Pathobiology

ABNORMAL TRACE METALS IN MAN: LEAD

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INTRODUCTION

LEAD has been considered toxic to man for many years. Although its acute toxicity is relatively low, it accumulates slowly in tissues when exposure exceeds elimination, finally provoking the characteristic overt syndrome of chronic plumbism. Little is known, however, of its recondite biologic activity in small concentrations or after a lifetime of exposure to amounts "normally" found in food, water, or air, although a vast amount of experimental work has been done on larger exposures for the past 70 years.

The body of the "standard American man" contains approximately 80 mg. of lead, much of which is in bone, but with concentrations of more than 1 mg./kg. (wet weight) in the aorta, kidney, liver, and upper respiratory tract.[1,2] Lead was found in every human liver and in all but a rare kidney and lung from human bodies analyzed from the Orient, India, Middle East, Europe, Africa, and the United States.[3] It was present in all newborn infants and children.[4] Of American human tissues it was found in all specimens of aorta and pancreas, and in almost all prostates, spleens, and testes examined.[1,4] Therefore, exposure to lead appears largely world wide, although geographic variations in concentrations may exist.

It is the purpose of this report to answer, in so far as possible, three questions: (1) What are the sources of the lead found in human beings? Many surveys of food and water have been made,[5,6] but it appeared rewarding to reexamine the matter in order to ascertain whether or not exposures have changed in the past 20 years. (2) Is lead by any possibility an "essential" or necessary trace element for living organisms? To our knowledge, no one has proposed that this might be the case, although lead is more prevalent on this planet than are some essential trace metals, such as cobalt or molybdenum. (3) Is lead primarily

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an industrial contaminant, a product of a civilization based on metal, or is it mainly of natural occurrence? While man has been exposed to industrial lead from the beginning of history, are wild animals also exposed? A most important question regarding esoteric toxicity in small doses cannot be answered until lifetime studies of small mammals have been completed. Partial answers to these questions were obtained.

METHOD

Samples were ashed in a muffle furnace at 450°C. for 24 to 48 hours after drying to constant weight. Samples of 1 L. of water were evaporated to 5 to 6 ml., treated with 1 ml. HNO_3 and 1 ml. $HClO_4$, evaporated to dryness, and fumed to drive off the acids. The residues were taken up in deionized water with a resistance of one million ohms or more. Lead was determined by the microanalytic method of Sandell for biomaterial, which depends upon dithizone extraction.[7] Optical density was read at 520 mμ in a Bausch and Lomb Spectronic 20 colorimeter. Recoveries of known amounts of lead added to unknowns usually were 100 per cent. Limits of sensitivity were approximately 0.05 μg per sample. Small amounts of lead in reagents appeared in the blanks and were subtracted from the analytic results.

ORGAN ACCUMULATIONS OF LEAD IN MAN

In Table I are shown the mean concentrations of lead found in kidney and liver in various areas of the world,* by spectrographic analyses of tissues.[3] Levels in Africans were generally lower than in other races, especially in nonurban natives. Figs. 1-3 indicate the mean concentrations of lead in aorta, kidney, liver, lung, pancreas, and bone at different ages in American human beings. There appears to be an accumulation for five or six decades. Noteworthy are the presence of lead in the newborn, indicating placental transfer, and the low values in the bones of infants and children. Data in curves were analyzed for coefficients of correlation (r) and correlation ratios (Eta)[8]; significances are shown in the legends. The curves for liver and pancreas were not statistically valid either as curves or straight line functions.

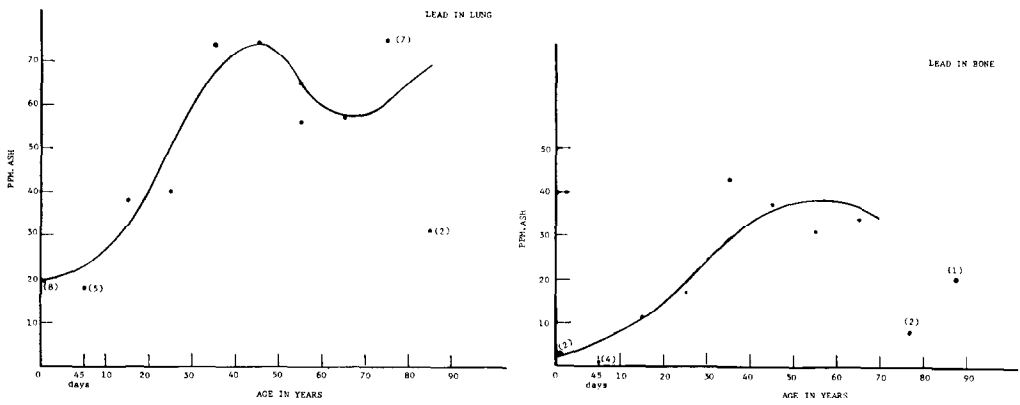
LEAD IN COMMON FOODS

Table II shows the lead concentrations by microanalytic chemical methods in a variety of foods. A few were devoid of lead and an additional few had small amounts. On the other hand, not many had high contents, most showing less than 0.5 ppm. These data are in general comparable to or lower than those obtained by Kehoe, Cholak, and Story 20 years ago.[5] An attempt to calculate the amount of lead per 100 calories of each food is also shown in the table.

LEAD IN WATER

A preliminary survey of potable waters in this area revealed little or no

*Tissues from the United States were collected by Dr. I. H. Tipton and Miss M. J. Cook; those from Africa by Dr. H. M. Perry, Jr., and those from other areas of the world by one of us (H. A. S.).



