EXPERIMENTAL STUDIES ON THE INHALATION OF LEAD BY HUMAN SUBJECTS

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I have only a short time at my disposal in which to connect up certain experiments which are related to the subject of this Symposium, based on the work of many years in the Kettering Laboratory on the general problem of the biological significance of lead. In order to do this I must cover the ground hastily and only in outline, and I shall have to rely upon your willingness to go to the literature later for the evidence on which certain statements of fact are based.

This work began in 1927–28 with an examination of the occurrence and distribution of lead in nature, especially in biological materials. This task has not been completed, but the general background has been established, and some of the facts are highly pertinent to our discussion here. The summarized results of the early work were published in 1933, and other publications have followed since.

Some years later, we began a systematic investigation of the metabolism of lead in human subjects under normal conditions, and then under artificial conditions involving the oral administration of lead, daily, over long periods of time (in one instance, for 4.5 years), at several levels of dosage. The results of these investigations have been published briefly and, because of their elaborate nature, the experimental procedures and findings have not been described minutely in all of their physiological significance. A full account will be given in a monograph which will deal both with methods and data, as they bear on this participant in the mineral metabolism of the body, as well as on a variety of medical and hygienic problems.

In 1950, we initiated the present phase of the work—one toward which the investigation of the fate of ingested lead had been moving—by entering upon a study of the behaviour of inhaled, particulate lead compounds in the human organism under carefully controlled conditions in the laboratory. These observations, as well as those concerned with the ingestion of lead by human subjects, could be carried out within physiological limits. Since members of the Laboratory staff had had experience in the field of industrial hygiene in the lead trades, there would be no risk of inducing even incipient manifestations of lead intoxication. Clinical and chemical (analytical) observations had been made systematically in a wide variety of such trades for many years and had established, beyond cavil, physiological criteria—levels...
of lead concentration in blood and urine—whereby harmless levels of absorption of lead compounds can be differentiated from those which are potentially or actually harmful. By the application of statistical methods of analysis to the clinical and chemical data, it had become possible to cover the possibilities and probabilities of a large group of adults in industrial populations and to express the standards of safety and danger in substantially absolute, mathematical terms. These have been stated, for practical application, in the literature\textsuperscript{3,7,8}. On these bases, within physiological limits, over periods of months or years, we have subjected members of the Laboratory staff—usually recruited for the purpose from among persons of appropriate physical fitness, who possessed qualities or aptitudes that would meet the requirements of a restricted regimen of daily work within a respiratory chamber—to the inhalation of air containing known concentrations of a specific lead compound in known states of subdivision.

The principal objective of these, as well as the experiments on the fate of ingested lead compounds, was that of acquiring an understanding of the basic physiology of human lead absorption, excretion and retention, at least descriptively. A more specific objective of the experiments now under way is that of appraising respiratory exposure to lead as to its contribution to the total exposure of the human subject, in relation to the standards of safety with which we are concerned in the field of occupational health, and of extending these standards to exposure to lead on the part of the general population. These experiments will be continued for some years, until certain of the more important variables, such as size of particles, behaviour of specific compounds, levels of dosage, and the temporal aspects of the exposure, have been explored. We have now completed six experiments on four persons (two have been duplicated), and four verbal reports of progress have been made, on matters of considerable practical importance, to certain professional groups. Only two of the experiments will be referred to in the paragraphs that follow.

**EXPERIMENTAL METHODS**

*Figure 1* illustrates one of the respiratory chambers, made by assembling standard metal partitions, into which have been introduced the necessary ventilatory and other equipment of dynamic experiments, whereby the desired conditions can be produced and maintained with a minimum of technical supervision. Within this chamber, the experimental subject carries out his work, mostly of a clerical nature, on 5 days of each week, for 7.5 hours per day. This schedule simulates the normal regimen of industry, with respect to the temporal relationships of exposure to lead in the atmosphere, but not that of the general population.

