THE HARBEN LECTURES, 1960

THE METABOLISM OF LEAD IN MAN IN HEALTH AND DISEASE

by

ROBERT A. KEHOE, M.D.

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ERRATA

Page

2. Left column, line 14, correct typographical error in "elsewhere"
5. Right column, line 5 from bottom, place comma after "occasionally,"
11. Table 12, last column should be headed:

Blood Lead in mg. per 100 g. whole blood by Spectrograph	*Blood Lead in mg. per 100 g. whole blood by Dithizone*

13. Left column, line 8 from bottom, place comma after "inconsistent,"
17. Reference 5 (b), place comma after "Stevens, C.D.,"
    9, place comma after "Kehoe, R.A.,"
19. Right column, line 7 from bottom, place comma after "it,"
20. Right column, line 8 from bottom, place comma after "experiments,"
21. Table 17, the heading Successive Periods of 28 Days should be in the box directly to the right, and the numbers below should read 1st, 1st, 2nd, etc.
43. Right column, line 3 under Fig. 13, place comma after "cipitation,"
44. Right column, line 8, "lunar months" should read "weeks"

48 and 49. Fig. 18 and Fig. 20, the first number (2) in the baseline of the sections identified as the "Period after termination of exposure" is an error of photography.

62. Left column, line 26 of main paragraph is line 38 of the same paragraph, reprinted in error. It should be deleted and substituted by "trations of lead in the two types of skeletal"
64. Left column, line 11, place comma after parentheses; line 9 from bottom, place comma after "obvious,"
69. Left column, line 32, "specification" should read "specifications"
70. Left column, line 9 from bottom, "hazard" should read "hazards"
73. Right column, line 9 from bottom, "As it will be shown" should read "As will be shown"
74. Right column, line 10 from bottom, "approximately" should read "approximated"
81. Reference 11, line 2 from bottom, place period after Part I.

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THE METABOLISM OF LEAD IN MAN IN HEALTH AND DISEASE

by

ROBERT A. KEHOE, M.D.
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LECTURE I

THE NORMAL METABOLISM OF LEAD

In the Chair: E. R. A. Merewether, C.B., C.B.E., M.D., F.R.C.P., F.R.S. (Edin.)
(Member of Council)

INTRODUCTION

The substance of these lectures has been gleaned from investigations of the past 30 years in The Kettering Laboratory, some of which have been designed systematically to explore certain aspects of the general problem, while others have arisen fortuitously out of the practice of forensic and occupational medicine and industrial hygiene in which the professional staff of the Laboratory has been engaged. The practical impetus for these investigations, as well as their economic justification and support, came out of certain problems posed by the introduction and use of tetraethyl lead as an antiknock additive in automotive gasoline. The toxicological and clinical observations on this compound and analogous lead alkyls, together with the details of a regimen of industrial hygiene which has provided the basis for satisfactory control of the occupational hazards within the industries concerned, would furnish the subject matter for this or another series of lectures. However, our present subject has a greater significance in relation to the public health, and even in relation to the use of tetraethyl lead, since the quantitative aspects of the respiratory absorption of lead on the part of the general population, especially the urban population, in consequence of the discharge of finely divided inorganic lead compounds from the exhausts of automobiles into the atmosphere, has, from the first, constituted the principal hygienic problem which has confronted this technological development. Moreover, it was apparent early in the third decade of this century, that the limiting factor in the use of lead compounds in this manner might well be the ultimate concentration of respirable lead in the atmosphere from this source, as a contribution to the total intake and absorption of lead on the part of the urban population or, more specifically, such part or parts of this population as might be subjected to the severest and most persistent exposure to this source of atmospheric contamination. Therefore, the entire subject of the occurrence of lead in the general human environment, and of its access to the human organism, had to be examined in detail.

In the early course of certain more or less randomized observations, it became apparent that a very considerable proportion of persons in the general population

of the United States of America was absorbing and excreting small quantities of lead regularly. While this fact had been postulated long before, and had been regarded by certain investigators and their countrymen as having been established for all practical purposes (1), it had been denied categorically, in respect to persons in the general population of the United States, after having been put to the test through the application of analytical methods of allegedly greater precision than those previously employed in the United States or elsewhere (2). Certainly the point was sufficiently important, practically, to warrant thorough-going and quantitative elucidation, and to this problem our attention was directed in what must be regarded as a somewhat pedestrian, or at least in a step-wise, manner. First, it seemed essential to settle upon analytical procedures which, when applied to a wide variety of biological materials, would provide reproducible results characterized by a fully defined, small error of both positive and negative sign. This was no easy task, and while fairly good analytical methods have been available for more than 30 years, new techniques, introduced a little more than 20 years ago by a number of investigators, have been developed to a high degree of reproducibility and precision when employed in skilled hands (3). Second, it seemed necessary to apply such analytical procedures to all of the materials in the human environment which may gain access to the human body, as well as to the excreta, fluids and tissues of the body itself. And third, it seemed imperative that such analytical results should be related, quantitatively, individually and collectively, to the diurnal rhythm and the physiological processes of the human organism over such period of time as might be considered to be realistic and representative of common experience. The task, stated otherwise, was to learn the facts concerning the general experience of a representative segment of the population, with respect to the quantities of lead taken into the human body from individual and combined sources from day to day, over a period of time sufficient to delineate the prevailing environmental conditions, and to determine the immediate and ultimate fate of the lead taken into the body, in terms of its absorption, its distribution in the tissues at various times, its excretion from the body under various conditions, and its residual retention, if any. In short, the objective was to establish a comprehensive portrayal of the pattern of the "normal" metabolism of lead in men residing in the United States of America, to the extent that this could be described in the terms of analytical chemistry. As will be appreciated by all of those who have undertaken to investigate any type of physiological behaviour, the term "normal" as applied to populations or groups of organisms, including man, is of necessity somewhat arbitrary, and, therefore, subject to definition. The meaning here is comparatively straightforward, in that persons who were not definitely ill, and whose exposure to lead, as inquired into in some detail, appeared to have been incidental and general, rather than occupational or specific, were regarded in this respect as normal. Only after the gathering of large numbers of data could normality be expressed somewhat tentatively and pragmatically, on the basis of a comparatively uniform pattern of behaviour established as a statistical norm. The facts established by a less intensive investigation of two groups of persons who were living under primitive and almost wholly natural conditions in another country, served to reveal the extent to which an environment almost wholly devoid of artificial factors gave rise to exposure to and absorption of lead compounds (4).

THE NORMAL METABOLISM

A great deal of information has been obtained as to the quantities of lead which are taken into the body in the food and beverages consumed by the "average" adult North American, and in the respired air. The data obtained over a period of years demonstrate clearly that a considerable portion of the ingested lead is natural in origin, being derived from the soil and water directly and by way of the vegetation and animal life that constitute the greater part of the human diet. An appreciable portion, on the other hand, is derived from the introduction of lead into food in a great number of ways. Some of the facts in these respects are illustrated in Tables 1 to 6.

Certain comments on the individual tables would seem to be helpful in clarifying their meaning and their applicability for present purposes. The data in Table 1, for example, are too few to depict the range of the lead content of the superficial layer of the earth's crust, but they convey some idea of the range of values that may be encountered. The samples represented as virgin soils have the virtue of being essentially free of artificial contamination with lead, while those designated as agricultural

TABLE 1

The Lead Content of Certain Soils

Source of Samples	*Number of Samples*	*Range of lead content of dry sample (mg. per kg.)*
Virgin Soils:		
State of Mexico	5	0.07 — 8.0
Yucatan Peninsula	38	0.80 — 25.0
Sarawac	4	1.20 — 30.0
Agricultural Soils:		
Northwestern U.S.A.	10	7.60 — 15.7
Urban Soils—Cincinnati area	4	28.0 — 360.0
Rural Soils—Cincinnati area	3	16.4 — 27.2

soils in Northwestern United States are probably, but less certainly, in this same category. The samples of urban soil in Cincinnati, on the contrary, include some to which lead compounds have been added in the form of paint, scraped, worn or weathered from the surfaces of houses and other stationary or mobile structures, as metallic residues from bearings, lubricants, containers, solder and insecticidal sprays, as well as those derived from the exhausts of automobiles. The uses of lead are legion, and in any area of modern human activity, some of the effects of these uses will appear in the superficial layers of the earth.

The waters within and on the borders of lands inhabited by man may be expected to contain dissolved and suspended compounds of lead in varying amounts. Only when samples of water are obtained from streams or bodies of water remote from and unaffected by common human activities, can they be expected to reveal their natural state in this respect. It is not surprising, however, that the natural waters of the earth, including the seas, contain minute concentrations of lead. The evidence assembled in Table 2, scanty as it is, is such as to establish this fact, and further, that the general, piped water supplies of a number of cities and towns in the United States contain quantities of lead little if any above the order of magnitude of natural waters. It is apparent that the ordinary methods employed in the treatment and distribution of water need not contribute appreciably to its lead content. Moreover, considering the sources of the water which is distributed in certain of the cities in this group, one may reasonably conclude that lead compounds were actually removed from the raw water in the water-treatment plants.

The second footnote in Table 2 is of somewhat more than purely academic interest in that we had hoped to find some spot or area on the earth where the soil might be free of lead, and thus furnish a site for further investigation. A coral island in a remote part of the sea, the soil of which would have no direct derivation from disintegrated stone, might, perhaps, fulfil this criterion, and permit one to search for any possible effects of such an environment on the local flora or fauna. The facts, with respect to the extraction of lead from sea water by this organism, and the accumulation of relatively high concentrations of lead in the skeleton, have deprived us of any such hope. It seems highly improbable, at present, that there is any area on this planet in which vegetation or animal life could remain entirely free of traces of lead compounds.

TABLE 2

The Lead Content of Various Waters

Source of Samples	*Number of Samples*	*Range of lead content (mg. per litre)*
Caribbean Sea	2	0.02*
Pacific Ocean	3	0.02*
Atlantic Ocean (Florida Keys)	2	0.003—0.005†
River water—Sarawac	1	0.005
Pond water—Sarawac	3	0.004—0.02
Well water—Mexico	1	0.009
Stream water—Mexico	1	0.009
Well water—U.S.A.	2	0.02—0.03
Water from general supplies of 35 towns and cities—U.S.A.	37	0.003—0.04

* Limit of sensitivity of analytical method then in use.
† Coral skeletons taken from these waters contained lead in concentrations ranging from 4.0 to 30.0 mg. per kg.

Table 3 furnishes data which show that common beverages may be contaminated with lead in their preparation or distribution, and also that these may (by chance or design) escape such contamination. Thus the lead content of the water in a specific building, and especially in a newly constructed building, may be high, despite the minuteness of its representation in the influent water, if the latter takes up lead from the distributing equipment within the building. The source of lead in the three samples referred to in the second item of Table 3 was traced to a preparation used to lute the joints of the piping in a new building. This source disappeared with the lapse of time. In other instances in our experience and that of others too numerous to justify citation, lead was contributed to the water by lead pipes or by lead-lined storage tanks, or by solder used in somewhat extensive and crude attempts to repair water heaters or other receptacles for water. It is not difficult to recognize, in these data, themselves, the presumptive likelihood of artificial sources of lead. There is nothing remarkable, it seems, in the results obtained by the analysis of coffee as prepared for drinking, or of three commercial samples of milk (human milk contains like concentrations of lead). Beer and wine may contain lead from equipment used in their production, in addition to that in the original ingredients which, themselves, may have been contaminated. The grapes which are made into wine may have been

TABLE 3

The Lead Content of Various Beverages

Article	*Description*	*Number of Samples*	*Range of lead content (mg. per litre)*
Water	From local taps	10	0.02 — 0.05
Water	" " "	3	0.37 — 0.92*
Coffee	As usually prepared	2	0.01 — 0.03
Milk	Local market	3	0.02 — 0.04
Beer	" "	21	0.01 — 0.09
Beer	" "	3	0.13 — 0.29
Grape juice	" "	7	0.04 — 0.40
Wine	Domestic and imported	10	0.05 — 1.51

* After standing over week-end in pipes of new building.

sprayed with a lead-containing insecticide, and this was certainly the source of the high values found in certain of the samples of grape juice; it was much less likely to have been responsible for that found in the wine, for the reason that the lead in the grape juice is precipitated (as tartrate) and appears virtually quantitatively in the discarded residue from the fermentation process. So far as we can establish by ordinary inquiry, wines are no longer "sweetened" with lead compounds; various other sources of contamination with lead exist, however, and can be discovered by careful investigation. One common source of the contamination, with lead, of wines imported into the United States (uncommon but not unknown in domestic wines) is the almost universal use abroad of a sheet-lead covering over the cork and the neck of bottles. Since the bottles are so stored usually as to maintain the cork in a moist state, the metallic lead is subject to corrosion, the products of which are slowly transmitted, in solution, by capillarity, to the wine within the bottle. In addition, unless the top of the cork and the neck of the bottle are cleaned thoroughly before the cork is removed and the wine poured out, a degree of contamination, which is not always negligible, results. It is necessary at this point to remember that some slight contamination of wine in this manner, while perhaps inevitable, may be entirely insignificant, as a source of frequently or regularly recurrent absorption of lead, quantitatively, especially, perhaps, in the United States, in which the use of wine, although increasing, is slight and irregular in the general population, as compared with that of many other countries. The contamination is likely to be much greater in wines that are stored in bottles for fairly prolonged periods of time, and is, therefore, more likely to be encountered by the connoisseur of the rarer (often somewhat older) wines, rather than by the more numerous consumers of the more common and more plentiful products of the vineyard. On the whole, however, this is not an unimportant source of dietary lead, and since it seems unlikely that there is any disadvantage in the use of plastic materials for this purpose, this source of contamination might well be disposed of by this means.

The articles listed in Table 4, with the exception of a few items designated as having been obtained from local (U.S.A.) markets, were so obtained in the field, and so handled and transported as to avoid external contamination. Some of them, as indicated, had been exposed to atmospheric dust or to direct contact with soil that could not certainly be removed, before being analyzed. With these exceptions, however, the analytical results portray the natural lead content of these articles and may be accepted as fairly representative of vegetation generally, in this respect. Certain oddities of the distribution of lead within a plant or its fruit will be apparent in the data as evidence of chemical or metabolic differences therein. One of these, for example, is the high natural lead content of the delicate skin on the nibs of cocoa beans as compared with other parts of the fruit. The various parts of the originally intact pod were separated out within the laboratory with meticulous precaution against contamination. It may be noted that the several parts of the pod tended to contain unusually high concentrations of lead, as compared with other types of vegetation.

The lead in vegetable products (Table 5) appears to have remained within the ordinary range of concentration of the original vegetation in some instances, and in others to have been appreciably augmented in the course of the processing of part or all of the plant for commercial use. Every step of the harvesting and processing of a food product may present some opportunity for contamination. Such evidences of contamination as are seen in these data, are not so remarkable for their occurrence as for their generally modest limits.

Roughly corresponding factors influence the lead content of animal products as the latter find their way from grazing lands or farm, or from the stream, lake or sea, to the table. Even the utensils in which they are cooked and served, and the tableware in which they are served, offer possibilities for a slight or, occasionally a significant degree of contamination. The first five items in Table 6 were obtained from range cattle in a fresh state after special handling to ensure their

TABLE 4

The Lead Content of Various Types of Vegetation

Article	*Source*	*Number of Samples*	*Range of lead content (mg. per kg.)*
Tea leaves, hand picked (dry) ...	Ceylon	1	0.02
Tea leaves, import package (dry)	China	1	43.2
Fruit of forest tree (wet)	Yucatan	2	0.15 — 0.30*
Foliage of forest tree (wet) ...	,,	2	0.25 — 0.60*
Bark of forest tree (dry)	,,	112	0.04 — 0.40*
Root of forest tree (dry)	,,	1	0.05
Latex of forest tree (wet) ...	,,	36	0.04 — 0.08
Bark of forest tree (dry)	Sarawac	6	0.04 — 0.25*
Latex of forest tree (wet) ...	,,	4	0.02 — 0.04
Cocoa pod—outer (dry)	Trinidad	4	0.14 — 0.87*
Cocoa pod—inner (dry)	,,	2	0.17 — 0.23
Cocoa pulp (dry)	,,	2	0.38 — 0.46
Cocoa beans (husks) (dry) ...	,,	3	1.38 — 1.60
Cocoa beans (nibs) (dry)	,,	1	0.03
Cocoa beans (husks) (dry) ...	,,	13	0.05 — 0.035*
Peas (green)	Mexico	1	0.03
Pea pods (green)	,,	1	0.05
Beans (green)	,,	2	0.15 — 0.26
Bean pods (green)	,,	1	0.04
Beans from first harvest (dry) ...	,,	3	0.04 — 0.40*
Corn (green grain)	,,	3	0.03 — 0.31
Corn (green stalk)	,,	3	0.05 — 0.11
Corn (green husk)	,,	1	0.26
Corn (dry grain, prior harvest) ...	,,	1	0.33*
Wheat (green grain)	,,	1	0.27
Wheat (dry grain, prior harvest)	,,	1	0.40*
Cherries (green)	,,	1	0.05
Apple (green)	,,	1	0.12
Pear (green)	,,	1	0.18
Peach (green)	,,	2	0.04 — 0.08
Fruit (green)	Variety, local market U.S.A.	16	0.003 — 1.00*
Radish (green)	Mexico	1	0.20
Pepper (green)	,,	1	0.94
Cabbage	Local market U.S.A.	4	0.10 — 0.24*

* Articles known to have been contaminated or believed to have been subject to some likelihood of contamination.

freedom from contamination. Their lead content is low, in comparison with the findings in the corresponding human tissues, as exemplified in Table 15. This is not surprising, in view of the natural lead content of the forage which constituted their food.

Before translating the data tabulated thus far, in illustration of the sources of lead in food and beverages, into their collective contribution to the daily ingestion of lead, recent observations recorded in Table 7 will serve to demonstrate the existence and the present order of magnitude of the atmospheric component of human exposure to lead in certain parts of the United States. How far these findings deviate from those which might have been found naturally, before the advent of modern man and his activities, is a matter for speculation, but there is little reason for doubt that a situation roughly comparable to the present, characterized by a somewhat lower order of magnitude of occurrence and, perhaps, of variability, of the concentration of lead in the atmosphere at the surface of the earth, has existed for a long time. Later

TABLE 5

The Lead Content of Various Vegetable Products

Article	*Source*	*Number of Samples*	*Range of lead content (mg. per kg.)*
Wheat bread	Local market	8	0.02 — 0.16
Bran flakes (breakfast food)	„ „	2	0.14 — 0.15
Crackers	„ „	1	0.24
Pretzels	„ „	1	0.25
Pancakes	As prepared for table	2	0.22 — 0.28
Spaghetti	„ „ „ „	2	0.06 — 0.21
Corn starch	Crude and refined	4	0.75 — 1.83
Corn syrup	Factory product	2	0.21 — 0.49
Ground corn	Factory product animal feed	4	1.85 — 11.22
Oilcake meal	„ „ „ „	1	3.90
Cocoa	As prepared for market, 20 brands	25	0.40 — 11.5

TABLE 6

The Lead Content of Various Animal Products

Article	*Description*	*Number of Samples*	*Range of lead content (mg. per kg.)*
Beef bone	Fresh—Western U.S.A.	1	3.60
Beef brain	„ „ „	2	0.13
Beef liver	„ „ „	2	0.29 — 0.40
Beef spleen	„ „ „	2	0.003 — 0.027
Beef kidney	„ „ „	2	0.12 — 0.38
Cooked beef	Local market	9	0.003 — 0.63
Cooked ground meat ...	„ „	3	0.15 — 0.18
Cooked sausage	„ „	4	0.16 — 1.60
Uncooked sausage	Mexico	1	0.27
Chili con carne	„	1	0.46
Lizard	„	1	0.10
Fish (fresh)	„	1	0.24
Fish (dried)	„	1	1.51
Crawfish	„	1	0.75
Eggs (chicken and turkey) ...	„	1	0.02
Eggs	Local market	6	0.003 — 0.12

discussion will concern itself with various aspects of this matter. For the present, there is need merely to include this source of exposure in the consideration of the complete metabolic pattern, so as to appraise its contribution in quantitative terms, so far as possible.

We come now to the consideration of the extent to which the natural and artificial sources of human exposure to lead in the "normal" human environment combine to provide a reasonably consistent pattern of intake and absorption. The quantities of lead derived from the foregoing sources

TABLE 7

The Concentration of Lead in the Atmosphere of Various Cities in the United States.
(In Micrograms per Cubic Metre)*

City	Order of Magnitude of Variability			Mean Concentration
	Diurnal	Seasonal	Geographic	
Cincinnati	1.2 — 2.2	1.2 — 3.0	0.5 — 1.5	1.2
Los Angeles	2.4 — 4.5	2.0 — 20.0	—	5.2
San Bernardino	1.5 — 2.0	1.2 — 2.0	—	1.5
Washington, D.C.	1.5 — 3.5	—	—	2.5

* The findings vary from year to year with various factors, and from season to season in any one year, and from the least active (population, business activity, vehicular traffic) to the most active area of the individual city. The degree of variability pictured here is of the proper order of magnitude for the time (year or season) or area within which the observations were made. Only the mean values, however, offer some basis for comparing one city with another. Even these provide for no more than crude comparison, since the conditions under which the observations were made, with respect to the year, the season and the specific locale, were not identical.

vary within certain limits determined by certain characteristics of a given geographic area or society. Therefore, while the general features of the intake of lead will be much the same among peoples generally, the quantities of lead may differ considerably from place to place, from time to time, and from nation to nation, since the natural environment varies in different parts of the earth, as does the manner of producing, harvesting, processing and distributing food, and also the indigenous cuisine, and the composition of the general and individual diet. The specific facts relative to the United States of America will not apply, necessarily, elsewhere.

In the course of a series of experiments, of which a more detailed account will be given later, the daily intake of lead in food and beverages by human subjects and the output in the feces and urine, were followed for weeks, months or years, according to the requirements of individual experiments. Duplicates of meals were composited as daily samples and the additional beverages, including water, were also obtained, as duplicates of those consumed, for analysis. All of the feces and all of the urine were collected daily, and paired samples of blood were obtained weekly. Some of the results of these experiments, as conducted systematically in the study of 10 normal, healthy adults, have been assembled in Tables 8, 11 and 12.

In Table 8, the distribution of the findings in the food (and beverages) is set down opposite that relating to the feces. It is clear that the patterns of these correspondingly distributed results are quite similar. There is a correspondingly wide variation in the quantities of lead involved in the two series, but only rarely do the quantities in either exceed 0.6 milligram, while the mean value in both cases is low in accordance with the great preponderance of low individual results.

The statistical correspondence in the two sets of analytical findings points to the presumption (reinforced by the close correlation which is found to exist between the gross intake and the fecal output of lead for functionally corresponding periods), that the ingested lead traverses the alimentary tract without being absorbed. That this is not strictly true is readily demonstrated by the regular presence of lead in the urine and blood, but the fact remains that the amount of lead evacuated in feces from a normally functioning alimentary tract is indicative of the amount of lead ingested during the functionally corresponding period. This fact has provided a comparatively simple and indirect means for determining the approximate intake of lead on the part of a representative segment of the human population. Effective use of this method has been made on several

TABLE 8

The Daily Occurrence of Lead in the Food and Feces of Ten Normal North American Adults During the Investigation of the Normal Metabolism of Lead

Lead in Milligrams per 24 hours	*Frequencies of Occurrence of Quantities of Lead*	
	In Food	*In Feces*
0.0 — 0.19	1407	1279
0.2 —	840	729
0.4 —	137	170
0.6 —	33	43
0.8 —	9	8
1.0 — 1.99	5	13
2.0 — 2.99	3	4
4.33	—	1*
5.78	1*	—
9.12	—	1*
Total Numbers	2435	2248
Mean	0.21	0.22
S.D.	± 0.16	± 0.20

Mean daily weight of food and beverages (except water) 2.9 kg. (S.D.±582)

* Excluded in the statistical calculations

TABLE 9

Lead Content of Random Samples of Feces of Persons in Various Categories of Employment in Three Cities in Ohio. Field Survey, 1955

Lead in Milligrams per Sample of Feces	*Frequencies of Occurrence of Quantities of Lead Indicated*
0 — 0.199	282
0.20 —	104
0.40 —	42
0.60 —	8
0.80 —	3
1.00 —	2
1.20 —	1
1.40 —	2
1.60 — 3.399	3
8.65 — 104.4	6*
	453
Mean	0.232
S.D.	± 0.288

* Excluded in calculation of mean value

occasions, one of which is illustrated by the observations referred to below.

In a recent survey of a fairly large group of persons employed under conditions which are known to result in a negligible degree of exposure to and absorption of lead, specimens of feces were collected so as to yield approximations of 24-hour evacuations. The data are displayed in Table 9 in a statistical arrangement similar to that of Table 8. The correspondence of these findings to those obtained in the more prolonged observations on experimental subjects can hardly be fortuitous.

The results of another survey of a relatively small group of widely scattered persons is given in Table 10. The minor differences in the statistical characteristics of this group may have resulted from the small size of the group, and the results may have been affected by the locale and dietary habits of these individuals. Nevertheless, the practical significance of the data lies in the extent to which this small number of observations fits into the normal pattern of the more extensive survey, thereby suggesting that they may represent fairly, but not comprehensively, the facts with reference to the quantities of lead likely to be encountered in the daily dietary of adults in all areas of the United States. Considering the degree of uniformity with which food and food products from all parts of the United States (and abroad) are distributed throughout the country, it would not be surprising to find that a relatively small sample could yield reasonably representative results in this respect. Such has been shown to be the case, in that numerous surveys of this type, involving large and small groups of adults in the general population, over a period of more than 20 years (since the development of the analytical methods now in use), have provided generally similar data of which Tables 9 and 10 are typical. The evidence shows that, during this period of years, the average daily intake of lead in food and beverages, on the part of adult citizens in the United States, has ranged from somewhat less than 0.15 to somewhat more than 0.35 milligram, with due regard to the quantity and variety of the food consumed by individuals. A glance at Table 12, in which the mean daily intake of lead of each of 10 experimental subjects, investigated under the well-controlled conditions of the laboratory, are listed opposite the mean weight of the food consumed daily by these individuals, reveals this degree of individual variation and indicates the influence thereon of the quantity of food consumed. Inspection of the diaries of these individuals, in which the composition of the diet from day to day is given, demonstrates certain well defined and fairly consistent qualitative differences which provide further explanation of the relatively high or low ingestion of lead.

TABLE 10

Lead Content of Random Samples of Feces of Normal Persons in Ten Widely Scattered Cities in the U.S.A.

Lead in Milligrams per Sample of Feces	*Frequencies of Occurrence of Quantities of Lead Indicated*
0.0 — 0.19	26
0.2 —	43
0.4 —	17
0.6 —	7
0.8 —	2
1.0 —	4
1.2 —	2
2.0 —	1
Total Number	102
Mean	0.398
S.D.	± 0.310

That lead is absorbed regularly, to some extent, from the alimentary tract (as well as from the respiratory tract) under the ordinary conditions portrayed above, is a reasonable presumption (subject to proof, on evidence to be adduced later) from the illustrative data in Tables 11 and 12. The variation in the daily output and concentration of lead in the urine, as well as the concentration in the blood, from day to day

TABLE 11

Distribution of the Frequencies of the Analytical Findings with Respect to the Excretion of Lead in the Urine and the Concentration of Lead in the Blood of Ten Normal North American Adults During the Investigation of the Normal Metabolism of Lead.

Milligrams of Lead Found in Consecutive Samples of Urine (Daily) and Blood (Weekly)

	Per day—Urine—per litre		*Blood per 100 g.—*	
			Spec. method	*Dith. method*
0.00 — 0.009	—	3	0	0
0.01	594	307	5	15
0.02	913	1012	99	166
0.03	551	762	68	26
0.04	236	283	33	6
0.05	103	82	4	0
0.06	48	26	3	2
0.07	22	9	—	—
0.08	9	4	—	—
0.09	2	—	—	—
0.10 or more	2	—	—	—
Total Numbers	2488	2488	212	215
Mean	0.0295	0.0320	0.0322	0.0264
S.D.	± 0.0135	± 0.0100	± 0.0117	± 0.0066

TABLE 12

Occurrence of Lead in the Food, Feces, Urine and Blood of Normal North American Adults, as Revealed by the Mean Quantities or Concentrations of Lead Found in Successive Samples Obtained During Investigation of the Normal Metabolism of Lead.