A. *B.*

Fig. 1.—Change in concentration of lead (ppm. ash) with age in *A*, lung (167 cases) and *B*, bone (79 cases), mean United States values.[1,3] Numbers in parentheses refer to numbers of cases in that decade, when less than 9. Bone ash varied from about 20 to 30 per cent of wet weight; lung ash 0.9 to 1.7 per cent. Statistical analyses[8] for the curve of the concentration in the lung showed: E = 0.28, S.E.$_E$ = 0.07, not significant; r = 0.21, p < 0.01. For that of bone: E = 0.58, S.E.$_E$ = 0.75, p < 0.05; r = 0.32, p < 0.01.

detectable lead, except in instances where lead piping was used. In view of the constant supervision of public health agencies on the lead content of potable water, this survey was not further developed. To determine solution of lead by soft water in a new piping system, analyses were made from a spring and a newly installed tap at the end of 200 feet of black polyethylene and copper pipes, the latter joined with lead solder. The results are shown in Table III. The total hardness of the water was 18 ppm. and the pH, 6.0.

To ascertain the presence of airborne lead, snow was collected from town areas and from a mountain more than a mile from a road. The elevation of the town was approximately 100 M., of the mountain 550 M. above sea level. The results are indicated in Table IV. Presumably the lead came from the combustion of petroleum products at or near ground level, as is inferred from the table.

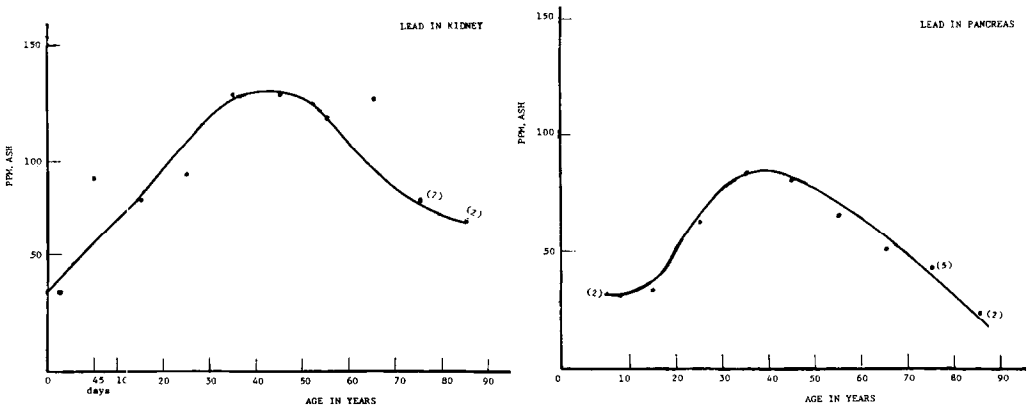
LEAD IN ANIMAL TISSUES

In order to ascertain whether or not exposure to lead occurs in animals other than man, the livers, kidneys, and a few other tissues from both wild and domestic animals were analyzed. The results are shown in Table V. It would appear from these examples that exposure to lead is not confined to man.*

SOURCES OF LEAD IN ANIMALS

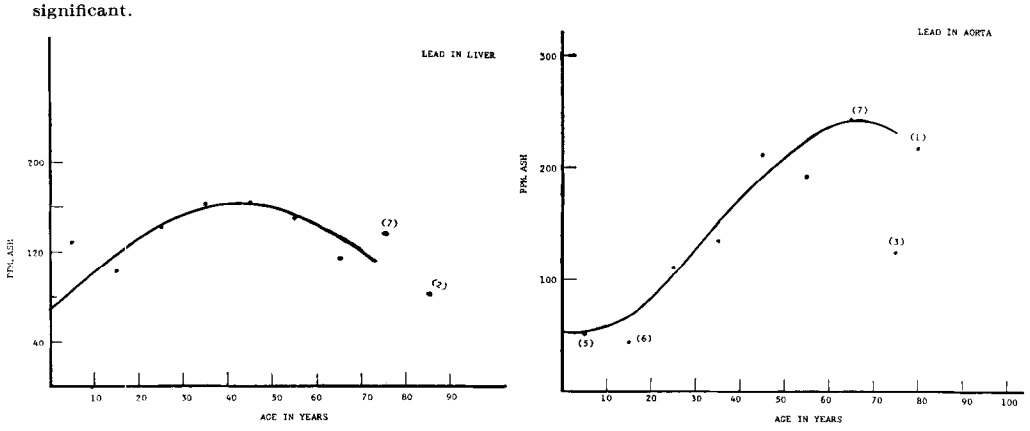
Table VI shows the results of analyses of vegetation, including some samples of food for animals and birds. The high concentrations in apple trees are noteworthy. Although spraying with lead arsenate was begun in 1894, it is doubtful that these trees were ever so sprayed, for they were seeded at some distance

*Tipton found 3.6, 0.16, and 0.27 ppm. lead in the kidneys of three female Tennessee deer and none in a male.[3]



A. *B.*

Fig. 2.—Change in concentration of lead (ppm. ash) with age in *A*, kidney (194 cases) and *B*, pancreas (143 cases), mean United States values.[1,3] Numbers in parentheses refer to numbers of cases in that decade when less than 9. Kidney ash varied from 0.8 to 1.3 per cent of wet weight, pancreas ash 0.7 to 1.6 per cent. Statistical analyses[8] for the curve of the concentration in the kidney showed: E = 0.61, S.E.$_E$ 0.045, p < 0.01. For that of the pancreas: E = 0.136, S.E.$_E$ = 0.082, not significant; r = 0.02, not significant.



