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Variability in the metal content of human organs

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The concentrations of the essential metals: magnesium, calcium, manganese, iron, copper, zinc, and molybdenum in human organs were found to be more constant than the concentrations of the presently nonessential metals: strontium, barium, aluminum, titanium, vanadium, chromium, nickel, silver, cadmium, tin, and lead. For the former the 80% range of concentrations for each metal in each organ, expressed as ninetieth percentile/tenth percentile, was usually less than 3.5 and almost always less than 7.0. For the latter the ranges were usually greater than 7.0 and often greater than 14. These ranges were equally valid for liver, kidney, lung, aorta, heart, spleen, and brain of 150 healthy adults who died suddenly and unexpectedly in the United States. The ranges for the same organs of 100 adults, many of whom were chronically ill, from 8 different parts of Africa, Asia, and Europe were similar but somewhat larger. The two populations were more alike with respect to the absolute concentrations of essential than of nonessential metals. In both populations aluminum and titanium were strikingly accumulated in the lung and cadmium in the kidney.

Nine chemical elements which occur in concentrations greater than one part per thousand comprise over 99 per cent of protoplasm. Nine more elements which occur in smaller concentrations are known to have specific biologic functions. These 18 elements are designated *essential*. At least a score of additional elements are also present in small but measurable concentrations in many mammalian tissues. They are currently designated *nonessential* since they are not now known to be required for any biologic function.

Although the essential elements are vital to living systems, the concentrations of some which are present in relatively small amounts and of most nonessential

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Table I. Ranges of metal concentrations in organs of Americans adults (frozen tissue)*

Metal	10th and 90th		
	Liver	Kidney	Lung
Essential			
Mg	340-750	360-680	260-550
Ca	55-170	130-430	160-400
Mn	1.0-4.0	0.82-2.7	0.15-0.81
Fe	95-430	72-200	200-940
Cu	5.0-21	3.0-5.4	1.4-2.8
Zn	34-92	49-120	13-27
Mo	0.33-1.5	0.21-0.50	
Nonessential			
Sr	0.008-0.040	0.033-0.14	0.050-0.19
Ba	< .001-0.015	< .001-0.029	0.029-0.29
Al	0.62-4.4	0.51-3.0	29-190
Ti	< .1-0.33†	< .1-0.12†	1.0-15
V			< .02-0.26
Cr	< .002-0.071	< .002-0.087	0.063-0.95
Ni	< .09-0.19†	< .09-0.19†	< .09-0.48
Ag	0.0091-0.030	< .0009-0.0093†	< .0009-0.0046†
Cd	0.53-3.0	13-45	< .4-0.89
Sn	0.041-0.62	0.042-0.39	0.093-0.93
Pb	0.29-1.2	0.21-1.1	0.062-0.68

*Concentrations are expressed as micromoles of metal per gram of tissue ash. Values cited are limit of detectability and ninetieth percentile. Therefore < indicates that less than 90 metal.

†Indicate that less than 50 per cent of the values, and blanks indicate that less than 10 per

elements in human tissues have not been well defined. Methodologic problems are partially responsible; chemical assay is cumbersome since elements must be treated individually, while spectrographic analysis for many elements simultaneously is frequently less accurate. In addition, data which have been collected by different workers are often not easily correlated because the concentrations are expressed in units which are not comparable. Finally the few available surveys of many elements have not been performed systematically; in particular, most of the populations examined have been chosen because of their convenience to highly industrialized areas where exposure may be unusual.

Large and unexpected differences in the concentrations of individual metals in human organs have recently been observed.[1, 2] In seeking associated phenomena, a study was made of several variables, including the subjects' geographic origin, age, sex, race, and disease. Despite shortcomings, both in the techniques of collection and in the methods of analysis, some striking correlations between the first two of these variables and metal concentrations were found, such as those reported for renal cadmium.[3]

Further examination of the extensive data which have been presented elsewhere[1, 2] revealed a marked difference in the variability of concentrations of essential and nonessential metals. The material presented here involves 18 metals which are found in relatively small amounts but which are readily assayed by