Identification of Subjects	*Food and beverages consumed daily*		*Feces*	*Urine*			*Blood lead in mg. per 100 g. whole blood*	
	Weight	*Lead content*	*Lead content per day (mg.)*	*Volume per day (ml.)*	*Output of lead (mg./day)*	*Concentration of lead (mg./l)*	*by Spectrograph*	*by Dithizone*
	(kg.)	*(mg.)*						
M.R.	—	—	—	1778	0.026	0.021	0.032*	
E.B.	3.30	0.35	0.34	1147	0.037	0.031	0.029	
I.F.	3.16	0.24	0.26	1057	0.032	0.034	0.028	
S.W.	3.13	0.23	0.29	1594	0.040	0.031	0.040	
M.O.B.	2.45	0.21	0.33	1022	0.032	0.035	0.033	0.028
F.C.	3.20	0.25	0.21	921	0.023	0.028	0.030	0.025
M.B.	2.99	0.21	0.22	1152	0.038	0.038	0.030	0.023
I.S.	2.52	0.18	0.18	1161	0.024	0.025	0.030	0.026
S.B.	2.70	0.12	0.12	941	0.025	0.031	0.038	0.026
L.D.	2.66	0.17	0.22	974	0.023	0.025	0.025	0.019

* Average of all determinations

TABLE 13

Concentration of Lead in Urine of Small Groups of Normal Persons Residing in Four Western Countries.

Lead in mg. per litre	*Mexico*	*U.S.A.*	*France*	*Germany*
0.00 -- 0.009	5	—	—	—
0.01	10	7	11	5
0.02	7	6	6	4
0.03	4	8	8	2
0.04	3	5	5	1
0.05	—	3	2	1
0.06	—	1	1	—
Total Numbers	29	30	33	13
Mean	0.022	0.029	0.030	0.027
S.D.	± 0.017	± 0.016	± 0.014	± 0.012

TABLE 14

Concentration and Partition of Lead in Blood of Small Group of Normal Young Men in U.S.A.

Lead in mg. per 100 grams	*Frequencies of Occurrence of Concentrations Indicated*		
	Whole blood	*Erythrocytes*	*Plasma*
0.000 — 0.0049	—	—	27
0.005	—	—	—
0.010	—	2	—
0.015	2	4	—
0.020	9	11	—
0.025	12	6	—
0.030	5	3	—
0.035	2	1	—
Total Numbers	30	27	27
Mean	0.027	0.024	0.0015
S.D.	± 0.005	± 0.006	±0.001

TABLE 15

Range and Mean Levels of Concentration of Lead in the Tissues of Fifteen Persons Presumed to Have Had No Unusual or Abnormal Exposure to Lead.

Tissue	*Milligrams of Lead per 100 Grams of Fresh, Unfixed Tissue*	
	Range	*Mean*
Brain	0.01 — 0.09	0.04
Lung	—	0.02
Heart	—	0.04
Liver	0.04 — 0.28	0.12
Spleen	0.01 -- 0.07	0.03
Kidney	0.015 -- 0.16	0.05
Muscle	0.010 -- 0.17	0.03
Flat bone	0.21 — 1.11	0.65
Long bone	0.67 — 3.59	1.78

TABLE 16

Concentration of Lead in Skeleton of Persons Presumed to Have Had No Unusual or Abnormal Exposure to Lead in Association with Age.

Identification	*Age*	*Rib*	*Femur*
E.S.	3	—	2.22
Female	6	1.02	1.14
E.I.	20	1.11	—
E.H.	51	0.47	—
N.R.	64	—	0.80
A.P.	70	0.39	3.59
J.W.	75	0.60	2.89
A.C.	95	0.56	1.36

and from person to person, is shown by the combined data of Table 11, while the variation among individuals, over considerable periods of time, is indicated by the differences in the mean values relative to urine and blood in Table 12. Incidentally, the tabulation of the mean values resulting from the analyses of duplicate samples of blood by two totally different methods, one chemical and the other physical, will convey some impression as to the probable precision and reproducibility of these results. On the basis of these data, obtained under carefully scrutinised conditions, it may be said that the daily output of lead in the urine of a group of normal human adults ranged generally from 0.01 to somewhat more than 0.08 milligram, and is found rarely to be slightly in excess of 0.10 milligram, the mean value being approximately 0.03 milligram. In individuals (Table 12) the mean value may vary from 0.023 to 0.040 milligram.

The concentration of lead in the urine (in the temperate but variable climate of the United States in and around Cincinnati, Ohio) of the entire group of subjects (Table 11) varied from somewhat less than 0.009 to somewhat more than 0.08 milligram per litre (there being a clearly defined but not always sustained trend towards high values in summer and low in the winter, in a generally, but inconsistent inverse relation to the urinary volume). Here again, the variation from individual to individual is demonstrated, statistically, by the mean levels of lead concentration listed in Table 12.

The concentration of lead in the blood of this group of subjects varied from 0.01 to 0.06 milligram per 100 grams, and the combined results yielded a mean value slightly more or less than 0.03 milligram per 100 grams with due regard to the two sets of analytical results. It will be noted in the distribution of the analytical findings, as well as in the mean values, that the results obtained by the spectrographic method of analysis were usually relatively low. A rigid comparison of the two methods has shown that there is a greater variability in the results of the spectrographic method, which amounts to a lesser degree of reproducibility in the results. The error may occur on the high side or the low, but in a large series there is a preponderance of low results. Accordingly, the results of the use of the dithizone method, in this Laboratory, are usually preferred, while the specificity of the spectrographic method and its sensitivity to extremely low concentrations of this element give it a unique advantage at times, especially in its application to very small samples or unusual materials.

In order to provide a simple illustration (to be supplemented later) of the fact that findings comparable to those obtained under experimental conditions in the Laboratory can be had by the examination of the urine and blood of other widely scattered groups of adults who have had no unusual or occupational exposure to lead, the data in Tables 13 and 14 have been taken, more or less at random, from many others. Table 13 has the further virtue of indicating the type of variability that may be found in comparable groups of persons in several countries. The results under the subheading 'Mexico' were obtained in our

investigation of this and other features of the metabolism of lead in a primitive society (4). They are relatively low, but are not clearly outside the range of the results obtained in the study of certain individuals within the United States, and hence they are not especially remarkable.

The data in Table 14 portray the range of concentration of lead in the blood of a small and very homogeneous group of young men whose lives and experience had been such as to preclude opportunities for casual or brief occupational exposure to lead compounds. Thus none of the analytical results extended into what may properly be called, in terms of larger and more varied groups, the upper normal range. The additional information in this table relates to the partition of lead in the blood between the erythrocytes and the plasma. The concentration of lead in the plasma is so low, and so avid is the selective absorption of lead by the erythrocytes, that the actual concentration in the plasma at any time can be estimated with greater accuracy by calculating the difference between that in the whole blood and that in the erythrocytes, than by direct chemical analysis unless unusually large samples of blood (and plasma) are obtained, since the quantities of lead to be determined are in the range associated with relatively low analytical precision. The results on plasma noted in Table 14 were obtained by direct analysis, but all that has been ascertained is that the concentration of lead in none exceeded 0.005 (0.0049) milligram per 100 grams of plasma. Evidently, in most instances, it was appreciably lower than this, for only rarely are concentrations found in excess of this value, with due allowance for analytical accuracy, even when the concentration of lead in the whole blood is elevated 10-fold above the mean normal level. Regardless of the nature of the combination of lead with the erythrocyte, there must be an equilibrium of sorts between it and that in the plasma, since the urinary excretion of lead is a regularly continuing phenomenon. Moreover, for the same reason, this equilibrium must be quite labile. It is interesting to note that tetraethyl lead and its principal degradation products in the body (5) are not taken up by the erythrocytes, since even at the height of intoxication by tetraethyl lead, when the rate of the urinary excretion of lead is greatly elevated, the concentration in the whole blood is but slightly or not at all elevated (6). This point is of consequence here because it suggests, without affording proof, that the combination of inorganic lead in the erythrocyte is of a somewhat loose chemical nature.

In further consequence of the absorption of lead under the conditions of normal life, lead is distributed in a fairly characteristic manner throughout the tissues of persons of all ages. Analytical results that are believed to be roughly indicative of the facts, as they relate to the tissues of adults in the "normal" population of the United States, are listed in Table 15. It cannot be held that the data are sufficient in number or type to be regarded as certainly or adequately representative. They are factual, however, as far as they go, and they are credible, if not sufficiently substantiated, in a strictly representative role, because of their orders of magnitude and the modest limits of their variability, as compared with the corresponding attributes of the lead content of the blood and urine as portrayed previously.

Certain observations of other investigators (7, 8) have suggested that lead accumulates progressively in the body with the years, under the usual (normal) conditions of life unattended by occupational or other types of abnormal exposure to lead. We have commented elsewhere (9), to the effect that this view has not been substantiated by the evidence offered in support of it, and we have attempted to obtain more satisfactory information on this point. The results on the rib or femur (or both) of the eight deceased persons whose bones are represented in the last two lines of Table 15 (such tissues were obtained at necropsy from only eight of the 15 cadavers), have been arranged according to the age of the individuals at the time of death, in Table 16. Here again, the data are too few to be representative. Such special virtue as they may possess is based on the high probability that none of these individuals had absorbed lead from unusual or occupational sources during their lives. It is extremely

difficult, under present conditions, to obtain numbers of specimens of human bones (and other tissues) which fulfill this specification, and until this can be done, no direct and certain answer to this question can be obtained. It can only be said that these data are consonant with the indirect evidence of balance experiments which point undeviatingly to the conclusion that, under the ordinary conditions of modern life in the United States, the output of lead from the body of the normally functioning man, over long periods of time, is very nearly equivalent to the intake. Such evidence will be examined in some detail in the second lecture. We shall draw upon it, to some extent, as further basis for the development of a concept of the "normal" metabolism of lead, which may now be stated in connection with a summary of the facts presented thus far.

SUMMARY

Facts

1. The lead content of the food and beverages consumed daily by the adult person in the United States of America varies from somewhat less than 0.10 mg. per day to somewhat more than 2 mg. per day occasionally, and may average (for any one individual) as little as 0.12 or as much as 0.35 mg. per day. The mean intake of lead from this source, on the part of fairly large groups of persons with variable diets, is somewhat less or more than 0.30 mg. per day.

2. The lead inhaled from the general ambient atmosphere varies from about 0.01 to as much, perhaps, as 0.09 mg. per day, according to where one lives, and where he spends the 24 hours of the day.

3. Most of the lead ingested with food and beverages under normal conditions traverses the alimentary tract and is evacuated in the feces. (Some portion of that absorbed is returned to the alimentary tract in the biliary, pancreatic and alimentary secretions.) Thus the lead content of the feces of normal persons is almost equivalent to that in the food and beverages over any considerable period of time, ranging from 0.12 to as much as 0.34 mg. per day, on the average, in the individual instance, and averaging somewhat more or less than 0.30 mg. per day in the case of groups of normal adults, dependent upon social and occupational conditions which influence the quantity and quality of the food and beverages consumed regularly.

4. The available evidence (to be presented later) has demonstrated that half or more of the lead inhaled in finely dispersed form from the ambient atmosphere is discharged from the body in the expired air. Accordingly, the lead retained in the lung, to be absorbed promptly or slowly, as the case may be, may amount to as little as 5 micrograms per day in certain parts of the United States, or as much, perhaps, as 45 micrograms per day in others. It is possible that this range may be extended somewhat below and above these limits in extreme instances, but it is unlikely that the higher of the two values is attained frequently anywhere in the United States. The indirect evidence of balance experiments (conducted in Cincinnati) indicates that the quantity absorbed from the respiratory system accounts for an output of lead of the order of 8 milligrams per year, thus approximating 20 micrograms per day.

5. The lead absorbed into the body from day to day is dealt with by a series of mechanisms which result in the excretion of lead (a) into the alimentary tract, as indicated in paragraph 3 above (this is completely masked, in all but prolonged balance experiments, by the larger quantities of ingested lead in transit), in quantities ranging from somewhat less than those which appear in the urine, to quantities which may average twice that amount per day (perhaps as much, at times, as 0.08 mg.); (b) in the urine, in quantities ranging from 0.01 to 0.08 mg. per day, and averaging about 0.03 mg. per day; (c) in the sensible sweat, under suitable conditions, in amounts which can only be estimated roughly from the fact that the concentration of lead in the sweat from the entire surface of the body, under induced experimental conditions, tends to approximate that in the urine. In addition, some of the absorbed lead is distributed regularly into the tissues, in which, at all times, with only a limited degree of variability, a characteristic pattern is maintained.

6. On account of its accessibility to sampling and analysis, the blood assumes an importance that far exceeds that of any other tissue, as a clue to the total quantity, "the body burden," of lead in the tissues generally, during life. As the circulating tissue of the body, it conveys the stream of absorbed lead into the tissues, as it does, also, the counterstream of lead from the tissues. It is in a continuous state of dynamic equilibrium with the internal and external environment of the body, with respect to lead, and in view of the ability of the erythrocytes to combine with, as well as to release, the lead within the bloodstream, the state of the body in this respect appears to be portrayed admirably by the concentration of lead in the blood, if due allowance is made for a factor which will be dealt with later in these lectures. The lead in the blood of any one normal individual varies but little in its concentration from day to day over long periods of time, and changes significantly (beyond the analytical deviation) only with a more than fleeting change in the rate of absorption of lead, i.e., a change in the environment or the dietary regimen. This essentially steady state varies from individual to individual within the limits of 0.015 to 0.040 mg. per 100 grams, averaging, in large numbers of normal persons, somewhat less than 0.03 mg. per 100 grams of whole blood.

7. It suffices for present purposes to indicate that the lead content of the bodies of normal persons in the United States may be represented, on the basis of the concentration of lead in the principal "lead-seeking" tissue, the skeleton, by the range of 0.2 to 1.0 mg. per 100 grams of rib, or 0.7 to 3.5 mg. per 100 grams of femur (weight in the fresh state). These concentrations, in association with the normal pattern of distribution in the other tissues, in a person of 80 kilograms in weight, point to the presence of total quantities of lead in the body ranging from somewhat less than 100 to somewhat more than 400 milligrams. The significance of the topmost value in this range, in relation to the metabolic process under examination, may be appreciated more fully by recognizing that if it had resulted from a progressive accumulation of lead in the body over such a period as 30 years, it would have amounted to somewhat less than 0.04 milligram of lead per day.

BASIC CONCEPT

It appears from the foregoing facts, that an equilibrium is established at an early age between the human organism and its usual or normal environment in the United States, whereby the stream of lead absorbed into the body from the environment is balanced by a counterstream of lead issuing forth from the tissues and from the body via excretory routes. No doubt this equilibrium is disturbed from time to time by the variability of the environmental conditions, and for a time the absorption of lead exceeds the excretion, or *vice versa*. There is good reason to believe, however, that the end result of the operation of these variables is the maintenance of an essential balance between absorption and excretion over the span of life of an individual.

Inasmuch as there is a highly significant difference in individuals within the same general (normal) environment, with respect to the actual levels of intake, output and retention of lead which are maintained, it is highly probable that such difference will exert a greater influence on the lead content of the bodies of normal persons (as defined herein) of any age than those which might result from the operation of the factor of time (age) alone. On the other hand, it may be that some slight accumulation of lead occurs in the tissues (or in specific tissues) of the human body under normal conditions during life. Thus far, any such phenomenon has been too small to detect, and it seems likely, in view of the variability referred to, and the minuteness of the quantities represented therein daily, that this will continue to be the case.

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THE HARBEN LECTURES, 1960

THE METABOLISM OF LEAD IN MAN IN HEALTH AND DISEASE

by

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LECTURE II

THE METABOLISM OF LEAD UNDER ABNORMAL CONDITIONS

In the Chair: R. F. GUYMER, T.D., M.A., M.D., F.R.C.S.
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The normal metabolism of lead, as visualized in the terms of the preceding lecture, is a remarkably stable and uniform process. Before proceeding to the examination of the "abnormal" metabolism of lead, it is necessary to define the meaning of this term, according to our usage, and to establish the intent and scope of the presentation which is to follow. There can be little doubt that the behaviour of lead in man is affected by certain types of disease. Such effects, however, have been explored but little, and mention will be made of them only in passing. We must also omit a full discussion of therapeutic procedures designed to "mobilize" lead from the body, in favour of a brief statement of certain facts. The distribution of lead in the tissues and the rate of the excretion of lead from the body can be modified considerably by the administration of chelating agents such as British-Anti-Lewisite, derivatives of ethylenediaminetetra-acetic acid, and certain other similar compounds. The induction of specific metabolic disturbances such as those occasioned by gross increases and decreases in intake of calcium and phosphorus, or those involving drastic changes in the acid-base equilibrium of the body, exert little or no effect upon the rate of excretion of lead or on the concentration of lead in the blood; such minor changes in the metabolism of lead as are seen in association with these procedures are no greater or more prolonged than those occasioned by the accompanying changes in the throughput or temporary increases in output (diuresis) of water.

Abnormal lead metabolism, as defined for present purposes, is characterized by *quantitative* changes which result from abnormal, that is to say, unusual, conditions of exposure, as these are induced by a wide variety of industrial operations, and also by conditions which occur from time to time in the environment of the home or elsewhere. The emphasis upon the quantitative aspects of the matter derives from the fact that the *pattern* of the metabolism of lead, as we now know it is modified but slightly, and often not at all, by gross increases in the severity of exposure or in the rate of absorption. This is not to say that there is not some subtle change in the behaviour of the lead in the tissues, or some intrinsic change

in the susceptibility of the tissues to the presence of lead, whereby intoxication ensues. The nature of any such mechanism is unknown, but it is clear that its activation depends upon the presence of an adequate concentration of lead in the tissues (presumably at the right point or in the proper state). Thus to all present appearances, the metabolic process associated with saturnine intoxication differs only *quantitatively* from the normal process.

When the rate of the absorption of lead is increased beyond the range described in our somewhat arbitrary terms as "normal," there is a prompt change in the rate of the excretion of lead. This is seen first in an increase in the output of lead in the urine (provided there is no impairment of the renal secretory apparatus). It is associated with an increase in the lead content of the body, as demonstrated a little later in the intact organism by an elevation of the lead content of the blood. If the increase in the rate of absorption is maintained at a sufficient level and with sufficient uniformity over an appropriate period of time, there will be a *progressive* increase in the rate of the urinary excretion of lead, in the lead content of the body, and as an indication of the latter, in the concentration of lead in the blood.

1. THE INGESTION OF LEAD REGULARLY

General Experimental Procedures

The foregoing facts are illustrated by the results of a series of balance experiments, in which each of a series of young, healthy, human subjects has taken an aqueous solution of a lead salt in a known quantity with each meal on every successive day over a period of months or years.

Briefly to describe the experimental procedure, intelligent and reliable subjects were selected, after a comprehensive investigation of their previous and current personal, physiological, and medical status. In a preliminary series of observations, each subject was instructed in the collection of duplicate quantities of everything eaten and drunk, including medicines of any type taken at any time (only with the knowledge and on the advice of the supervisory physician), and food or beverages taken between meals; he was instructed further in the techniques of collecting all urine and feces, both under the ordinary conditions of daily life and in the course of the incidental illnesses of a minor type that commonly interrupt or modify the daily routines of otherwise healthy persons. Various clinical observations were made and recorded weekly (and at other necessary times), at which time duplicate samples of blood were obtained by venipuncture for analysis. A diary listing the food and beverages consumed, and recounting briefly the routine and any unusual activities of the day, was kept for the private information of the principal investigator.

At some point in this experimental regimen, after the characteristics of the normal metabolism of lead had been established, the experimental ingestion of lead was initiated by providing the subject weekly with 21 small containers, in which the desired quantity of a lead salt in aqueous solution had been measured out, so as to facilitate the ingestion of the correct dose with each meal.

Further details of procedures, which have been perfected by experience, need not be elaborated at this time, except to say that every effort was made to eliminate fortuitous and especially systematic errors in the performance of the subject and in the handling of the analytical work. No doubt, errors of sampling, especially those concerned with duplication of the food consumed, occurred from time to time, but there is little reason to doubt that those of positive and negative sign have tended to cancel each other during the prolonged periods of observation. Likewise analytical errors were inevitable, but constant checking of the analytical precision in several ways gave reasonable assurance that these would not be cumulative or systematic, and that errors of positive and negative sign would occur with approximately equivalent frequency.

In the first of such experiments after brief examination of the normal metabolic pattern, one milligram of lead was ingested daily by Subject M.R. (in addition to that which occurred in his food and beverages), over a period of 1,456 days (because of certain fortuitous omissions, the total quantity of lead administered in this way was

1,443 milligrams). The observations were carried out for an additional 280 days after the experimental ingestion of lead had been terminated, at which time the experiment was concluded at the wish of the subject.

Over the period of eight years, additional experiments of this type were conducted, in which comparable information was obtained as to the responses of three other experimental subjects to the daily ingestion of 2, 3, and 0.3 milligrams of lead respectively, as aqueous solutions taken with the meals. (Earlier experiments of this general type were carried out prior to the development of the analytical methods now in use in the Laboratory. The results, while similar, are not strictly comparable, quantitatively.) None of these was so prolonged as the first, each having been designed, primarily, around a question that could be answered in a shorter period of time. Moreover, the patience and endurance of even the most imperturbable and compliant human subject have limits. It is neither possible nor necessary to speak of the many details of these experiments at this time, nor to deal with the many experimental findings which have been or are to be presented elsewhere. Instead, certain portions of the data have been assembled in tabular form or arranged graphically, in

Table 17

Lead Intake and Output in a Healthy Human Subject (M.R.)

Successive Periods of 28 Days		Lead Ingested Milligrams	Lead Eliminated—Milligrams		
			Total	In Feces	In Urine
Control Period	1	7·26	10·57	9·92	0·65
Test Period—					
1 mg. of lead as lead acetate or lead chloride in solution, taken daily in doses of 0·333 mg. each with meals	1	36·62	29·05	28·16	0·89
	2	37·97	30·41	29·21	1·20
	3	37·79	38·69	37·62	1·07
	4	37·66	32·63	30·95	1·68
	5	42·76	34·75	32·97	1·78
	6	38·67	38·07	36·32	1·75
	7	35·74	33·12	31·81	1·31
	8	35·62	33·15	31·43	1·72
	9	35·59	35·86	35·55	2·33
	10	42·81	39·55	37·78	1·77
	11	38·43	34·81	31·74	2·07
	13	36·19	36·58	33·97	2·61

illustration of facts which are pertinent. The first of this series of experiments is presented fairly fully, in order to demonstrate the method of assembling the data for study, after which corresponding parts of others of the series are shown for comparative purposes.

Experimental Results

In Table 17, the early findings of the experiment in which subject M.R. was under observation for a little less than five years, are arranged to show the lead content of the food and beverages, and that of the feces and urine, as these have been composited for each of a series of 28-day periods (originally tabulated daily, summed up for each week, and then for each period of four weeks). The primary purpose of this table is to present the summarized findings of the initial period before the administration of lead in solution, in juxtaposition to the early months of the experimental ingestion. Only two points in the assembled data call for special notice, namely, the general trend toward a progressive increase in the urinary lead output as the experiment continued, and the lack of such increase in the fecal lead output. Both of these phenomena will appear more strikingly later.

Table 18

Lead Intake and Output of Normal Subject (M.R.) During Oral Lead Administration

Successive Periods of 12 Weeks	Lead Ingested Milligrams	Lead Eliminated—Milligrams			Lead—Mg. Lost (—) or Retained (+)
		Total	In Feces	In Urine	
1st	112·84	101·48	98·32	3·16	+11·36
2nd	118·74	108·95	103·74	5·21	+ 9·29
3rd	107·22	105·51	100·15	5·36	+ 1·71
4th	118·79	111·57	105·57	6·00	+ 7·22
5th	110·18	111·22	104·66	6·56	— 1·04
6th	116·22	121·59	114·15	7·44	— 5·37
7th	109·44	93·41	86·57	6·84	+16·03
8th	125·45	118·86	112·47	6·39	+ 6·59
9th	117·11	114·81	108·97	5·84	+ 2·30
10th	105·48	98·86	91·22	7·64	+ 6·62
11th	107·57	109·19	102·25	6·94	— 1·62
12th	114·24	102·06	94·03	8·03	+12·18
13th	113·14	100·68	94·02	6·66	+12·46
TOTAL ...	1,476·42*	1,398·19	1,316·12	82·07	78·23

* Approximately 22.00 mgs. in drinking water, 372.32 mgs. in food and other beverages, and 1,082.10 mgs. administered in solution.

The corresponding results of a more prolonged period during which one milligram of lead was ingested daily (in addition to that contained in the diet), have been combined for successive periods of 7 weeks in Table 18. These data demonstrate more clearly than those in Table 17, the uneven but generally progressive increase in the urinary output of lead, and they establish the occurrence of an irregularly progressive increase in the deficit in the total output of lead, as compared with the total intake. Apparently, under these conditions lead was accumulating in the body of the subject. It is apparent, however, that there were times in the course of this experiment when the output of lead from the body was very nearly equivalent to the intake; there were also three periods, as shown in Table 18, when the output was somewhat greater than the intake. We shall examine these irregularities a little later.

The facts with reference to the sources and quantities of ingested lead, the avenues and the extent of the output, and the magnitude of the deficit referred to above, during the entire period of the experimental administration of lead, are summarized in Table 19. It may be noted here, for what it may be worth later, that the quantity of lead excreted in the urine during this period was practically equivalent to that retained in the body of the subject. A rough calculation will serve to show that approximately 70 milligrams of lead were excreted in the urine during the period of

3

Table 19
Lead Intake and Output of Normal Subject (M.R.)
During Four-Year Period of Oral Administration of Lead

	Milligrams	Per cent of Total Ingestion
Ingested :		
In drinking water	30·00	1·5
In food and beverages	498·47	25·3
Administered in solution ...	1,442·80	73·2
TOTAL	1,971·27	100·0
Eliminated :		
In feces	1,739·31	88·2
In urine	113·77	5·8
TOTAL	1,853·08	94·0
Retained	118·19	6·0

abnormal absorption more than would have been excreted under normal conditions. This calculation is made by multiplying the gross urinary volume during this period, by the mean concentration of lead in the urine of this subject before lead was administered, and subtracting this product from the total output of lead in the urine. Disregarding the indeterminable quantity that may have occurred in the feces as a true excretion, which may have been of about the same magnitude as that excreted in the urine, this quantity (70 mg.), when added to that retained in the tissues, adds up to 180 milligrams that may credibly be taken to have been the minimum quantity of lead actually absorbed from the alimentary tract in the course of this experiment, roughly 13 per cent of that administered, or somewhat less than 10 per cent of the total quantity ingested.

At this point in the description of this experiment, it might serve the purposes of brevity and, at the same time, contribute information for comparison, if we were to introduce data corresponding to those of Table 19, but derived from another experiment, in which subject E.B. ingested two milligrams of lead per day, in addition to that in his diet, over the period of somewhat less than two years (684 days). This experiment was carried out in precisely the same manner as that of the first experiment and in concurrence with the latter part of it. The corresponding data are summarized in Table 20, in which it can be seen that approximately twice the daily dose of lead per day resulted in the accumulation

Table 20
Lead Intake and Output of Normal Subject (E.B.)
During Two-Year Period of Oral Administration of Lead

	Milligrams	Per cent of Total Ingestion
Ingested :		
In drinking water	12·00	0·8
In food and beverages	120·48	8·5
Administered in solution ...	1,286·85	90·7
TOTAL	1,419·33	100·0
Eliminated :		
In feces	1,236·19	87·1
In urine	73·07	5·1
TOTAL	1,309·26	92·2
Retained	110·07	7·8

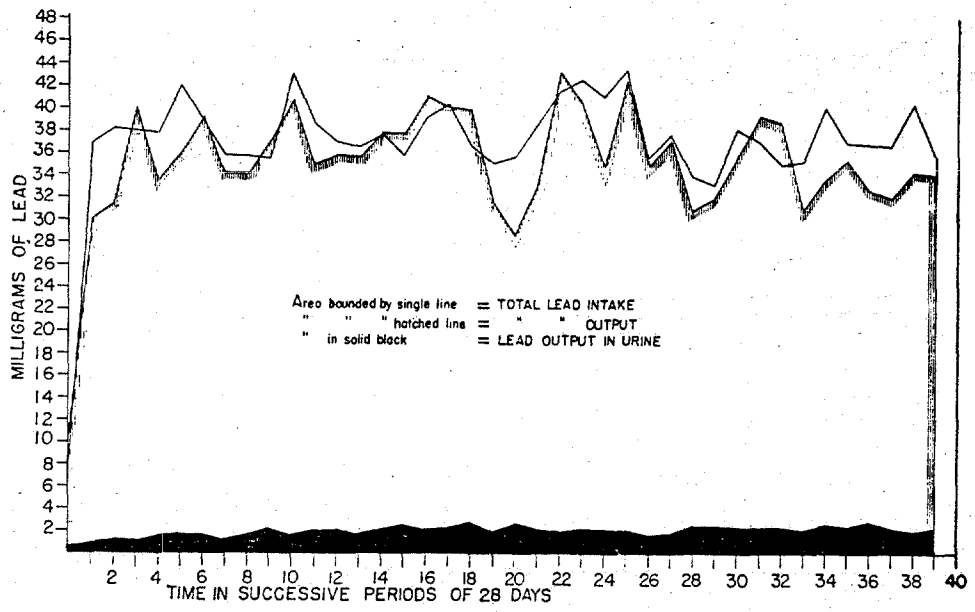

Fig. 1. Graphic representation of the quantities of lead taken in food, beverages and in solution (with meals) in each of 39 successive periods of 28 days, and the quantities eliminated in the urine and feces (combined) in the corresponding periods. Subject M.R.

of approximately the same quantity of lead in the body of subject E.B. in half the time. Again, the quantity excreted in the urine during the administration of lead was approximately the same as that retained in the body of the subject. The quantity of lead absorbed during the period of the administration of lead, arrived at by the same procedure as that indicated in the case of subject M.R. above, was certainly not less than 165 milligrams, which is about 13 per cent of that administered, and almost 12 per cent of the total quantity ingested. (The total quantity absorbed may well have been of the order of 200 milligrams, or 15 and 14.5 per cent, respectively, of the administered lead, and the total quantity of ingested lead.)