A. *B.*

Fig. 3.—Change in concentration of lead (ppm. ash) with age in *A*, liver (207 cases) and *B*, aorta (102 cases), mean United States values.[1,3] Numbers in parentheses refer to numbers of cases in that decade when less than 9. Liver ash varied from 0.8 to 1.8 per cent of wet weight, aortic ash from 0.5 to 3.4 per cent. Statistical analyses[8] for the curve of the concentration in the liver showed: E = 0.22, S.E.$_E$ = 0.066, not significant; for that of the aorta E = 0.396, S.E.$_E$ = 0.084, p < 0.05.

from orchards over 100 years old which has now virtually disappeared except for dead or dying old trees in the midst of a forest of marketable hardwood. In Table VII are the concentrations of lead found in a variety of building and other materials to which laboratory animals might be exposed. The impossibility of obtaining a strictly lead-free environment is clear from these results, although low levels in food are possible to achieve by careful choices.

DISCUSSION

The present report is the second of a series on the presence and sources of "abnormal" trace elements in man (and animals). It attempts to obtain data which will lead to a decision as to whether or not certain metals are essential,

TABLE I. LEAD IN ADULT HUMAN KIDNEY AND LIVER FROM VARIOUS AREAS OF THE WORLD. MEAN VALUES, PPM. ASH. (From Tipton, et al.[1,3,4])

AREA	NUMBER OF SAMPLES	KIDNEY PPM.	LIVER PPM.
United States Mainland—A*	88	120	150
—B†	18	92	120
Honolulu	5	84	150
Alaska	2	57	37
Cairo	3	110	200
Beirut	6	76	125
Bombay	9	88	74
Delhi	10	41	55
Vellore	13	98	92
Bangkok	9	91**	74**
Manila	4	51	77
Hong Kong	10	100	213
Taiwan	9	160	125
Tokyo	10	98	94
Kyoto	11	37**	105
Nigeria	19	37‡	94
Lambarene	6	57	104
Welkom	5	38**	60
Uganda	4	28	25
Usumbura	11	23‡	20**
Bern	9	50	100
Total and range	261	23–160	20–213

The median per cent of ash in kidneys was 1.1 (90% range 0.8-1.3) and in livers 1.3 (90% range 1.0-1.8).

No geographic variations in concentrations of lead in the liver or kidney from data from 7 cities of the United States were found, maximum deviations from the mean being 30 per cent for kidney and 25 per cent for liver.

*U. S.—A = Accidental deaths.

†U. S.—B = Cardiovascular deaths.

**Trace In one, not used in mean.

‡None detectable in one, not used in mean.

or are industrial or natural contaminants, and whether or not they accumulate in man. The first report dealt with cadmium.[9] We are interested in the 29 common trace elements found in man in easily detectable amounts.[1] Of these, lead ranks twenty-third in order of magnitude of abundance in the universe.[10] It ranks sixteenth in the earth's crust and ninth in sea water, from which all life evolved. In alfalfa (lucerne) it ranks eighteenth of 20,[11] and in coal, eighth of 14.[10] In the body of man it ranks seventh (omitting all bulk elements), being exceeded only by essential iron, zinc, and copper, and by rubidium, strontium, and aluminum.[2] Its concentration considerably exceeds those of manganese, molybdenum, and cobalt in the whole body and in such tissues as the liver, spleen, kidney, lung, and muscle.[2]

For a working hypothesis, one can suspect a trace metal to be essential for mammals if it has the following characteristics: (1) It is ubiquitous on the earth's crust and therefore readily available. (2) It is present in plants and in at least one mammalian organ or tissue. (3) It shows biologic activity in vitro, affecting one or more common enzyme systems. (4) Its molecular weight is (probably) below elements in the lanthanum series. (5) It is relatively nontoxic to mammals orally, a dose equal to the total body pool being readily tolerated. Lead satisfies only the first two of these criteria.

TABLE II. LEAD IN FOOD

SAMPLE	μG/GM WET WEIGHT	μG/100 CALORIES*
Condiments		
Table salt, iodized	0.0	——
Pepper, black	0.40	——
Sugar, white, granulated	0.0	——
Sugar, white, granulated	0.07	1.8
Molasses, New Orleans	0.53	20.4
Baking powder	1.50	——
Yeast, dry	1.17	——
Sea Food		
Shrimp, frozen, uncooked	0.31	27.2
Shrimp, fresh	0.45	39.4
Lobster, claw meat, Maine	2.50	111.0
Crabmeat, canned, Japan	0.06	4.8
Clams, fresh frozen	0.15	31.3
Oysters, canned, American	0.13	26.0
Scallops, fresh	0.15	15.0
Anchovies, fillets	0.87	29.9
Kippered herring, Norway	0.30	15.0
Sardines, canned, Portugal	0.75	25.0
Swordfish, Atlantic	0.17	17.0
Haddock, Atlantic	0.27	27.0
Mean	0.49	——
Meats		
Beef, chuck	0.20	11.3
Beef, marrow	0.07	——
Lamb, chop	0.15	8.0
Lamb, marrow	0.37	——
Pork, chop	0.16	5.3
Gelatin, dry	0.57	14.3
Egg, whole	0.0	——
Egg, whole	0.15	9.0
Mean	0.21	——
Grains and Grain Products		
Wheat, winter, seed treated	0.19	5.6
Wheat, crushed, Vermont	1.39	40.8
Wheat, Japanese #4	0.0	——
Wheat, Japanese #6	0.24	7.1
Flour, wheat, all-purpose	0.23	7.0
Flour, wheat, all-purpose	0.52	14.9
Flour, wheat, Japanese #5	0.52	15.3
Bread, stone ground, whole wheat	0.86	34.4
Wheaties	0.10	2.5
Puffed Rice	7.49	214.0
All-Bran cereal	0.21	7.0
Grapenuts	0.10	2.8
Oats, seed	0.62	15.5
Oats, feed	0.60	15.0
Oats, quick cooking	0.56	14.0
Rye, seed	0.20	6.0
Buckwheat, seed selected	0.19	5.4
Rice, American, polished	0.06	1.2
Rice, Japanese, #2 polished	0.07	1.5
Rice, Japanese, #5 unpolished	0.0	——
Rice, Japanese, 204 samples	0.10	2.8