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Percentiles			
Aorta	*Heart*	*Spleen*	*Brain*
390-820	450-950	290-610	240-500
700-2000	55-200	70-200	82-240
0.073-0.31	0.22-0.73	0.091-0.35	0.18-0.58
29-120	61-130	160-750	39-86
0.79-2.2	3.9-7.0	1.1-2.0	3.8-8.0
17-43	31-59	15-29	8.0-17
0.17-0.89	0.012-0.081	0.012-0.068	0.0057-0.049
0.018-0.12	< .001-0.020	< .001-0.024	< .001-0.013
0.76-5.2	0.37-2.6	0.36-4.4	0.22-1.4
< .1-0.52†	< .1-0.10†	< .1-0.29†	
< .002-0.19	< .002-0.16	< .002-0.062	< .002-0.038
< .09-0.34†	< .09-0.46†	< .09-0.090†	
< .0009-0.0092	< .0009-0.0046†	< .0009-0.0046†	< .0009-0.015
< .4-0.53†		< .4-0.44†	
0.042-0.32	< .04-0.23	< .04-0.29	
0.17-1.4	< .03-0.087	0.033-0.43	< .02-0.19

are tenth and ninetieth percentiles of the sample except where < occurs, in which case values cited per cent of the values equalled or exceeded the minimum measurable concentration of a particular

cent of the values, equalled or exceeded the minimum measurable concentrations.

emission spectrography. Their concentrations are considered in 7 human organs. The presentation is designed to emphasize marked differences in the observed *ranges of concentrations* for individual metals, in particular the greater constancy among essential as compared with nonessential ones. The same spectrographic assay technique was used throughout in order to render all results comparable. Absolute values of concentrations are cited for purposes of orientation, but they are justified elsewhere.[4]

Two autopsy populations were examined. The first reflects the situation in urban United States and consisted of apparently healthy American* adults. The second was intentionally made diverse with respect to geographic origin and hence to race, environment, and also disease; it consisted of foreign* adults many of whom had been chronically ill. Since, in addition to the different method of choosing subjects, the tissues from the United States were preserved by freezing and the foreign ones with formalin, the analytic results for the two populations have been treated separately.

Materials and methods

Material for analysis was obtained from 150 Americans over 20 years of age who had no evident disease prior to their sudden accidental deaths. One hundred and ten were Caucasoid

*Throughout the presentation the term "American" refers to subjects from the United States and the term "foreign" to subjects from the eastern hemisphere.

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Table II. Range (80 per cent) of metal concentrations in American organs*

Metal	90th/10th percentile						
	Liver	*Kidney*	*Lung*	*Aorta*	*Heart*	*Spleen*	*Brain*
Essential							
Mg	2.2	1.9	2.1	2.1	2.1	2.1	2.1
Ca	3.1	3.3	2.5	2.9	3.7	2.8	2.9
Mn	4.0	3.3	5.4	4.2	3.3	3.8	3.2
Fe	4.5	2.8	4.7	4.0	2.1	4.7	2.2
Cu	4.1	1.8	2.0	2.8	1.8	1.8	2.1
Zn	2.7	2.4	2.1	2.5	1.9	1.9	2.1
Mo	4.4	2.4					
Nonessential							
Sr	5.0	4.3	3.8	5.2	6.5	5.5	8.6
Ba	> 15	> 29	10	6.8	> 20	> 24	> 13
Al	7.1	5.9	6.5	13	7.0	12	6.3
Ti			15				
V			> 13				
Cr	> 36	> 44	> 15	> 95	> 80	> 31	> 19
Ni							
Ag	33	> 10		> 10			> 17
Cd	5.7	3.4					
Sn	15	9.2	10	7.6		7.3	
Pb	4.2	5.2	11	8.2		13	> 9.5

*Whenever the value of the tenth percentile was below the minimum measurable concentration, the full 80 per cent range for a metal in a tissue could not be determined. In this situation, a value for the 80 per cent range has been tabulated only if the ninetieth percentile exceeded the minimum measurable concentration by a factor of at least 7. The > indicates that the tabulated values are minimum ones of this type.

and the rest were Negroid; 112 were men. They came from 8 large metropolitan areas scattered throughout the continental United States. Their average age was 44 years. Further data about race, sex, and geographic origin are not presented here because they were not obviously correlated with metal concentrations; however they are tabulated elsewhere.[1] Although, even among adults, metal content varied somewhat with age,[5] the effect was relatively small and is not considered here; however, it too is tabulated elsewhere.[1] A sample of every organ was not available for every subject, but more than 100 samples each of liver, kidney, lung, aorta, heart, spleen, and brain were collected.