*Figure 2* shows some of the details of the design of the chamber; the intake of air, the course of distribution of the stream into the chamber, the use of a fan below and at the end of the influent tube (instead of a louvred distributor on the leaves of which some of the lead might be deposited), to dissipate the influent air throughout the room. The air is removed by a large, perforated tube located around the sides of the chamber near the floor, which leads to an electrostatic precipitator from which the clean air passes into one of the main stacks of the laboratory to the outside.
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Influent air A enters an intake blower through which it passes into a sound muffler and then on beyond a lateral leg to enter the chamber through the centre of its top at B, where the air stream is distributed by fan C which is suspended from the ceiling of the chamber by light chains. Effluent air E is withdrawn from the chamber by a second blower through properly spaced orifices in the peripheral duct at floor level and through an electrostatic precipitator (rectangular box at lower left). An air stream at F, valved and equipped with a pressure gauge, divides into two, one of which is by-passed through a small flask containing a small quantity of tetraethyl lead (armoured by means of a removable rectangular metal box) and then rejoins the main stream, which then passes to a bunsen burner. A stream of propane at G, with valve and pressure gauge, is led to the bunsen burner, from which the excess of air and the products of the combustion (lead sesquioxide, carbon dioxide and water) at H enter the lateral leg of the influent pipe at I.

In Figure 3, the room is shown equipped as an office. It can also be equipped as a laboratory in which microscopic and other suitable manipulations can be carried out.

Note the small (stoppered) ports to right and left of windows, an electrical outlet above the back of the chair, a telephone and an inter-communication unit. The floor is covered with asphalt tile, and every surface, including the walls of the chamber, ducting and furniture, is lacquered (joints of partitions are covered with Scotch tape) so as to facilitate cleanliness. The floor is mopped once daily, and every surface and object in the chamber is wiped off once daily, by the subject, to prevent any accumulation of lead-bearing dust, which, through the movements of objects or the subject, might redisperse particles of lead oxide agglomerated into sizes foreign to the experiment. The typewriter and other similar equipment (calculator, dictating equipment) are cleaned by vacuum periodically.

Not shown in the photograph are the two air-locks, a small one for books, records and the like, which can be introduced and removed without disturbing the composition of the air of the chamber, and a larger one for exit and entrance, which serves also as a double-locker room for the subject's street and work clothing (a regimen of changing clothing and bathing is maintained by the subject). There is another closet, adjoining and included in the chamber, in which there is a wash-basin for the subject. The electrostatic equipment for cleaning the effluent air is also situated within it, and there is space for the housekeeping implements (mop, dust-cloth, etc.) for the chamber. A shower, a clean place for eating lunch (if desired), and additional storage space are available within the room (separate from all others) in which the chamber (now two chambers) is situated.

A built-in small bench for convenience in the use of sampling equipment (the air of the chamber is sampled twice daily by an electrostatic precipitator operated by the subject, and other samples are taken from time to time) is situated along one side of the chamber (not shown), and other ports and electrical outlets are available here and elsewhere.

The experimental design requires the subject to collect duplicate samples of everything he eats and drinks in the course of each day, to collect all urine voided each day, and to collect all faeces passed each day. This regimen,
laid down in detailed written and verbal instructions, and attended by advice and guidance, as required on the basis of the subject's inquiries and his log of daily activities, is maintained throughout the period of the observations, which includes a period of not less than six months, preceding his intermittent sojourn within the chamber, during which the pattern of his normal lead metabolism is ascertained.

A brief description of the clinical observations made on the subject must suffice for present purposes. The prospective subject is given a thorough physical, physiological and psychological survey, and a series of tests of his organic integrity are carried out prior to his acceptance. Haematologic, respirometric, roentgenographic, electrocardiographic and encephalographic records are made as base lines for future comparisons. Other observations, as indicated by any unusual findings, are made during the period before exposure to lead is initiated.