*From McCance, R. A., and Widdowson, E. M.[27]

TABLE II—CONT'D

SAMPLE	μG/GM WET WEIGHT	μG/100 CALORIES*
Grains (Cont'd)		
Corn, frozen	0.58	16.5
Corn meal, New Hampshire	0	——
Corn, 50-year old, on cob	0.16	4.5
Corn oil	0.0	——
Vegetable shortening	0.27	3.4
Mean	0.37	——
Vegetables		
Potatoes, white, raw	0.12	13.8
Cabbage, white	0.0	——
Cabbage, red	0.02	10.0
Kale, organically grown	1.26	504.0
Lettuce, garden, organically grown	1.04	36.6
Lettuce, commercial	0.03	27.2
Kohlrabi, leaves, organically grown	0.28	112.0
Broccoli, frozen	0.07	49.0
Beet greens	0.36	144.0
Swiss chard, organically grown	0.75	300.0
Spinach	0.16	64.0
Cauliflower leaves, organically grown	0.09	82.0
Celery, green	0.10	100.0
Chicory, fresh	0.81	810.0
Escarole, fresh	0.27	270.0
Beans, string, frozen	0.01	1.1
Beans, string, canned	0.03	3.3
Beans, red kidney, dried	0.16	5.3
Beans, yellow eye, dried	0.21	7.0
Beans, navy, dried	0.0	——
Peas, frozen, fresh	0.02	3.0
Peas, split, dried	0.0	——
Peas, canned	0.11	12.7
Tomato juice, canned	0.08	53.3
Tomato, fresh	0.02	13.3
Apple, raw, McIntosh	0.38	76.0
Pear, raw	0.03	7.5
Mean	0.21	——
Fluids		
Milk, whole, fresh local	0.0	——
Milk, skim, dried, packaged	0.79	24.2
Milk, skim, dried, bulk, same	0.02	0.6
Milk, evaporated, #1	0.05	3.2
Milk, evaporated, #2	0.04	2.6
Cola, #1	65/L.	13.0
Cola, #2	18/L.	3.6
Mineral water, bottled, Hot Springs, Ark.	5/L.	——
Ginger ale	10/L.	——
Tea, Orange Pekoe	1.37	——
Cocoa, dry	0.10	2.0
Cider, apple, local	90/L.	18.0
Vinegar, cider, local	100/L.	——
Beer, canned	40/L.	8.0
Wine, red	50/L.	——
Cigarettes		
Filtered, whole	24.11	482.0/pack

*From McCance, R. A., and Widdowson, E. M.[27]

TABLE II—CONT'D

SAMPLE	μG/GM WET WEIGHT	μG/100 CALORIES*
Spices		
Cinnamon	0.11	
Nutmeg	0.41	
Cloves	0.10	
Allspice	0.64	
Chili powder	0.18	
Bay leaves	0.55	
Animal Foods		
Dog food	0.0	——
Beet pulp	1.80	360.0
Calf food, prepared	0.32	32.0
Bird seed, wild	0.65	——
Wheat, poultry	0.02	0.6
Rye, seed, dried milk and corn oil diet #1	0.37	9.3
#2 (bulk milk)	0.20	5.0
#3	0.20	5.0
#4	0.20	5.0
#6	0.26	6.5
#9	0.20	5.0
Poultry wheat, dried milk and corn oil diet	0.08	2.0
Dog meal, A, 1954	94.0	Spectrographic Method†
1958	1.9	
Dog chow, B, 1954	14.8	
1958	0.40	
Rabbit chow, 1954	trace	Chemical Method†
1958	1.7	
Rat diet 1958	1.9	
Wheat and milk diet, 1958	0.7	

*From McCance, R. A., and Widdowson, E. M.[27]

†These analyses were done in 1954 and 1958 by Robert E. Keenan, Principal Spectrochemist, United States Public Health Service, Occupational Health Field Headquarters, Cincinnati.

TABLE III. LEAD IN POTABLE WATER (μG/L.)

SOURCE	Pb	PIPING AND REMARKS
Tap, laboratory, cold	2.3	Brass, town water supply
hot	4.5	Brass
Spring, forest, piped #1	0	600 feet galvanized, copper in house
Spring, forest, unpiped #2	0	
Spring, field, piped #1	4.2	Lead, 75 years old
Spring, field, piped #2	112.5	Lead, 50 years old
Well, artesian, piped	0	Galvanized
Spring, forest, old, at source	0	Rock walls
after rebuilding	0	Poured cement walls
through pipes, turbid	24.0	First run through 210 feet black polyethylene, 10 feet copper and hot water heater "glass-lined"
filtered	10.0	
six weeks later	3.3	
Mineral water, bottled	5.0	From Hot Springs, Ark.

TABLE IV. LEAD, CADMIUM, AND NICKEL IN MELTED SNOW (μG/L.)

SAMPLE LOCATION	AGE (DAYS)	Pb	cd	Ni
A—Edge of town 100 M. elevation				
1. Open porch 10 M. high	0	0	0	0
2. 300 M. from street, open lawn	0	5.25	0.38	0
3. 3 M. from street, lawn	0	12.0	0.5	0
4. Side of street, plowed and fresh	0+	77.0	0.75	0
B—Top of mountain, 550 M. elevation				
1. Open lawn 20 M. from house, fresh	0	0	0	0
2. Same, old	8	3.9	0	0
3. Forest, 100 M. from house	2	1.0	0.5	0
4. Near auto exhaust 5 minutes	0	1858	0.98	0.56

Note: Location "*A*" was on the grounds of the Brattleboro Retreat, bordering a fairly well-traveled road. The area is suburban, verging on rural. Sample A-1 was from one of the buildings, which lies approximately halfway between location of samples A-2 and A-3 and 4. Oil is used for heat.