Material for analysis was also obtained from 100 subjects over 20 years of age from 8 different geographic areas of Africa, Asia, and Europe: Ruanda-Urundi, Nigeria, India, Formosa, Thailand, Hong Kong, Japan, and Switzerland. Race, age, sex, and some information about the cause of death have previously been tabulated for 95 of these subjects.[3] A sample of every organ was not available for every subject, but 67 or more samples each of liver, kidney, lung, aorta, heart, spleen, and brain were collected. Moreover at least 5 samples of each organ were collected from 7 of the 8 geographic areas; no aortas and only two brains were obtained from Ruanda-Urundi.

All samples were collected at autopsy and individually preserved, the American ones by freezing and the foreign ones in metal-free formalin as previously described.[3] All samples were ashed by the same technique in one laboratory; all of the preserving formalin was ashed with each foreign sample.[3] The ash was then analyzed spectrographically by both anode and cathode layer techniques for a total of 18 metals, 7 essential and 11 nonessential. The details of the analytic method, including standardization, recovery, and reproducibility, are described elsewhere.[4] For most concentrations of most metals, the standard deviations of the levels found

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on repeated assay were less than 20 per cent of the amount known to be present; moreover precision described in this way did not depend on concentration.[4]

In tabulating the data, each of the 18 metals in each of the 7 organs was considered separately. For each of the resulting 126 cases, the highest 10 per cent and the lowest 10 per cent of the individual concentrations were discarded in order to avoid a disproportionate effect from a few aberrant results. The only absolute concentrations cited below are the resulting values for the tenth and ninetieth percentiles of the samples or the limits of detectability when tenth percentiles were not measurable. The 80 per cent ranges of concentrations are ratios of the ninetieth to the tenth percentiles. When this range was narrow for a particular metal in a particular organ, most subjects had relatively similar concentrations. On the other hand, a large range indicated that concentrations varied considerably from subject to subject.

Results

American organs preserved by freezing. Table I cites the range, *tenth and ninetieth percentiles,* of concentrations for each of 18 metals in each of 7 organs. The relatively low concentrations of the nonessential metals are obvious. Marked accumulations of cadmium in the kidney and of aluminum, titanium, and perhaps vanadium in the lung reflect unusually high organ specificity.

Table II indicates the 80 per cent range of concentrations, *ninetieth percentile/tenth percentile,* for each metal in each organ. Essential metals tended to have smaller ranges than nonessential ones. Specifically, of the 44 ranges tabulated for essential metals, three fourths were less than 3.5 and none exceeded twice that value, in fact none exceeded 5.5. In contrast, of the 50 ranges in which nonessential metals had at least a 50 per cent occurrence, most were greater than 7.0 and a quarter exceeded 14.

Foreign organs preserved in formalin. Table III cites tenth and ninetieth percentiles for each metal in each organ. The formalin-preserved foreign tissues resembled the frozen American tissues more closely with respect to essential than nonessential metals. The minimum concentrations of the former were particularly similar and the maximum concentrations of the latter particularly dissimilar. Only for splenic manganese and aortic copper among the essential metals did the American and foreign tenth percentiles differ by a factor of more than 2; whereas the tabulated ninetieth percentiles of nonessential metals usually differed by a factor of more than 2. Moreover in 11 instances, all involving barium, aluminum, and titanium, the foreign ninetieth percentiles were more than 5 times the American values. Of the nonessential metals investigated, lead was much more concentrated in American than in foreign aortas, but tin was the only metal more concentrated in several organs of the American subjects. Chromium, nickel, silver, and cadmium in addition to barium, aluminum, and titanium were more concentrated in several organs of the foreign subjects.

Unusually high concentrations of renal cadmium and pulmonary aluminum, titanium, and probably vanadium were again observed. Moreover cadmium was 4 times as concentrated in the liver as in any other organ except the kidney; this distribution characterized the American as well as the foreign material. The high organ specificity of the other 3 nonessential metals may have involved aortas as well as lungs.