After the acceptance of the subject, blood films are made daily and examined by standardized procedures for enumerating the "stippled" erythrocytes and the reticulocytes. In a measured portion of each day's urine, certain porphyrins, including coproporphyrin III, are determined quantitatively. The subject is interviewed weekly by the physician responsible for his clinical supervision, and his weight, blood pressure, pulse and respiratory rates, and general bodily status are recorded. At this time each week, a measured sample of urine is examined for reaction, sugar, albumin and microscopic constituents, and the blood picture is obtained. Neurological and psychological examinations are repeated at intervals during the experiment, and an interview with a psychiatrist is had from time to time (as a part of a somewhat irrelevant investigation conducted by the psychiatric staff).

On each day of the experimental period, with the exception of a brief "vacation" just prior to the initiation of the experimental exposure to lead, his daily intake (in duplicate) of food and beverages, and his output of faeces and urine are collected for chemical analysis. Once each week, duplicate samples of blood are drawn for chemical analysis. At regular intervals, after the initiation of the respiratory exposure to lead and during the period spent within the chamber, the lead content of the exhaled air is determined by a technique to be illustrated later. By this means, the degree of retention of lead in the respiratory system is determined, and the total quantity of lead made available experimentally for absorption within the body can be calculated from the data on the respiratory volume and the actual duration of each day's exposure. (The lead inhaled from the atmosphere outside the respiratory chamber during the days and hours of freedom from confinement can be calculated with approximate reliability, from the average lead content of the atmosphere of the laboratory and that of the subject's home and urban environment. Thus the total intake and the total output of lead daily and during the entire period of an experiment can be ascertained with fair precision. The only item of data that is missing is the initial quantity of lead within the body of the subject. This also is amenable to indirect estimation from the preliminary pattern of the lead metabolism, as set against that of certain "normal" persons whose bodies, fortuitously, have come to be available to us for analysis.)
**Figure 1.** External view of respiratory chamber made of standard metal partitions

**Figure 2.** Schematic plan of chamber and equipment
Figure 3. Photograph of interior of chamber equipped as an office

Figure 4. X-ray diffraction patterns
Figure 5. Particles of lead sesquioxide from the air of the chamber precipitated by hot-wire and visualized by the electron microscope.
In Figure 4 is the X-ray diffraction pattern of the lead compound employed in the experiments with which this report is concerned, superimposed on that of the pure compound, lead sesquioxide. The upper pattern is that of the lead compound introduced into the atmosphere of the chamber; the lower one is that of a highly purified sample of lead sesquioxide. For historical reasons in relation to the problem of tolerable concentrations of lead in the air, as well as those of ease of manipulation, we chose to use lead oxide in initiating these experiments. The sesquioxide can be produced in a finely divided form, and in high purity, by the combustion of a small quantity of the vapour of tetraethyl lead in a stream of propane burned to completion in a bunsen burner. This is a readily reproducible means of providing particles of the specific lead compound of a specific range of size at a predictable and steady rate.

Figure 5 displays the particles of lead oxide as they occurred in the air of the chamber, in a photograph of a hot-wire precipitate visualized by the electron microscope. Note certain minute, discrete particles, and other larger obviously agglomerated clumps, none of which approach 1 μ in any dimension. The size of these particles, as represented in Figure 6, ranges up to 0.17 μ, the mean size, however, being 0.05 μ. Because of the method of generating the particles, little variability was observed throughout the experiments. One could be certain that particles of this size would not be entrapped within the upper respiratory tract to any measurable extent, and that any appreciable retention of such particles within the respiratory tree would occur within the alveoli. The extent of such retention could not be left to conjecture, however, and some means of measurement had to be devised. The procedure adopted is not entirely satisfactory from the standpoint of strict accuracy, but it has the virtue of simplicity, and it yields results which vary only within reasonable limits. The apparatus is illustrated in Figure 7. Note the direct flow of expired air from the face-piece to the electrostatic
precipitator, the volume in the terminal Douglas bag being determined later. The procedure requires the subject, while breathing normally within the chamber, to exhale, by way of a short tube, to the outside of the chamber, through an electrostatic precipitator and on into a Douglas bag.

