March 3, 1960

David W. Fassett, M.D., Director
Laboratory of Industrial Medicine
Eastman Kodak Company
Kodak Park Works
Rochester 4, N.Y.

Dear Dave:

Herewith are the two copies of my contribution to the book. I hope the text will be to your liking. I could have done better if I had started sooner and taken more time, but I am fairly well pleased with the result. You (or Frank Patty) may think I have been a bit wordy in spots, or that there is some unnecessary repetition. This may be true, but I am not inclined to think so. Perhaps I wouldn't be sufficiently critical. I am convinced, however, that there have been some islands of confusion or lack of understanding in this general problem, and I've tried hard to eliminate them.

Something might have been said on toxicity per se. In my view, the intrinsic toxicity (in the sense of lethel concentrations or dosages) of these compounds, even of lead arsenate, for example, which combine's two elements, is almost wholly irrelevant so far as occupational exposure and absorption are concerned, and therefore, I have simply omitted reference to toxicity. The only important question relates to the rate and duration of a relatively prolonged and not immediately dangerous absorption and this, after all, is not a question of relative toxicity but rather the characteristic behavior of lead in the body.

I shall be glad to have any comments or criticisms which seem to you to be justified. I have edited the text most carefully, but I shall be surprised if you do not find some errors that have slipped past me. I believe the manuscript is fairly satisfactory in matters of form.

Sincerely yours,

Robert A. Kehoe, M. D.

RAK:ss

Enclosure (2 copies of manuscript)

THE RISK ASSOCIATED WITH THE ABSORPTION OF LEAD BY THE GENERAL POPULATION IN THE UNITED STATES

The Conditions Under Which the Ingestion of Lead is Hazardous

by

Robert A. Kehoe, M.D.*

From the Kettering Laboratory in the Department of Environmental Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio 45219

* Professor Emeritus of Occupational Medicine

The discussions of this meeting are concerned with the degree of risk of lead poisoning, if any, to which persons in the general population of the United States of America are subjected through the occurrence of lead in their general environment. In examining this problem, it is necessary, first, to differentiate between general environmental conditions, and those which have long been known to be potentially hazardous in certain lead trades and lead-using industries. It is also necessary to recognize certain other situations in which lead poisoning occurs, when, through innocence, ignorance or irresponsibility, the non-occupational environment of an individual, a family, or some other group may be rendered dangerous by personal behavior, or through the utilization of materials or equipment commonly known to be dangerous. An example of unusual behavior is that of the infant, usually poorly cared for, who habitually, for weeks or months, eats dangerously large quantities of lead-containing paint from the surfaces of outer or inner walls, woodwork, furniture, or toys, in his home. Further examples are furnished by the owner of an isolated cabin or camp, or even a permanent home, who conveys water into his house from a spring or other source through a long stretch of lead pipe; or by the frugal collector of maple sap, who preserves his wooden pails against disintegration by coating them generously, inside and out, with a paint high in its lead content; or by the art-conscious but technically incompetent potter who puts out a badly glazed

brand of tableware with which to beguile aesthetic housewives into feeding their families dangerously.

The foregoing are but a few examples of serious dangers associated with the ingestion of lead compounds, as variants of a host of recorded and assembled (1, 2, 3) human experiences which, collectively, have been responsible for numerous and sometimes fatal cases of non-occupational lead intoxication - incidents and epidemics which have come and gone over the centuries, some of which have been investigated and elucidated in times past and present. But while some of these have been informative, with respect to the quantitative relationships between dosage and time in the induction of lead poisoning, it is only in those respects that they are pertinent to the subject under discussion here. For the object of present concern is not the incident or the mischance that has yielded the unusual case of lead poisoning within the general population, but is, rather, the prevalent, regular exposure to and absorption of lead, which are the common lot of people who live in the environment of a modern technological nation.