A graphic view of the gross quantitative relationships between the ingested lead (food, beverages, and that administered), that in the feces, and that in the urine, during 39 of the 52 periods (each of 28 days) over which lead was administered to subject M.R., is shown in Figure 1. Certain trends are clearly visible—the general course of the increase in the urinary output of lead, the essentially parallel variability of the total intake and output of lead during the total period portrayed, and the comparative constancy and yet the slightness of the discrepancy between the intake and output, as referred to previously in Table 19.

A further series of charts have been drawn up to reveal certain simple but significant facts. Thus in Figure 2, the output of lead in the feces may be seen to have a well-defined relationship to the lead ingested (since the amount administered was the same each day, the variability here derives from that of the food); it also bore a direct relationship to the regularity of the emptying of the alimentary tract. (In assembling the analytical results on the lead in the food and feces, for scanning as they were obtained, it could be noted that the failure of the subject to defecate during any 24-hour period resulted in a discrepancy between intake and output which was never fully counteracted subsequently; evidently, a greater degree of absorption of lead occurred when the retention of the contents of the alimentary tract was prolonged. In this manner, this factor came to light.)

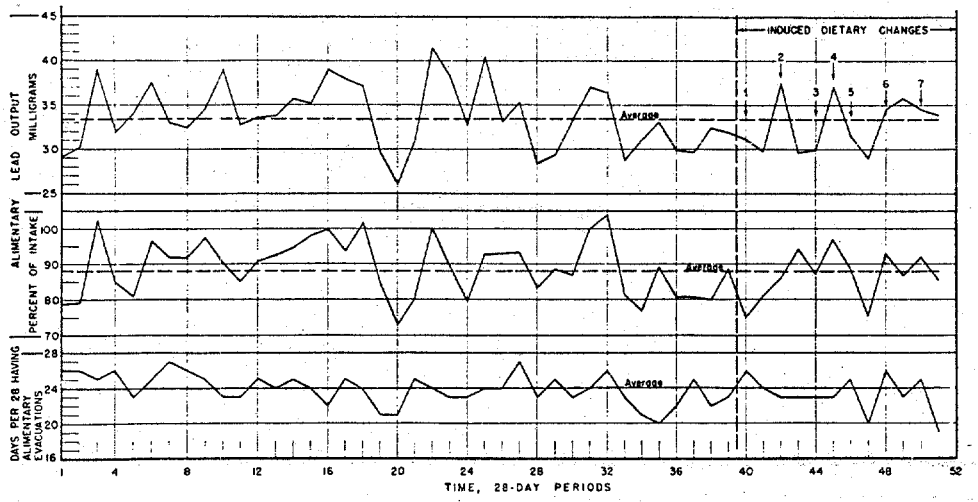

Fig. 2. The relation between the total lead output in the feces (uppermost series of connected points), the total intake of lead in food, beverages and in solution (middle series of connected points), and the irregularity (lag) of the fecal evacuations (lowermost series), as represented for each of 31 periods of 28 days, during a prolonged period in which 1 milligram of lead was ingested (with meals) daily. Subject M.R.

Certain facts with respect to the lead content of the urine and blood during the entire period in which lead was administered, are shown in Figure 3. The mean daily output of lead in the urine, the mean daily concentration of lead in the urine, and the average concentration of lead in the blood, for each 28-day period, are plotted. A point of outstanding importance is the general upward slope of the three curves. There are frequent peaks and valleys in each of them, as well as certain less frequent downward swings in the two representations of the urinary lead (which will be remarked upon later), but despite the frequent or infrequent recessions, their eventual course mounts to progessively higher values. There is no evidence of the achievement of an equilibrium with the experimental conditions.

A further point of importance is the somewhat lesser rate of increase (more gradual slope of curve) in the concentration in the blood, as compared with that in the urine. This difference is not as evident at a glance, as it is when the sharp and frequent deviations of the curves are ironed out in fitted (straight line) curves, as illustrated in the case of the urine in Figure 4 below. (The lag on the part of the blood is the more pronounced, the higher the rate of absorption from the alimentary tract, i.e., the larger the dose of soluble lead ingested daily.) This phenomenon would seem not to be especially remarkable when one reckons with the fact that the concentration of lead in the blood of the normal individual is approximately 10 times that in the urine. Indeed its unusual feature is not that this discrepancy occurs but that it is not considerably greater, for such would certainly be the case but for the capacity of the erythrocytes to take up lead and thus retard somewhat its passage from the blood stream into both the tissues and the urine. As we shall see later, the usual limitation of the rate of the urinary excretion of lead does not depend on a normal incapacity of the renal apparatus to excrete lead beyond a certain low level, but upon the limited availability of lead for excretion. Thus when a sufficient quantity of lead is available in the body, the urinary excretion of lead may be augmented thirty-

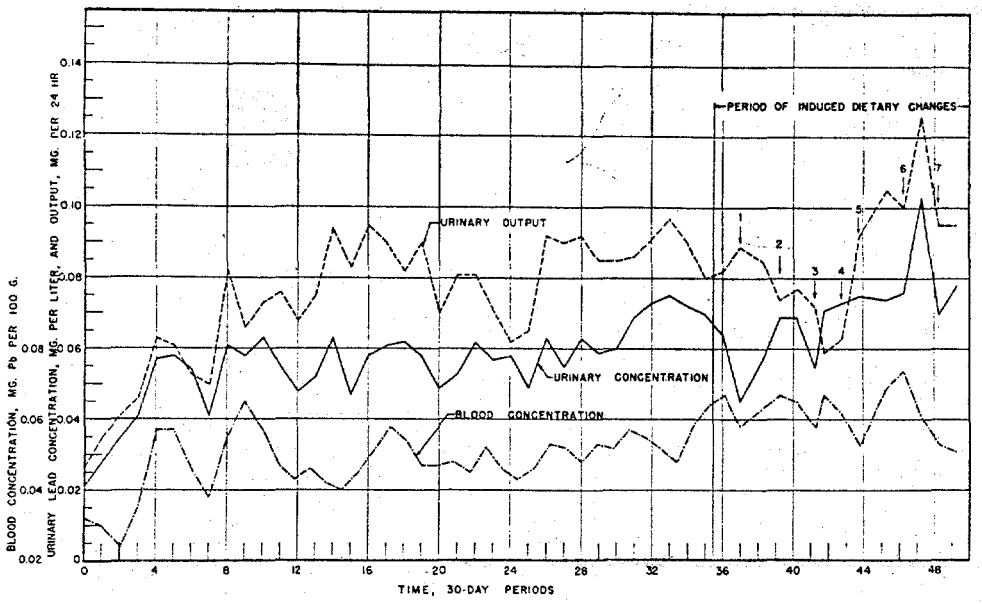

Fig. 3. Mean daily output of lead in urine, and mean daily concentration of lead in urine and blood, in each period of 28 days, during a prolonged period in which 1 milligram of lead, in solution, was ingested, daily, with meals. Subject M.R.

fold or even more. At such a time the concentration in the blood is likely to be increased only eight or tenfold. On the other hand, under circumstances associated with abnormal absorption of lead, and also with an impairment of the renal excretion of lead—a situation which occurs only rarely—the concentration of lead in the blood may be elevated by as much as twentyfold.

In Figure 4, the total output of lead in the urine, and the total volume of the urine, for each 28-day segment of the total period involved in the experimental administration of lead, are plotted in parallel. By this means, one is enabled to see that the volume of the urine is an important factor in the urinary output of lead, and also that (in Cincinnati) there is a well-defined seasonal factor which influences the output of water and the output of lead in an essentially parallel manner. Many (but not all) of the minor irregularities in the output of lead over the entire experimental period appear to be explainable on this basis, while the low points separated from each other by larger, serrated, upward loops, coincide with the peaks of summer heat, approximately a year apart. And yet, despite all of these deflections, the main course of the curve is steadily upward. Whether this curve is best fitted by a straight line may be questioned, but such a question at this point in our discussion may be dismissed as of little importance. The important point is the fact that there is no evidence here to suggest that the upward trend will diminish with further time. For aught one may suspect to the contrary, this same course might have continued upward through the remaining lifetime of the individual, so long as the experimental conditions were maintained, and, as we shall see later, this, in all likelihood, would have resulted disastrously for this experimental subject in somewhat more than three additional years. [The special experimental conditions represented in the latter part of the curves by the arrows under the heading "induced dietary changes," will not be dealt with here beyond the brief comment that they represent a series of crucial tests

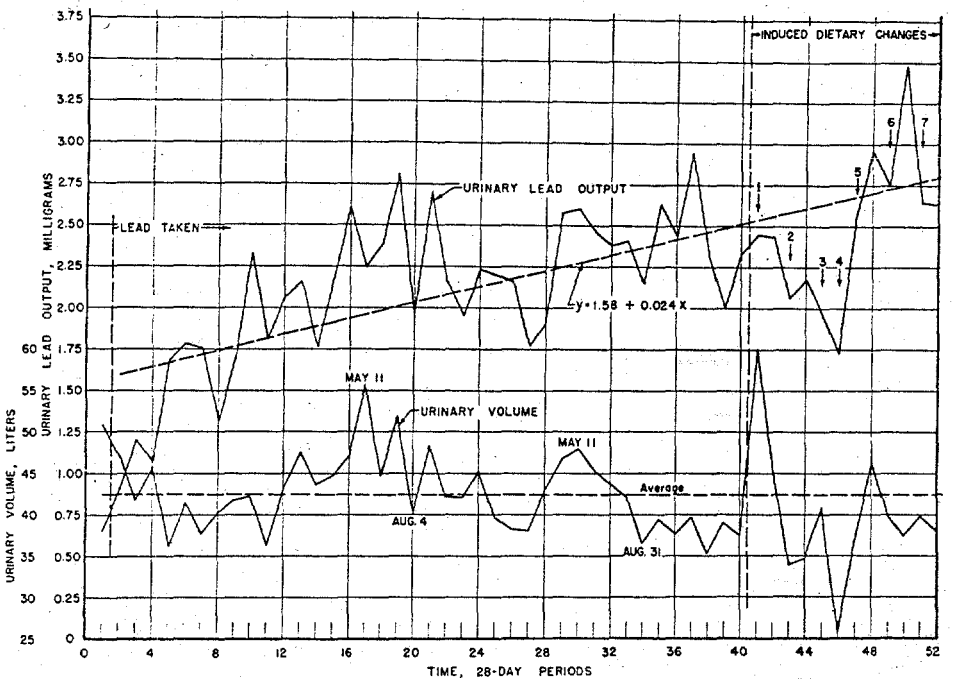

Fig. 4. The relation between the gross output of lead in urine and the gross volume of the urine, in successive periods of 28 days, during a prolonged period in which 1 milligram of lead, in solution, was ingested daily, with meals. Subject M.R.

of certain dietary or therapeutic methods of altering the retention of lead in the body, which can be seen to have influenced the output (and intake) of water, and thus only indirectly and insignificantly, the output of lead. These were, in sequence, (a) the administration of milk in large volume, (b) the administration of large doses of ascorbic acid, (c) deprivation of dietary calcium, (d) the deprivation of both dietary calcium and phosphate, and (e) the administration of excess of calcium, (f) the administration of excess of phosphate, and (g) the administration of excess of calcium and phosphate, one administered in the morning, the other in the evening, to diminish their direct interaction. Each of these procedures was continued for 28 days, after which the subject resumed his usual regimen for 28 days, with the exception of procedures (c) and (d), the latter of which followed immediately in the wake of the former.]

In view of the apparent physiological and practical importance of the influence of the urinary volume upon the output of lead from the body, and in recognition of the dearth of quantitative information, derived from controlled conditions of experimentation, on this matter, the opportunity to carry out certain detailed observations of this type, in the course of this experiment, was too tempting to pass by. Since also there was little or no information as to diurnal variations in the concentration of lead in the blood, under fairly constant but abnormal conditions with respect to the absorption of lead, the blood and the urine of subject M.R. were sampled at intervals of two hours throughout a period of 24 hours on each of three different occasions during the period of administration of lead. The first observations were made five and one-half months after the initiation of the experimental ingestion of lead, the second, 19 months later, and the third, 10 months after the second. No additional experimental variable was introduced into the first series of observations, but in order still further to intensify the variability of the throughput of water, the second and third

sets of observations were carried out as urinary dilution-concentration tests, the subject first being given an excess of water at the start of the observations, and then being deprived of water until the regimen of sampling had been completed. The results are plotted in Figure 5.

It will be noted that the concentration of lead in the blood varied only insignificantly (only one result, on 9th January, 1940, ranged above the upper limit of analytical variability) during any one of the 24-hour periods, but that the level of concentration increased step by step in the

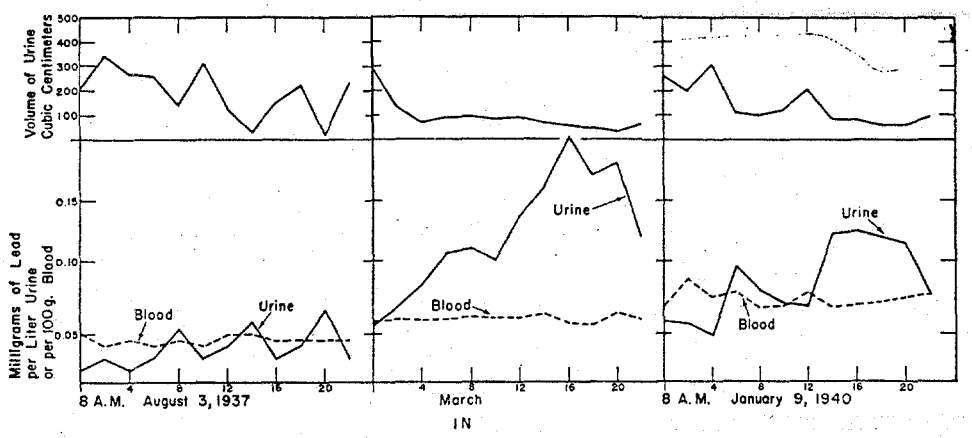

Fig. 5. Diurnal variations in the concentration of lead in the urine and blood (lower sections), in relation to normal (left, upper section) and induced (centre and right upper sections) variations in the volume of the urine, during three 24-hour periods in the course of a prolonged period of experimental ingestion of lead. Subject M.R.

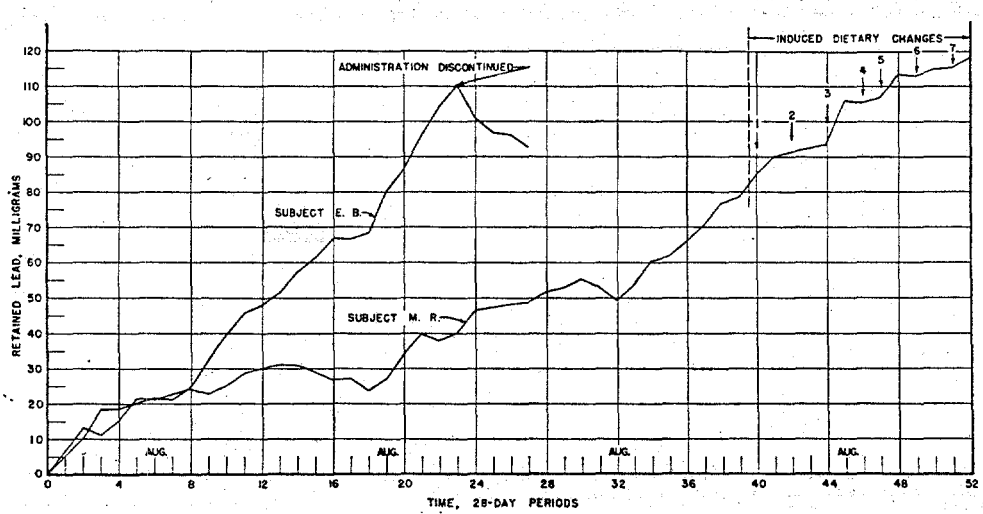

Fig. 6. The cumulative difference between the gross intake of lead in food, beverages and that ingested in solution, and the gross output in the feces and urine, in successive periods of 28 days, during prolonged periods of experimental ingestion of lead. Subject M.R. (1 mg. per day in solution) and subject E.B. (2 mg. per day in solution). Each point represents the total quantity of lead retained in the body of one of the subjects at the corresponding period of the experimental sequence.

successive periods. The urinary concentration of lead, on the contrary, varied widely within each period, in inverse relation to the urinary volume. The extreme expression of this variability occurred when, on the same day (3rd March, 1939), while the concentration of lead in the blood remained essentially constant at 0.053 mg. per 100 grams, the concentration of lead in the urine ranged from 0.05 to 0.21 mg. per litre, at the opposite poles of the urinary volume. This high degree of variability should be noted and remembered in relation to the frequency with which attempts are made to establish the general level or rate of the current absorption of lead by an individual, through the analysis of a sample of urine of small volume.

Next in Figure 6, is another aspect of the abnormal metabolism of lead, as revealed in the two experiments in which subjects M.R. and E.B. ingested 1.00 and 2.00 milligrams of lead daily, respectively, in addition to that in their respective diets. The cumulative retention of lead (the gross difference between intake and output in the bodies of these subjects) is plotted on a month by month (28 day) basis, the resultant two curves being practically the same except for their slopes and their representation in time. That is, subject E.B. reached practically the same end-point as that of subject M.R. in about half the time, as shown previously in the end results, Tables 19 and 20. It may be noted that the points on these curves could hardly be fitted by any other than straight lines, and that there is no suggestion of a terminal levelling off. There are evidences in both curves, however, of a recurrent levelling and downward trend, in the form of four notches in the four-year curve (M.R.) and two in the two-year curve (E.B.), these occurring at the same time of year in both instances, namely, in the summer season.

The meaning of Figure 6, in its simplest terms, is clear, but the very simplicity of the facts may be deceptive, and perhaps some further consideration should be given to them. These two experimental subjects, as well as a third (subject I.F.) who ingested three milligrams of lead, as a dissolved salt, every day for four months, suffered no deviation from a state of well-being during these experiments, and, therefore, it might be concluded that these daily dosages of lead have been proved, thereby, to be harmless. So they were, for the period of time represented in the experiments. If, however, there is a point at which the accumulation of lead in the body becomes, of itself, dangerous (evidence will appear, subsequently, to show that this is the case), we must view these experiments in a different light. Unless these subjects, if continued indefinitely under their respective conditions of lead intake, should, at some time, achieve an equilibrium whereby the intake and output of lead would come into balance, they might well be threatened with lead intoxication at some time. It is important to recognize, therefore, that no evidence of an approach to such an equilibrium is offered by the results of these experiments. We shall return to this matter at a later and more appropriate point.

As to the seasonal variation in the lead metabolism of subjects M.R. and E.B., no satisfactory interpretation can be given. It is pertinent, however, to call attention to the fact that the excretion of lead in the sweat of these subjects, to whatever extent it may have occurred, is not accounted for in these curves or in any other representations of our data. If such data were available for inclusion, they would further increase the loss of lead from the body, and would increase the negative metabolic balance, thus deepening the notches in the curves of Figure 6. It is evident, then, that there was a greater excretion or a lesser absorption of lead by these subjects in the summertime, but the reason for this phenomenon is a matter for speculation. Was it temperature *per se*, or sunshine, or the greater seasonal recreational exertion of young persons, or the greater use of fresh vegetables and fruit during the summer months, or was it some more subtle change in the general metabolism of the body?

A further experimental variable, that of dosage, remains to be examined for its comparative effects upon the patterns of response of the several subjects. These effects can be illustrated in a few charts and comprehended promptly and with little further explanation. It may be of

interest to mention the fact that the dosage of 0.3 mg. of lead per day, taken by subject S.W. (in addition to that in his diet), was selected by means of a rough calculation, in the belief that it might result in an amount of alimentary absorption equivalent to that being absorbed in the respiratory tract. This subject had just completed a period of 13 lunar months of observation under normal (control) conditions, during which his output in the feces and urine had exceeded his intake in food and beverages by 8.58 milligrams. This excess was regarded as having been absorbed from the atmosphere in the respiratory tract. If our estimate of the appropriate dosage for use in this experiment had turned out to be correct, the intake and output of lead, charted in the usual manner, would have been in balance, and the actual amount of the respiratory absorption would have been indicated by this indirect procedure. This turned out not to be the case, but it eventuated that this was the least dose which, when ingested, would be absorbed to such an extent as to yield incontrovertible evidence thereof within a few months. This fact and certain others are shown in a series of charts.

Figure 7 portrays the mean daily alimentary intake and output of lead by subject S.W., during the 11.5 lunar months of the control period, and for the 17 months thereafter, during 15 of which, the dose of 0.3 mg. of lead was ingested daily. This chart is introduced merely to demonstrate again, for emphasis, the familiar relationship of the alimentary output of lead to the alimentary intake, over the entire period of the observations. The extent and the abruptness of the changes associated with the initiation and the termination of the period of experimental ingestion of lead are apparent.

The situation is different, however, when evidence is sought of the absorption of lead from the alimentary tract, under the conditions of this experiment, by examining the data as they are set down graphically in Figures 8 and 9. The two lowermost curves of Figure 8 represent the mean quantities of lead excreted per day in the urine by subject S.W. during each 28-day period of this entire experiment (the period of ingestion being superimposed, for purposes of comparison, upon the control period). In three of the periods of 28 days during the experimental ingestion of lead,

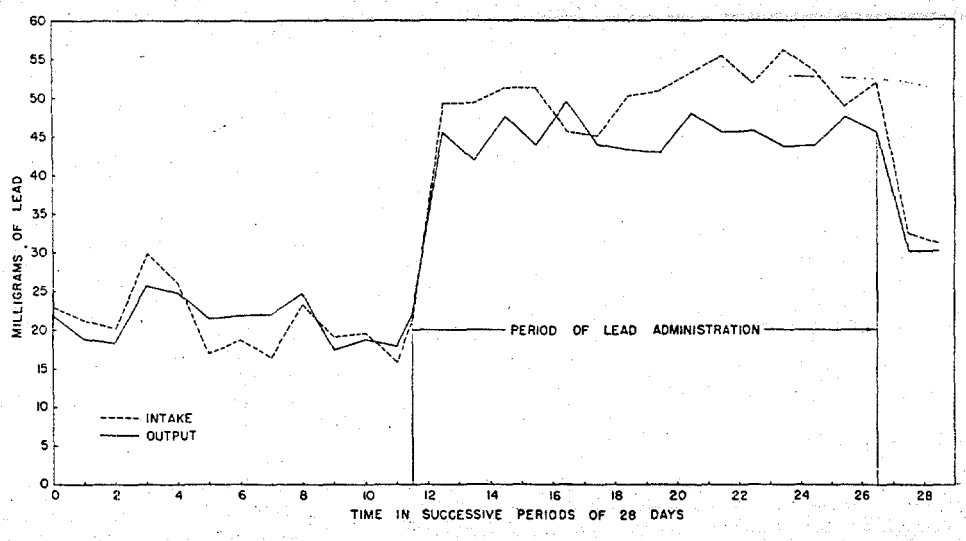

Fig. 7. The gross intake of lead in food and beverages and the gross output of lead in the feces, for each period of 28 days in sequence, are plotted as indicated, in the initial and final sections. The lead taken in solution along with the food, is added to that in the food, in each successive period of 28 days, during the total period in which 0.3 mg. of lead was ingested daily. Subject S.W.

the output of lead in the urine was significantly greater than it had been in the corresponding part of the control period, and, during the latter part of the period of ingestion, the general trend of the urinary output of lead appeared more and more to deviate from strictly normal levels. Most of the time, however, during the period of ingestion, the difference between the two curves may be seen to have been negligible. The over-all difference is barely of statistical significance. The other curves in Figure 8, with the exception of that of subject I.F. (3 mg. of lead per day), whose period of ingestion was too brief to bring out the main or ultimate slope of this curve, reveal their own trends and diverge from each other and from the baseline in a generally definitive manner. These elongated curves are plotted on approximately the same seasonal basis, and although there is some degree of conflict in their seasonal trends, simple inspection is a sufficient means of differentiating them in relation to the daily dosage of ingested lead.

Figure 9 provides a comparison of curves which differ in their construction from those in Figure 8, only in that each point represents the mean concentration, instead of the mean quantity, of lead in a series of 28 samples of urine each of which was one day's output, these being plotted in temporal sequence. The visual comparisons are facilitated by the inclusion of a straight line representing a mathematically derived slope for each curve (except that representing the control period of subject S.W.). There was a barely significant increase in the concentration of lead in the urine of subject S.W. during the period of ingestion. The other curves bear much the same relation to each other as those in Figure 8. In Figure 9, however, the inadequacy of the curve (subject I.F.) which is intended to represent the response to the

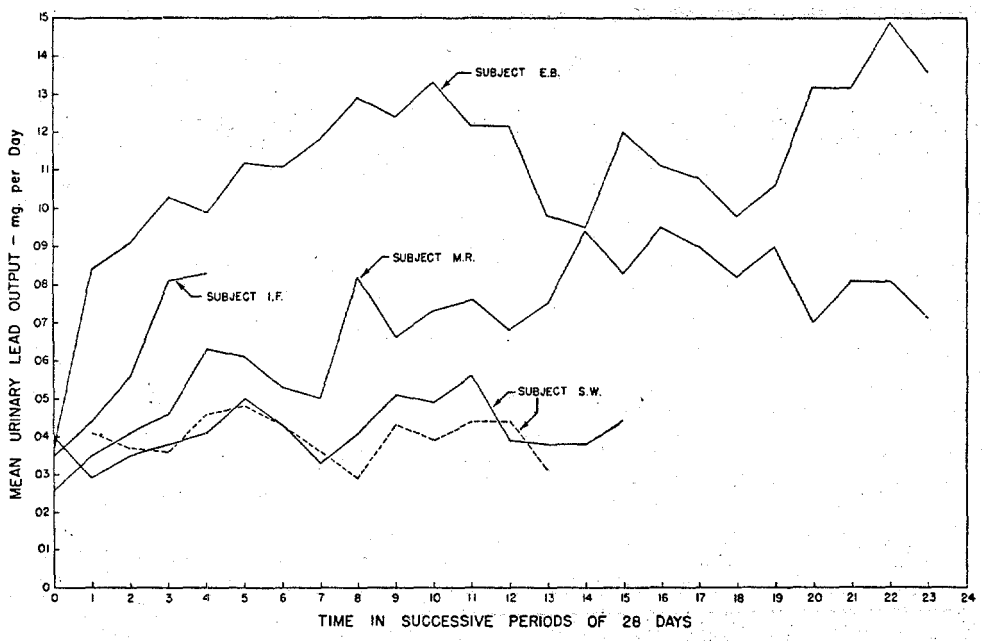

Fig. 8. The mean daily output of lead in the urine of each subject as identified, in successive periods of 28 days, including the preliminary (control or base-line) values of subjects M.R. (1 mg. per day), E.B. (2 mg. per day), and I.F. (3 mg. per day). Subject S.W. is represented by two curves, one broken, portraying the period during which no lead was taken with meals, and the other, continuous, covering the period during which he ingested 0.3 mg. of lead per day. The points plotted in the case of subject M.R. represent only the first 23 of 52 periods, which could be compared with those of subject E.B.