In the first of the six experiments referred to previously, the normal lead metabolism of Subject M.O.B. was followed for 36 weeks, after which his exposure to air containing particles of lead sesquioxide of a mean diameter of 0.05 μ and in a concentration equivalent to 0.075 mg lead/m³ was initiated and continued for approximately 7.5 h/day (the time within the chamber was recorded precisely, daily) on 5 days of each week for 92 weeks. After termination of the experimental exposure to lead, the clinical and chemical observations were continued for an additional period of 148 weeks, at the end of which period (actually some months previously) the subject was believed to have returned to his initial (pre-experimental) state with respect to the lead content of his body and his current lead metabolism. This initial experiment, conducted over the period of almost 5.3 years, continuously, with only brief periods of respite for the subject (none during the period of exposure), and well after the second experiment on another subject had begun, was used as a pilot study for subsequent details of experimental design, while serving to demonstrate the response to one level of dosage.

In the second experiment, Subject F.C. was followed in a preliminary manner, as described, for 76 weeks (the time was extended beyond original expectations, because of the prolongation of the exposure of Subject M.O.B. within the one chamber available at that time). After this he entered the chamber on the schedule outlined above, under the same conditions as those of the first experiment, except for the doubling of the concentration of lead in the air. The resultant concentration, equivalent to 0.15 mg lead/m³ air, was based, for obvious reasons, on the standard generally advocated at that time by industrial hygienists in the United States in relation to occupational exposure. The period of exposure under these conditions was 88 weeks, after which the observations on this subject were continued well beyond the

![Figure 7. Illustration of equipment employed in determining lead content of expired air](image-url)
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76 weeks that will be indicated for present purposes in his charts (Figures 12-15).

EXPERIMENTAL RESULTS

The results that have primary relevance to the subject of this Symposium can best be demonstrated in a series of four charts for each of the two subjects. In the first pair (Figure 8, Subject M.O.B. and Figure 9, Subject F.C.), the lower line shows the mean daily weight of the food (exclusive of that of the drinking water), as calculated from the data of each day in every period of 28 days, on the scale indicated on the right. The upper intertwining curves, as indicated, represent the mean daily intake of lead in food and all beverages, including drinking water, and the mean daily output in the faeces only, both of these values having been calculated for each 28-day period, from the analytical data representative of each day. The calculations have been plotted against the scale indicated on the left. Each point on each curve, therefore, represents the mean value (the weighted average) of 28 determinations. There are many interesting features of these findings, but they
have been observed before and discussed elsewhere\textsuperscript{4-6} and need not occupy our time here. Suffice it to note that the lead in the faeces bore the same relationship to the lead in the food, during the periods of the respiratory exposure of the two subjects, as it did in the other two periods. This provides the proof of the correctness of our expectation that none of the inhaled lead would be caught in the upper respiratory tract and subsequently swallowed. As we turn then to later charts which give evidence of an increase in the absorption of lead during the period of respiratory exposure, we are assured that such absorption took place in the lungs of the subjects. The proportion of the inhaled lead that was entrapped in the lungs of the two subjects varied somewhat from time to time. However, many determinations of the proportion retained in the lungs of subjects M.O.B. and F.C. during respiration within the chamber averaged 37 per cent and 36 per cent, respectively.