Table IV indicates ninetieth percentile/tenth percentile for each metal in each organ. A comparison with Table II indicates that ranges of concentrations

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were larger for the foreign organs than for the American organs. In general, however, the ranges continued to be smaller for essential than for nonessential metals. Specifically, for most essential metals, the tabulated ranges were less than 3.5; only 2, both involving iron, exceeded 7.0. In contrast for most nonessential metals, the tabulated ranges were at least 14; only 5, three of which involved strontium and one barium, were less than 7.0.

Discussion

The variations in concentrations tabulated above could presumably be lessened by more precise analytic techniques and more homogeneous sampling. Although it might seem ideal to limit subjects to healthy individuals who died suddenly and accidentally, as was attempted for the Americans, and to limit samples to single types of cells, or perhaps single fractions of such cells, it was difficult to obtain even the less adequate material considered here. The difference in the method of preserving the American and the foreign material was apparently relatively unimportant; analyses of both frozen and formalin-preserved kidney and liver from 24 subjects failed to show significant differences related to method of preservation. The data for cadmium and zinc have previously been presented[3] and are typical of the data for the other 16 metals considered here.

Since the populations under discussion had no recognized deficiency of essential trace metals nor toxicity from nonessential ones, the observed 80 per cent

Table III. Ranges of concentrations in organs of foreign adults (formalin-preserved

Metal	*10th and 90th*		
	Liver	*Kidney*	*Lung*
Essential			
Mg	390-820	450-720	300-600
Ca	62-250	160-450	170-600
Mn	1.5-4.2	0.73-2.0	0.25-1.3
Fe	95-570	68-200	200-680
Cu	7.7-32	3.1-*16*	1.6-*8.5*
Zn	44-*230*	35-175	13-36
Mo	0.53-1.7	0.14-0.42	
Nonessential			
Sr	*0.018*-0.075	0.047-0.16	0.073-0.16
Ba	< .001-*0.12*	*0.018-0.17*	*0.068*-0.34
Al	*1.3-18*	*1.1-31*	49-330
Ti	< .1-0.49†	< .1-*0.84*†	0.72-21
V			< .02-0.27
Cr	0.0039-*0.16*	*0.010-0.27*	0.10-1.1
Ni	< .09-*0.39*†	< .09-*0.46*	< .09-0.68
Ag	< *.0009*-0.033	< .0009-0.0092†	< .0009-0.0069†
Cd	< .4-*6.7*	*5.2*-62	< .4-*1.3*†
Sn	< .04-*0.24*†	< .04-*0.14*†	< *.04*-0.62
Pb	*0.14*-1.4	*0.077*-0.72	0.077-0.75

*Numbers in italics indicate where American and foreign tenth or ninetieth percentiles differed by

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ranges of the metals placed some limits on concentrations incompatible with normal function. Control mechanisms required to assure correct amounts of essential trace metals for specific vital processes may explain the relatively small ranges of concentrations of such metals among the entire group of subjects examined. The greater *upper limits* of concentration that were found for most nonessential trace metals among foreign as compared with American subjects may reflect the chronic illness of the former, but more probably it reflects their wider exposure to unusual environmental conditions associated with their wider geographic distribution.

The apparently universally high pulmonary concentrations of aluminum and titanium in adults may well occur because these metals enter the body predominantly via the respiratory tract where they are immobilized. By analogy with equine kidney,[6] it seems likely that the renal cadmium is strongly bound to a protein, but the underlying reasons for the predilection of this metal for kidney remain unexplained. Finally, the arbitrariness of the distinction between essential and nonessential metals must be re-emphasized. Chromium, with its effect on glucose metabolism,[7] seems particularly likely to be transferred from the nonessential to the essential category. Vanadium, which is essential in some protovertebrates and which increases both phospholipid[8] and monamine oxidation[9] in mammalian tissues, is another candidate for such a transfer from nonessential to essential.