The question, as I choose to restate it for my purposes, is threefold. What are the facts with respect to the magnitude of the total exposure to lead to which citizens of the United States are being subjected? Is such exposure hazardous to a certain segment (or segments) of the population now or in the near future? If not, what margin of safety exists, or should exist? I am scheduled to speak only of the hazard of ingested lead, and I shall fulfill to this mandate. However, it must be evident to all of us, that this is but one facet of the matter at issue, and that it cannot be dealt with, at this or any other time, in independence of the respiratory absorption of lead. Therefore, in order to determine the threshold value of the alimentary factor in relation to public safety, the respiratory component must be held constant, and vice versa. This,

for all practical purposes, is what has been done in an experimental approach to this matter.

The Total Magnitude of the Current Exposure of the General Population to Lead

In the course of a series of investigations carried out in the Kettering Laboratory during the past forty years, but more specifically, those of the past twenty-eight years (because of the essential uniformity of the analytical method employed during that period), it has been possible to visualize, in a fairly comprehensive manner, the daily contribution made to the alimentary intake and absorption of lead by the food and beverages consumed generally in the United States (4,5). By indirect measurements, on the one hand (5) and by calculations based on physiological parameters on the other, a reasonably satisfactory approximation of the quantities of lead breathed in from the ambient atmosphere by adults in the population has also been arrived at. (The latter quantities vary from time to time and from place to place, and also, to some extent, from individual to individual, as do, also, the quantities ingested in food and drink. There is no present means, however, by which the respiratory intake can be measured, directly, so as to obtain a statistically valid array of findings. Therefore, they must be expressed as a range of estimated values, for which, at present, there is little virtue in an average value. The range, however, is not extensive in the absolute sense, and there is little doubt that the order of magnitude encompassed thereby is realistic.)

The food and beverages consumed daily by an adult in the United States contain lead in amounts which range from somewhat less than 0.1 to 4.0 milligrams (occasionally more). The lowermost and the highest values occur infrequently, the large proportion of the quantities grouping themselves regularly around the mean value of approximately 0.3 mg. per day (this mean value is derived from

a large number of results obtained from a sizeable group of adults; the mean values for individuals obtained by daily observations over periods of months or years, range from 0.12 to about 0.38 mg. per day, their variance being due to the differences in the gross quantities and the choices of food and beverages consumed, habitually, by different individuals of different size, occupation, and appetite.

The quantities taken in daily with the inspired air may range from somewhat less than 0.015 to 0.09 (15 to 90 micrograms) per day, (no doubt, being considerably closer, as the usual experience, to the lower than to the higher value), depending upon where and in what manner one resides and where and how he works; i.e., upon the quality of the air breathed during the 24 hours of each day, with respect to lead content, and upon the rate and depth of the respiration during sleep, work and recreation.

The quantities of lead absorbed into the human body from the sources indicated above may be estimated with fair accuracy on experimental evidence which shows that somewhat less than 10 per cent of that ingested under ordinary circumstances is absorbed daily from the alimentary tract, while from 25 to 50 per cent of that inhaled (5), dependent upon the size, shape and density of the particles inhaled, is retained and absorbed in the respiratory system. The average quantity absorbed daily in the alimentary tract of the adult is of the order of 0.03 milligram (30 micrograms), while a reasonably satisfactory estimate of that absorbed in the respiratory system would not be far from 0.2 milligram or 20 micrograms (5,6).

The Significance of the Current Exposure of the General Population to Lead, from the Aspect of Hazard

If there is to be a satisfactory answer to the question as to whether the current trend in the absorption of lead by the general population is hazardous, the answer must come, it seems, from quantitative, physiological information as

to the fate of lead absorbed over long periods of time (extended, in the final sense, to the human lifetime), and from the facts of toxicology and clinical medicine, as to the conditions under which intoxication by lead occurs.