Location "*B*" was near an old farmhouse close to the top of a mountain at the road's end, one mile from a country road and nearest other house. It lies approximately four miles from the nearest highway and is 400 M. higher. Oil is used for heat. Auto engines run approximately 5 minutes per day. Sample B-2 and B-3 were exposed only to chimney smoke from wood and oil.

TABLE V. LEAD IN ANIMAL TISSUES

SAMPLE	μG/GM WET WEIGHT	REMARKS
Liver		
Salmon, young, Miramachi R.	0.88	First return to river
Salmon, 4 years+, same	0.71	4 trips to river
Starling	2.12	Shot, 22 cal. bullet in neck
Robin	1.10	Killed accident
Ruffed grouse	0.56	Found dead
Red squirrel, female	1.37	Trapped
Red squirrel, male	2.08	Trapped
Rat, Long-Evans, 33 days old	0.39	
Same 28 days old	0.83	
Same 145 days old	0.0	"Lead-free" diet
Rabbit, wild	0.57	Trapped
Deer, #2	0.0	Shot
Deer, #3	0.36	Shot
Deer, #4	0.50	Shot
Deer, #5	0.45	Shot
Pork, #1	0.82	
Pork, #4	0.26	
Beef	0.67	"Organically" raised
Rat, Long-Evans weanling, 28 days	0.37	Rockland Farms
Rat, Long-Evans weanling, 31 days	0.83	Rockland Farms
Human (mean)	2.0	Ref. 2
Kidney		
Ruffed grouse	26.17	Found dead
Gray squirrel, male	1.47	Shot
Rabbit, wild	2.91	Trapped
Deer, #1	0.57	Shot
Deer, #2	0.72	Shot
Deer, #3	0.45	Shot
Deer, #4	0.40	Shot
Deer, #5	1.40	Shot

TABLE V—CONT'D

SAMPLE	μG/GM WET WEIGHT	REMARKS
Kidney (Cont'd)		
Deer, #6	0.34	Shot
Deer, #7	1.17	Shot
Deer, #8-a	0.20	Shot
Deer, #8-b	0.0	Shot
Pork, #1	0.98	
Pork, #3	0.84	
Pork, #4	0.26	
Beef	0.51	"Organically" raised
Human (mean)	1.24	Ref. 2
Bone		
Beef, foreleg	0.16	
Human (mean)	6.6	Ref. 2
Muscle		
Beef	0.20	
Pork	0.16	
Lamb	0.15	
Human (mean)	0.14–0.19	Ref. 2
Heart		
Chicken	1.71	
Gray squirrel	0.50	
Human (mean)	<0.2	Ref. 2
Aorta		
Human (mean)	2.51	Ref. 2
Male, aged 82	2.13	

Essentiality of Lead.—From its ubiquity in almost all natural material and in wild animals, and from its concentration in the biosphere, one might infer that lead is an essential trace element. The prevalent belief in the toxicity of lead, however, has argued against such an hypothesis, although another metal equally or more toxic (cadmium) has been considered as possibly essential.[12]

Lead, like cadmium, when it acts at all upon an enzyme system or a living organism, is inhibitory,* mainly, perhaps, by binding free sulfhydryl groups.[13] On living organisms, lead (chloride) immobilized *Daphnia magna* at concentrations of 0.01 to 1.0 ppm. and was lethal to various fish at 0.1 to 50 ppm., which is in the range of toxicity of zinc and nickel; these three metals were considerably less toxic than copper, cadmium, mercury, and silver ions.[14] It is not as toxic orally for mammals as cadmium and mercury, but is more so than copper, manganese, silver, vanadium, zinc, chromium, molybdenum, cobalt, nickel, and

*This statement is not strictly true. Pb^{++}, along with four other trivalent ions, may further activate phosphoglucomutase which requires Mg. or Mn.[28] Lead has been shown to act as a constrictor of the arteries of the dog's hind limb when perfused in low concentrations.[29] No known enzyme, however, has been shown to require lead, although experiments aimed at finding one have been few.

TABLE VI. LEAD IN VEGETATION

SAMPLE	μG/GM WET WEIGHT
Apple, wild, 6″ diameter tree, #1	0.02
Leaves	4.49
Twigs	20.75
Bark	22.00
Apple, 14″ diameter tree, once cultivated, #2	0.11
Leaves	0.0
Twigs	4.78
Apple, wild, 4″ diameter tree, #3	0.09
Leaves	5.5
Hemlock bark, wild	10.1
Twigs	3.0
Needles	3.2
Spruce twigs, wild	1.6
Needles	2.04
Pine twigs, wild	4.2
Needles	1.8
Sumac berries	0.75
Sawdust, pine, local	1.6
Wood chips, northern New Hampshire	1.83
Peat moss, Sphagnum, #1	1.7
Same, #2	1.6
Hay, fertilized field, #1, tractor baled	1.25
Hay, fertilized field, #2, tractor baled	1.7
Hay, unfertilized field, tractor baled	1.1
Elm, center, grown 1865-1870 (Cd, 0)	0.16
Section grown 1900-1910 (Cd, 0)	0.12
Outer section, 1940-1947 (Cd, 0.01 ppm.)	0.33
Late growth, 1956-1959 (Cd, 0.04 ppm.)	0.74
Bark and cambium (Cd, 0.08 ppm.)	3.9