One other point is worthy of comment as background information for the proper interpretation of the later charts. Careful scrutiny of Figures 8 and 9 will reveal some fairly wide variations in the intake of lead in the food from time to time. It is noteworthy that these variations parallel, and are clearly responsible for, almost all of the variations in the lead content of the faeces. Most of the lead ingested in the food is evacuated unabsorbed with the faeces (as we have demonstrated in earlier experiments). Nevertheless almost every increase or decrease in the lead intake in food is accompanied by a corresponding increase or decrease in the urinary excretion of lead. It is important to remember this fact in connection with the variability of the urinary excretion under the conditions of an essentially constant level of experimental respiratory exposure to lead. In short, the lead taken in daily with food is an important factor in the daily output of lead in the urine, and this factor must be kept in mind constantly in any appraisal of the significance of the urinary excretion of lead. The daily intake of lead in the food of the individual varies with the type and quantity of food consumed; it varies, then, with the dietary habits and the appetite, with the seasons, with the home-life (cuisine), and with the locale of the individual subject or of different subjects. For example, Subject F.C. changed his boarding house in the 14th month (28 days) of the control period, with the result, of somewhat unusual proportions, indicated at that point in Figure 9. It may be noted that the weight of the food increased, probably with enhanced appetite, at this time, and that as it decreased some five months later, with accommodation to the no-longer-new dietary regimen, the lead in food and faeces decreased. These influences are reflected in Figures 11 and 13, in which the sharp upturn and falling off of the urinary lead output and concentration would, otherwise, be disconcerting. Because of this and other apparent vagaries in the urinary lead excretion of this subject from time to time, the curves of the lead content of the food, in the control period, and that of both food and faeces, in the other two periods, have been repeated on the latter chart.

In Figures 10 and 11, the mean daily urinary output of lead by the two subjects is plotted, in parallel with the mean daily volume of the urine voided, for each 28 days of the entire experimental period. In Figure 10 the lower dotted line shows the mean daily volume of the urine voided
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(including that of measured samples taken from time to time for other determinations), as calculated from the measurement of the volume each day over each period of 28 days, on the scale indicated on the left. The upper dotted line represents the mean daily lead content of the urine voided, as calculated, similarly, from the data of each period of 28 days. Note the peaks at the 5th point during the period of exposure, as a characteristic "overshooting" of the response, which also corresponds not precisely but generally, with an increase in the lead content of the food and faeces (Figure 8). Note, in contrast, the peak at the 19th point of the same period, which, after "equilibrium" has been attained, is in precise correspondence in time with a sharp increase in the lead content of the faeces, not precisely, but approximately, duplicated in the food (Figure 8). It must be borne in mind that each of these points is the weighted average of 28 determinations and not the result of a single fortuitous error of sampling, contamination, or
analysis. In Figure 11 note the "overshooting" of the response to exposure (5th and 6th points during the period of exposure) as in Figure 10, without a corresponding peak in food and faeces (Figure 9). Note also the consistently low volume of the urine of Subject F.C., the especially low volume (hot weather) during the early part of the period of exposure, and the higher variability (as compared to that of Subject M.O.B.) throughout the experiment.

Aside from the influence of the variable referred to above, several points of outstanding significance are revealed. First is the fact that the responses of both subjects to the experimental exposure were the same qualitatively; the urinary output of lead increased with equivalent promptness (at a somewhat more rapid rate in response to the larger dosage); it rose to a relatively high point in both instances, receded appreciably, and then flattened out (with appreciable variations, inconsistent in direction) to maintain an essentially horizontal curve, the level of which was well above the normal (control) base line. The horizontal character of these curves, developed after 6 (Subject M.O.B.) to 8 (Subject F.C.) months of exposure, varied sharply from the maintained upward slopes of the curves representing the urinary output of subjects to whom lead was administered daily along with their food. This variation was not unexpected but gratifying, in view of the corresponding behaviour of men employed in lead trades in which the occupational conditions, with respect to exposure to lead, are maintained in a fairly constant manner. We have observed, repeatedly, that individuals and groups of such employees reach a level of urinary lead excretion which characterizes the severity of their exposure. Further that this level changes but little thereafter for years (within the limits of physiological variability), except in response to increase or decrease in the severity of the exposure to lead. This, no doubt, is due to the intermittence in the exposure to, and the absorption of, lead, in association with freedom from exposure during the 16 or 16.5 hours of each working day and during the 2 days at each weekend. During a large part of these periods of freedom from exposure, the output of lead, on the part of the individual, is greater than the intake, and a point of balance is reached which must, it seems, depend upon both the time relationship and the dosage.

