS

Figure 1 Relative activity or abundance of isotope produced as a function of neutron activation duration is shown in terms of half-life fraction. Right curve is standard decay curve also in terms of half-lives.

Figure 2 Gamma spectrum for blood and plasma after 10^{13} neutrons cm^{-2} sec^{-1} activation, 15 days' decay, and 1000-minute counting.

Figure 3 Gamma spectrum for kidney and liver after 10^{13} neutrons cm^{-2} sec^{-1} activation, 15 days' decay, and 1000-minute counting.

Figure 4 Gamma spectrum for lung and bone after 10^{13} neutrons cm^{-2} sec^{-1} activation, 15 days' decay, and 1000-minute counting.



DBL 7012-6038

Fig. 1

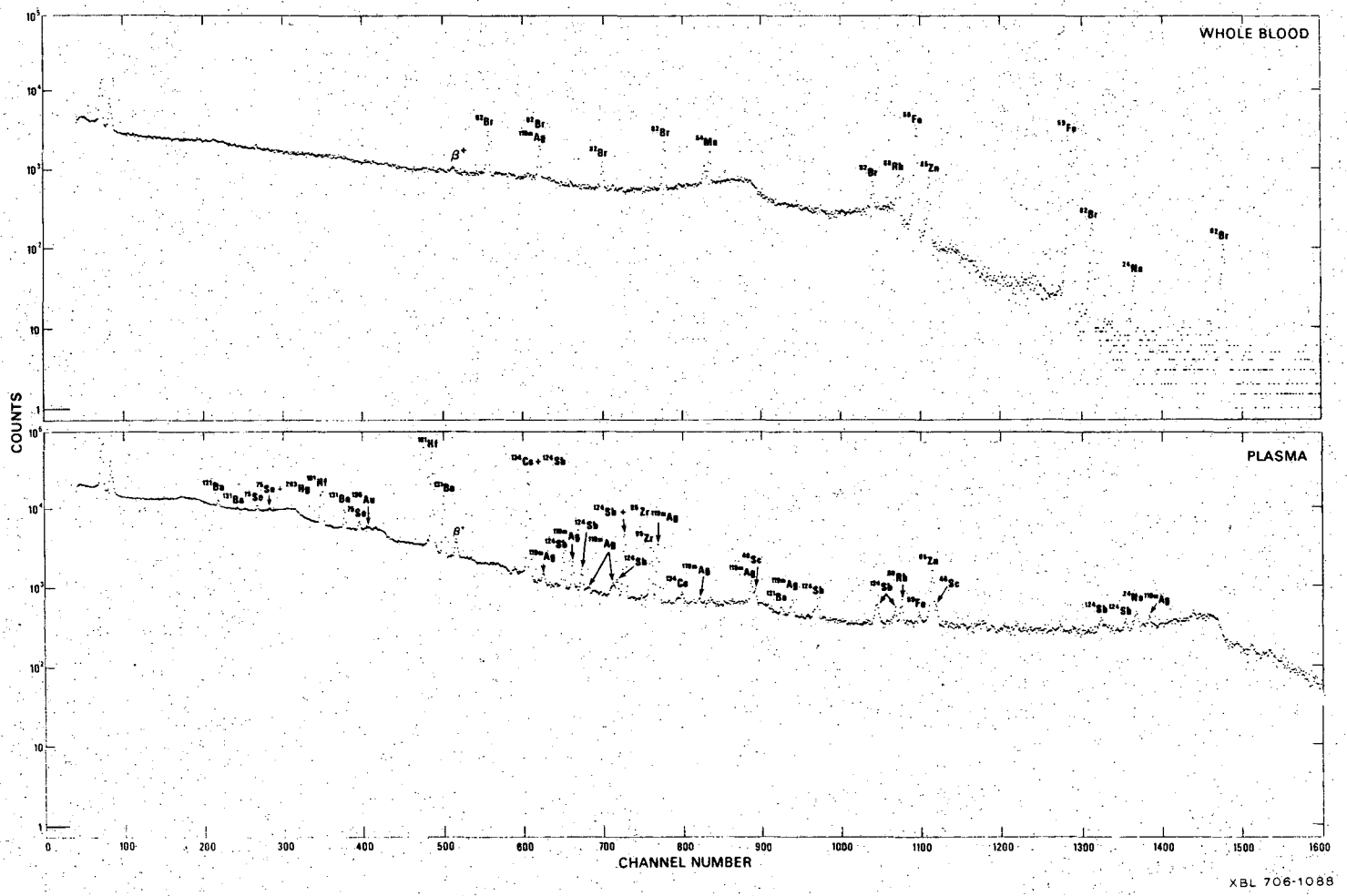


Fig. 2

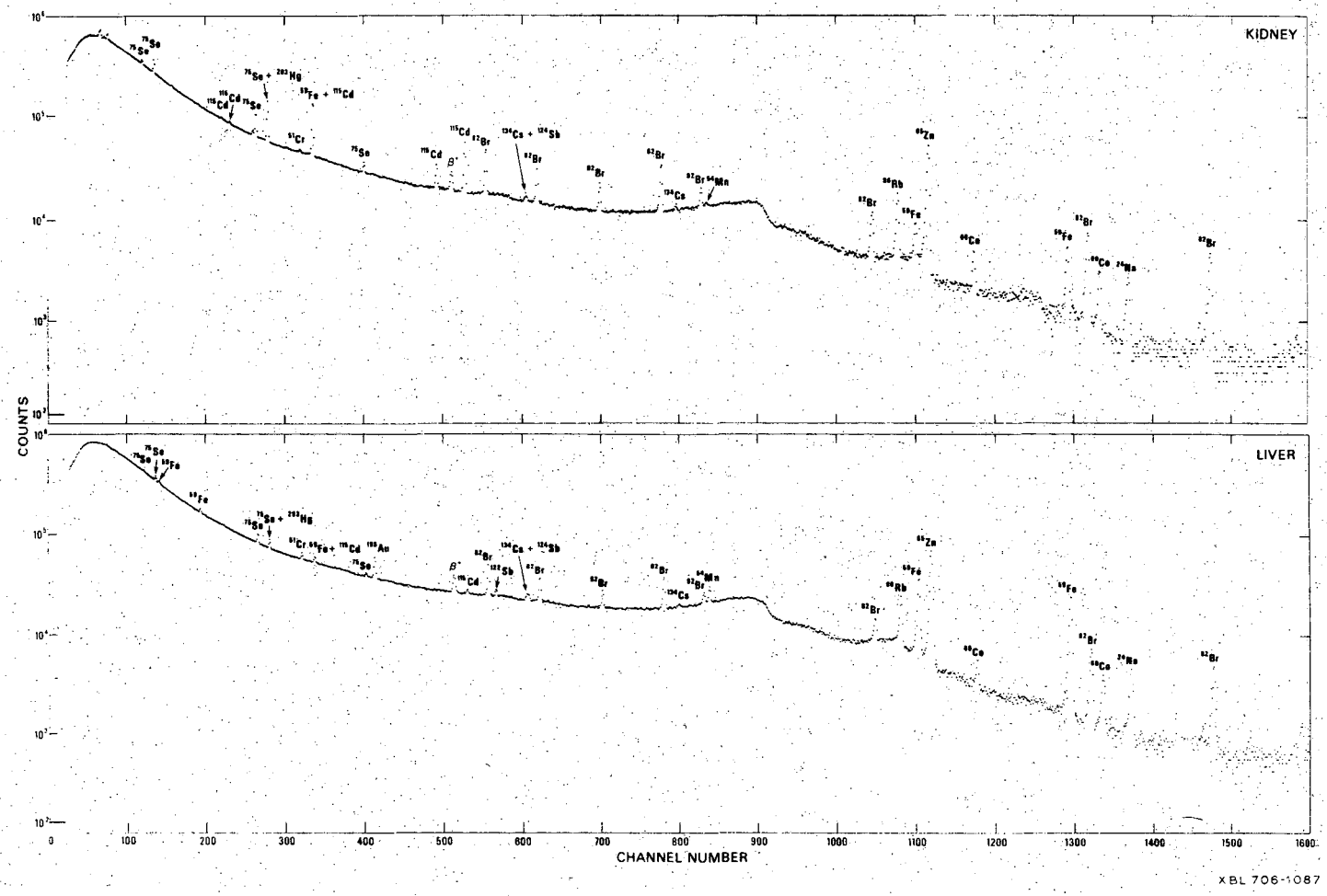

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Fig. 3

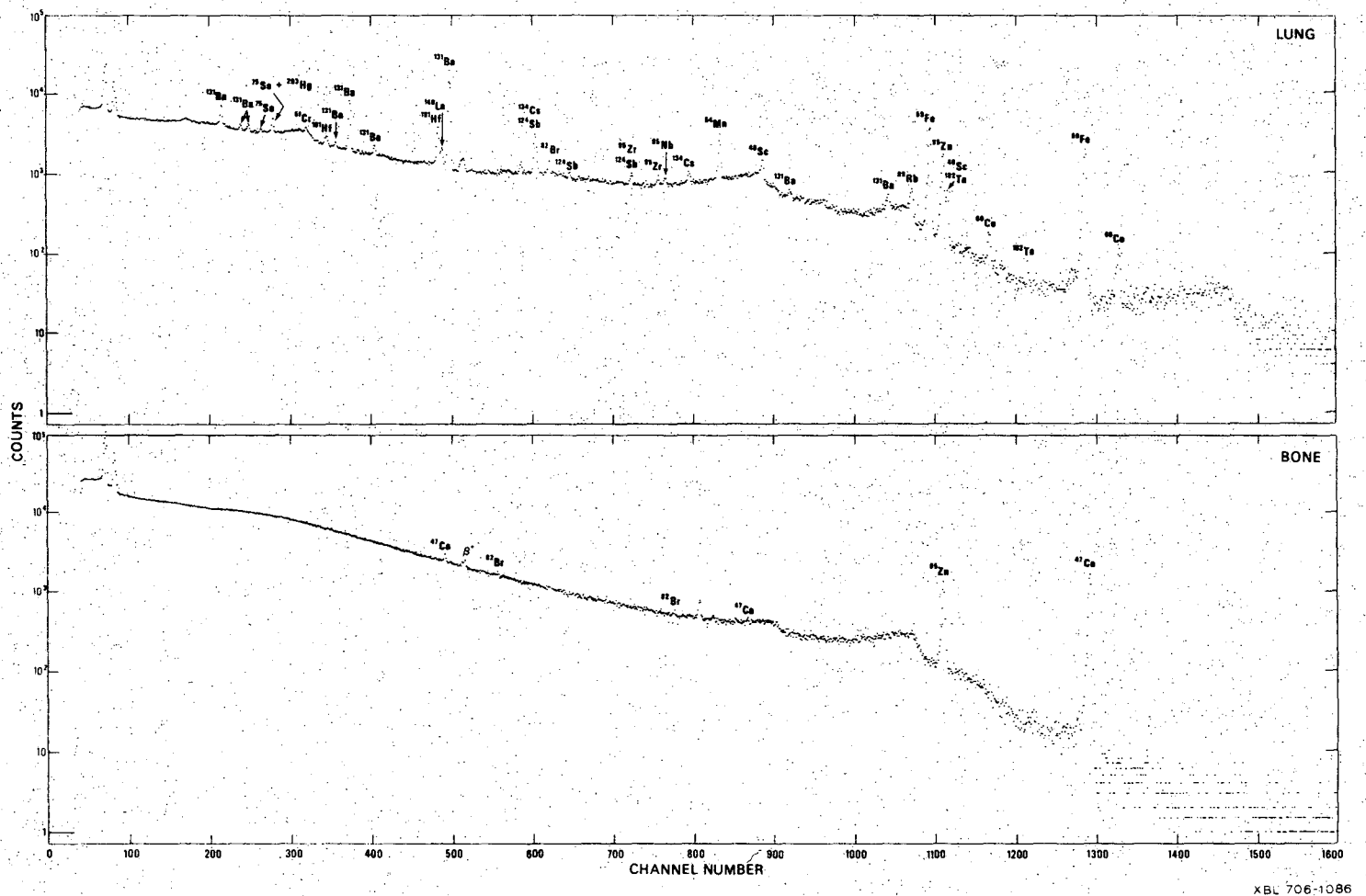
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Fig. 4

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