First, with respect to the metabolism of lead taken in and absorbed by typical representatives of the healthy, adult population, the facts, while seemingly not so comprehensive, in relation to a population of nearly two hundred million people distributed throughout the wide expanse of the United States, as to cover all of the possible environmental variations, are so uniform, physiologically, as to be convincing. The results of experiments carried out under exacting conditions in the Laboratory, supported in breadth by extensive sampling of selected and random groups in the population, have demonstrated, (a) that the intake of lead by typical, healthy, male adults is balanced for all practical purposes, by an equivalent output; (b) that there is no progressive increase, over prolonged periods of time, in the rate of the excretion of lead from the body, nor in the concentration of lead in the blood; and (c) that any increase in the concentration of lead in the tissues of the body, including the skeleton, which may occur over the span of life, is too small to be measured, being within the limits of the individual variability in the intake and output of lead (4,5). (The latter statement should not be misinterpreted to mean that the total quantity of lead found in the body does not increase with growth from childhood to adult life. The increase observed, however, is not accumulation, in the physiological sense, but is, rather, the maintenance of a balanced concentration of lead in individual tissues, that is to say, the maintenance of an equilibrium with the environment.

Second, with respect to whether the concentration of lead in the tissues of people, generally, in the population, and the quantities in their entire bodies and in the metabolic processes described above, constitute a risk - the risk of

intoxication by lead in any form known to physicians, physiologists and pathologists - the answer is in the negative. The toxic effects of lead upon the human body, as expressed in the more severe types of plumbism known classically, both before and since the days of Tanquerel des Planches (7), have not been seen frequently in recent years, but they still occur from time to time, especially among children, to display the immediate signs and symptoms and certain sequelae of the most damaging forms of plumbism. The milder types of lead poisoning are the more common manifestations of the disease in our time, in the adult, and, because of this, much attention has been focused upon biochemical evidences of disturbances in the rates of destruction and replacement of the erythrocytes and the degradation and synthesis of hemoglobin. These disturbances, while not confined to the effects of lead, are among the earlier and more subtle changes induced by lead, which may give warning of more serious symptomatic and organic effects to follow. Even these subtle chemical changes do not occur in association with the levels of the concentration of lead that are prevalent in the tissues, body fluids, and excreta of persons in the general population that have not been subjected to unusual types of exposure to lead. The evidence on this point is extensive and convincing (8,9,10,11), and from such evidence, obtained from unusual incidents and accidents within the general population, including those involving infants and small children, and from a wealth of systematic observation of groups of persons engaged in occupations that yield cases of lead poisoning, as well as those that do not, has demonstrated that there is a critical concentration (or a narrow range of concentration) of lead in the body (in the tissues, including the blood, and in the urine), below which none of the obvious or even suggestive manifestations of plumbism have been found. In the intact living body of man, the most readily available tissue for sampling is the blood. This tissue is the most precise indicator, under certain necessary and appropriate

conditions, of the lead content of the entire living body, and, specifically, of the soft tissues of the body. (The measurement of the rate of the excretion of lead in the urine can often but not always be counted on to yield the same type of information, but the difficulties of sampling, and the physiological variability of the excretory process combine to make this measurement more difficult of interpretation than that of the concentration of lead in the blood.)

The Margin Between the Current Levels of the Concentration of Lead in the General Population and Those Associated with the Occurrence of Lead Poisoning

The large proportion of cases of lead poisoning are associated with the absorption of relatively large quantities of lead. The quantities found in individual organs, in the blood, and in the urine, in typical lead poisoning, are many times larger than those found in the corresponding organs, blood and urine of persons in the general population. The skeleton, for example, may contain from ten to twenty times the usual levels found in persons in the general population. The liver, kidneys and brain, likewise, may contain eight to ten times the usual quantities, while the concentration of lead in the blood is similarly elevated, the values ranging, as a rule, from 0.1 to 0.8 mg. (150 to 800 micrograms) per 100 grams of whole blood, as contrasted with the highest value, 0.05 (50 micrograms) per 100 grams, found among persons in the population who have been screened, carefully, to eliminate all occupational factors (5,8). Occasional cases of lead poisoning are found, usually after an intervening period of freedom from exposure occasioned by a delay of some weeks before the blood has been sampled, in which the concentration of lead in the blood is at the level of 0.08 ±0.005 mg. (80 ±5 micrograms) per 100 grams. The latter is the lowest concentration that has occurred, in the experience of the Kettering Laboratory, in association with the onset of lead poisoning in a child or adult, i.e., without an interval of freedom from exposure of more than a few days. This value is not, as some ill-informed persons have believed, the critical level above which