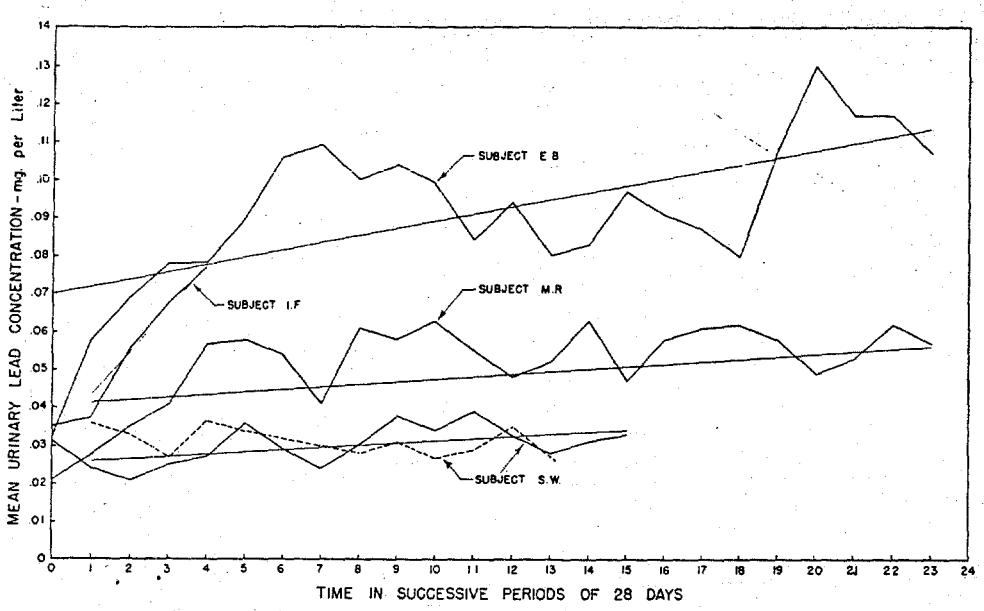

Fig. 9. The mean daily concentration of lead in the urine of subjects S.W., M.R., E.B., and I.F., plotted for comparative purposes in exact accordance with the arrangement in Figure 8.

ingestion of 3 mg. of lead per day (plus that in the food), seems evident, for while the two adjacent and more prolonged curves tend to level off somewhat after an initial sharp rise, this one, seemingly, portrays only the initial slope. One would like to know what would have been its future course had the experiment been prolonged.

The occurrence or nonoccurrence of significant changes in the concentration of lead in the blood of the four subjects during these experiments is shown graphically in the curves of Figure 10. The two which represent the two periods of the experiment involving subject S.W. cannot be differentiated, nor could these two sets of data be differentiated by statistical means. It is possible that these curves would have diverged significantly, if this subject had adhered to the same experimental regimen for a longer period of time. This is not certain, however, and the fact is clear that the absorption of lead at this level of oral dosage is so minute as to be barely demonstrated only by a slight increase in the rate of the urinary excretion of lead, without the confirming evidence of an increase in the concentration of lead in the blood.

The curves which show increases in the concentration of lead in the blood, in association with varying rates of absorption of lead, slope much more gently upward from the base line than do those indicative of the rates of the urinary excretion of lead (Fig. 9), and they tend to differentiate themselves from each other to a lesser extent and more gradually than do the corresponding urinary slopes. On the other hand, it follows that every demonstrable change in the blood is more significant, in terms of the degree of absorption of lead which induced it, than is a comparable degree of change in the urinary output or concentration of lead.

A passing reference was made, at the beginning of this discussion of the metabolism of lead under abnormal conditions, to means of hastening the elimination of lead from the body—"deleading", as this has often been spoken of. The accomplishment of this purpose has been a persistent goal of medical therapy, and many remedies, among which were potassium iodide in an earlier period, ammonium

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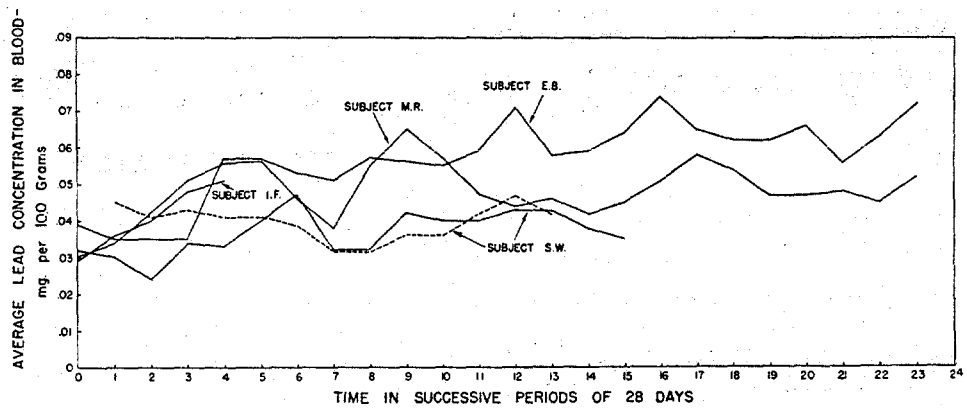

Fig. 10. The mean concentration of lead in the blood of subjects S.W., M.R., E.B., and I.F., plotted for comparative purposes, as in Figures 8 and 9.

chloride more recently for a time, and sodium citrate still more recently and on different theoretical grounds. None of these agents is of any practical value in speeding the elimination of lead from the body. (Whether they may yield therapeutic benefit otherwise, is another matter.) An obstacle to the clarification of this and certain other questions of clinical and legal medicine, has been the almost utter lack of precise information concerning the manner and the proportional extent, and, more particularly, the rate and duration, of the elimination of lead from the body, following varying periods of abnormal absorption. Every physician has known, or considers that he knows, about the cumulative characteristics of lead, but few have concerned themselves to know anything definite about the eventual outcome of the ordinary processes of elimination. It is almost as though, in general medical belief, lead accumulates in the body in the absolute sense and without expoctation of a reversal of the process, except through

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It would be an astonishing

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ged observations of the rate and

extent of the excretion of lead by patients or industrial employees who had terminated their occupational exposure to lead temporarily or permanently (10). The experiments described herein elucidate the matter still further, however, because of the completeness and the quantitative character of the information which they supply on all aspects of the matter.

In addition to the fact that, after the termination of a period of abnormal absorption, a variably prolonged period of elimination of the accumulated lead ensues —that is, an excess of output over intake— there is also a variation in the rate of this loss, from one individual to another, dependent upon, (a) the amount of lead which accumulated during the period of abnormal absorption, and also (b) upon the length of time involved in the accumulative process. These features of the elimination of absorbed and retained lead are illustrated, in part, in Figure 11, in which are represented graphically the cumulative retention of lead by each of this series of experimental subjects, during a period of daily experimental ingestion of a known quantity of lead, and the accumulative loss of lead during a period following the termination of the experimental ingestion of lead. Figure 11 also includes the

graphic representation of the corresponding behaviour of two subjects who ingested only such lead as was contained in their food and beverages.

The legend of Figure 11 provides the additional information required to clarify certain of the details of the manner of representation employed, but some comment may be required to bring out the more important relationships. First, it should be noted that it contains a family of related and similar curves. The two subjects represented in the two lowermost and substantially identical curves, eliminated more lead in their urine and feces, which lead accumulated in the bodies of these subjects are indicated by the primary slopes of the respective curves, which varied directly with the quantities of lead ingested daily. The actual quantities accumulated varied correspondingly, being represented, in the intermediate and final periods, by the points on the curves. Despite the fact that two of the curves (those of subjects M.R. and E.B.) tended to coincide in their early courses (during the first 8 months of each), the metabolic behaviour of the individuals was clearly differentiated otherwise, according to dosage.

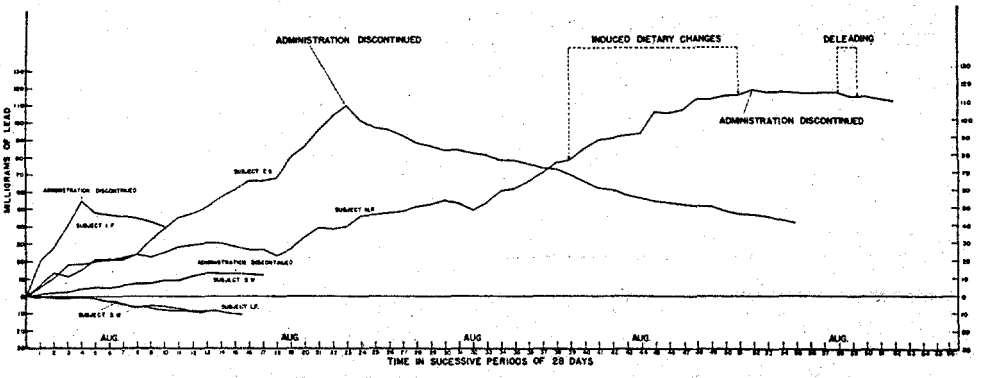

Fig. 11. The cumulative difference between the gross alimentary intake of lead, and the gross output of lead in the feces and urine, in successive periods of 28 days, over the periods of time indicated. The two lowermost curves represent the negative balance as observed in subjects S.W. and I.F., under normal (base-line) conditions. The upward slopes of the four above the base line represent, from below upward, the relative rates of accumulation, and the points give the quantities of lead accumulated by subjects S.W., M.R., E.B. and I.F., during the periods indicated, in which they ingested, in solution, daily 0.3, 1, 2, and 3 mg., respectively, of lead. The downward slopes of the three curves identified as pertaining to subjects I.F., E.B. and M.R., represent the rates of the progressive losses of lead, following the termination of the respective periods of experimental ingestion of lead, while the points indicate the quantities of absorbed and accumulated lead remaining within the bodies of the respective subjects.

month by month, than they ingested with their food and beverages. As indicated in the first lecture, this is readily explained by the lack of any representation in the analytical data of the lead inhaled and absorbed from the atmosphere. The other curves, which, from below upward, represent the behaviour of subjects S.W., M.R., E.B., and I.F., who, in addition to the lead in their diets, ingested 0.3, 1, 2 and 3 mg. of lead per day, respectively, show that each of these subjects ingested more lead than he eliminated. The relative rates at

When the intake and output of lead of the three subjects were followed after the termination of the experimental ingestion of lead, the situation was reversed and the lead that had been accumulating now diminished. The eliminative process, in each instance (after a brief period of relatively rapid decrease in two of the three), proceeded at rates which were appreciably lower than the respective rates of accumulation, and appeared to vary inversely, among the three, with the length of time over which the accumulation had

occurred. The different rates at which the previously accumulated lead was eliminated are illustrated most strikingly by the prolonged observations on subjects M.R. and E.B., and the difference between these two subjects was especially pronounced, despite the fact that the total quantities of lead which they had retained (the one in four years, and the other in two) were very nearly identical. If it be assumed that the metabolic reactions of the two subjects were much the same, the conclusion is almost inescapable that the respective rates of elimination depended upon some factor associated with the length of time required to accumulate a given quantity of lead in the two instances. Such a factor may be visualized, in contemplating the evidence that the large proportion of the retained lead had gone into the osseous tissues of the two subjects in which, in the two periods of time, disproportionate quantities of the retained lead had found their way into the more sluggishly metabolizing regions of the respective bony structures. It has been observed at necropsy, that when lead has been absorbed rapidly, it is unevenly distributed in a bone, being found in relatively high concentration in the more vascular and more rapidly metabolizing areas; but when lead is absorbed very slowly, or at a low level intermittently, or when a long period of time has elapsed since the occurrence of abnormal absorption, the concentration of lead in all parts of the bone tends to be more nearly uniform (11). It may be noted, in this relationship, that under normal conditions, lead is found in higher concentrations in the relatively avascular long bones of the skeleton than in the flat (Table 16, Lecture I), whereas the opposite relationship obtains in fatal cases of lead poisoning (Table 27, Lecture III).

It is of interest to examine Figure 11 further, from the aspect of the absolute length of time that may be required for the elimination of a given quantity of lead retained in the body during a period of abnormal absorption. This obviously is related directly to the foregoing discussion of the rates of elimination, but from the practical viewpoint, it is important to think in definite temporal terms. It may be observed that subject M.R. eliminated very little of his retained lead during the period of 10 months (actually only 7 to 10 milligrams). This was due in part to the unfortunate circumstance that, with the termination of the period of experimental ingestion, this subject altered his mode of living somewhat, and, as is likely to happen at such times, the quantity of lead in his diet changed. In this instance it was increased appreciably for approximately two months. Despite this experimental variable, however, it was evident that the elimination of the lead which he had retained during the experiment would require a long time. Subject E.B., on the other hand, began promptly to eliminate the lead which he had retained, and he continued to do so at a fairly steady but gradually diminishing rate, for about 30 months, after an initial period of about two months of relatively rapid loss. During the total period (32 lunar months, 896 days) he eliminated approximately 70 of the 110 milligrams he had accumulated in his body in 23 lunar months (half of the retained lead had been eliminated in 23 lunar months). Neither of the other subjects was followed long enough (the importance of doing so was not evident at the time, and it would have been difficult to do so in either case) to provide results which can now be compared with those obtained in the case of subject E.B. There is good reason, from the trends of the other two curves, and in view of the comparability of the other aspects of their metabolic patterns, to infer that subject I.F. reduced his retained lead by half in something more or less than eight months, while subject M.R. could hardly have reached a similar state (that of half of his experimentally induced "body burden") in much less than five years. These are, of course, rough estimates, but they provide some support for a "rule of thumb," which in the case of subject E.B. is based on reasonably firm ground. One may state such a rule in his case, and may perhaps apply it, with some reservation, to other situations involving approximately two years of abnormal absorption, to the effect that about twice the length of time was required to eliminate the accumulated

lead, as that involved in its accumulation. The other subjects fall on one side or the other of this estimate, as will also those individuals whose abnormal absorption of lead has resulted in accumulation over short or long periods of time.

Another incidental feature of Figure 11 is concerned with the lack of any visible effects in association with the "induced dietary changes" (which have been referred to previously) in the case of subject M.R., and with the correspondingly negative effect of the indicated attempt at "deleading." The latter, introduced into the experiment only after an interval of time sufficient to permit the normal eliminative processes to demonstrate their operation, but before there had been any considerable diminution in the body burden of lead, consisted in providing subject M.R. with a diet very low in calcium, and in the administration of ammonium chloride in increasing dosage up to the point of tolerance, over a period of six weeks. The effect, in terms of the elimination of lead during this period, was clearly negligible. It has been an accepted fact for some time that this type of eliminative regimen is ineffectual, and mention is made of it here only for the sake of a full representation of the details of this experiment. This experimental procedure was not without point at the time it was undertaken.

In the conduct of the group of experiments concerned with the ingestion of lead, opportunities presented themselves for seeking answers to a number of questions that are of interest to physiologists and also to clinicians. Only a few of such questions were pursued in a manner that required a departure from a simple and ordinary routine of performance on the part of the subjects. The data, on the other hand, have been examined by various means and in various relationships in search of significant items of evidence. They will be returned to again and again, no doubt, as further questions arise. One such procedure was that of examining the data obtained during the period following the termination of the experimental ingestion of lead. This period, when lead was being excreted in greater quantities than those being absorbed, was especially favourable for the determination of the relationship between the urinary and the true alimentary excretion.

Tables 21 and 22 display the observed facts, as well as the calculations and the assumptions, on which are based the estimation of the urinary and the alimentary excretion of lead by subjects M.R. and E.B. respectively, during the terminal periods of these two experiments. The steps in the calculations were those of (1) summing up the excess of the output of lead of each subject over the intake, follow-

Table 21

Lead Intake and Output of Normal Subject (M.R.) During the Period of 280 Days After the Termination of the Oral Administration of Lead

Ingested lead :		
In food and beverages		92·18 mgs.
Eliminated lead :		
In urine	15·99 mgs.	
In feces	83·43 mgs.	
TOTAL		99·42 mgs.
Excess of Elimination		7·24 mgs.
Excess excreted in urine	10·11 mgs.*	
Excess excreted by alimentary tract	—2·87 mgs.	
TOTAL		7·24 mgs.

*Arrived at by calculating what would have been the normal urinary output for this period, by multiplying the total volume of the urine during this period by the mean normal concentration of lead in the urine of this subject, and subtracting this product from the total amount of lead eliminated in the urine during this period.

ing the termination of the period of abnormal absorption, for a period of time sufficient, presumably, to cancel out the errors of sampling of the food and feces; (2) of calculating what would have been the normal output of lead in the urine during this period, and subtracting this amount from the actual output during the period (the normal output was taken to be the product of the total volume of the urine in litres, during this period, multiplied by the mean normal concentration of lead in the urine of the subject as originally determined, expressed in the proper decimal of a milligram per litre); and (3) of subtracting the value in (2), which will represent the excess of lead excreted in the urine, from the total excess, and regarding this difference as the excess of lead actually *excreted* via the alimentary tract. This method is not strictly precise, but it is correct in principle, and can be expected to yield results that err only slightly, and are certainly of the correct order of magnitude. According to Table 21, subject M.R. excreted a quantity of lead in his urine of the order of 7 to 10 mg. (dependent upon which value is accepted) in excess of that which was taken into his body and absorbed during the period of 280 days with which we are concerned in this relationship; during this same period he did not excrete any of the retained lead by way of the alimentary tract. The actual excess of the gross output of lead over the gross intake during this period was almost negligible, in view of the evidence to which attention was called previously, that a normal subject may eliminate approximately 6 mg. of lead (8 mg. per year) during such a period as this. The elevation of the output and the concentration of lead in the urine after the termination of the abnormal absorption provides adequate evidence, however, of the excretion of previously absorbed lead in the urine. The quantity of lead so excreted in excess of that normally excreted, is more nearly correct, in all probability, than is the quantity indicated by the gross difference between intake and output, for the reason that, under the conditions of these experiments, errors in the sampling of the urine are less numerous and smaller than those associated with the duplication of the food consumed daily. We may reasonably take it, from these observations, therefore, that satisfactory evidence has been afforded in Table

Table 22

Lead Intake and Output of Normal Subject (E.B.) During the Period of 448 Days After the Termination of the Oral Administration of Lead

Ingested lead :		
In food and beverages		148·20 mgs.
Eliminated lead :		
In urine	35·61 mgs.	
In feces	153·04 mgs.	
TOTAL		188·65 mgs.
Excess of Elimination		40·45 mgs.
Excess excreted in urine	19·13 mgs.*	
Excess excreted by alimentary tract	21·32 mgs.	
TOTAL		40·45 mgs.

* Arrived at in the same manner as the corresponding value in Table 21.

21 of the excretion of the excess of lead via the urine, but that it has yielded no valid evidence that any of the retained lead was excreted by subject M.R. via the alimentary tract.

The evidence in Table 22 is different. Subject E.B., when considered in the same manner as subject M.R. eliminated approximately 40 milligrams of lead more than he took in during the period of 448 days of these observations. The same methods of calculation indicate that approximately equal amounts of the retained lead were excreted in the urine and feces.

The meaning of these somewhat disparate results in the two instances is not entirely certain. It seems improbable that there was any great difference in the operation of the basic metabolic mechanisms of these two subjects. Rather, it is probable that the principal difference in their excretory behaviour during these corresponding experimental periods lay in the difference in the quantities of lead in active transit in the two instances. We have observed that, when the quantities of lead being excreted by certain patients were quite large, in the absence of continuing respiratory exposure to particulate lead compounds, the alimentary lead appeared to be appreciably greater than that which could be accounted for by the lead ingested in food and beverages. It seems likely, therefore, that the alimentary excretion of lead begins to contribute to the total excretory process, when the lead in transit reaches a suitable threshold, and that it contributes proportionally more, as the quantity of lead in transit increases. We have observed persons whose true alimentary excretion of lead appeared to be three or four times that in the urine (in the absence of renal impairment), and we have also seen others, as in the case of subject M.R., whose alimentary excretion of lead appeared to be negligible. There is no doubt, of course, that lead is excreted in the bile, but at its point of discharge into the alimentary tract it has a long way to go and a long time in which to be absorbed before being evacuated.

2. THE INHALATION OF LEAD INTERMITTENTLY

General Experimental Conditions

A further series of experiments, involving the response of experimental subjects to the inhalation of inorganic compounds of lead dispersed in particulate form in the atmosphere, was initiated following the completion of those concerned with the ingestion of abnormal quantities of lead. In these experiments, the same general procedure described previously, with respect to the intake of lead in food and beverages, and the output in the feces and urine, was followed faithfully. In the experimental provision of abnormal conditions of respiratory exposure, certain almost insurmountable difficulties were encountered. There was no simple means whereby such exposure could be maintained continuously so as to produce conditions comparable to those of the daily ingestion of lead with meals, whereby the rate of absorption of lead into the body varied only slightly from hour to hour and from day to day. It seemed more readily feasible, and also, fortunately, more in accordance with our immediate purpose, to establish experimental conditions similar to, but more uniform than, those associated with occupational exposure to lead. Accordingly, after a period of observation sufficient to portray the individual and seasonal characteristics of the metabolism of lead of the experimental subject (36 or more weeks), he entered a respiratory chamber in which the appropriate conditions had been established. on a schedule of approximately 7.5 hours per day on five days per week, and continued on this schedule, after the manner of employment in industry, for such a period of time as would reveal his metabolic response to the experimental conditions. Allowing for the time required to change clothes before entering the chamber in the morning, to take lunch outside the chamber at noon, and to bathe and change clothing at the end of the day, the period of approximately 37.5 hours per week (the time spent within the chamber was recorded daily), simulated closely the normal work week of 40 hours.

The experimental programme was designed to establish one by one the effects of each of the following variables—the concentration of lead in the atmosphere, the size of the dispersed particles, the nature of the compound of lead, and the influence of the duration of the exposure (both that

per day and per week over variably prolonged periods of time)—upon the absorption and excretion of lead, its retention within the body during the period of the experimental exposure, and its loss from the body after the termination of the exposure. It was anticipated that by varying the temporal relationships of the intermittent exposure, a trend could be established whereby eventually, by extrapolation, one could estimate the effects of continuous exposure.

Up to the present time the experiments have concerned themselves with only one compound of lead, the sesquioxide, at two levels of concentration and in three distinct ranges of particle size. The schedule of exposure, in experiments that have been completed, has been limited to 7.5 hours per day on five days per week. In the present discussion, in the interest of brevity, we shall deal with certain details of one of these experiments, merely mentioning two others in order to call attention to certain variables of immediate importance in relation to industrial hygiene. At the time the experiments were initiated, the most generally accepted standard for good industrial hygiene in the lead-using industries in the United States of America, with respect to the potential severity of the respiratory exposure of workmen to lead, was the limitation of the concentration of dispersed lead in the air of industrial establishments to 0.15 mg. per cubic metre. This standard was based largely upon experience in industries in which finely divided lead oxides constituted the sole or the main contaminants of the air. Half of this concentration, 0.075 mg. of lead, as the sesquioxide, was selected as the level at which to conduct the first (exploratory) experiment. This was followed by an experiment in which the concentration of lead (as sesquioxide) was 0.15 mg. per cubic metre. In order to avoid any possibility of the entrapment of particulate lead in the upper respiratory tract of the subjects (to be swallowed partly or wholly) in these two experiments, the size of the particles was made so minute as to cause them to behave, for practical purposes, as a gas. This was accomplished by the complete combustion of a very dilute stream of tetraethyl lead in propane, in a small Bunsen type of burner, whereby the sesquioxide of lead was dispersed in pure form in particles of the mean size of 0.05 micron. In a third experiment, which will be referred to with the utmost brevity, the only experimental variant was the larger size of particles of lead sesquioxide which ranged somewhat above and below two microns in diameter.

In case this type of experimentation, as well as that involving the ingestion of lead, should appear to be somewhat hazardous and therefore to pose a question of professional ethics, let me hasten to point out that long experience in industry with a wide range of conditions imposed, or at least permitted, by the current status of industrial hygiene, had yielded clear evidence on this point. Our efforts to define and achieve occupational safety, with respect to exposure to lead, had resulted in the development and adoption of certain physiological criteria, which, if adhered to rigidly and consistently, could be relied upon to ensure the freedom of our experimental subjects from any but the most improbable hazard. Such criteria, which could be applied with an unusual degree of precision under the controlled conditions of these experiments, as compared with those of the industrial environment, will be set forth clearly at a later and more appropriate point in these discussions.

It should be said further, that the experimental subjects were members of the staff of the Laboratory and associates in the day's work, to whose safety and welfare one could not be even slightly indifferent on either personal or professional grounds. Perhaps one could justify the imposition of some risk upon human volunteers who were made fully aware of the nature and the apparent extent of the risk to be taken in the interest of science and humanity, but it should be understood that there was no such attitude in the minds of either subjects or investigators. Nevertheless, both as part of the experimental procedure, as well as an extra precaution, a physician, who had no responsibility for the experimental regimen otherwise, but was responsible for the medical supervision (in the

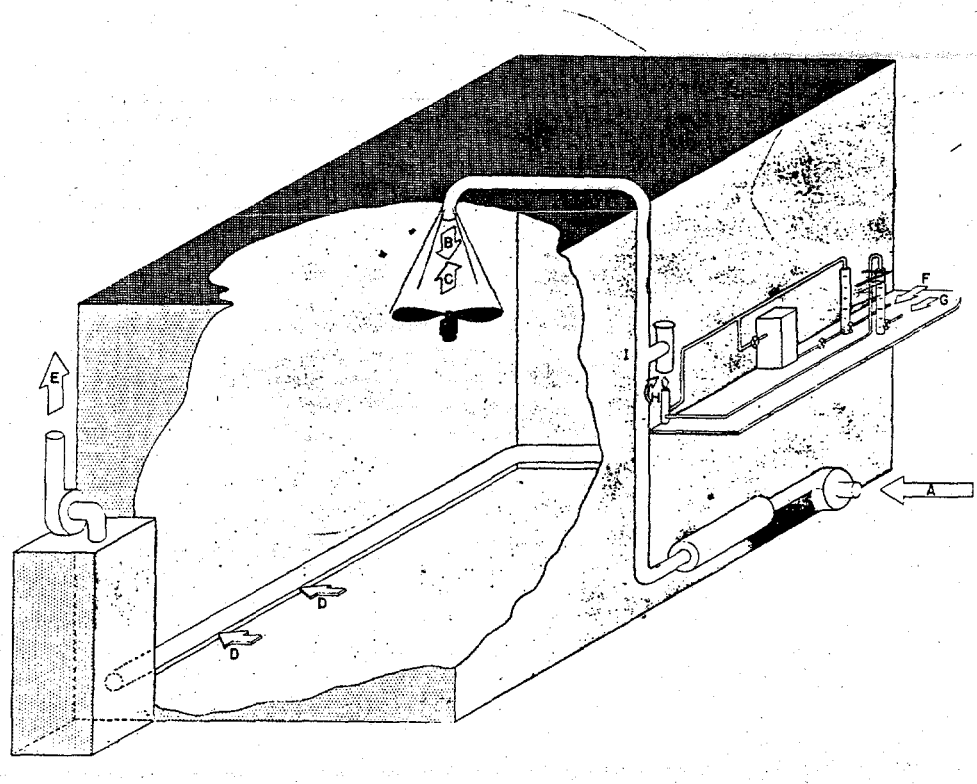

Fig. 12. Scheme of respiratory chamber. Air enters at "A" and is impelled through a sound muffler to the orifice at "B" into the chamber, having picked up, via the Venturi at "I", the products of combustion at "H". A stream of propane, entering the meter at "G", is joined in the burner by a measured stream of air, a measured portion of which has passed through an armoured flask over a small quantity of tetraethyllead. The combustion results in the quantitative conversion of tetraethyllead to lead sesquioxide. The stream entering the chamber is met by a countercurrent of air from the fan at "C" and is distributed. The mixed air of the chamber is withdrawn, through properly spaced ports "D" in the large duct (around the inside base of the chamber), through the electrostatic precipitator, by the (balanced) exhaust pump at "E" from which it enters a large vertical stack.

occupational sense) of the personnel of the Laboratory, was given full authority to terminate the exposure to lead at any time when, in his judgment, its continuation was prejudicial to the welfare of an experimental subject. This prerogative was exercised in one experiment in which lead was being ingested, and the exposure of the subject to lead was discontinued summarily. This, in my view then and now, was an excess of caution, but the established policy of the Laboratory could not be violated.

Experimental Procedures

The design of the respiratory chamber and the apparatus for providing the desired stream of air and the concentration and type of particulate lead therein, during the conduct of the experiment which is the main theme of the following discussion, is illustrated in Figure 12. The cubical room (10 feet in each dimension), constructed of a standard variety of double-wall, insulated, steel panels, was first sealed with plastic tape at all joints and then sprayed with a thin film of plastic (which could be removed and reapplied as frequently as might be desirable). In order to minimize any deposits of particulate lead within the distributing system of the chamber, the large tube (three inches in diameter), which delivered the stream of air containing the lead, was made smooth at the bends

and was kept completely unobstructed at its point of discharge into the chamber. A fan directed its counterstream of air upward toward and around the discharge end of the distributing tube, and scattered the incoming stream of air, with a fair degree of uniformity, throughout the chamber. Air was exhausted from the chamber, at a rate sufficient to balance the incoming stream, through appropriately distributed ports into a large duct situated around the inner wall of the chamber just above the level of the floor. In addition to the facilities illustrated in Figure 12, the chamber was equipped with two air locks, one for entrance and exit with a minimum of disturbance of the atmosphere of the chamber (which was brought to the desired state each morning before the entrance of the Subject); the other, of small volume, was used to introduce and remove books, papers and other articles, according to the needs of the Subject. There was also a telephone by which the Subject could give or obtain information or acquire needed articles without leaving the chamber.