Reference to dosage leads to the second point of importance, in that the level at which equilibrium was reached varied directly in these two subjects, with the concentration of lead in the air which they breathed. Starting from slightly, but significantly, different base lines (Subject F.C. had a lower base level of lead output than did Subject M.O.B., in accord with his lower output— and intake— of water), the mean daily output of lead by Subject M.O.B., at equilibrium, was 0.055 mg, and that of Subject F.C. (at twice the concentration of lead in his respired air), at equilibrium, was 0.07 mg.

A third point, which will be emphasized in the presentation and discussion of further data, is the fact that, in neither instance did the respiratory exposure of the subjects to lead result in a consistent increase in their urinary output of lead to a level which could be regarded as even approaching the threshold of danger.

Since the urinary excretion of lead by industrial employees is expressed more conveniently and (under suitable conditions of sampling) somewhat
more satisfactorily in terms of the concentration of lead, than in terms of lead output per unit of time, the data have been so represented in Figures 12 and 13. In Figure 12 the (slightly) lighter dotted line (consistently above the other throughout the control period and that of exposure) represents the results of the analysis of the urine by a colorimetric method with dithizone (Figure 9); the heavier and generally lower dotted line gives the results of a spectrographic method (Figure 9), discontinued after the 22nd lunar month after

These lines show the mean daily concentration of lead in the urine, calculated from the respective data of the two methods of analysis for each
day of every period of 28 days. Note the parallelism of the curves of this figure with that of Figure 10, as evidence of the satisfactory quality of this manner of expressing the urinary excretion of lead.

In Figure 13 the single line without dots portrays the deviations in the mean daily concentration of lead in the urine, on the background of the lead in the food during the control period, and on that of both food and faeces during the remaining periods of the experiments, in order to show the influence of the alimentary lead on the urinary excretion of lead. The mean daily lead content of the food and faeces are plotted as in Figure 9, except that the scale is on the right. The mean daily concentration of lead in the urine, as determined by the dithizone method alone, is plotted, as in Figure 12, on the scale at the left. Note the similarity of the curve to that of Figure 12, but the augmentation of the variability. The peaks during the period of exposure correspond to the periods of maximum ambient temperature during the summer months of the successive years.

The facts indicated in these figures are much the same as those pointed out in connection with Figures 10 and 11, so that little further discussion is required. It is worthy of note, however, for the benefit of those who have specific numbers in mind, as unvarying physiological criteria for industrial danger, that the mean daily concentration of lead in the urine of Subject F.C., during the 5th month of the period of exposure, was 0.14 mg/l, and during the 15th month, was 0.16 mg/l. Neither of these values, of itself, is indicative, necessarily, of a dangerous level of lead absorption, but the higher of these two results, if maintained consistently for some months, is potentially dangerous under ordinary conditions of life in the temperate zone. It is important to recognize, therefore, that both of these values, spaced about one year apart, came during the peak of the hot weather in the respective years. They also occurred in association with elevated levels of lead intake in the food. Their unusual character is demonstrated by the fact that the average concentration of lead in the urine, after equilibrium with the exposure had been reached, was approximately 0.085 mg/l. This chart (Figure 13), more than any other portrayal of the data of these two experiments, illustrates the difficulty of visualizing the lead metabolism of an individual, as a consistent pattern, on the basis of a few observations of the rate of the urinary excretion of lead. Such evidence should give pause to those whose limited experience and over-confidence in a specific value, voiced or recorded without due qualification, enable them to accept arbitrary diagnostic criteria or to promulgate arbitrary legislative or administrative standards.