one may properly conclude that the person concerned is suffering from lead poisoning. It is, rather, as stated above, the level below which no case of poisoning induced by inorganic lead, however mild, has been found in our nearly thirty years of extensive experience with all types of lead poisoning, during which the current, sensitive methods of analysis have been employed. It is not certain, in the absolute sense, that this is the actual threshold level between safety and danger, for it may be (and is believed by certain other investigators to be) slightly in error on the low side. It is also not beyond the bare possibility, in view of the extent of the reduction which may occur in the erythrocytic content of the blood (to which the predominant portion of the lead in the blood is bound), that a bona fide case of lead poisoning may be found at the onset of symptoms, at a slightly lower level. This has not occurred, in our experience, as yet, despite the fact that no correction of the analytical finding has ever been made for a lowered erythrocytic content. (Due allowance must be made, here, for the analytical deviation, which is of the order of 0.001 mg. or 1 microgram per 100 grams of whole blood; and for the calculation, which increases it by a factor of 10, in expressing the result in terms of 100 grams of blood.) This error can be and is partially counteracted, when the result obtained is near, above or below, the critical value, by multiple analyses, by enlarging the sample of blood, or by special manipulations.

In the analytical sense, there is a small margin between the upper limit of the concentration of lead in the whole blood of persons in the general population (who have not sustained any unusual exposure to lead), that is 0.06 mg. (60 micrograms) of lead per 100 grams, and the lowermost limit of concentration which, occasionally, may be associated with the onset of (mild) lead intoxication. In the physiological sense, however, if the accuracy of the analytical findings can be substantiated, the difference is not slight, for many months of potentially hazardous occupational (or experimental) exposure to lead

are required to elevate the concentration of lead in the blood by an increment of 0.02 mg. (20 micrograms). The reason for this lies in the fact that most of the absorbed lead, in the process of its distribution in the body, goes selectively into the skeleton, leaving only a small proportion (5 to 8 per cent) distributed within the soft tissues, including the blood. Thus, a difference of 0.02 mg. (20 micrograms) per 100 grams of whole blood, as has been demonstrated (4), may be indicative of an increase of more than 100 milligrams in the body burden of lead. It is such physiological facts as these, with their background in known analytical variance, that must be understood before one can consider intelligently the quantitative relationships in this field of toxicology.

Lead Poisoning from the Ingestion of Lead

Returning now to the assigned topic - namely, the conditions under which lead poisoning may be induced as the result of the ingestion of lead - it is possible to describe such conditions in a fairly precise manner. They may be stated in principle, as follows:

1. Lead poisoning may be induced in a short period of time by a high level of regular, daily, oral dosage, and in a longer period of time by a relatively low level of daily, oral dosage.

2. The requirements are that the dose of lead taken regularly, so as to maintain an essentially constant rate of absorption of lead from the alimentary tract, shall be large enough to lead to a progressive accumulation of lead of critical proportions within the lifetime of the individual.

3. The presence of critical quantities of lead in the intact, living body - the potentially hazardous body burden - can be identified by the finding of a critical concentration of lead in the fluid tissue, the blood, and, with somewhat lesser precision, by the finding of a critical elevation of the rate of the excretion of lead in the urine.

4. The actual onset of lead poisoning cannot be predicted, nor can this specific illness be identified, with certainty, on the basis of any analytical finding in the tissues, body fluids or excreta. Only the danger of lead poisoning can be recognized by such means. It is a fact, however, that the likelihood of the actual occurrence of lead poisoning in the individual case is greatly augmented if the concentration of lead in the tissues of the body increases rapidly in response to relatively high dosage. It appears, from this fact, that if lead is absorbed slowly, some mechanism in the body (beyond the distribution of the major portion into the skeleton) inhibits its toxic effects, possibly by binding it as it is absorbed. The failure of such a mechanism is also indicated by the fact that persons with high body burdens are often precipitated into a bout of intoxication, by a sudden, brief increase in the rate of their absorption of lead.