This chamber was equipped as an office, with a small desk on which a typewriter, calculator, or other necessary office equipment could be used by the experimental Subject, whose regular work in the handling of certain records, including some of the data of the experiment in which he was engaged, occupied his time throughout the workday. (A second chamber, designed in a similar manner, was equipped as a simple type of laboratory in which certain procedures which would not result in further contamination of the atmosphere of the chamber could be carried out. This additional chamber made possible the conduct of two experiments simultaneously, thus expediting the investigation, and at the same time making provision for the use of a Subject whose capabilities could be employed in technical activities.) In addition to these activities, sufficient to occupy most of his time (which otherwise would have borne heavily upon him), the Subject initiated, supervised and terminated the operation of an electrostatic precipitator through which a metered stream of air within the chamber was aspirated for a scheduled period of time during the forenoon and afternoon of each day. This entire assembly was installed before the Subject entered the chamber in the morning and again during his lunchtime. At the end of the day, the Subject also mopped the linoleum floor of the chamber, and dusted the few flat or irregular surfaces of the objects within the chamber with a moist cloth so as to prevent the accumulation of any particles that may have agglomerated and separated out of the air within the chamber during the day. The Subject also kept a complete diary of pertinent information, including the time of all of his entrances, departures and re-entrances into and from the chamber for any reason, thereby recording the precise duration of his respiratory exposure to the atmosphere of the chamber. Once each week, while the Subject remained within the chamber, his exhaled air was passed through an electrostatic precipitator into a Douglas bag until a suitable volume had collected therein. By this means the lead in a measured volume of expired air could be determined. A schematic representation of the apparatus for this purpose is shown in Figure 13.

Clinical observations, similar to those concerned with the physical state of Subjects of the experiments involving the ingestion of lead, were made at regular intervals, usually on Saturday mornings, but also on certain other occasions when the Subject was not required to be within the chamber. These included a complete physical examination, a fairly comprehensive hematological examination, a clinical analysis of a measured quantity of urine (to be included in the total recorded volume of the urine of that day). In addition, blood films were made daily for determination of the presence and numbers of reticulocytes and erythrocytes showing basophilic granulation, and a small measured quantity of fresh urine was examined daily for its content of various porphyrins. (None of the results of these observations will be included in this necessarily abbreviated account, beyond the statement that there were no systematic or progressive changes in any of the physiological qualities of the Subjects in respect to any of these matters. The Subjects were selected

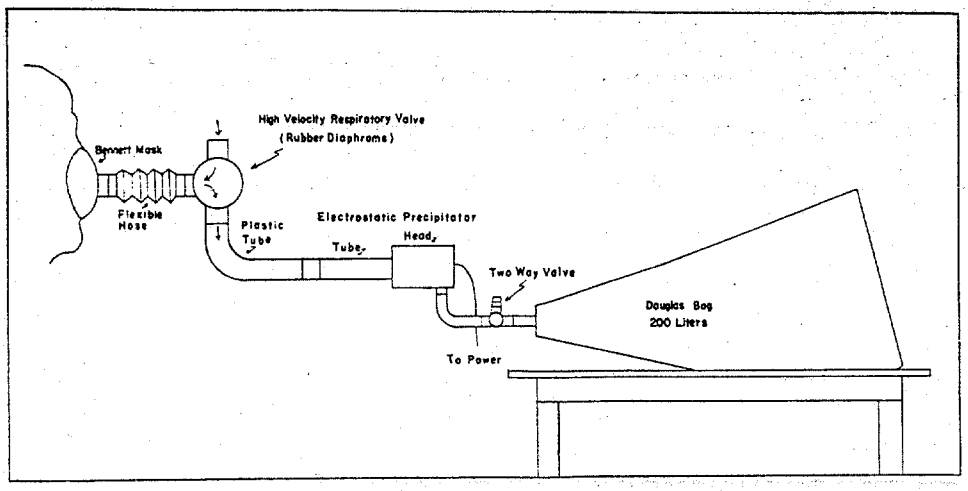

Fig. 13. Schematic representation of equipment and method for determining the proportion of particulate lead exhaled.

for their healthy normal characteristics, and these characteristics were not altered by the experimental conditions. One of the subjects has since been the victim of a disease of unusual type which results intermittently in discomfort and partial disability. Suffice it here to say that nothing in the onset, nature, and course of this disease has suggested to ourselves or to consulting physicians that there may be a relationship between it and his experience as an experimental subject.)

In the experiment dealt with in some detail in the paragraphs that follow, the compound of lead dispersed in the air was, as indicated previously, the sesquioxide. The identification and the essential purity of the dispersed compound are demonstrated by the comparison, in Figure 14, of the X-ray diffraction pattern of a sample collected from the air by electrostatic precipitation with that of the pure compound.

The range of sizes of the dispersed particles in the atmosphere of the chamber in this experiment is illustrated by the electron-microphotograph in Figure 15, and more precisely by Figure 16, which demonstrates the regularity of the distribution of the sizes.

Experimental Results

After the acceptance of subject F.C. as suitable for the second of this series of experiments, preliminary observations for the purpose of defining the pattern of his normal intake and output of lead were initiated in anticipation of their completion in time for his introduction into the respiratory chamber. Meanwhile, the first of

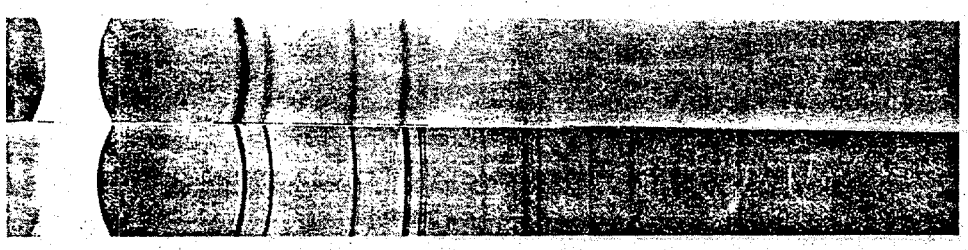

Fig. 14. X-ray diffraction pattern of lead sesquioxide. Above is that of particulate lead removed from respiratory chamber; below is the reference standard.

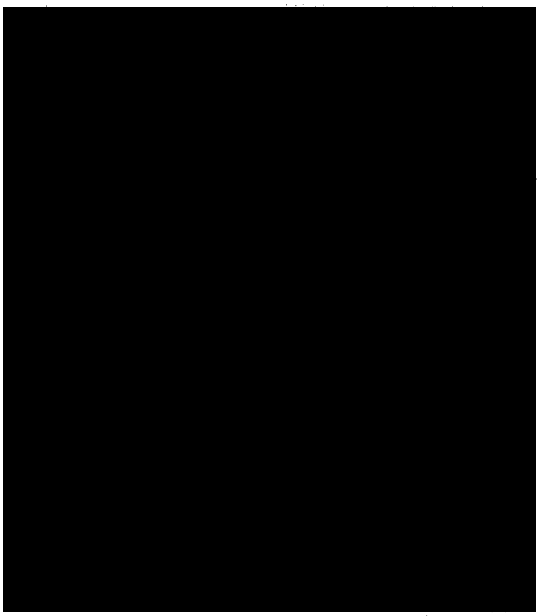

Fig. 15. Electron-photomicrograph of particles precipitated from atmosphere of the respiratory chamber in accordance with their proportional occurrence therein.

these experiments was in progress, and because of the variability of the response of the subject of this experiment, it had to be continued for a much longer period of time than had been anticipated. Accordingly, the preliminary (control) period, in the case of subject F.C. persisted for 72 lunar months. Unexpectedly, this circumstance turned out to be advantageous, for during the latter part of this period, when this subject would otherwise have been well along in the period of experimental exposure, there was an abrupt change in the lead content of his food. The results of this change, while readily explainable on the basis of previous experience, would have created a problem of interpretation had they occurred fairly early in the period of respiratory exposure. The data of the preliminary period have been summarized in Table 23. There it may be observed that the quantity of lead in the food and beverages during the last 16 weeks of this period was almost twice what it had averaged previously. The subject, a bachelor, had moved from one boarding house to

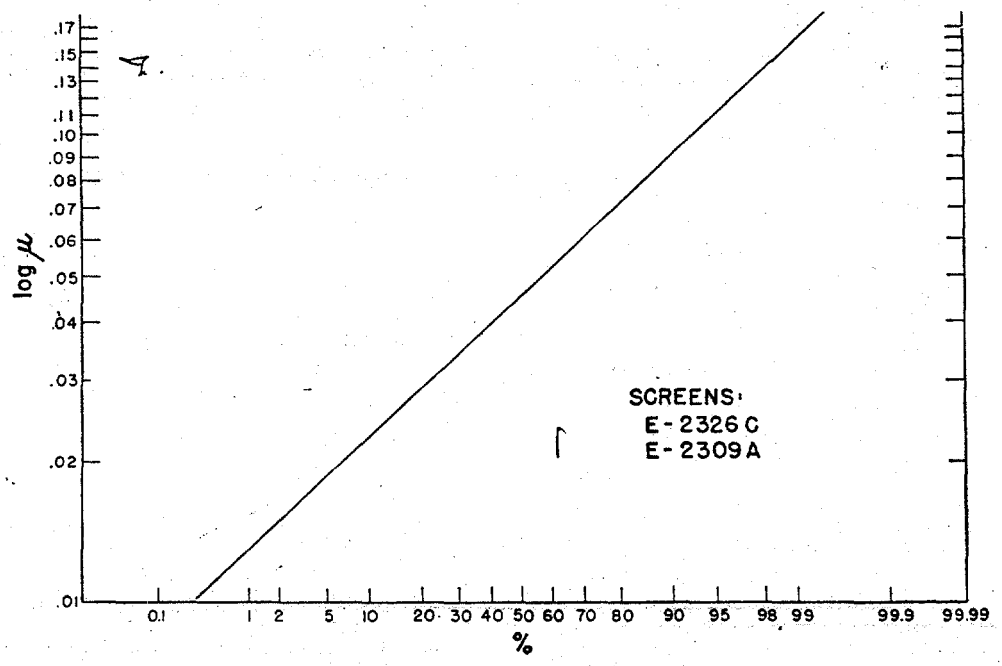

Fig. 16. The distribution of particles of lead sesquioxide in the atmosphere of the respiratory chamber according to their size.

while being unusual in his experience, was not especially noteworthy except for its persistence. It was not to be taken as an indication of a poor quality of food, or of unsatisfactory methods of handling it in this new household. The average quantity of lead in the food per day was slightly under 0.4 mg. during the first of these two periods of eight weeks, and 0.32 mg. during the second. Comparable results had been obtained occasionally in the second month of the control period, and also appeared again from time to time later in the experiment.

and in a different manner in a series of charts. Attention is called to the limited variability of the lead intake in the food during the 40 weeks represented in Table 24; to the discrepancy between the total output of lead and the alimentary intake, and yet the essential equivalence of the quantities of lead in the food and feces at all times; and to the output of lead in the urine, which increased steadily from the first period of four weeks through the fifth of such periods, and then after diminishing slightly, remained practically constant thereafter. This last phenomenon, i.e., the

Table 23

Lead Intake and Output of Normal Subject (F.C.) During Period of Preliminary Observation

Successive Periods of 8 Weeks	Lead Ingested Milligrams	Lead Eliminated—Milligrams			Lead—Mg. Lost (—) or Retained (+)
		Total	In Feces	In Urine	
1st	13·59	11·95	10·45	1·50	+ 1·64
2nd	13·31	15·13	13·63	1·50	— 1·82
3rd	13·16	13·82	12·45	1·37	— 0·66
4th	11·51	11·59	10·41	1·18	— 0·08
5th	9·30	8·93	7·88	1·05	+ 0·37
6th	9·24	9·05	8·16	0·89	+ 0·19
7th	12·75	13·74	12·86	0·88	— 0·99
8th	22·21	17·61	15·85	1·76	+ 4·60
9th	18·17	15·05	13·76	1·29	+ 3·12
TOTAL ..	123·24	116·87	105·45	11·42	+ 6·37

apparent steady state of the subject with respect to the rate of the urinary output of lead, after several months of intermittent respiratory exposure, appeared to be an adequate confirmation (if it should persist), as well as an explanation, of observations made repeatedly under the conditions of occupational exposure. It had been noted, with some doubt as to the mechanisms involved, that groups of workmen introduced into an occupational environment in which they were subjected almost wholly to respiratory exposure to lead at a substantially uniform level of intensity, responded with a prompt and progressive increase in their urinary output and concentration of lead for some months, after which the excretory rate levelled off and showed little further change, so long as the conditions under which their work was being done remained unchanged. In view of the fact that the same phenomenon had occurred and had persisted over the period of almost two years in the first experiment, it was anticipated that it would do so in this case as well, but the respiratory exposure was continued uninterruptedly through an additional period of 48 weeks, thereby extending the total duration of the exposure to 88 weeks, in order to determine the outcome. The point having been settled conclusively in the affirmative, the exposure was terminated, and the other procedures of the experimental regimen were continued for another period of 80 weeks.

The principal results of the entire series of observations made in this experiment, with respect to the metabolism of lead, are

Table 24

Lead Intake and Output of Normal Subject (F.C.) During Period of Inhalation of Lead Oxide

Successive Periods of 4 Weeks	Lead Ingested Milligrams	Lead Eliminated—Milligrams			Lead—Mg. Lost (—) or Retained (+)
		Total	In Feces	In Urine	
1st	4·16	4·53	3·52	1·01	— 0·37
2nd	4·89	5·63	4·06	1·57	— 0·74
3rd	6·11	8·34	6·59	1·75	— 2·23
4th	6·95	8·62	6·71	1·91	— 1·67
5th	6·18	8·00	5·61	2·39	— 1·82
6th	6·06	9·00	6·66	2·34	— 2·94
7th	6·22	8·53	6·52	2·01	— 2·31
8th	5·07	7·29	5·44	1·85	— 2·22
9th	6·20	8·83	6·90	1·93	— 2·63
10th	5·22	7·91	6·07	1·84	— 2·69
TOTAL ...	57·06	76·68	58·08	18·60	—19·62

portrayed in Figures 17, 19 and 21. In the first of these (Fig. 17), the mean values of the daily intake of lead in the food and beverages, the daily output of lead in the feces, and the weight of the food consumed daily by Subject F.C., as determined for each period of 28 days, are plotted in sequence. The curves representative of the food and feces parallel each other, their peaks and valleys corresponding closely in the time of their occurrence, with those of the weight of food consumed. This correspondence is the more striking at the points in these curves which deviate most markedly from their general course. The largest and most persistent upward swing occurred toward the end of the control period, as commented on previously. The weight of the food consumed during this period was considerably greater than it was at any other time during the experiment. However, the ingestion of lead in the food, by this subject, was not in the upper normal range, with the exception of the two occasions, during the control period, and one other about midway in the period of experimental exposure.

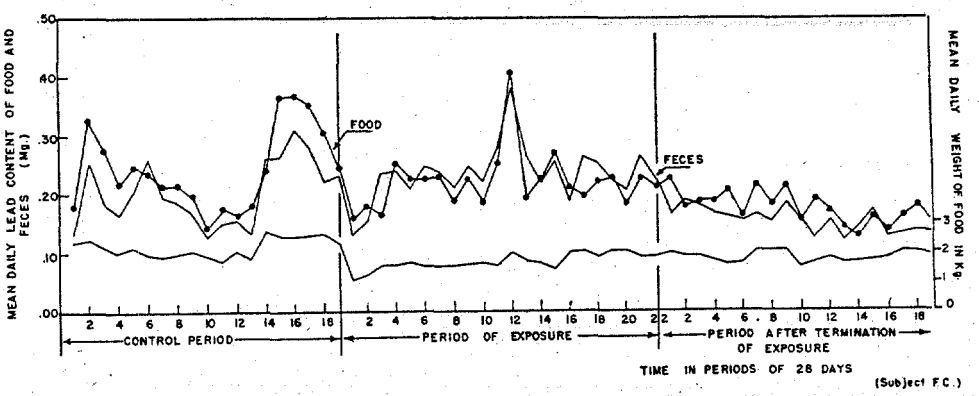

Fig. 17. The large connected points represent the mean quantity of lead (left axis) found in each of a series of 28 daily composite samples of food and beverages, plotted in temporal sequence during the entire period of the metabolic observations. The successive points of changed direction in the lighter line intertwining with the foregoing curve, represent the mean daily output of lead in the feces, plotted in like manner. The lowermost line indicates the mean daily weight of food, plotted similarly (right axis). First experiment in which subject F.C. was engaged.

Reference was made to the avoidance of the entrapment of any of the particulate lead in the air of the chamber in the upper respiratory tract of the subject. It is evident, from the relationship of the lead in the food to that in the feces during the period of exposure, that the particles of the lead compound escaped such entrapment. In order to emphasize this point, and also to illustrate the manner in which such entrapment is revealed graphically when it occurs, Figure 18 is interposed at this time. Figure 18 corresponds in every way in its representation to Figure 17, except that it portrays the results of another experiment engaged in by this same subject months later. Indeed, as may readily be seen, the first major period in Figure 18 corresponds to the last major period of Figure 17. The intervening period of 80 weeks, between the conclusion of his first period of intermittent exposure and the initiation of his second, resulted in the restoration of this subject very nearly to his original normal state with respect to his body burden of lead. At this time he returned to the respiratory chamber on the same schedule as before. The only variant in the experimental conditions, as compared to those of his first period of exposure, was the size of the particles of lead sesquioxide which now ranged up to a maximum of four microns in diameter (90 per cent of the particles were smaller than two microns, and 50 per cent were under 0.9 micron, in diameter). The larger particles were trapped in the upper

somewhat more than half of that inhaled (55 per cent) was found in the exhaled air of this subject under these conditions, it appears that approximately 40 per cent of the inhaled lead that separated out of the air in some part of the respiratory tract found its way subsequently into the alimentary tract. Furthermore, since according to the results of previous experiments, only 10 to 12 per cent of that swallowed was absorbed in the alimentary tract, as opposed to the essentially complete absorption of that which was deposited upon the membranes of the respiratory tract, one might suspect that the extent of the absorption of lead under these experimental conditions, as revealed by the excretion of lead in the urine, may have been appreciably less than it had been when the subject had inhaled the more highly dispersed particles.

initial and subsequent response to the induced respiratory exposure to the finely dispersed lead in the air of the chamber. The initial response is prompt, after which it progresses in degree for 20 weeks, then diminishes. The seasonal factor is not notably involved in this decrease, as the urinary volume, which was at its minimum some three months earlier, discloses. (This phenomenon of an apparently excessive response before levelling out, has occurred with regularity in experiments involving exposure to the highly dispersed sesquioxide in the air of the chamber.)

Despite the variability of the output of lead in the urine during the period of exposure, the trend during that period is unmistakable. A peak in the mean output of lead was reached at about 0.086 mg. per day after about 24 weeks; this was

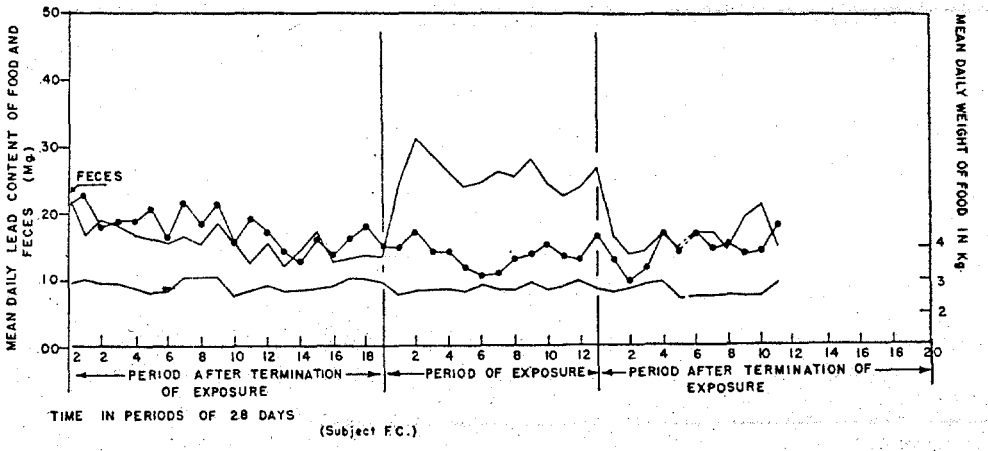

Fig. 18. The comparable data of a second experiment in which subject F.C. was engaged, are plotted in exactly the same manner as in Fig. 17. The difference in the relationship between food and feces, with respect to lead content, in the middle section of this, as compared to that of the chart immediately preceding (Fig. 17), lies in the size of the particles of lead sesquioxide dispersed in the air in this experiment.

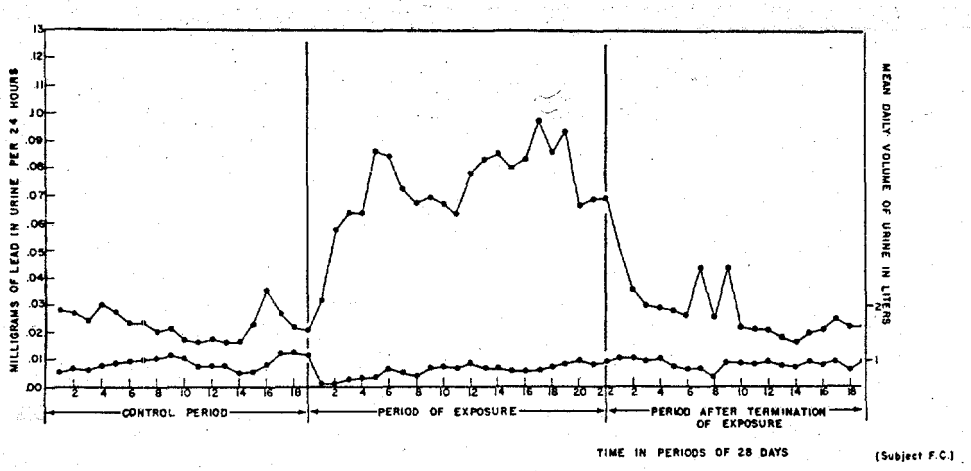

Fig. 19. The connected points of the upper curve represent the mean daily output of lead in the urine, in each period of 28 days, plotted in sequence throughout the first experiment in which subject F.C. was engaged. The corresponding points in the lower line depict the mean daily volume of the urine (right axis) in each period of 28 days.

exceeded on only two subsequent occasions. The average height of the plateau, during the period of the respiratory exposure, was somewhat above the level of 0.07 mg. per day, which was maintained during the last 12 weeks of the exposure, this being only slightly higher than it had been 68 weeks earlier. Following the termination of the subject's intermittent occupancy of the respiratory chamber, the output of lead in the urine decreased precipitously, thereby demonstrating that the previously persistent elevation of the lead output in the urine had been maintained by the repetition of the exposure from day to day and not by the accumulation of

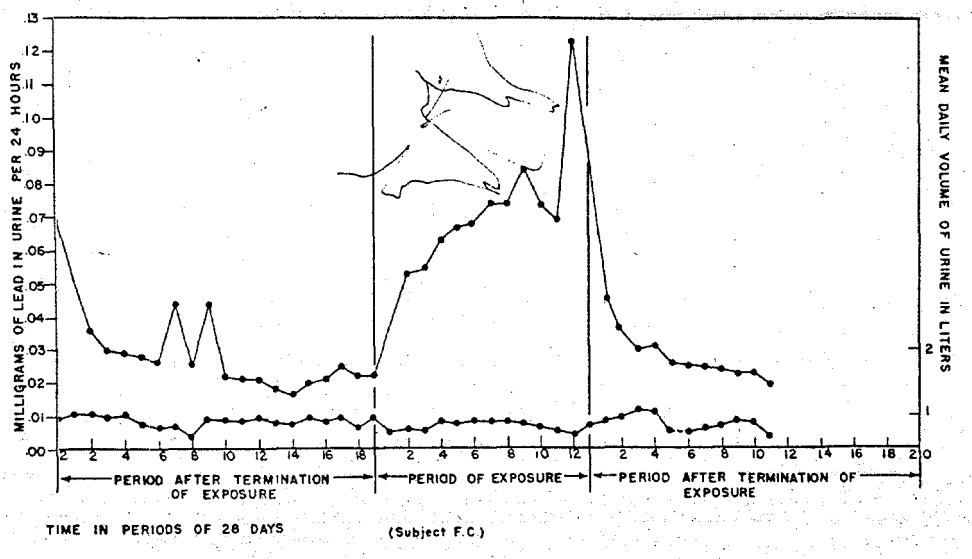

Fig. 20. The data of the second experiment in which subject F.C. was engaged, are plotted exactly as those of the first experiment (Fig. 19). The only variable was the larger size of the particles of lead sesquioxide in the second experiment.

slowly absorbable lead within the respiratory tract. The further downward trend of the urinary output of lead (interrupted at two points in the curve by the coincidental occurrence of relatively large quantities of lead in the food, as seen in Fig. 17) illustrate the decremental decrease of the lead retained in the body of the subject during the period of respiratory exposure.

Digressing again, at this point, briefly to consider the response of this same subject F.C. to respiratory exposure to the same quantity of lead in coarser dispersion in the atmosphere of the chamber during his second experiment, attention is called to Figure 20, analogous in its temporal relationships to Figure 18. Here it may be seen that the subject has reacted somewhat differently than he did during his first intermittent sojourn in the respiratory chamber. The rate of his absorption of lead during the entire second period within the chamber was certainly no less than it had been during the first, as judged by the output of lead in the urine during these two periods. The level mounted at about the same rate during the early months of the two periods; it reached a somewhat higher level during most of the intermediate months of the second experiment than it had in the first; and it was at a higher level at the end of the 52 weeks of the second period of exposure than it had been at the corresponding time in the first. These differences are not great, but they are too consistent to be ignored. It is in the *pattern* of the response to the two sets of conditions, however, that the greatest dissimilarity appears. There is no definitive evidence in Figure 20 that the urinary output of lead reached a maximum and then levelled out. One is on somewhat uncertain ground in interpreting this apparent fact, because of certain experimental variables which cannot be harmonized entirely. The second period within the chamber began some three years later than the first; the two did not coincide, exactly, in their seasonal relationships (the second began 12 weeks earlier in the year than had the first); and they were not of the same duration (the second having been terminated at the end of 52 weeks, and the first only after 88 weeks). One cannot be sure what would have happened had the second period within the chamber been extended. Nevertheless, the evidence, as it stands, denies the occurrence of the steady state in the second experiment, and there is reason to suspect that no such state would have been reached later. This reason lies in the fact that most of the lead which was diverted from the respiratory tract to the alimentary tract, persisted in the latter throughout the intermittent periods of freedom from further respiratory exposure (16 hours per day on five days of the week, and 64 hours over the weekend). Since, as has been noted, approximately 20 per cent of the lead in the air inhaled by subject F.C., while in the respiratory chamber, gained entrance into the alimentary tract, this experiment tended, to that extent, to simulate the experiments in which lead was ingested with every meal and was being absorbed from the alimentary tract at an approximately constant rate. Under the latter conditions, the rate of the urinary excretion of lead increased progressively at a nearly constant rate. Under the conditions associated with this second experiment in which subject F.C. engaged, the quantity of lead swallowed during, and for a time after, the day's respiratory exposure, was smaller than it had been in any of the experiments in which lead was ingested (being of the approximate order of 0.1 to 0.15 mg. per day), but this quantity, available for continuing absorption for a day or more, may have been sufficient to offset the equilibrium which otherwise would probably have been achieved, and to cause a modest progressive increase in the absorption of lead and in the corresponding rate of its excretion.

The fact that the general level of the absorption of lead by subject F.C., during the second experiment, was as high as it had been during the first, is also of interest. There is no doubt, of course, that an appreciable portion of the lead which was inhaled during the second experiment was diverted to the alimentary tract, where its absorption would be considerably less complete than that in the respiratory tract. However, another factor, associated with the size of the particles, operated in the

opposite direction. The determinations of the lead in the expired air of this subject, under the conditions of the two experiments, demonstrated that approximately 64 per cent, by weight, of the inhaled lead was being exhaled when the particles were uniformly small (0.05 micron in diameter), while only 54 per cent (by weight) of the larger particles of the second experiment (2 microns in diameter) were so disposed of.