We come now to the data on the blood, which are of prime importance in the appraisal of the status of individuals, with respect to the relative quantities of lead in their tissues generally, and the significance of such quantities in relation to hazard. It is necessary to qualify the foregoing statement somewhat. The lead content of the blood, while clearly indicative of the general level of the lead absorption of an individual who is being subjected to exposure to lead, is somewhat less representative of the facts when an interval of some months of time has elapsed since the termination of a mild degree of occupational or other abnormal exposure. Moreover, the lead in the blood is essentially valueless as an indication of the extent of
the individual’s absorption of certain organic lead compounds, tetraethyl lead being the outstanding example. (Tetraethyl lead is decomposed in the living organism, and the ultimate residuum of lead in the body from this source is probably inorganic in character. However, tetraethyl lead and its intermediate decomposition products are not held in combined form in the erythrocytes, as are the inorganic compounds of lead, and hence are not in demonstrable equilibrium with the other tissues of the body with respect to their lead content. The rate of the urinary excretion of lead, following the absorption of tetraethyl lead appears to be the sole indication of the relative quantity absorbed, in the intact animal or man.)

Figures 14 and 15 display the average of 8 samples of blood collected at weekly intervals (2 per week) for each 28-day period of the two experiments. In both figures each point on the dotted line from left to right represents the average of 8 determinations of the concentration of lead in the blood, 4 by the dithizone method and 4 by the spectrographic method, during the respective periods of 28 days throughout the experiment. In Figure 14 note the relatively low variability of the concentration of lead in the blood from point to point, and the general trends during the periods before, during and after the experimental exposure. While in Figure 15 note the lack of variability from point to point during all but the period of exposure, and note the greater response of Subject F.C. to the higher level of exposure, as compared with Subject M.O.B. Two items of interest and importance are worthy of comment. First, the level of lead concentration in the blood of each subject increased more gradually in response to the experimental exposure, and declined more gradually after the termination of the exposure, than did that in the urine. Subject M.O.B. reached a stable concentration of lead in his blood at about the 7th month, whilst Subject F.C. arrived at a similar state of apparent equilibrium at about the 11th month. Some of the variability indicated in the blood of both subjects may be attributed to analytical deviations, the quantities of lead in these samples (10 ml) being minute. The analytical error is much too small (two methods of analysis were employed in parallel analyses) to influence the general trend of these data, however, or to alter significantly the recorded values, since the unsystematic error is as likely to occur on the high as on the low side.

The average concentration of lead in the blood of Subject M.O.B., at approximate equilibrium, was 0·04 mg/100 g, and that of Subject F.C. was 0·045 mg/100 g. Since Subject F.C. started at the average level of 0·025 mg/100 g, and the base level of Subject M.O.B. was higher by approximately 0·003 mg/100 g, the differential is somewhat greater than the average figures, at equilibrium, indicate. The fact is clear, in any case, that Subject F.C. absorbed more lead than did Subject M.O.B., as was to be expected in accordance with the experimental conditions. The data obtained during the period after the termination of the exposure, i.e., the excess of the output of lead over the intake, in both instances, demonstrated that both subjects had retained (accumulated) some lead in their bodies during the period of exposure. Calculations made from these data indicate that the total amounts accumulated during exposure and eliminated in the subsequent period were of the order of 18 to 21 mg, in the case of Subject M.O.B., and 25 to 30 mg, in that of Subject F.C. There are good reasons for the belief that the last
small residue of the lead that is absorbed during a period of abnormal exposure remains in the body for a long time. It is probable that somewhat more lead was retained by our subjects, during their exposure, than was eliminated in the extended period of the observations after the exposure had been terminated. This probability, plus the intrinsic, composite, random error of the experimental procedures, makes it necessary to express the retained lead in their orders of magnitude rather than in absolute values.

![Graph of lead concentration in blood](image1.png)

*Figure 14. Concentration of lead in the blood of subject M.O.B.—experiment no. 1*

Even so, the probable error of the estimates is small, considering the total amounts of lead involved in the experiments, and little, in way of assumptions, need be made in arriving at the approximate amounts.