TABLE VII. LEAD IN COMMON MATERIAL

SAMPLE	μG/GM WET WEIGHT
Scotch tape, filament, glass	1.67
Scotch tape, black plastic	196.00±
Salt, rock, crude, road	0.37
Calcium chloride, crude, road	0.0
Sheet rock	0.75
Sheet rock, plastic	0
Tar paper, building	8.1
Whitewash, old	3.2
Cement, old	0.25
Fabulon, plastic	0.25
Krylon, plastic	0.57
Cork, rubber, A. H. T. Black	1.47
Newsprint, blank, unused	2.41
Paper, shredded, excelsior #1	1.35
Paper, shredded, excelsior #2	2.65
Paper towels	9.78
Polyurethane foam	0.55
Cellophane excelsior, white	2.4
Hytron disinfectant	3.75
Polyethylene, copper colored	1.04

probably arsenic.[14,15] Calves have survived 2 Gm. per day for two to three years, but poisoning in man has been reported from the use of drinking water containing 0.18 to more than 1.0 ppm., or 0.4 to 2.5 mg. daily in addition to lead in food. Of the total bodily content in man (80 mg.) it is probable that 1 or 2 per cent ingested daily would produce poisoning eventually. Acute toxicity is low; the body pools of antimony, arsenic, and cadmium, taken as single doses, are within toxic limits.[14,15] All of the essential trace metals have a wide margin of safety and their total bodily contents can be given orally, limited only by gastrointestinal irritation.[15] No essential metal, insofar as is known, has a molecular weight above 127 (iodine) and most of them are below 97 (molybdenum). Therefore, the available data imply that lead is not an essential trace metal, but this point cannot be proved. If it is, then, like cadmium, its action is inhibitory.

Accumulation With Age.—Accumulation of lead with age in 6 tissues of American human beings appears to follow a fairly consistent pattern, reaching a maximum in the fifth or sixth decade. In 4 tissues the highest mean concentrations were four to ten times those at birth or in childhood; the curves would be much steeper if total amounts per organ were calculated during the growing period. In the liver and pancreas increases in concentration were smaller.

Concentrations in the liver, kidney, and pancreas were in the same general ranges as those reported by Butt and others[16] from Los Angeles, when calculations for different methods of reporting are made. Those for the lung were less, perhaps as a reflection of airborne lead. Total bodily contents based on these data[1,2] are lower, however, than from other calculations.[6] Although individual variations were wide, three of these curves are statistically significant. Accumulation in the aorta, which rises sharply in early decades, was an unexpected finding; the explanation that lead accompanies calcium is not wholly valid in view of the rapid accumulation in young adults who would not be expected to have much aortic calcification. The apparently low values in bone ash, as compared to ash of other tissues, are functions of the high ash content of bone.

According to these spectrographic analyses [1,2] calculations can be made of the approximate amounts of lead in the major tissues and organs of the "standard" man. These turn out about as follows: muscle, 4.8 mg.; skin, 3.3 mg.; skeleton, 46.2 mg.; blood, 1.6 mg.; gastrointestinal tract, 0.6 mg.; liver, 3.4 mg.; lungs, 0.7 mg.; kidneys, 0.4 mg. From these approximations almost half of the total body pool is in tissues other than bone. Some lead was found in all organs examined except brain and heart, where its occurrence was sporadic. Therefore, the idea that bone is the main area of storage must be revised, although it is the tissue of highest concentration (6.6 ppm. wet weight) (Kehoe and coworkers[5] found 18.8 in long bone and 4.7 ppm. in rib).

Lead Balance.—Monier-Williams gives the following figures for an approximate daily lead balance in a normal individual (in England):

	Intake	*Excretion and Storage*	
From food =	0.22 mg.	Feces	0.30 mg.
From water	0.10	Urine	0.05
From inhaled dust	0.08	Stored in Bones	0.05
Totals	0.40 mg.		0.40 mg.

According to Kehoe[17] the average balances should be adjusted somewhat as follows:

Intake		*Output*	
From food	0.31 mg. (0.1–4.0)	In feces	0.32 mg.
From water	0.02	In urine	0.03
From air	0.02		
Totals	0.35 mg.		0.35 mg.

He has calculated that somewhat less than 10 per cent of ingested lead is absorbed and that the output exceeds the amount of food and water by about 20 μg per day, which probably comes from air. He does not believe that lead in normal amounts continues to accumulate in tissues for a lifetime, but that a balance is achieved.

If the total body pool is about 80 mg.,[2] approximately 2 mg. per year or 6 μg per day would be retained for 40 years, neglecting the small level present at birth. It would be difficult to detect 6 μg by usual methods. If 10 per cent of ingested lead, or 35 μg were absorbed per day, the calculated 6 μg would represent retention of approximately one-sixth, with urinary excretion of five-sixths.* These rough approximations fall within the known values for balances on average American adults.