tissue)*

Percentiles			
Aorta	*Heart*	*Spleen*	*Brain*
230-920	430-860	270-590	260-490
360-1900	75-350	67-290	67-290
0.11-*0.69*	0.27-0.086	*0.19*-0.74	0.26-0.62
29-*260*	61-200	130-1300	47-94
1.9-12	3.4-8.5	1.2-3.8	4.7-10
15-54	26-49	15-36	8.7-27
0.12-0.87	0.014-*0.19*	0.013-0.11	0.0064-0.096
0.036-0.50	*0.017-0.24*	*0.009-0.18*	*0.015-0.19*
0.94-*51*	*0.87-20*	*0.95-18*	0.38-*10*
< .1-*2.3*	< .1-*0.52*†	< .1-*0.59*†	< .1-*0.42*†
< .02-*0.065*			
< .002-*0.59*	*0.0058-0.38*	< .002-*0.14*	0.003-*0.12*
< .09-*0.85*	< .09-0.38†	< .09-*0.31*†	< .09-*0.24*†
< .0009-*0.032*	< .0009-*0.011*†	<.0009-*0.012*†	< .0009-0.022
< .4-1.3†	< .4-0.68	< .4-*1.1*†	
< .04-0.21	< .04-0.13†	< .04-*0.11*†	
< *.02-0.16*	< .02-*0.26*	0.023-0.48	< .02-0.20†

a factor of more than 2. Otherwise, the conventions are those of Table I.

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Table IV. Range (80 per cent) of metal concentrations in foreign organs*

Metal	90th/10th percentile						
	Liver	*Kidney*	*Lung*	*Aorta*	*Heart*	*Spleen*	*Brain*
Essential							
Mg	2.1	1.6	2.0	4.0	2.0	2.2	1.9
Ca	4.0	2.8	3.5	5.2	4.7	4.4	4.4
Mn	2.8	2.8	5.3	6.3	3.2	3.0	2.4
Fe	6.0	2.9	3.4	8.8	3.2	10	2.0
Cu	4.1	5.0	5.3	6.1	2.5	3.2	2.2
Zn	5.3	5.0	2.8	3.6	1.9	2.4	3.1
Mo	3.3	3.0					
Nonessential							
Sr	4.1	3.4	2.2	7.2	14	8.2	15
Ba	> 120	9.2	5.0	14	14	20	13
Al	14	28	6.7	54	> 23	19	26
Ti		> 8.4	20	> 23			
V			> 14				
Cr	41	26	11	> 300	70	> 74	40
Ni			7.6	9.4			
Ag	> 37	> 10	> 7.7	> 36	> 12	> 13	> 24
Cd	> 17	12					
Sn			> 16				
Pb	10	9.4	9.7	8.0	13	21	> 10

*Conventions are the same as in Table II.

Table V. Differences in the metal concentration of infant and adult organs (frozen American tissues)*

Metal	*Liver*		*Kidney*		*Lung*	
	10th and 90th percentiles (adults)	*Infant median*	*10th and 90th percentiles (adults)*	*Infant median*	*10th and 90th percentiles (adults)*	*Infant median*
Ca	55-170	420				
Fe	95-430	970	72-200	610		
Cu					1.4-2.8	6.1
Ba			< 0.001-0.029	0.061		
Al					*29-190*	*2.8*
Ti			< 0.10-0.12	0.63		
Cr	< 0.002-0.071	0.38	<0.002-0.087	0.81		
Ag	*0.0091-0.030*	*1.3*			< 0.0009-0.0046	0.010
Cd			*13-45*	*< 0.4*		
Sn					0.093-0.93	< 0.04
Pb			0.21-1.1	0.10		

*The figures are micromoles of metal per gram of tissue ash. Numbers in italics indicate when the infant median was more than 10 times the adult ninetieth percentile or less than one tenth of the adult tenth percentile.

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Addendum. There are no extensive data for children comparable with those presented for adults; however, the livers, kidneys, and lungs of 10 infants who died in St. Louis Children's or Maternity Hospitals at less than one month of age give some measure of the changes in metal content which depend on age. These organs were preserved in the same manner as those of the American adults and were analyzed by the same laboratory with the same techniques; but, unlike the American adults, the patients were all from one geographic area and they were not healthy immediately prior to demise.

Table V indicates the 14 instances when the median value for the infants was more than twice the ninetieth percentile or less than half of the tenth percentile previously cited for American adults. For renal cadmium and pulmonary aluminum, the infant median was less than one tenth of the adult tenth percentile, suggesting that these metals accumulated during childhood. The significance of the markedly increased hepatic silver in infants is not clear.

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