The interpretation of certain of the findings of these experiments may appear to have been based on the assumption that the particles of lead sesquioxide, which were deposited upon the respiratory membrane during the exposure of this subject to the contaminated atmosphere of the respiratory chamber, were absorbed fairly promptly. This, however, is not an assumption, but a fact—a noteworthy and, in some respects, a remarkable fact. The oxides of lead are not very soluble, and it might be suspected that they would not be absorbed rapidly. On the other hand, one is not dealing with a simple aqueous medium in considering the interaction of solid particles of submicroscopic dimensions with the extensive surface of the complex, hydrated chemical system, the pulmonary membrane. No special effort was made to determine the actual speed of the pulmonary absorption of the lead compound employed in these experiments in either of the states of subdivision described. The absorption in the lung in both instances, however, occurred with a degree of promptness which resulted in a definitive increase in the lead content of the urine within the first few days after the initiation of the respiratory exposure of the subject. The relative completeness of the absorption from the lung from day to day is demonstrated by the fact that there was a significant decrease in the concentration of lead in the urine voided on a series of Mondays as compared to that found in the urine voided on a corresponding series of Fridays. This could not have been the case had there not been a significant degree of clearance of lead from the lung during the weekend. The still more pertinent fact, which demonstrates, in a conclusive manner, the virtually complete absorption of the particles of lead from the lung membrane, is the development of what amounts to an excretory balancing of the pulmonary absorption, after a period of time sufficient to build up an appropriate burden of absorbed and retained lead in the body of the subject. This is not actually an equilibrium or a steady state. It is rather a series of intermittent disturbances of the equilibrium, now in one direction, and then in another, of essentially equivalent proportions, which may be postulated as having occurred in the following sequence. During the 7.5 hours of exposure, the subject absorbed more lead than he excreted, and then during the 16 hours thereafter the process was partially reversed; during the 5 successive days of exposure, he accumulated lead in his body, and during the 2 days of freedom from exposure he reduced the quantity thus accumulated. But when the accumulated lead reached a level at which the quantity lost during the period of freedom from exposure balanced that gained during the period of accumulation, the progress of the accumulation ended, and the weekly or monthly rate of the urinary excretion became essentially constant. This pattern of excretory behaviour can be expected to occur only when both exposure and absorption wax and wane to a sufficient extent and with regularity. It would not occur if the exposure were constant or if its irregularity were to be masked by the retention of unabsorbed, but absorbable, lead within the body in the intervals between periods of exposure, whether as an expression of a slow rate of absorption from some site within the body (as in the case of an accumulation of slowly absorbable lead from the lung), or as the result of the diversion of lead into such a site as the alimentary tract, from which it would continue to be absorbed for many hours after the primary exposure had come to an end.

The final representation of the data of the first experiment in which subject F.C. was engaged, appears in Figure 21. Here are shown the variations in the concentration of lead in the blood, as determined in duplicate samples obtained on the same day of each week, and averaged for each successive period of 4 weeks, in the form

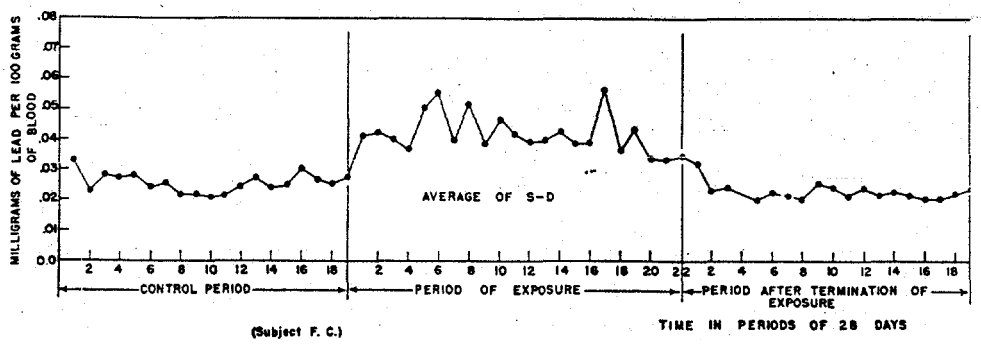

Fig. 21. The average concentration of lead in the blood in each successive period of 28 days (8 samples), is plotted as a series of connected points in sequence, throughout the entire period of the first experiment in which subject F.C. was engaged.

of a sequence of points plotted in the manner of the preceding charts. The plateau effect, as noted in Figure 19, is clearly evident, for while there is at times a somewhat greater variability in successive or adjacent points than might be expected (certainly more than can be interpreted precisely), the general shape of the curve during the period of exposure is not subject to question. It slopes upward, moves upward and downward, uncertainly, for a time, and then continues on its level way for 48 weeks with but two deviations. Certainly this behaviour on the part of the blood provides convincing evidence of the general but less inconsistent pattern of the

tion, in sharp contrast with upward slopes of the curves terized the blood, in this res- xperiments in which lead was ılarly. The decrease in the of lead in the blood followed t relatively brief course after ɔn of the period of exposure, vel which was indistinguish- e initial (control) period after ks. It should be noted in this at it was never very far above vel; the height of the plateau ıut 0.042 mg. per 100 grams, ighest average concentration ıg any period of 28 days (there such period after the concen- ed off) was 0.056 mg. per 100

ı arises naturally concerning ıantity of lead which was retained in the body of subject F.C. during the course of these experiments, and the same question has presented itself in the four other experiments of this type that have been completed and in the seventh which is now in progress. This question cannot be answered directly from the data, but an estimate can be arrived at in either of two straightforward ways. The total respiratory yield of lead during the entire period of time, dating from the first to the last day of the exposure of this subject, can be calculated (a) from the estimated volume of his respired air, as verified by measurements made during various periods of the day; (b) from the concentration of lead in the air breathed during the hours spent within the respiratory chamber (this comes to about 98 milligrams); (c) from the concentration of lead in the ambient air in the relevant parts of Cincinnati (this was of the order of two micrograms per cubic metre); (d) from the percentage of lead retained in the lungs of the subject during the period spent in the respiratory chamber (approximately 36 per cent); and (e) application of this percentage to the air exhaled under ordinary conditions. The addition of the total quantity of lead contributed by the atmosphere, to that found in duplicate samples of the food and beverages, constitutes the total effective intake of lead, against which can be set the total output in the feces and urine as measured.

The other procedure is that of determining the amount of the excess of lead eliminated from the body of the subject during

the period after the termination of the exposure, taking the additional precaution of comparing the diminishing slope of the curve representing the rate of the urinary excretion of lead with those of the experiments in which known quantities of lead were ingested and reasonably well documented quantities of lead had been accumulated.

The result obtained by the application of either of these methods is not altogether satisfactory because of the relatively small quantities of lead which are involved from day to day, because of the inevitable variability of these quantities from day to day, which are not rendered more precise, necessarily, when they are composited together over a long period of time. All that can be said is that such results represent an order of magnitude which is probably not greatly in error, and (if there is any comfort in the fact) that they are in reasonably close agreement. On these bases of estimation, it appears that the quantity of lead retained by Subject F.C. during his first period of exposure in the respiratory chamber was not much less than 50, nor much more than 70 milligrams.

CONCLUDING REMARKS

It would be futile, and to some extent misleading, to attempt, in several brief statements, to summarize the pertinent facts which have come to light in the description of these experiments and in the discussion which has accompanied the description. Students of physiology, experimental medicine, and clinical medicine will examine the findings in different ways, while the physician who is concerned with preventive medicine in industry—that is, industrial hygiene—will view them in a still different light. It may be wise, therefore, as it seems necessary at this time, to leave their interpretation to these investigators.

For the purposes of these lectures we shall undertake, at our next meeting, to draw out and examine the more important facts in relation to practical problems with which we are confronted at this time.

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THE HARBEN LECTURES, 1960
THE METABOLISM OF LEAD IN MAN IN HEALTH AND DISEASE

by

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LECTURE III

PRESENT HYGIENIC PROBLEMS RELATING TO THE ABSORPTION OF LEAD

In the Chair: J. C. AINSWORTH-DAVIS, M.A., M.D., F.R.C.S.
(Chairman of the Executive Committee of the Council)

The natural environment of this planet is such that the occurrence of lead in the tissues, body fluids and excreta of its human inhabitants is inevitable. On the other hand, the artifacts introduced into the environment by the past and current activities of mankind have provided numerous unanticipated and often unrecognized opportunities for human absorption of a wide variety of lead compounds. Most of these contributions to the alimentary or respiratory intake of lead are small, but sometimes single or multiple factors produce dangerous conditions. This occurs most frequently in connection with the occupations of individuals and groups. In the United States of America, for example, occupational lead poisoning, although reduced in severity now, in comparison with earlier periods, occurs more frequently, according to somewhat untrustworthy statistics, than any other occupational disease. The large proportion of cases of lead poisoning are occupational in origin, but cases occur from time to time in the adult population as the result of a variety of conditions in the household. Moreover, permanently disabling and fatal cases of lead intoxication occur among children between the ages of 1 and 3 years with distressing frequency and regularity, in many North American cities.

From the broader aspect of the public health, the contamination of the atmosphere with lead from a number of sources may increase under the influences of modern technology, especially in industrial and urban centres, and therefore, this potential source of public exposure to lead requires periodic investigation. More importantly, the opportunities afforded for the contamination of food with lead, in a country in which the processing of food materials is a complex industry of very large and widespread proportions, must be kept under constant surveillance. The variety and volume of the beverages consumed by the public must also be considered in this relationship, and not even the drinking water of a nation can be ignored, despite the comparative ease with which the lead content of urban water supplies can be controlled. The general exposure of the population to lead from these combined sources must be kept within appropriate limits, and, therefore, no standard promulgated for the safety of the public, with respect to the concentration

of lead in individual items of food or beverages, or in the air, has independent validity.

Of the many medical and hygienic problems that arise out of the matters mentioned above, as well as those which stem from other sources, four have been singled out for consideration on the background of the facts concerning the metabolism of lead, which have been the burden of the two preceding lectures.

1. THE DIAGNOSIS OF LEAD INTOXICATION.

Lead poisoning, in a variety of forms, has been known to physicians for centuries, and like many another matter that is "common knowledge", there have been many false ideas and many more hazy concepts of its nature and significance. This is neither the time nor the place to deal with the manifold facets of this situation, which has been further obscured and complicated by the socio-economic and legalistic aspects of workmen's compensation laws and procedures. Suffice it here to consider the contributions to the clarification of these problems which derive from the establishment of sound physiological criteria by which the magnitude and significance of the absorption of lead by an individual patient can be appraised, not by hearsay, nor by the generally inadequate and quantitatively unreliable history of the patient's exposure to lead as recounted by himself, nor even by the appraisal of his environment, but by the determination of the lead content of his urine and blood, or that of his tissues (post-mortem).

Systematic analyses of the lead in the atmosphere of industrial establishments over sufficient periods of time, in concert with clinical examinations and determinations of the lead in the urine and blood of the populations at risk in lead-using industries, have yielded data which have revealed the relationships which exist (a) between exposure to lead and absorption of lead, and (b) between the absorption of lead and the incidence (and to a lesser extent, the severity) of lead poisoning. The extent of the absorption of lead by men in industry is clearly related to the severity and the duration of their occupational exposure to lead. Under the somewhat variable conditions which exist in a specific industry or series of industries, this relationship, to be sure, is not as well defined, quantitatively, as it has been shown to be in our well-controlled experiments in the laboratory. On the other hand, the greater range of severity in industrial exposure to lead generally, as compared with the modest range which is compatible with the complete safety of experimental subjects in the laboratory, has yielded unmistakable evidence of a correlation between exposure and absorption. This fact is illustrated in Tables 25 and 26, from the aspect of the absorption of lead, by the data obtained in the investigation of five industrial populations (selected more or less at random from many other corresponding series of data which cover the desired range of findings without unnecessary replication). The environmental conditions under which these groups of men worked were such as clearly to differentiate them, in increasing order of severity from left to right in Tables 25 and 26, on the basis both of periodic inspections, and analyses of the air at the breathing zone of the workmen. The gradation of the absorption of lead among the groups, as indicated by the ranges and the distribution of the frequencies of occurrence of various levels of the concentration of lead in the urine (Table 25), requires little comment, despite the overlapping of the findings in the higher rubrics in the four columns to the right. The mean values show the order of severity satisfactorily, except for the fact that the exposure associated with one of the occupations of the group listed under the sub-heading "Slight and Severe" was considerably greater and more difficult to control than that of the others. As we shall see later, certain individuals in this group (those employed in the job referred to above) were in danger, while the majority of the group was not. This situation exists in many industries. In the absence of quantitative measurements of the severity of the exposure associated with specific jobs or areas within an industrial plant, it has often produced unexpected cases of poisoning and has contributed greatly to the unwarranted belief that the "susceptibility"

TABLE 25

Comparison of Various Occupational Groups with Respect to the Concentration of Lead in Their Urine, in Association with Varying Degrees of Severity of Exposure to Lead Below and Above the Threshold of Danger.

Lead in Urine	*Frequencies in Ascending Order of Severity of Exposure to Lead—Left to Right*				
			Near Threshold		
mg. per litre	*Demonstrable*	*Slight and Severe*	*Safe*	*Unsafe*	*Very Severe Very Dangerous*
0·00 — 0·039 ...	41	35	—	3	2
0·04 — 0·079 ...	156	98	11	7	2
0·08 — 0·119 ...	9	56	22	10	13
0·12 — 0·159 ...	—	35	16	14	14
0·16 — 0·199 ...	—	27	7	11	9
0·20 — 0·239 ...	—	8	2	3	9
0·24 — 0·279 ...	—	7	2	4	6
0·28 — 0·319 ...	—	4	3	3	5
0·32 — and over ...	—	3	—	2	19
Total Number	206	273	63	57	79
Mean	0·051*	0·102*	0·130*	0·152*	0·238
S.D.	±0·014	±0·069	±0·059	±0·024	±0·151

* Calculated from a different arrangement of the frequencies.

TABLE 26

Comparison of Various Occupational Groups with Respect to the Concentration of Lead in Their Blood, in Association with Varying Degrees of Severity of Exposure to Lead Below and Above the Threshold of Danger.

Lead in Blood	*Frequencies in Ascending Order of Severity of Exposure to Lead—Left to Right*				
			Near Threshold		
mg. per 100 g.	*Demonstrable*	*Slight and Severe*	*Safe*	*Unsafe*	*Very Severe Very Dangerous*
0·00 to 0·019 ...	—	—	—	—	—
0·02 — 0·039 ...	11	85	4	1	—
0·04 — 0·059 ...	24	122	30	18	9
0·06 — 0·079 ...	1	50	22	21	12
0·08 — 0·099 ...	—	7	5	6	17
0·10 — 0·119 ...	—	6	1	6	14
0·12 — 0·139 ...	—	2	—	1	5
0·14 — 0·159 ...	—	—	—	—	4
0·16 — 0·179 ...	—	—	—	—	1
0·18 — 0·199 ...	—	—	—	—	1
0·20 — 0·219 ...	—	—	—	—	2
0·22 and over ...	—	—	—	1	10
Total Number	36	272	62	54	75
Mean	0·042*	0·050	0·060	0·075	0·130*
S.D.	0·008	±0·019	±0·016	±0·041	±0·091

* Calculated from a different arrangement of the frequencies.

of individuals to lead poisoning is highly variable.

We shall return to Table 25 later, in considering the relationship between severity of exposure and degree of hazard. Table 26 deals with the analytical findings in the blood of the same individuals and groups (the groups are the same, but certain discrepancies in the frequency of sampling are apparent) represented in Table 25. In keeping with the lesser degree of physiological variability of the concentration of lead in the blood, versus that in the urine, as noted in experimental subjects, as well as with the relatively slighter dependence of the concentration of lead in the blood upon the daily or immediate rate of absorption of lead, the results in Table 26 are more indicative of the true status of these men, with respect to the extent of their body burden of lead at the time of sampling, than are those in Table 25. The distribution of the results within and among the industrial groups is, therefore, more clearly indicative of the relative status of the individuals and groups. Here, there is no doubt as to the gradation of absorption from left to right, except in the " Slight and Severe " group, in which certain individuals in one occupation differ significantly from the main group. (The lack of a bi-modal distribution of the results is due to the small number of persons in this divergent subgroup.)

Alike, in Tables 25 and 26, the subheadings indicate the point at which safe levels of absorption are differentiated from those which are dangerous. The basis for this differentiation is the purely practical criterion of the non-occurrence or the occurrence of cases of lead poisoning within these populations. As the environmental conditions in the industrial plants in which these men were employed were appraised from time to time over periods of years, and as the employees were investigated periodically by clinical and analytical means, a definitive correlation between the levels of lead concentration in the urine and blood, and the non-occurrence or occurrence of lead intoxication, was established. The data listed in these tables, as indicated, are recent examples of the sharpness of the analytical criteria that may now be applied. Experience and the accumulation of voluminous data have spoken for themselves, in proclaiming that cases of lead poisoning occur only when certain limits of concentration of lead in the urine or blood (or in both) have been exceeded. The critical concentration of lead in the blood of child or adult, below which, in our experience (during the period of exposure, not weeks or months later), no case of even the mildest type of poisoning has been induced by the absorption of inorganic compounds of lead*, is approximately 0.08 mg. (80 micrograms) per 100 grams of whole blood. Due allowance must be made for an analytical error which rarely exceeds 0.01 mg. (10 micrograms) on either the positive or negative side, within the range of concentration of 0.01 to 0.10 mg. per 100 grams (somewhat greater in the higher range), as calculated from the results obtained by the analyses of 10 grams of whole blood. The qualifications, with respect to the known precision of the preparatory and analytical methods, are essential, since the methods and the facilities used by highly competent analysts vary in the type and quality of the equipment, reagents and manipulative procedures, to such an extent that the magnitude of the deviation, although it may be uniform within a specific laboratory, varies from laboratory to laboratory, almost without exception. Aside from carefully controlled procedures for the preparation of samples, two methods of analysis, one essentially chemical and colorimetric, the other physical and densitometric, have been employed in parallel in these investigations, and are applied, as a rule, to duplicate samples of blood, in order by their combined qualities to promote precision, sensitivity and specificity, and also to detect the fortuitous contamination of a sample which occurs from time to time, inevitably. *Parallel* analyses are not readily applicable to the urine because of the difficulty of obtaining duplicate specimens as the urine is being voided. The division of a specimen after single or

* It seems wise to remind physicians and analysts that the determination of lead in the blood in an attempt to appraise the degree of absorption of tetraethyl lead, and, in all probability, other lead alkyls, is futile. Because of the metabolic behaviour of these compounds in the body, the concentration of lead in the blood bears little or no relationship to their absorption and distribution in the tissues.

multiple voidings is fraught with gross possibilities for error, since, after even slight cooling, the sample, following the precipitation of the phosphates, is no longer homogeneous. The factor of physiological variability, however, renders imperative the analysis of multiple samples of the urine of an individual.

The concentration of lead in the urine, or the output of lead in the urine per unit of time (on the part of individuals without renal damage or impairment of function) which corresponds to the threshold level in the blood, is a range rather than a single value, because of physiological factors (other than the rate of absorption or the body burden of lead) which result in a considerable variability in the rate of the urinary excretion of lead.

The value in the individual case may be as low as 0.15 mg. per litre and as high as 0.24 mg. per litre, dependent upon the number and volume of the urinary samples which have yielded an average result, and also upon the climatic conditions (prevailing temperature) under which the samples were obtained. The objective of the investigation of the urine by analytical means is the determination of the current rate of the urinary excretion of lead. Attention has been directed repeatedly toward this matter in these discussions. Further emphasis on it is justified, however, for despite the absurdity of the performance, a single result obtained from a sample of urine, collected without special precautions and analysed by a nondescript method, is often advanced as definitive diagnostic evidence in case reports and in medico-legal reports and testimony. Such results are likely to be grossly misleading and should be discarded in favour of purely clinical evidence until and unless they have been confirmed conclusively. Unfortunately, their status as numbers, fortified by the semblance of technical precision, catches the poorly disciplined or ill-informed mind, and acquires an authority that can hardly be matched by the superior but non-quantitative judgment of the most competent and experienced clinician.

The significance of the data in Tables 25 and 26 goes beyond their diagnostic relevance, as we shall see later. They are presented in this relationship, however, for the sole purpose of defining the ranges of the concentration of lead in the blood and urine which are associated with the occurrence of lead intoxication. No such range, in either instance, is indicative of the existence of intoxication. There is, however, a critical level of concentration of lead in the human body, at or above which, under suitable conditions, individuals may develop intoxication. Such a situation, as revealed by the excretion of lead in the urine, or as shown more precisely by the concentration of lead in the blood, when accompanied by symptoms and signs compatible with the known effects of lead, as revealed by clinical investigation of a patient, provides a sound basis for the diagnosis of lead intoxication. The actual existence of intoxication, however, is established on clinical grounds alone, for there are no analytical findings which, of themselves, are indicative of illness. They merely denote the conditions in the background, without which the diagnosis of lead poisoning cannot be made or substantiated.

It is difficult to establish this concept in the minds of physicians and laymen who are unduly impressed by the historic toxicity of lead compounds. The facts, however, are as crystal clear as present physiological knowledge and skill in clinical observation can make them. Lead occurs naturally in the human body; within certain limits of concentration therein, whether useful or not, it is harmless; above a well-defined, critical concentration it is capable of causing lead poisoning; the higher the concentration above the critical point, the more likely it is to cause poisoning in the individual person (higher incidence in groups); even the highest concentration yet found does not, of necessity, cause intoxication, or so it seems, and, therefore, there must be some conditioning, biochemical factor (release of lead ions from chemical bonds?) which initiates a toxic effect. It is obvious that further clinical and physiological investigation may identify toxic effects which are not now recognizable. A phenomenon which may well belong in this category—one, which, in fact, we tend to regard as the first sign of lead intoxica-

tion, is the alteration wherein certain porphyrins, principally coproporphyrin III, occur in the urine in concentrations well above the normal range. This abnormality, as is well known, is not induced by lead alone, but when other causes can be excluded, it seems reasonable to regard it as an early sign of lead intoxication, in the absence of other clinical evidence of illness. The acceptance of this view does not alter the threshold values which are set forth in Tables 25 and 26, for abnormal concentrations of porphyrins have not been found in the urine of men in the safe categories of occupational exposure to lead as defined therein.

In practice, in the clinical investigation of alleged or suspected cases of lead poisoning, it is desirable and feasible to secure analytical data on both the urine and blood of the patient. If the interval of time between the examination of the patient and the termination of highly abnormal exposure to lead, whether occupational or non-occupational in origin, has been sufficient to diminish the concentrations in the urine and blood below threshold levels, the analytical results will have little value. (It may be possible, in some instances, to fit the analytical findings into points on a curve which represents the diminishing rate of excretion of lead in the urine, and the corresponding decrease in the concentration of lead in the blood, with lapse of time after the termination of abnormal absorption, and so to determine the probable status of the individual in this regard at the termination of his exposure. However, this procedure will often involve fruitless speculations.) In such cases, only clinical judgment can yield a tenable diagnosis. When the physician in industry is presented with a diagnostic problem at the onset of the illness of regular workmen, the analytical findings in the urine and blood at that time make their maximum contribution, on the background of results obtained previously at intervals on the same individual. Atypical symptoms or clinical signs lose their potential significance as "unusual" manifestations of lead intoxication, when considered in relation to insignificant exposure as defined by analytical data, while plausible but non-specific symptoms or signs find a secure basis in concentrations of lead in urine and blood which denote harzardous absorption of lead. Bizarre clinical patterns of illness, in concurrence with dangerous levels of lead absorption, continue to pose diagnostic difficulties and medico-legal controversies, but it is pertinent commentary on the "protean" manifestations of lead intoxication, that they have come to be fewer in number and much more comprehensible, as exposure to lead and the resultant absorption have been given quantitative significance. This simplification and clarification of the clinical pattern of lead poisoning is partially due, in all likelihood, to the fact that some of the more serious effects of this disease are seldom seen in American industry. On the other hand, analytical evidence which is capable of demonstrating the probable insignificance of the absorption of lead as a factor in an illness of obscure etiology, has had a salutary effect in divesting speculative diagnoses of their capacity to become presumptive and then definitive, through authoritarian medical and legal pronouncements. It is obvious that one cannot, without self-deceit or lack of perspicacity, employ the clinical syndrome of lead poisoning as a criterion for defining the level or range of lead concentration in the blood which is required for the induction of illness, and then, simultaneously, use this range as the criterion for defining the clinical pattern of the disease. On the other hand, sound investigative procedure often calls for this very device, when, one after another, individual variables in such an association can be held constant while the manifestations of the others are being observed. Through such a device, probability increases to a point which approaches certainty. During the past twenty-odd years since the present methods of analysis came into use, thousands of observations have been made, and the correlation between analytical results and the clinical features of plumbism has been put on an unassailable basis.

TABLE 27

The Concentration of Lead in the Tissues of Children Fatally Poisoned by Lead, or Suspected of Having Been So Poisoned.**

Tissue	*Milligrams of Lead per 100 Grams of Fresh, Unfixed Tissue*						
	Case Identification						
	A.J.	S.J.	D.S.	V.W.	L.D.	C.B.	D.E.M.
Brain	0·29	0·58	0·24	0·42	0·50	0·09***	0·14****
Liver	3·27	4·00	3·91	4·40	2·96	1·80	8·00
Kidney	0·61	0·88	—	2·59	1·74	1·10	5·5
Flat Bone	10·65	26·80	17·00	17·90	—	9·80	8·0
Long Bone	—	13·15	—	—	—	5·60	—
Blood	—	—	—	—	—	0·46*	—

* Obtained during life.

** Illustrative data from case material so selected as to exclude results that may have been influenced by chelation therapy.

*** Not characteristic of encephalopathic plumbism.

**** Poliomyelitis.

The problem of post-mortem diagnosis is presented not infrequently, in connection with a belated or neglected history of exposure to lead, when the cause of death, especially in an infant, is left in doubt, in the absence of definitive pathologic processes or in the presence of a non-specific form of encephalopathy. The analytical evidence at such a time may exclude lead as an etiological factor in the fatal illness, or it may demonstrate *not that lead was the cause of death, but that lead had been absorbed to an extent compatible* with such a diagnosis if, in afterthought, the type and course of the terminal illness of the child was such as to justify it.

An illustrative series of results obtained by the analysis of tissues taken from the bodies of children, post-mortem, are given in Table 27. In all but one of these cases, the diagnosis of lead poisoning had been arrived at before death occurred, and the analytical findings had demonstrated clearly that each child had absorbed grossly abnormal quantities of lead within a period not too far removed from that of his terminal illness. In scanning these data, it is enlightening to compare the levels of the concentration of lead in the skeleton with those in the soft tissues, and to reflect that the deposition of lead in the skeleton is the product of the rate of absorption and the time over which such absorption occurred, whereas the concentration of lead in a soft tissue, such as the liver, reflects the summation of the effect of the stream of lead being absorbed currently (shortly before death) from the environment, with that of the stream flowing from the skeleton, into which relatively large amounts had been absorbed previously. When the lead content of the skeleton is found to be high and that in the soft tissues is relatively low, the time involved in the absorptive process was relatively long, while the rate of absorption shortly before death was relatively low. Attention is called to the fact that the concentration of lead in the flat bone, in these cases, is higher than that in the long bone, this relationship being the reverse of that which obtains in the normal skeleton (cf. Table 15, Lecture I).

In one case, that of L.D. in Table 27, no data relative to the skeleton are available. This is an example of the usefuless of even scanty data. It is always desirable to have information concerning the skeleton, but skeletal tissues are not always obtained by the pathologist in the absence of a toxicological consultant. In this instance, the high concentrations of lead in the liver and kidney are sufficient proof of a potentially dangerous degree of absorption of lead,

while that in the brain is quite high, only one in the series being higher.

The coincidence of the relatively high concentrations of lead in the brain, in five of the seven cases illustrated in Table 27, with the common encephalopathic character of the clinical pattern of lead poisoning in children, is not, it seems, fortuitous. It had been our experience, until the recent appearance of the two exceptions recorded in Table 27, that the concentration of lead in the brain, in encephalopathy due to lead, was always equivalent to, and usually greater than, 0.20 mg. per 100 grams of fresh brain tissue (there is a moderate degree of variability in the concentration in different areas of the brain). In case C.B. the finding of 0.09 mg. per 100 grams of brain was a surprise, for this represents only twice the mean normal concentration and is barely beyond the normal range. This child, in life, was convulsing and otherwise dangerously ill, when first seen, and the concentration of 0.46 mg. per 100 grams of whole blood was indicative of a rapid and highly dangerous rate of absorption of lead. The relatively low concentrations of lead ranging from 0.20 to 0.60 tissue are evidence of the relative brevity of the child's severe exposure, and, therefore, it is reasonable to assume that the shortness of this period of absorption was responsible for the unusually low level of absorption into the brain. It is likely, we believe, that the symptoms were more intimately associated with circulatory dynamics than with the direct effects of lead in the brain. In any case, because of the frequency of the occurrence of concentrations of lead ranging from 0.20 to 0.60 mg. per 100 grams in the brains of children that have died with encephalopathic plumbism, we have come to consider this to be an important diagnostic criterion. In one instance, that of the case designated as D.E.M., this criterion led us to suggest that the diagnosis of lead encephalopathy was in doubt, and that further investigation of the case was indicated. A thorough examination of the brain resulted in the demonstration of characteristic lesions of poliomyelitis. Certainly this child had absorbed abnormal quantities of lead, and the two diseases may have developed concurrently, but the symptomatology cannot be attributed solely to the effects of lead.

The use in Table 27 of data derived exclusively from cases of lead poisoning in childhood should not be construed to indicate that the diagnostic significance of analytical results differs in any respect in fatal cases of lead poisoning among adults. As it happens, however, fatal cases of lead poisoning are seen but rarely among adults, and the facts could be illustrated much more satisfactorily by the more numerous cases that occur among children. These data serve, moreover, to introduce the subject of lead poisoning in early childhood, and to call attention to the frequently tragic outcome of such cases.