By spectrographic analyses, Perry and Perry[18] found 120 μg per L. of urine (± S. E. 35.5) or 169 μg per day to be the urinary excretion of 24 people in St. Louis. This amount is higher than usually measured. Kehoe and associates found 29 μg per L., or about 10 per cent of the amount ingested.[5]

The lead concentration in foods found in this study by chemical methods and those reported in 1940 by Kehoe and others,[5] on the basis of results obtained by spectrographic methods, are in similar or lower ranges. Many of their raw materials came from Mexico and a few analyses gave much higher values than ours. There appears to be no obvious increase in lead content of common foods during the past 20 years, as estimated by these data. The use of lead glazes on utensils has diminished considerably as a donor to food.[6]

Lead in Food.—According to our data, a normal diet of 2,300 calories with 100 Gm. protein and 250 Gm. carbohydrate will contain about 0.14 mg. of lead plus a variable amount in vegetables and drinks. Analysis of an institutional diet for one day with beverages of approximately 2,040 calories and weighing 2,526 Gm. wet, showed 258 μg of lead, of which 54 was in the 550 calorie breakfast, 69 in the 800 calorie lunch, and 135 in the 690 calorie dinner (which included gelatin). A diet low in lead can be calculated, using meats, dried legumes, eggs, and fresh milk as the proteins (lead ± 9 μg/100 Gm.), certain Japanese wheat and rice as the carbohydrates (no lead), cabbage and lettuce (4 μg/100 Gm.), corn

*Retained "normal" tissue lead is probably quite strongly chelated to protein, most likely to sulfhydryl groups. Perry and Perry[18] found only a 2.2 fold mean increase of urinary lead in eight patients after daily intravenous injections of disodium calcium ethylenediaminetetraacetate for 10 days. Zinc, on the other hand, increased more than tenfold, suggesting that large amounts are relatively loosely bound. This chelating agent did not mobilize tin, silver, nickel, or molybdenum and increased the excretion of cadmium, manganese, and vanadium less than twofold.

oil and butter. Such diets would contain about 15 μg of lead per day. Contrariwise, diets high in lead can be made up of lobster, whole wheat bread, oatmeal, dried milk, frozen corn, kale, and chicory, washed down with apple cider and colas, which would contain more than 1.3 mg. of lead. A reasonably liberal diet, however, appears to have about the same amount as calculated by Kehoe and others,[5] i.e., approximately 0.29 mg. per day or less. Thus, exposure from food may be somewhat sporadic. If these calculations are correct, it becomes obvious that lead from other sources (most likely air) makes up a small proportion of the intake, and that only a minor fraction is stored in the tissues.

Contrary to common belief, little lead may enter some foods from solders on cans, although the amounts vary with the type of food and the tin content of the solder.[19] In one series of experiments, average values of lead in solution after six months' contact in cans sealed with a tin (2.5 per cent), silver (2.5 per cent), and lead (95 per cent) solder were (ppm.): Evaporated milk 0.38, orange juice 0.04, green beans 0.02, corned beef hamburger 0.05.[19]

Because most foods of whatever nature contain lead in quantities of 0.5 ppm. or less, it is obvious that diets containing large amounts of low-calorie vegetables may have much larger quantities of lead than would more concentrated diets. Table II shows that 1,000 calories of American grain products supply an average of about 0.12 mg. of lead, while 500 calories of leafy vegetables might have as much as 1.0 mg. For practical purposes, therefore, the intake depends more upon the nature of the diet rather than on a choice of specific foods.

Lead in Water.—Water in these days of galvanized and copper piping probably contributes little lead to the body pool. Standards for purity of potable water set a limit of 0.1 ppm.,[20] or about 0.2 mg. per day, a relatively large amount. Analyses of water from 51 locations on 16 major rivers of the United States made twice in 1958 and 1959[21] showed detectable lead by the spectrographic method only 7 times: the Arkansas at Coolidge, Kansas (0.1 ppm.), the Columbia, near Clatskamie, Oregon (0.02 ppm.), the Delaware at Philadelphia (0.08 ppm.), the Mississippi at Delta, Louisiana (0.01 ppm.), and at Burlington, Iowa (0.08 ppm.), the Ohio at Cincinnati (0.03 ppm.), and at East Liverpool, Ohio (0.02 ppm.). The few water supplies analyzed in this area showed at most a few micrograms; most of these waters were soft and acid and therefore liable to dissolve lead from pipes and joints.

Lead in Air.—The amount of lead which air can contribute to the human pool was not measured. Presumably a major portion of airborne lead comes from additives to gasoline used for the past 35 years.* That lead (and cadmium) can accumulate in snow from air is shown in Table IV, where low-lying areas near a road rapidly became contaminated while snow from a 30 foot elevation showed none. Thus a portion of the lead absorbed by man probably comes from gasoline or petroleum as an industrial contaminant.

*The estimated domestic consumption of tetraethyl lead in 1960 was 536 million pounds, or about 150 thousand long tons of lead. This represents approximately 15 per cent of the over-all lead consumption in the United States. About three quarters of this lead was exhausted into the air during driving, from 27 to 40 per cent of that amount settling rapidly.[17]

The amount of lead in air depends upon the locality, in one survey varying from an average of 9.5 $\mu g/M.^3$ in Philadelphia to 0.05 μg in Minneapolis; and 0.1 to 0.9 in nonurban areas. In general it was larger in the largest cities.[17] According to Tabor and Warren,[22] of 754 samples of air, 83 per cent contained less than 1.6 $\mu g/M.^3$ and 5.4 per cent contained 3.9 to 2.4 μg; lead was detected in all but 10 samples. At a respiratory volume of 15 $M.^3$ per day, the amount inhaled in a few localities could reach 0.06 to 0.3 mg. but would usually be less than 0.02 mg., provided that all the air inhaled was equally contaminated.

Variations in amounts of lead found in various sections of an elm tree 97 years old by ring count suggest increasing exposures during the last 100 years, especially in the past 30, for there is little circulation in the center of large trees. Presumably this increment represents airborne lead.

The concentrations of lead found in one brand of cigarettes were in the range of those previously reported,[23,24] e.g., 19 to 80 ppm. The amount in tobacco smoke found by spectrographic analyses[24] was, however, only about 1.0 to 3.3 μg per cigarette, providing 20 to 66 μg per pack. This lead is believed to come mainly from lead arsenate [24] and offers to smokers an additional source of airborne metal about equal to that from motor exhaust.