Experience has shown conclusively that lead intoxication does not occur, even in infants and children or in "unusually susceptible" industrial employees, until and unless the concentration of lead in their blood has reached or exceeded 0.08 mg (80 μg)/100 g whole blood. (It is conceivable, of course, that some highly unusual individual, with some, at present indefinable, physiological defect, might develop toxic manifestations due to lead absorption at a blood level lower than that indicated above. In some twenty years of experience since the present methods of analysis came into use in the Kettering Laboratory, and after tens of thousands of analytical results have been obtained from a large number of employees in a wide variety of lead
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trades, and from many cases of real and alleged lead poisoning, we have never encountered a single person in whose blood, at the onset of lead intoxication, a lead concentration of <0.08 mg/100 g was found.) For the purposes of industrial hygiene in the lead trades, we consider that the concentration of 0.07 (70 µg)/100 g leaves little margin of safety for the individual employee, and we act or advise in the belief that his methods of working or the conditions of his work environment should be improved so as to lessen his hazard. If the concentration of lead in the blood reaches the level of 0.08 mg (80 µg)/100 g, as determined by multiple analyses, we advise his removal, summarily, from his job, regardless of his apparent state of good or ill health. If it is feasible (it usually is), and if the man is not ill, he is transferred to another job in which no exposure to lead is involved (a little absorption of lead is sufficient to maintain a high level of lead concentration in the body, once it has been attained, or to retard its gradual reduction). Such a man is not permitted to resume the job until his blood level has returned to the normal range (under 0.06 mg (60 µg)/100 g, and ideally) until the situation which was responsible for his excessive absorption of lead has been corrected. That the "ideal" handling of such a situation is not always achieved is due to the lack of understanding of the problem on the part of both employer and employee, coupled with certain hard facts of social and economic life that do not always yield readily or promptly to hygienic considerations. There is an undue apprehension among uninitiated and inexperienced persons, lest the insidious, toxic effects of lead, absorbed in any quantity, should ultimately induce disastrous effects; there is a corresponding disregard of danger among those whose long experience in the lead trades, especially those concerned with old processes and commodities, has inured them to the "occasional" case of seriously disabling lead intoxication. These curiously persistent and contrasting views are equally expressive of ignorance and of the common human proclivity for prejudice, especially in old or traditional fields of thought and activity.

From the aspect of specific criteria of industrial hygiene in the lead-using industries, the most significant result of these experiments is the fact that no hazard of lead poisoning is associated with the inhalation of air containing a fully respirable and absorbable compound of lead in the concentration of 0.15 mg/m³, over the period of nearly 2 years. The experiments were carried out under conditions that simulate those of industry except for their strict uniformity and their virtually complete elimination of the ingestion of lead in connection with the day's work. It must be emphasized that the adoption of this level of lead concentration in air as a criterion of absolute safety in industrial employment would make no allowance for longer hours of work and exposure; for such diseased states as may interfere with the normal disposition of absorbed lead within the body and its excreta, and, above all, with the situations in the lead trades in which the ingestion of lead is a highly significant factor in the composite occupational absorption of lead. The issue may be raised that the duration of the "occupational" exposure of Subject F.C. was somewhat less than 2 full years, whereas actual occupational exposure may continue for many years, or indeed during a lifetime of employment. This point cannot be dismissed lightly, nor can it be disposed of entirely by the experimental evidence, unless one takes the

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position that no further lead accumulated in the body of either experimental subject after the equilibrium with the experimental environment had been reached. Certainly the rate of accumulation, if any, within that period, was low, but it cannot be said now, with certainty, to have been nil. We believe it to have been negligible, for the reason that progressive accumulation of lead in the body at a rate as low as 0.04 mg/day (as demonstrated in an experiment on the ingestion of lead) is associated with a significant, progressive increase in the rate of the urinary lead excretion. Of one thing, however, we are sure, in consequence of long experience in the medical supervision and clinical monitoring of industrial employees, i.e., that men whose regular rate of urinary lead excretion, over a period of many years of stabilized exposure, is represented by a concentration of lead of not more than 0.10 mg/l or by a lead output of not more than 0.12 mg/day, are not in danger of developing any form or degree of lead intoxication. On this criterion, the margin of safety of Subject F.C., for an indefinite period of exposure to the prescribed experimental conditions, was large.

References