2. LEAD POISONING AMONG CHILDREN

To those who are familiar with the history of lead poisoning among children in Queensland, Australia, in the first three decades of this century (1, 2), it may not be surprising that similar cases occur as the result of somewhat similar environmental conditions in the United States. In Queensland, principally in Brisbane, large numbers of children were poisoned by the ingestion of lead in paint applied on the exterior surfaces of homes built of wood. The most commonly accessible painted surfaces were those of the side walls and railings of the verandas, from which, after the weathering which resulted rapidly in the tropical climate of this city, lead carbonate came off as a powder on the hands and fingers of small children who were confined, for their greater physical safety, during their daily sojourn out of doors, on these verandas.

In older sections of many North American cities, children of the same age group as those in Queensland (largely 1.5 to 3 years), and characterized by some of the same habits of eating, or putting fingers, thumbs and other objects in their mouths, ingest the crumbling and flaking paint from surfaces that had been painted repeatedly in earlier periods of better maintenance. The interior paints of an earlier day contained much larger quantities of lead pigments than those which are marketed and used at present, and this problem,

therefore, while not entirely eliminated in modern homes by changes in paint technology, is not increasing greatly in its scope with the further growth of cities. The circumstances of life conspire to make this a serious problem of public health, however, in that young children, in the poorer areas or slums of our cities, live under unsatisfactory conditions of housing, and in addition are likely to be left too much to their own devices; some of them are unwanted and unloved, while the mothers of others are compelled to leave them in the care of children but little older than themselves, while they (the mothers) engage in employment outside the home. The children develop aberrant appetites, interests and habit of eating (pica), and tend to deviate psychologically in other respects from those with more favourable social and physical environments.

In Cincinnati, in the period extending from 1928 through 1949, when interest in this subject, and the alertness of the house staffs of the two principal hospitals with which we were associated, were relatively undercultivated and somewhat intermittent, 45 cases of lead poisoning among children, 12 of whom died, were brought to the attention of the Kettering Laboratory. These were verified, with respect to the clinical significance of their absorption of lead, by analytical means, and confirmed by adequate clinical investigation in three local hospitals. They were also investigated in a somewhat desultory manner, from the aspect of the social and environmental conditions out of which they had arisen. Paint from toys, furniture, and the interior woodwork of houses, was implicated as the source of lead in most of these cases; old storage battery casings, used for fuel, were responsible for several cases; toys of lead-containing alloys were involved in a few instances, one of which, in an infant, was fatal; and a nipple shield made of lead was convicted in one case.

In 1950 and afterward, with an increasingly intense and concerted diagnostic effort on the part of the staffs of two hospitals, the recorded cases of lead poisoning among children in Cincinnati increased in number. There were 12 in 1950, 18 in 1951 and variable numbers of that order of magnitude in the years since, culminating in 28 cases in 1959, of which 6 were fatal. (Of 128 cases entered into the records of the Kettering Laboratory, mostly from Cincinnati, several from neighbouring cities, and two from distant cities, in the period from 1928 through 1955, there were 35 fatalities.) Sanitary inspectors in the Department of Health of Cincinnati collaborated in the investigation of the homes from which these children had come, and an aroused professional and official concern led to the enactment, in 1960, of local legislation, which, with appropriate official and legal action and the intelligent co-operation of the manufacturers and distributors of paints, can be expected to eliminate the large proportion of these cases in the not too distant future among the children of Cincinnati. The problem is widespread, however, within the country, as is attested especially strikingly by the evidence adduced in Baltimore and New York. So long as present conditions, with respect to housing and maintenance of the interiors of houses, persist in the poorer districts of Cincinnati and other North American cities, cases will continue to occur with tragic consequences.

A curious phenomenon, in connection with these cases, is their seasonal incidence. They occur sporadically, throughout the year, but, in the Eastern and North Central States, to the extent of the available records, almost all of the cases occur between the months of May and September in accordance with an essentially Gaussian curve of frequencies. This fact has been responsible for much speculation concerning a seasonal factor (or factors), which may coincide with the presence of dangerous quantities of lead in the bodies of children, in the induction of intoxication. There can be no doubt that the temperature (and humidity) of the summer months along or near the 39th parallel of the northern hemisphere provides a significant factor of stress, and the experiments of Baetjer (3), have demonstrated an effect of this factor, in association with lead poisoning. No evidence has been found, however, of a profound disturbance in the metabolism of lead in association with elevated ambient

temperatures. On the contrary, it is clear that these children have been ingesting large quantities of lead up to the very day of the onset of their illness. Roentgenographic examination of the abdominal region of the sick child reveals, frequently, the presence of irregularly shaped, radiopaque objects along the course of the alimentary tract, and the feces, which often contain grossly demonstrable flakes of paint (sometimes painted splinters of wood) yield variable but large quantities of lead on analysis. By the latter means, the nature of the source of the ingested lead is often rendered apparent, and an investigation in the home, and an analysis of paint scraped from a tooth-marked wooden object—a window sill, the railing of a play-pen, the arm of a highchair, the orally accessible part of a toy—complete the record in this respect. It is not always so easy, however, for when no one has been caring for a child and observing its activities, there is no direct source of information, and often there is no physical clue to the source of the ingested lead. Under such circumstances a thorough search of the child's environment may call for numerous analyses, before the source of the absorbed lead shall have been disclosed. As a generalization, it may be said that no great mystery attaches to these cases. The exposure to lead, in immediate temporal relationship to their onset, has been readily demonstrable, and the extent of the absorption of lead has not been slight or dubious but of gross and obviously dangerous proportions. Two questions of major importance arise out of their occurrence. (*a*) What factor or factors operate to cause the absorption of lead by these children to reach a critical level in the summer months? (*b*) Why is it that encephalopathy is so frequently the presenting form of lead poisoning in children up to four years of age?

It is obvious of course, that the accumulation of lead within the tissues of these children will usually have reached a dangerous level some weeks or months before the onset of the convulsive seizure which so frequently is the alarming episode that brings the child to the hospital. Such an occurrence on a specific day, which, in terms of the quantity of lead in the body of the child, differed little from many a preceding day, had some exciting cause—perhaps a fall, a blow on the head, an unusually hot day or succession of days, or some other added stress. The stage was set, and as is true of lead poisoning in the adult, some necessary 'trigger mechanism' was all that was required to initiate a toxic response. Generally, however, the length of time involved in the period of abnormal absorption of lead is short in the case of the child, as compared to that of the adult whose exposure to lead is occupational in origin. It may be as brief as 30 days, or even less under unusual circumstances, although it may continue, at a much lower rate of absorption, for six months or even a year. (We have seen two cases of lead poisoning in young adults, whose abnormal exposure to lead, by ingestion, was limited to 30 days, and we have also seen several children who continued, probably intermittently, to absorb lead at rates which did not result in actually dangerous levels of accumulation in their bodies for periods of time somewhat shorter or longer than one year.) The usual brevity of the period of absorption, coupled with the unusually high rate of absorption which is common in childhood, means, however, that the child is especially vulnerable to the initiation of the intoxication, for the danger of acute saturnism is the greater, the more rapid the absorption of lead, so long as the quantity absorbed is sufficient to raise the concentration of lead in the body to the necessary level. It means, also, in most instances, that the abnormal absorption began several months, at least, before the onset of illness. It is likely, therefore, that some feature in the lives of many of these children or in the character of their surroundings, leads to a gross increase in their exposure to, and absorption of, lead during the first half of the year. An alternative explanation of the facts may lie in the frequency with which some stimulus, associated with the summer months, operates to bring about the onset of an intoxication for which the way had been prepared weeks or perhaps months previously.

The frequency of the occurrence of encephalopathy in the child is an expression, we believe, of the rapid rate of the

absorption of lead by these children. Saturnine encephalopathy, as we have observed it occasionally in the adult who has been subjected to exposure to inorganic lead, may or may not occur in response to *brief*, as well as highly severe, exposure to lead, but it has not occurred except under the conditions of *severe* exposure. When such exposure has been brief, the adult patient with cerebral symptoms may recover promptly, even abruptly; when the exposure has been prolonged, and associated with multiple episodes of minor severity, recovery is much less likely to follow promptly, and the outlook for eventual, complete recovery is relatively poor. In the case of the child, the facts with respect to the duration of the exposure are often in doubt, but the severity is always great, and, as the data in Table 27 have indicated, the quantity of lead absorbed by the children who die is large. Moreover, the concentration of lead in the brain, in encephalopathic plumbism, is greatly increased over normal levels, and while this may, in a sense, be coincidental, the probability is high that it is an important factor in the character and the outcome of the disease.

In view of the apparent similarity of the conditions of housing in the poorer districts of many cities in North America, and in consideration of the fact that the recorded incidence of lead poisoning among children varies greatly with the quality and accessibility of the diagnostic facilities in these cities, or in any one of them in different periods, the conclusion is virtually unavoidable that the large proportion of such cases escape recognition. It is this fact which justifies this somewhat lengthy discussion, and points to the urgent need for special consideration of the requirements of differential diagnosis of lead poisoning in the small child. The strictly clinical aspects of this problem have been discussed fully in numerous publications, of which only two recent articles (4, 5) have been selected for citation because of their appraisals of certain recent methods of therapy. These and earlier articles demonstrate clearly that the careful application of non-specific clinical methods will usually identify cases of lead poisoning in infants and children, and will differentiate them from other types of disease. The fact is, however, that the less serious forms of lead poisoning—colic for example—are rarely seen or recognized in the inarticulate and neglected child, and that it is the children with varying degrees of encephalopathic involvement, who are brought to the public clinic or to the pediatric wards of the hospitals. Whether or not lead poisoning is regarded then and there to be a possibility, depends, to a very large extent, upon the clinical experience of the physician. Whether or not a definite diagnosis of lead poisoning is made promptly, and appropriate therapy initiated without delay, will depend, in no small measure, upon the availability of analytical facilities for the determination of the concentration of lead in the blood. Often, the differential diagnosis by other means cannot be made promptly, and in some instances, not at all, with certainty. Time after time, in our association with a completely competent and thoroughly indoctrinated pediatric staff, the prompt exclusion or conviction of lead as an etiological factor in a specific case has rested upon precise information as to the concentration of lead in the blood. It is evident, therefore, that this analytical procedure, in and of itself, when properly carried out on satisfactory specimens of blood, is the most important clue to the existence of this disease in an infant or small child. Even more important, perhaps, is the fact that it is the best of all specific procedures for use in case-finding, or in the exploration of the effects of environmental conditions which pose the threat of lead poisoning to children.

The emphasis on the determination of the concentration of lead in the *blood* for diagnostic purposes in the small child, in contradistinction to the application of this procedure to the *urine*, is entirely intentional. It is not to be denied that satisfactory results may be obtained in many instances by the analytical investigation of the urine. We relied upon it before we had gained sufficient experience with analytical results on blood to be certain of their meaning. There are, however, altogether too many cases in which this cannot be done, and since lead poisoning is often a

fatal disease in the child, such exceptions should not be disregarded. It often happens that a satisfactory sample of urine cannot be obtained, or that obtaining such a sample is too difficult to be practicable, if there is a suitable alternative. The urine of a co-operative or even a semi-conscious male child can usually be obtained without contamination, but this is not true in the case of the female child, for it is advisable to collect the urine from the patient in the container from which it is to be taken for analysis. Any intermediate container, and especially the use of a catheter, in-dwelling or otherwise, is a likely source of a contamination of a type and degree which is rarely appreciated or avoided by anyone who lacks quantitative chemical training or careful indoctrination and supervision. Urine voided by the female child is likely to undergo some degree of contact with the perineum, and if this occurs, the urine will usually have been contaminated appreciably and, sometimes, grossly. An even more serious difficulty exists, however, in that the urine excreted by a very sick child may fail completely to contain lead in any significant relationship to the amounts available in the body. It is not unusual to find a low concentration of lead in the urine of a child that is very ill, at a time when the concentration in the blood is very high. The corresponding situation in the adult is very rare—so rare, indeed, that it scarcely justifies consideration in relation to diagnosis, although there are other reasons, as indicated previously, for obtaining additional information by the analysis of the blood. The nature of the presumed impairment of the kidney that is responsible for this phenomenon has not been investigated, but it is reversible in many, if not most, instances, for, as the child recovers, the rate of the urinary excretion of lead mounts until it reaches its usual relationship (in terms of concentration or daily output) to that in the blood. Meanwhile, of course, the concentration in the blood will have diminished gradually, and the somewhat paradoxical relationship, for a time, will have been that of a progressively decreasing concentration of lead in the blood in association with a progressively increasing concentration and output of lead in the urine.

A further important fact, with reference to the blood, and one which is true also of the urine, with the exceptions noted above, is that the significance of the concentration of lead therein, in relation to the likelihood of the onset of intoxication, is no different in the child than in the adult. We have not seen a case of lead intoxication in an infant or child, at or within a few days of the time of the onset of illness, in whose blood the concentration of lead was lower than 0.08 mg. (80 micrograms) per 100 grams. The intoxication, once developed, tends to persist after the concentration of the lead in the blood has dropped well below the threshold level, but illness is not initiated at lower levels. This fact, added to the more frequent observation that illness is not always associated with high concentrations of lead in the blood, has misled some investigators into the belief that there is no relationship between illness and the concentration of lead in the blood. It is true that the discovery of significantly high concentrations of lead in the blood, is not, in itself, diagnostic of lead intoxication. On the other hand, there can be no doubt that there is a level of concentration in the blood, below which, lead poisoning does not occur in the child or in the adult. In the light of extensive experience this critical level is very little above or below 80 micrograms of lead per 100 grams of whole blood. The individual who has absorbed lead to that extent is in grave danger of developing lead intoxication, if and when the conditioning state or stimulus comes into being.

3. OCCUPATIONAL HYGIENE IN THE LEAD USING INDUSTRIES

The danger, indicated in the preceding discussion, that intoxication by lead will occur, if the concentration of lead in the blood, or the rate of the excretion of lead in the urine, exceeds threshold levels as defined herein, constitutes one of the basic considerations in the prevention, by medical means, of occupational lead poisoning. The fact that such poisoning will not occur if these threshold levels are not reached or

exceeded, provides the one additional feature of sound preventive medicine that is required to eliminate lead poisoning, as an occupational hazard, from even those industries in which serious obstacles are afforded to wholly and continuously successful environmental control, or in which, from time to time, the hazard incurred by an individual workman or a small group of workmen may differ markedly from that associated with the usual operating conditions. This is not to say that the fortuitous consequences of a highly unusual circumstance, such as a mechanical or human failure or other emergency, can always be avoided. It can be said, however, with full assurance based on many years of experience, that cases of lead poisoning, in connection with all of the regular operations of a highly hazardous industry, can be eliminated utterly, through careful and persistent application of this principle of preventive medicine. What is required is the will to do so, and the economic and administrative backing of managers who believe in the complete protection of their employees against the avoidable hazards of their work. There must also, of course, be a parallel and equally meticulous control of environmental conditions, as these are influenced by the processes and equipment employed in the operations, and by the associated procedures and equipment of environmental hygiene, together with satisfactory maintenance of all equipment, careful housekeeping, and attention to such supervision and indoctrination as may be required to insure against carelessness and disregard of instructions on the part of operating personnel. All of the appropriate armamentarium of industrial hygiene should be put to use for the control of the conditions of work, and for the protection of the workmen. The special virtue, however, of a medical regimen which includes determinations of lead in blood or urine (or both) and the interpretation of the results of such analyses, lies in its direct applicability to the *individuals* who comprise the industrial population, as well as to the specific *groups* of individuals who represent the several occupations in which the industrial population, as a whole, is engaged.

A man can work in freedom from the risk of lead poisoning, so long as the concentration of lead in his blood or the rate of the excretion of lead in his urine remains within the limits defined by the threshold values indicated above. If his work is potentially hazardous, as it may be, at times, under unusual circumstances or during operating stresses within the industry, or if, under ordinary circumstances, his freedom from hazardous absorption of lead is difficult to maintain, he may approach or reach the threshold level. At such a time, he can be transferred to a job in which his exposure to lead is negligible or greatly reduced, and after a period of relative freedom from exposure, sufficient to lower the body burden of lead to the desired point, he may be returned to his former work. Such a man may be paired with another man whose work is substantially free of hazard, and provision may be made thereby for a schedule of rotation which will insure the avoidance of significant hazard by both men.

Such procedures as those indicated above can be carried out satisfactorily, only if arrangements have been made in advance whereby all of the difficulties inherent in such an administrative and employment policy can be surmounted. Admittedly, certain industries are so constituted or organized that such arrangements are extremely difficult to effect; policies and agreements, with respect to wages, promotions, grievances, seniority and similar features of labour relations, may operate as obstacles to such plans; or there may be no jobs which are sufficiently free of exposure to lead. Generally, however, the implementation of such a programme, developed in advance of casualties, and designed in the strictly professional terms of industrial hygiene, will be found to be acceptable to both employers and employees. If the circumstances are such that the regimen of medical supervision cannot be made to include the temporary removal of workmen from hazardous exposure, there remains but one alternative—the operations of the industry must then be so designed as to eliminate truly hazardous conditions, and so to avoid the necessity for such a procedure. This alternative may be the

method of choice in the large proportion of industries in which the hazards of exposure to lead may be controlled by conventional engineering methods at moderate cost, and it is recommended highly as the best and often the most economical manner of dealing with the problem. There are, however, a number of extremely useful products, such as for example, electric storage batteries, in the manufacture of which, large quantities of metallic lead and of lead compounds are so handled as to become significant sources of human exposure. Not all of the plants in which such batteries are made are of the best design, from the aspect of industrial hygiene, and not all of them are operated so as to achieve the best results obtainable by the application of appropriate methods of industrial hygiene. Even the best of them have certain hazardous operations, and the maintenance of safe working conditions for the employees engaged in these operations requires intelligently designed and constantly applied technical and medical measures of industrial hygiene. It is in the medical supervision of such employees that a properly planned programme for the analysis of the blood and urine of employees can have its most effective and salutary application. Indeed, the question may properly be raised as to whether a wholly satisfactory regimen of medical supervision can be maintained in actually hazardous industries without resort to such a programme. Certainly the current status of industrial health in many of the plants engaged in the manufacture of electric storage batteries in the United States is evidence of the need for the consistent application of sounder, more specific, and more stringent standards, with respect to the permissible limits of the absorption of lead.

It may be useful to view the present position of industrial hygiene, generally, in the lead-using industries of the United States, and to consider how this situation has come about. As stated previously, the more severe forms of occupational lead poisoning are encountered infrequently, but the frequency of occurrence of the less severe cases demonstrates clearly that occupational exposure to lead has not been controlled adequately. On the one hand, there are young industries in the more recently industrialized areas of the country, in which knowledge and experience are lacking, and there are old, well established industries, in which the ideas and practices of the past are entrenched; in neither of these has the science and art of industrial hygiene been developed. On the other hand, some industries have pioneered or shared in the development of measures both of environmental control and of medical supervision, and have eliminated lead poisoning from among their occupational hazards and liabilities. As examples of what to avoid and of what to strive for, these opposite extremes of the present situation are not unimportant, but the more general state of affairs is the more deserving of attention, especially from the aspect of preventive medicine. As one takes stock of this matter, the striking fact is that the role played by the physician has diminished greatly in importance, while that played by the engineer has enlarged. As a corollary to this, the principal techniques of industrial hygiene in the lead-using industries in recent years have been those of analytical chemistry and engineering, and not those of medicine. The abdication of medicine has been nearly complete in many instances, having often reduced itself to the level of the nominal supervision of a laboratory technician who, at arbitrary intervals, examines a series of blood films for "stippling," and of making sober interpretations of these non-specific, non-quantitative and often irrelevant findings, in lieu of the critical observations of environmental conditions and work-a-day practices, and the periodic examinations of the personnel, that would give meaning to medical supervision. In consequence, conditions of work which fall short of adequacy are condoned, and some degree of impairment of the health and well-being of workmen is accepted as the natural consequence of employment in a dangerous occupation. Under such conditions, some workmen have occasional episodes of minor or incipient intoxication or continue in a state often referred to, ambiguously, as "lead absorption," which, apparently, while not being clinical "lead poisoning" is the nearest approximation that can be sustained

by the individual without complaint or disability. From time to time, inevitably, these conditions give rise to frank cases of occupational lead poisoning among "unusually susceptible" persons who are often, if not usually, relatively new employees. This is the state of the science and art of industrial hygiene in the United States, in its medical aspects, that yields an unnecessary incidence of occupational lead poisoning. Clearly it is in need of an infusion of methods of preventive medicine that are in accord with physiologic and toxicologic facts. The medical procedures of an earlier day in the lead trades have been plagued by gross inadequacies based upon their non-specificity, on the one hand, and their lack of quantitative significance, on the other. They have made a poor showing, indeed, in comparison with the specific and quantitatively precise methods of the industrial hygiene engineer. Preventive medicine, in the strict sense of the word, was ineffectual in practice, prior to the development and application of specific and precise methods for determining the magnitude of the absorption and excretion of lead by exposed workmen. Instead, the control of the environment according to specifications was the method of choice, and despite the fact that the adequacy of the specification depended basically upon competent and persistent medical interpretation of the hygienic status of the exposed personnel, the latter, being relatively unsatisfactory and difficult of attainment, was characterized more by default than by its application in the specific instance.

The principle of environmental control is, of course, basic in industrial hygiene. As it was first expressed in relation to occupational exposure to lead by Sir Thomas Legge (6) as the result of his clinical observations and the analytical work of his associate Duckering, it was a profoundly significant contribution to the armamentarium of industrial hygiene. It is a principle, however, which is difficult to apply to many industrial operations, and even in its best application, it leaves something to be desired, in so far as the safety of certain individual workmen is concerned. Moreover, it has not been extended, by the conjoined efforts of the engineer and the physician, so as to apply broadly to the variety of the compounds of lead or to the various physical forms of these compounds dispersed in the air. It is, in fact, an approximate expression of good practice for the lead-using industries, which, when employed in co-ordination with a sound programme of medical supervision, can be expected to yield a satisfactory control of hazards due to lead. With the development of sound methods for the interpretation of the status of the individual workman, the physician may now resume his former position of professional responsibility, and find security and satisfaction in the precision and efficacy of technical procedures that lie within his own domain.

Some objection has been raised to the technical difficulties and also the expense of establishing and maintaining a medical regimen which includes a programme for the sampling and analysis of the urine or blood (or both urine and blood) of workmen. The difficulties, while real, are far from insurmountable, being more formidable in anticipation than in their vanquishment. The laboratory in which such analyses are carried out must be specially designed, properly equipped, and capably manned; the containers for samples must be selected for the purpose and prepared with an eye to the avoidance of even the most minute contamination with lead; and the procedures for the collection of samples must be carried out by properly trained or carefully supervised persons. Even so, samples will be contaminated with lead occasionally. Attention to minute details, therefore, is mandatory; everyone concerned must know what he is doing and why he is doing it, and the technique must be essentially faultless, for lead is everywhere in the environment, and unless it is excluded by satisfactory technical means, it finds its way into samples in the process of their collection and while they are being analysed. The minuteness of the quantities of lead which are to be determined, and the facilities and techniques required to collect satisfactory samples and to carry out such determinations with adequate precision, contribute to the cost of the entire activity, but they do not render it prohibitively expensive, if reasonable judg-

ment is exercised in the economical employment of the analytical regimen. One may be inclined to ask how it is that a medical procedure which is so important to the safety of many men should be so carefully weighed in economic terms. What is a reasonable cost in such a situation? An acceptable answer would be, that if it is essential it must be borne, but that it should be used only to the extent of its essentiality. A further question is often raised in this relationship, to which attention is given here because it relates to the frequency with which workmen in the lead trades are to be examined in this or in any other manner, whether the periodicity is determined by official or legislative regulation, or as a matter of policy or design within an industrial organization. Nothing is more frustrating to a wise and competent industrial physician, or to a responsible and prudent management, than to find that the procedure in such a matter is dictated by a statute or by an official authority, and that their own knowledge and judgment may not be exercised. It is hard to resist the impulse to condemn utterly, as senseless, the regulation of such matters by official or legislative fiat, for such regulation cannot create the knowledge and judgment without which, the task cannot be done; it can only hope or imply that these exist, on the one hand, or interfere with their application, on the other. The point is, that the periodicity of the application of any specific medical measure of industrial hygiene, if it is to be effective, must be determined by the nature and the degree of the hazard that is being guarded against. With specific reference to the proper utilization of medical information obtained by the analysis of the urine or blood for their content of lead, frequently repeated observations are wholly unnecessary and wasteful of effort and money, unless the hazard of a specific man or group of men in a specific operation or area are such as to result in a rapid increase in their absorption of lead. In some industries in which lead or its compounds are employed, the environmental conditions, with respect to exposure to lead, are stable, uniform and well controlled, and the men are well-trained and indoctrinated in appropriate performance. In others some processes and areas are much more difficult to control than others. In still others, all or most of the processes are potentially hazardous, and uniformity of both human exposure and performance are difficult of attainment. Periodic medical surveys of the personnel, in co-ordination with careful observation of the conditions under which men work and of their manner of working, will disclose the degrees of hazard to which men are subjected, and will show clearly how the medical procedures must be scheduled so as to provide the necessary information at the proper time. It may be that the status of the workmen in a specific industrial establishment can be determined by the analytical investigation of a representative group of employees once per year or even once in two years. Or it may be that every man in an occupational group will have to be sampled at intervals of one month, if the risk is large and unpredictable. Within these extremes of scheduling, a programme can be adapted to the requirements of safety within an industry. When so designed, it can be counted on to reveal the sites of hazard that require the application of more satisfactory measures of environmental control, and to demonstrate faulty operations, faulty performance on the part of the men, or faulty maintenance of operating equipment or of housekeeping. Inasmuch as the extent of the analytical effort and of its cost will depend upon the severity of the hazard of lead absorption, it can be expected, automatically, to indicate the need for better environmental control, which, if achieved, will reduce the need for analytical information and lower its cost. It is not likely, however, after once having been instituted as a part of the medical regimen of a lead-using industry, that this regimen will ever be abandoned. The security of mind which is afforded to all who are involved in responsibility for the safety of workmen, and the satisfaction of the workmen with a regimen that protects them, are assets which are not lightly to be regarded. With respect to the attitude of the workmen, it has been our experience that, once their natural resistance to inconvenience or

to their initial dread of venipuncture have been overcome, as these so easily are overcome by the ministrations of doctor or nurse, they will offer vigorous resistance to any reduction in the established schedule of sampling and analysis. This is a consideration of sufficient importance to justify some caution in fitting the scope and frequency of these observations to the actual needs of the situation in the beginning.

The sampling of the urine has been something of a problem under certain circumstances. There are two general methods which can be employed satisfactorily, in our experience. Other investigators or industrial physicians have employed other procedures with success. Workmen can be instructed verbally and also in writing, as to the means of avoiding contamination of specimens of urine with lead, and in the collection of physiologically representative samples of large volume. A container with a capacity of four litres can be so prepared as to be chemically clean, sealed in a paper or plastic bag, and given to a workman, after he has bathed and changed his clothing, to take home with him (or, if need be, the container can be delivered to his home). There, he is to keep it in a place which is reasonably secure against accident or tampering, and to void directly into it at intervals until a suitable volume (2 to 3 litres, up to a mark) has been obtained. He is not to collect unusually dilute or unduly concentrated voidings (such as would be associated with the convivial drinking of unusual quantities of beer, ale, or other beverages, or with a period of restricted consumption of liquids), but to obtain a composite sample representative of his ordinary manner of living. This type of sample is likely to be a very good representation of the general rate of the urinary excretion of lead, as the latter is expressed in terms of the concentration of lead therein, rather than on the basis of time. (As ample data have demonstrated, this is as satisfactory a means of expression, for comparative purposes, as is that based on time, and it obviates the necessity for the collection of the time-honoured, but not always practicable, twenty-four or forty-eight-hour specimen.)

A second and alternate method of collecting the urine, and one that has the advantage of being accomplished under the eye of the examiner, is that of obtaining a single voiding of somewhat more or less than 100 ml., in a small container. This can be obtained when the workman has presented himself, after bathing, for an examination (as a normal part of the procedure of examination along with the collection of blood, if desired) or it can be obtained at the bathing and clothes-changing quarters, at the end of the work of the day (or shift), or at its beginning. By such means, contamination of these samples can be avoided, and a further advantage can be gained by the judicious use of the bathing facilities, in that the samples will have a uniform relationship to the day's work and its exposure to lead. These samples of small volume will be somewhat less satisfactory than those of large volume, because of the factor of physiological variability, but this disadvantage can be overcome by the numbers of samples which represent the group or by increasing the frequency of the sampling in the individual instance. The statistical array of data representative of a group of men engaged in comparable work will be entirely satisfactory in portraying the status of the group, while individuals at either extreme of the statistical array can be checked by the collection and analysis of additional samples. Moreover, when an individual who has been exposed to the inorganic compounds of lead is found to be in a dubious state, the necessary facts can be established by an analysis of his blood. The latter procedure, as has been indicated previously, is always desirable when, as in private or medico-legal practice, the patient may not be available later for re-examination.