Industrial Contamination.—A further suggestive answer to the question on possible contamination with industrial, especially airborne lead, is found in analyses of human tissues from various areas of the world. Concentration in the kidneys, for example, showed the following major geographic differences (ppm. ash, median values): United States 94, Switzerland 45, Africa 36, Middle East 72, and Far East 82. Values for liver concentrations were: United States 130, Switzerland 59, Africa 66, Middle East 86, Far East 110. Therefore, the Swiss and African tissues analyzed appear to have a bit less lead than do those from other areas. This difference also held for lung tissue.

Immediate sources of lead in wild animals apparently lie in foliage and seeds. Remote sources from forests are probably not the result of industrial contaminants,* but more likely of natural lead in soil. The upper lithosphere has an average lead concentration of 16 ppm., most of it unavailable to plants.[25] The absence of lead in the fertilizers examined suggests that both natural lead, and, in locations contaminated by exhaust fumes from leaded gasoline, airborne lead, may be the remote sources in vegetables and other foods to which domestic animals and man are exposed. Unlike cadmium,[9] probably little or no lead was transferred to food from these fertilizers.

Man has been exposed to lead from the beginning of the age of metals. During the time of the Roman Empire, water pipes and cisterns were made of lead (in Pompeii, for example), and lead vessels were in common use. Lead oxide has been the principal white pigment of paint for over 2,000 years. It is not known whether exposures from all sources have decreased or increased during the past 100 years; waterborne lead from piping has virtually disappeared in this country, but airborne lead almost certainly has increased. Direct contact of

*In suburban areas of Connecticut, considerable lead has been found in juniper bark (25-50 ppm.), shrubs (50-100 ppm.), soil (25 ppm.), yew, and turf from a golf green (10-50 ppm.), presumably from spray residues or gasoline fumes.[23]

lead with foods has lessened owing to government standards. It was impossible to estimate from our data, in these days of tractors and leaded gasoline, the proportion of natural as compared to industrial lead in food.

In 1949, Monier-Williams [6] wrote: "If we assume that lead at these low levels of intake, is absorbed from food as readily as it is from water, we arrive at 0.8 mg. as a safe lead intake from all sources, 1.15 mg. as the maximum permissible and 1.50 mg. as a dangerous intake. Admittedly this estimate is based on a number of assumptions and approximations, but if it is sound it indicates that a total lead intake of roughly 1 mg. daily is the maximum permissible." Kehoe considers 0.6 mg. as the upper limit,* with twice that amount probably injurious in 10 years or more.[17,34]

In the lithosphere and biosphere lead has a great affinity for sulfur, being more strongly chalcophile than many metals of biologic interest.[25] It displaces copper from the sulfhydryl groups of bovine serum albumin,[26] for example. It is also a lithophile element, its ionic radius making it possible for lead to displace potassium, strontium, barium, and, in certain minerals, calcium in carbonates and phosphates.[25] It has been implicated, and discounted, as a cause of many chronic diseases, including hypertension and atherosclerosis; the voluminous work on the toxicity of lead has usually failed to prove it a culprit, although hypotheses are legion.

In one condition, however, toxic amounts of lead have apparently led to disease after recovery from toxicity. Henderson in Queensland described the curious coincidence of plumbism in childhood (from paint) followed decades later by chronic nephritis leading to uremia.[30] The kidneys showed a characteristic pathologic pattern apparently secondary to loss of renal substance, which was unlike any of the known renal diseases. Danilovic has reported similar cases of chronic nephritis confined to a small area in Yugoslavia; the source of lead was in a millstone where local grain was ground.[31] Porritt has called attention to the correlation between lead water pipes and toxemia of pregnancy in England and Wales.[32] That a metallic insult to an organ in childhood may cause apparently irreversible changes leading to death many years later is of considerable interest to the hypothesis that certain "abnormal" trace metals may influence chronic disorders in man.

From our data it would appear that the daily amounts usually ingested by American adults are much lower than the limits set by Monier-Williams and by Kehoe, unless foods high in lead are chosen,† and that they seldom approach or exceed the values which have been considered eventually harmful. Whether or not the lead accumulating in tissues is in inactive "depots" or exerts biologic activity is unknown, as are the lifetime effects of these relatively small amounts.

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*Regulations under the Food, Drug and Cosmetic Act of Connecticut set limits in food at 7 ppm.,[23] an amount which would almost surely cause chronic plumbism if applied to all food.

†Warren and Delavault have analyzed several English and Canadian vegetables from a variety of locations for lead by chemical methods.[33] Many of his values are higher than ours, especially when the vegetables were grown near highways. Some samples of potatoes, for example, had 3 to 12 ppm., of oats 1 to 6 ppm., and of brassicas 1 to 3 ppm. This much lead in food would exceed the "safe" limits for human tolerances. Geographic differences in the lead content of vegetable foods require further investigation.

Larger quantities may be regularly ingested, however, in certain local areas affected by natural or industrial lead in soil or water.

SUMMARY AND CONCLUSIONS

1. The concentrations of lead in a variety of foods, tissues, vegetation, and manufactured products were measured by a microanalytic chemical method and data on human tissues obtained by spectrographic methods were analyzed statistically.

2. Lead seems to be ubiquitous.

3. Lead accumulates with age in the American human kidney, liver, lung, bone, pancreas, and aorta up to the fifth or sixth decade.

4. No obvious increase in exposure from foods or fluids during the past 20 years was demonstrated, although airborne lead has probably increased. This latter increment to the total body burden is usually small.

5. Wild animals and birds are exposed to lead.

6. Lead is probably not an essential element.

7. Lead in human tissues appears to come both from natural sources and from industrial contaminants, although the proportions from each source could not be estimated.

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