The foregoing details of procedure may appear to be wholly redundant, in a broad presentation of the physiological principles and facts with which we are here engaged. Experience has shown, however, that attention to these details, which is so necessary in order to obtain valid information, is honoured frequently in the breach. Therefore, at some risk of wearying or even offending those to whom the facts are well-

known, it seems wise to speak of them for the benefit of those who, otherwise, now or later, may waste valuable time and effort in learning, as we have done, by trial and error.

4. EXPOSURE TO LEAD IN THE REALM OF THE PUBLIC HEALTH

The facts concerning the metabolism of lead are of paramount importance in the development of criteria for public safety. Modern technological developments pose certain problems with respect to the composite exposure of men, generally, to lead in the food and beverages which they consume, and in the air which they breathe. No standard of safety in relation to any one of these general sources of exposure has validity, in itself, but each may achieve validity, in practice, when considered in relation to the others.

It is fair to say that, at the present time, in the United States, the absorption of lead on the part of the public, generally, from all sources, is attended by no hazard. This is not to say that there may not be situations productive of danger and of actual cases of lead poisoning within the population. Attention has been called emphatically, herein, to lead poisoning among children. Cases of lead poisoning also occur among adults, as the result of the contamination of food and drinking water, and even of the air in the home (e.g., from the use of battery cases scavenged from dumps or heaps of refuse, as fuel). On the whole, however, the food and beverages of the nation contain but little more lead than that which occurs naturally in them, while the ambient air, even in the more heavily contaminated areas of our cities, is contaminated with lead only to the extent of a few micrograms per cubic metre. The facts in these matters, as they now obtain, have been given in a fairly representative manner in Lecture I, in which, also, the normal metabolism of lead, as we have chosen to speak of it, has been described. We have found no reason to believe or to suspect that the quantities of lead involved in this normal metabolism of lead have increased within the past twenty-odd years. Indeed, if we were to rely upon the available evidence, without some reservation of judgment based upon recognized improvements in the techniques of sampling and analysis (which have reduced the opportunities for contamination of samples at our hands), we should be justified in concluding that the over-all exposure to lead, on the part of the "average" adult citizen of the United States, has decreased in the past decade.

The food and beverages of the country represent the largest source of lead intake, under the ordinary conditions of life, and they are most open to opportunities for artificial contamination. It appears that this source has undergone some decrease in recent years. The data obtained by the analysis of the feces of 453 persons (Table 9, Lecture I) involved in a field survey in 1955 yielded the somewhat surprising mean lead content of 0.23 mg. per sample. (The relationship of these data to the lead in food and beverages has been demonstrated in Lecture I.) The mean value of a corresponding series of results obtained in 1934 in the investigation of a group of 307 persons of comparable type from the same general area of the country (7) was 0.32 milligram. The difference between these two values is barely significant, statistically, and so is not to be taken too seriously, but the frequency with which the mean lead content of the food and feces of various large and small groups of persons had been found to exceed 0.3 mg. per day (8) in the period prior to the year 1950, and the more recent and fairly regular finding of mean quantities appreciably less than 0.3 mg. per day have not gone unnoticed. (Note the mean lead content of the food and feces of the experimental subjects listed in Table 12, Lecture I; the three subjects, E.B., I.F., and S.W., were under study prior to 1945, while the investigations concerned with the last six subjects began in 1950; the last three subjects are now under observation and will continue so through 1961.) These and other similar results provide only the proof of the variability of individuals, in this respect, but the coincidental factor of time is, at least, suggestive. It seems reasonably certain that if any change has occurred it has not been in the direction of an increase.

The lead content of drinking and culinary water, as supplied to town and city

dwellers from a common source, is not a problem in the United States, with the exception of certain of the older communities in the New England area, in which, even now, lead pipes are said to be in use. Throughout the greater part of the country, the methods employed in the treatment, if any, and in the distribution, of water supplies, are such that the concentration of lead therein rarely exceeds 0.03 mg. per litre. There is no present reason, therefore, for the persistence of the standard of 0.10 mg. per litre which was adopted by the United States Public Health Service many years ago, but was reduced to 0.05 mg. per litre in 1960. Obviously, opportunities for the ingestion and absorption of lead from this source should be as few and as insignificant as possible, in view of the ease with which this can be accomplished when the general water supply of a community is subject to control. On the other hand, there is no reason for concern, when, in emergency, the water supply of an entire community, or a sizeable segment of it, contains lead in a concentration approaching 0.10 mg. per litre, for a few weeks or months. This, to our knowledge, has occurred in times of severe drought, when water had to be transported in highway and rail tanks that had not been made chemically clean. The quality of the water made available under such circumstances should be known, however, from this and other aspects, in order that proper steps may be taken to protect the public.

Two related questions arise concerning the ingestion of lead, both of which can be answered in straightforward terms, on the basis of the experimental observations that have been described in Lectures I and II. One of these is concerned with the matter of the average quantity of lead which may be ingested daily, without risk, over the span of life, in the food and beverages including water, if it be assumed that the quantity absorbed from the air remains essentially unchanged or undergoes no significant increase. The other question involves the opposite side of the same coin, namely, the quantity of lead which, when ingested, will result in a dangerous degree of absorption within a definite period of time.

The answer to the first of these questions is based in part on the observation (Lecture II) that the oral administration of 0.3 mg. of lead (as lead acetate, in solution) per day (in addition to that contained in the food and beverages, thus bringing the total quantity ingested per day up to approximately 0.6 mg.) to experimental subject S.W., for a period somewhat longer than a full year, resulted in a barely detectable increase in the rate of the excretion of lead in the urine, but in no demonstrable increase in the concentration of lead in the blood. This is as near as one might expect to get to the least incremental increase in the oral dosage of lead that would yield a detectable response. On the background of the evidence provided by other similar experiments, in which larger dosages of lead were administered orally, the conclusion is fully justified that the quantity of lead which accumulated in the body of subject S.W. was slight indeed, and that such a rate of accumulation could continue for many years, probably for an entire lifetime, without any likelihood of reaching a potentially dangerous level. On the other hand, the ingestion of approximately twice this quantity of lead daily (1.3 mg. per day, by subject M.R., Lecture II) gave rise to a progressive increase in the rate of the excretion of lead in the urine and in the content of lead in the blood and other tissues of the body. The retention of lead in the body of subject M.R., continuing over the period of four years, at an essentially constant rate, resulted in the accumulation of 120 mgs. therein, at the average rate of approximately 30 mgs. per year. One cannot be certain that such a rate of accumulation would continue indefinitely, but since there was no evidence of a gradual diminution in the rate within four years, there are no grounds for the assumption that it would not. As it will be shown later, there is reason to believe that this would be dangerous if it were to continue unabated. It is unlikely that the ingestion of 0.6 mg. of lead daily for many years would be a source of danger to an adult. The accumulation of lead in the body, under these conditions, appeared to be of the approximate order of 8 mgs. per

year, at which rate it would be insignificant for many years and probably for a lifetime. At any rate it may be said, with reasonable assurance, that the quantities of lead in the food and beverages available to a population should be such that individuals may choose what they will in quality and quantity, without running the risk of ingesting more than 0.6 mg. of lead per day, on the average, over any prolonged period (years) of time.

In considering the problem of public health involved in the possible contamination of food and beverages with lead, from the aspect of any type of regulatory action, the conclusion arrived at above would seem at first to be wholly academic and impractical. And so it would be, were it not for the feasibility of ascertaining the facts, as they apply to persons or groups in the population, by the application of methods of investigation that have been described herein. There are, of course, other approaches to the more specific hazards presented by the discovery of the contamination of certain items of food or drink, which occupy established and quantitatively ascertainable places in the dietary habitude of the population. Tolerances may be, and indeed have been, applied to these in accordance with their importance in specific instances. These represent special situations, however, and even they need to be fitted into a general or all-inclusive standard.

The second question raised above, concerning the risk of lead poisoning in relation to the degree of contamination of food with lead, can now be answered with reasonable accuracy. Various statements have been made in the literature concerning the dose of lead which, when ingested, i.e., taken by mouth, daily, can be expected to cause lead poisoning. These estimates have been based on indirect evidence, and they have varied so widely as to have dubious worth. No doubt the conditions out of which they came, as interpretations, were variable and subject to a large margin of error. The carefully controlled conditions of the experiments relating to the ingestion of lead in solution have provided opportunity for much more precise estimates of the relationship between time and dosage, on the one hand, and a toxic effect, on the other. This is made possible by the establishment of the association between the concentration of lead in the blood (also the rate of the urinary excretion of lead) and the induction of lead intoxication. The fact that this association, in the quantitative sense, has a statistical, rather than a strictly individual basis makes it the more applicable as a general, rather than an individual, human experience. There is a high degree of probability, therefore, that if the experiments involving the ingestion of lead by our experimental subjects could have been continued until the threshold concentration of 0.08 mg. of lead per 100 grams of whole blood had been reached, we should have observed the early clinical evidence of a dangerous degree of absorption of lead, at least to the extent of an abnormal degree of elevation of coproporphyrin III in the urine. Fortunately it is unnecessary to go to such an extreme of experimental zeal, even if it were feasible, since it is possible to extend the curves in which the concentration of lead in the blood has been plotted against time (cf. Fig. 3 and Fig. 10, Lecture II) so as to establish approximately the length of time required to reach the threshold concentration in the blood. The result of this extrapolation, in the case of subject M.R., whose average daily intake of lead in food and beverages, together with that taken in solution, was 1.27 mgs., came to somewhat more than 7.5 and somewhat less than nine years (while the mathematical treatment of the extrapolation would yield a more precise value, such a value, without qualification, would be misleading); the corresponding result in the case of subject E.B., who ingested 2.35 mgs. daily, was approximately four years, while that of subject I.F., who ingested the average quantity of 3.27 mgs. daily, approximately eight months. Whether or not these subjects, or their counterparts in the population, would develop episodes of lead intoxication at or near the time indicated in each instance, is, of course, open to question, but that they would incur such danger is reasonably certain. With respect to the factor of time in association with still larger oral dosages taken regularly, we have had the oppor-

tunity recently of investigating the illness of two young adults, whose ingestion of unusual quantities of lead began at the same time and terminated in the nearly simultaneous onset of acute intoxication. The entire period of exposure was limited to about one month, during which the dosage of lead, while variable from day to day and from one to the other person, is believed (on the basis of simulated experience) to have averaged between 5 and 10 mgs. per day. It is interesting in this connection to consider the problem of susceptibility, and that of the exciting or enabling feature of lead intoxication to which reference has been made. As these matters have been viewed critically over the years, human susceptibility to lead poisoning has diminished steadily in importance, in favour of the influence of the variability of human experience whereby the quantities of lead being absorbed by individuals were significantly different. Likewise, and as something of a corollary observation, the variability in the time of onset of intoxication among individuals, under seemingly similar environmental conditions, has tended to be greater when the exposure to lead has been fairly uniform at a moderate level of severity. It seems that the onset of intoxication often coincides with the occurrence of a *sharp increase in the rate of the absorption of lead* by an individual. This observation has led us to suspect that the "trigger mechanism" of lead intoxication is that of overburdening the tissues with unbound or ionic lead, whether through an unduly rapid rate of absorption or through the loosening, under appropriate but presently unknown conditions, of chemical bonds within the tissues.

It is of further interest to consider the order of magnitude of the contribution made to the body burden of lead in subjects S.W., M.R., E.B., and I.F., at the time when each of them, by extrapolation, would have reached the concentration of 0.08 mg. of lead per 100 grams in his blood. This can be arrived at by extending the upward sloping curves of Figure 11 (Lecture II), for these subjects, for the lengths of time required in each instance to bring the concentration of lead in the blood to that point. The concentration of lead in the blood of subject S.W. (total daily oral dose of 0.6 mg. of lead) did not increase demonstrably during the experimental period, but apparently he added approximately 8 mgs. per year to his body burden, under the conditions of the experiment. On the reasonable and modest assumption that his body, prior to the experimental ingestion of lead, contained a quantity of lead of the order of 100 mgs., a period of 12.5 years of continuing ingestion at the same rate would be required to double, and 25 years, to triple, his body burden. His assumption of risk in so doing must certainly be considered to be negligible, in view of the fact that the body burden of lead of ordinary (normal) individuals in the general population is found, from time to time, to be of that order of magnitude (See Table 15, Lecture I).

As judged by similar means, subjects M.R., E.B., and I.F. might be expected to have added quantities of lead of the order of 270, 250, and 110 mgs. respectively to their initial body burden, if each had continued on his experimental regimen until he had reached the threshold level in his blood (i.e., in 9, 4 and 0.64 years, respectively). It will be noted that the total body burden, at the time the blood reaches its critical level, tends to be greater as the daily rate of intake and absorption diminishes, whereas the time factor involved in reaching the critical concentration in the blood, under these circumstances, is disproportionately large. This is in keeping with the relative inaccessibility of the lead which moves slowly into the relatively more dense and less vascular areas of the skeleton. Evidently it is not the body burden of lead, *per se*, which is the primary factor in providing the conditions in the body that are necessary to induce lead intoxication, but, rather, the manner in which the lead is distributed, with specific reference to its immediate metabolic accessibility, is the important factor. That is to say that the concentration of lead must be sufficiently high at the point or points of vulnerability, if intoxication is to be induced.

Notwithstanding the importance of the lead in human food and beverages, as the principal source of that which enters into

the "normal" metabolism of the population of the United States, generally, the finely divided lead in the ambient atmosphere cannot be ignored, as the observations noted in Lectures I and II have indicated. In so far as the quantities in the air are dispersed as particles less than 1 micron in diameter (as the large proportion of these appear, on somewhat scanty evidence, to be, under prevalent atmospheric conditions); and to the extent that the particles are retained within the lungs, rather than deposited in the nasopharynx, trachea and bronchi, or returned to the atmosphere in the expired air (the results of the respiratory experiments indicate that such retention ranges from 35 to 45 per cent); and, further, to the degree that the highly dispersed compounds of lead in the atmosphere are capable of being absorbed (as most of the lead in the general atmosphere seems to be); the air-borne lead in the general human environment has greater significance in the human economy, quantity for quantity, than that in the food and beverages. Whereas less than 10 per cent of the lead which occurs commonly in the food and beverages is absorbed (the absorption is proportionately greater when the quantities (concentrations) of comparably soluble compounds of lead are large), virtually all of that retained in the lungs is absorbed. Therefore, a given quantity of lead drawn into the respiratory tract in inspiration, if it meets the necessary specifications as to particulate dimensions and some degree of solubility, may contribute three to four times as much absorbed lead to the tissues of the body as would the same quantity of lead taken in with food and beverages. Likewise, a given quantity of lead actually *retained* in the lungs may yield ten to twelve times as much absorbed lead as would an equivalent quantity which enters the alimentary tract. On the other hand, it must not be forgotten that when the particles of lead compounds in the atmosphere exceed 1 micron in diameter, few of them reach the finer air passages of the lungs. Most of the particles between 2 and 5 microns in diameter will be captured in the upper respiratory tract and will eventually be deposited in the nasopharynx, to be swallowed or expectorated, and so absorbed to a much lesser extent than if they had been retained in the respiratory tract.

It seems advisable, in passing, to refer briefly to a potential source of inhaled lead to which undue speculative significance has been ascribed recently. The occurrence of lead in tobacco (along with arsenic and certain other mineral constituents) has given rise to calculations of the amounts of lead that might be absorbed in the respiratory tract, from this source. The calculations have failed to take into account three factors which are highly pertinent, namely: (a) the extent to which the lead in tobacco appears in the smoke which enters the mouth, as differentiated from that which remains in the ash of the burning cigarette, cigar or pipe tobacco; (b) the degree to which the smoker draws the smoke into his lungs; and (c) the actual length of the time, per day, involved in smoking. While the latter two factors cannot be ignored in any strictly quantitative appraisal of the absorption of lead from the smoke, there is no urgent need for their investigation, for the reason that only a small proportion of the available lead is found in the smoke; much the larger proportion of it remains in the ash. When this matter was brought somewhat forcibly to our attention by persistent questions, we were taken aback by the realization that we had no direct information on the subject. It was plain to be seen that there was no such difference between smokers and non-smokers, within the groups of persons whom we had investigated, as to justify the suspicion that this was a significant factor in the absorption of lead. The explanation was supplied by an associate (Cholak) in the Kettering Laboratory, who determined the quantities of lead removed from the smoke of each of several cigarettes by millipore filters, the quantities of lead in the residual ash of each cigarette, and the quantities of lead in individual cigarettes (ashed in the manner of the usual preparatory procedure for analysis, rather than by smoking). The average weight of each of several cigarettes was approximately 1 gram, of which the weight of the ash (obtained by the usual preparatory method) averaged approximately 150 mgs., and the lead content of the ash of the

individual cigarette averaged 0.015 mg. (15 micrograms). The smoke obtained by the simulated smoking of several cigarettes yielded about 0.5 microgram of lead per cigarette, while the ash of the "smoked" cigarette contained about 14 micrograms of lead. No doubt, results which would vary somewhat from these could be obtained by a more elaborate investigation of various types and brands of tobacco, burned (in smoking devices) at different rates and in different volumes, with and without the various filters or separators used currently in certain cigarettes or pipes. These somewhat scanty data add up to the fact, however, that the large proportion of the lead in tobacco can be expected to remain in the ash of cigarettes, cigars or pipe tobacco, rather than to be carried into the upper and, to some unascertained extent, the lower, respiratory tract. This, for the present, at least, provides a sufficient explanation for the fact that the lead content of the urine and blood of individuals is not altered significantly by their habits of smoking. It is likely that the situation of the habitual chewer of tobacco differs appreciably from that of the smoker, while cases of lead poisoning have been traced to the use of snuff, the "bright" colour of which, in some instances, at one time, was obtained or augmented by the addition of lead-containing pigments (9).

As for the lead in the air, and, in particular, that in the air of towns and cities, the principal issue which has generated a degree of concern in hygienic circles is the prospect of a progressive increase in the concentration of lead with the increasing use of automotive fuels containing tetraethyllead and, recently, other lead alkyls. This matter cannot be dealt with fully within the scope of these lectures, for various aspects of it have been under investigation since the year 1923, and the available data are too varied and voluminous for present consideration. Certain significant facts require presentation, however, in relation to the apparent trend toward the official establishment of an upper limit of concentration which is permissible in the general atmosphere. Legislative action in this direction appears to be imminent in certain areas of the United States, and, while no hygienic urgency requires such action, it will probably come about, as legislative and administrative standards are applied to other potentially noxious constituents of the atmosphere.

Certain facts with respect to the concentration of lead in the atmosphere in various cities in the United States have been presented in Table 7 (Lecture I). Additional data are available, and others are being obtained in current investigations in various parts of the country. Without attempting to summarize the available evidence, several pertinent findings may be mentioned briefly. There is a significant degree of variability in the concentration of lead in the atmosphere of one city as compared with another; there is further variation in different parts of individual cities as, for example, the industrial areas, the business and commercial areas, areas of heavy motor traffic, suburban residence areas, and essentially rural areas. There is a significant seasonal variability, which tends to be characteristic of a given community or type of community, or to be associated with the geographical location of a community. These point to the operation of a multiplicity of factors both as to the sources of the lead in the air, and the meteorological conditions—temperature, precipitation, and local and general air movements occasioned by temperature inversions, and the direction and velocity of winds—which influence the distribution and the dilution of lead derived from various sources. Among important known sources are the effluents from industrial plants, the combustion of coal and of waste materials in dumps and in public, industrial and private incinerators, the exhausts of motor vehicles which use leaded gasoline as fuels, and windborne dust from the surface of the earth, some of which is virgin soil and some is soil contaminated in varying degrees with pulverized lead compounds from a variety of sources. The complexity of the sources, the variability of meteorological conditions, and the changing patterns of community activities, offer serious obstacles to the interpretation of present trends and to predictions with respect to future trends. It is possible, but by no means certain, for example, that the contribution made by

automobile traffic (the discharge of lead from motor exhausts) will result in a further more or less general, increase in the lead content of the air at the breathing level of many people. On the other hand, this factor may have reached its peak of influence in the United States and certain other countries. Observations in Cincinnati over the period of the past 15 years give evidence of a decrease in the general level of the concentration of lead in the air, and a shift in the pattern of its distribution (10). These changes have coincided with a material reduction in the quantities of particulate matter (smoke, fly-ash and dust) in the air of the community generally, in association with successful efforts toward the abatement of common sources of air pollution, together with a demonstrable change in the geographic distribution of the population and alterations in the patterns of automobile traffic in the Cincinnati area.

The effects of changing conditions, with particular reference to the contribution made by automobile exhausts, has been investigated from time to time, by clinical and analytical surveys which involved determinations of the rate of the excretion of lead in the urine and the concentration of lead in the blood of representative groups of drivers of automobiles, attendants of service stations at which gasoline and oil are dispensed to motorists, and attendants and repairmen in parking and servicing garages. In some instances other small groups were included. The first of these investigations, which involved only the attendants of filling stations (and their urinary lead output), was carried out in 1924. Others followed (7, 11). The most recent survey, involving approximately 500 persons in Cincinnati, Dayton, and Columbus, Ohio, was begun in 1955 and completed in 1956, thereby providing recent analytical data, comparable in accuracy with those obtained in the investigation of normal subjects whose opportunities for any type of occupational exposure to lead were known to be negligible. Representative data of the latter type have been provided previously (Tables 11, 13 and 14, Lecture 1) in illustration of the "normal" metabolism of lead. They provide the background for the interpretation of those obtained in the survey of 1955-56, as the latter are grouped according to their frequencies of occurrence in Tables 28 and 29.

Little more than a glance is required to recognize the similarity of the findings of the survey (Tables 28 and 29) to those in Table 11. The numbers of observations in both cases are large, and if the final columns in Table 28 and Table 29 are

TABLE 28

Distribution of Persons in Various Occupational Groups According to the Concentration of Lead in the Urine—Field Survey 1955

Lead in Urine mg. per litre	*Service Station Attendants*	*Refinery Handlers*	*Garage Mechanics*	*Parking Attendants*	*Traffic Officers*	*Drivers of Motor Vehicles*	*All Persons*
0·00—0·009	1	1	4	1	—	1	8
0·01	—	1	2	4	9	28	44
0·02	74	49	39	21	5	11	199
0·03	33	22	33	12	—	2	102
0·04	13	9	30	7	3	2	64
0·05	5	—	21	2	—	—	28
0·06	3	4	16	1	—	—	24
0·07	—	—	4	—	—	1	5
0·08	1	—	1	—	—	—	2
0·09	—	—	2	—	—	—	2
Total Numbers ...	130	86	152	48	17	45	478
Mean	0·027	0·028	0·040	0·028	0·028	0·026	0·030
S.D.	±0·010	±0·013	±0·020	±0·011	±0·011	±0·010	±0·014

TABLE 29

Distribution of Persons in Various Occupational Groups According to the Concentration of Lead in the Blood—Field Survey 1955

Lead in Blood per 100 grams	*Service Station Attendants*	*Refinery Handlers*	*Garage Mechanics*	*Parking Attendants*	*Traffic Officers*	*Drivers of Motor Vehicles*	*All Persons*
0·00—0·009	—	—	—	—	—	—	—
0·01	1	2	—	—	—	—	3
0·02	42	30	8	1	7	17	105
0·03	71	46	43	26	9	19	214
0·04	14	8	72	20	1	9	124
0·05	2	—	25	—	—	—	27
0·06	—	—	4	1	—	—	5
Total Numbers ...	130	86	152	48	17	45	478
Mean	0·028	0·027	0·038	0·034	0·026	0·028	0·032
S.D.	±0·007	±0·006	±0·009	±0·006	±0·006	±0·007	±0·007

compared with columns 3 and either 4 or 5 of Table 11, the distribution of the results shows clearly that both sets of findings (i.e., in urine and blood) fit nicely into the same statistical universe. The correspondence in the mean values and their deviations merely confirm this relationship. There is, however, one group of persons in Tables 28 and 29, which differs significantly, in the quantitative, statistical sense, from the groups representative of other occupations. This group, comprising 152 men employed in the maintenance and repair of automobiles, is differentiated from the others by a significantly elevated concentration of lead in both urine and blood. This phenomenon was not unexpected, since a similar differentiation, on the basis of the urinary excretion of lead, alone, had been observed and commented upon previously (7). It is none the less significant in its present occurrence, as an indication of the sensitivity of the method of investigation in detecting a minor type of occupational exposure to lead. Many garage mechanics are subjected to a variety of opportunities for intermittent exposure to lead in the course of their day's work. Those who specialize in one or another type of work may have greater or lesser degrees of occupational exposure to lead, dependent upon their type of specialization. These activities, in a generally decreasing order of the significance of the actual exposure to lead involved therein, include the decarbonizing of motors, the repair of car bodies by soldering and by the removal and reapplication of paint, and the dismantling or repair (occasionally) of electric storage batteries. The exposure of these men, as a group, to the exhausts of motors, and to air-borne lead derived from accumulated deposits of finely divided lead on floors or other flat surfaces, is greater than that of filling station attendants, for example. Moreover, their work is dirty, and their clothing and hands are usually grimy, and their habits, with respect to cleanliness in the handling of food and beverages, are not especially circumspect. It is not remarkable that they give evidence of some occupational exposure to lead, and indeed it is only because of the brief and intermittent character of work involving opportunities for special types of exposure, that they escape actual hazard as a rule. Only very rarely is the garage mechanic the victim of lead intoxication, and such cases as we have encountered have arisen out of highly unusual circumstances associated with regular (specialized) employment in the removal of lead-containing carbon deposits from motors, under conditions which dispersed finely divided lead in significant concentrations in the air breathed (i.e., in the absence of satisfactory exhaust ventilation, or other respiratory protection) by the workmen.

The significance of the slightly elevated (relatively only, and well within the normal range) mean concentration of lead in the blood of the parking attendants (Table 29) is highly dubious, not only because of the slightness of the difference between this and the corresponding mean values for other groups, but also because of the small numbers of persons involved. All one can say is that this *might* be an expression of the relatively severe exposure of these men to the exhausts of automobiles in relatively enclosed areas which, at times, are insufficiently ventilated. The low mean concentration of lead in the urine of traffic officers (selected because of their situation at busy mid-town traffic intersections) is not to be regarded as especially significant, beyond the mere fact so disclosed, because of the small numbers of the observations.

On the whole, however, without undue emphasis on any specific occupational group, these data establish, clearly enough, the relative insignificance of the quantitative difference between the over-all exposure to lead of this entire group of persons and that of other persons in the ordinary walks of life that have no special occupational or geographical relevance to exposure to lead in the exhausts of automobiles.

On the purely hypothetical assumption that the lead content of the atmosphere in certain parts (at least) of urban and industrial centres will increase, what then should be the maximum level of such contamination that is compatible with public safety? There is no entirely satisfactory answer to this question at this time, and since there is no evidence of a present threat to the public health from this source, there is, it seems, no great or immediate urgency to obtain an answer. Our investigations have been carried on with this question in mind, however, for many years, and they have now reached a point at which such an answer can be obtained with a fair assurance of its relevance and adequacy, within a reasonable period of time. The factor at issue involves the rate of the absorption, excretion and accumulation of lead under conditions of *continuous* human respiratory exposure to air containing a low and somewhat variable concentration of lead when, during the different cycles of the day, and in the different locations of the individual, at work, at leisure and in sleep, his respiratory intake and retention of lead are subject to variation. It will not be possible to include all of these variables realistically in controlled experiments in the laboratory. What can be done is to vary the duration of exposure to known concentrations of lead in the air, under known conditions with respect to the respiratory volume and exchange, so as to provide data which can be employed by extrapolation, to predict the characteristics and the quantitative relationships of the metabolism of lead when the individual is exposed to the maximum permissible concentration during all hours of the day and night. Such experiments are in progress, and in due course the results will be available for practical application.

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The opportunity afforded to me to present these lectures in person, and to expand them somewhat in their publication, would not have been fulfilled with befitting grace, were I to fail to represent myself as spokesman for associates in the day's work, who, over the years, have contributed their ideas and their skills of head and hand to the accomplishment of a difficult task. They would not consider it important that they be named in this relationship, nor would this be appropriate, for their number is too great, and most of them are known to our colleagues for their work and publications. It is a necessity to me, however, to acknowledge their many contributions, not only for my personal contentment, but also because I have made use of skills which I do not possess, in the presentation of evidence which, but for such help, would not be acceptable. My grateful appreciation is expressed here, therefore, for many years of stimulating associations, and for the enthusiastic assistance of many members of the staff of the Kettering Laboratory. My deep thanks are due also to the industrial organizations that have financed these investigations, and have maintained their support of a broad programme of experimentation which could not always have been justified by their anticipation of practical benefits of any type.

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