The foregoing principles can be translated into quantitative terms on the basis of experiments carried out, within the limits of safety, in the Kettering Laboratory, by means of human subjects, and through certain clinical observations made under fortuitous circumstances. After varying periods of preliminary observation of the metabolism of lead as displayed in a series of young, healthy human subjects, lead was administered by mouth in soluble form, in three doses of equal size, taken with the meals. [These experiments have been described in detail, so that only the pertinent facts need be given here (4,5)]. One subject took 3 mg. of lead as the chloride, daily, for 18 weeks, in addition to that which occurred in his diet during that period. Another took 2 mg. (in addition to that in his diet), daily, for approximately 2 years; still another took 1 mg. daily for somewhat more than 4 years, while another took 0.3 mg. per day (plus the mean quantity of 0.32 mg. taken daily in the diet), over the period of 60 weeks.

There was a progressive increase in the output and concentration of lead in

the urine of the first three subjects, in the concentration of lead in their blood, and in the quantities of lead retained in their bodies (the cumulative difference between the intake of lead in the food and beverages plus that administered), and in the output of lead in their feces and urine). With some daily seasonal and incidental variability, the accumulation progressed at essentially constant individual rates throughout the periods of administration, there being no indication of any decline in rate, even after 4 years in the case of one subject.

The output and concentration of lead in the urine of the fourth subject, whose mean daily ingestion of lead amounted to 0.62 mg. (0.3 administered and 0.32 taken with food and beverages), increased slightly (barely significantly in the statistical sense), and there was a difference of about 12 mg. on the side of intake, between the intake and output of lead, at the end of 15 months - a difference too slight to be considered significant but for the consistency of the trend in this direction from month to month. There can be little doubt that the addition of 0.3 mg. of lead per day to that which occurred regularly in the diet of this subject was sufficient to bring about some slight accumulation of lead in his body. On the other hand, the rate of accumulation was insufficient to yield an elevation in the concentration of lead in the blood in the course of 15 months. It is believed that this experiment has gone about as far in the achievement of a positive result as is possible, and it is clear that a long time would be required, probably longer than the life expectation of this subject, to reach a potentially dangerous concentration of lead in the blood. It would seem, therefore, that the average intake of lead in the food and beverages of the nation should be maintained, for the safety of the public, to some quantity short of 0.6 mg. per day, so long as the respiratory intake and absorption of lead remains at or near its present level. In view of the experience of the past thirty years in the United States, during which there has been no increase

in the average oral intake, (there has been a slight trend toward a decrease), it should not be difficult to maintain a satisfactory margin of safety in this respect.

The other levels of dosage, namely 3, 2 and 1 mg., daily, continued regularly, in addition to the quantity, approximately 0.3 mg. per day in each instance, taken in with food and beverages, can be counted on, at some time, to yield dangerous levels of the concentration of lead in the tissues, body fluids and excreta. The period of time required to reach the point of danger (not necessarily of illness, but the distinct threat of illness), in each instance, can be arrived at, with sufficient accuracy for present purposes, by extrapolating on the curves yielded by the values in the blood during the respective periods of observation, to the level of 0.08 mg. (80 micrograms) per 100 grams. These periods turn out to be of the order of 8 months, 4 years and 8 years, under the three conditions.

The shortest period of time, approximately 30 days, which, in our experience, has intervened between the initiation of the ingestion of lead, regularly, and the onset of a typical bout of gastro-enteric plumbism, was associated with an alimentary intake of 10 to 15 milligrams of lead per day. Of particular interest, in this connection, were circumstances which fixed, conclusively, the duration of the period of the ingestion, and the quantities of lead taken daily by two adults, one male and one female, and the dates of the onset of intoxication in the two persons. The dosage and the temporal relationships of these two cases were practically identical.

A single oral dose, in sufficient quantity, of an inorganic (soluble) compound of lead, has been known to cause fatal poisoning within 24 hours. This fact, while of some general importance, especially because the resultant intoxication bears little resemblance to lead poisoning of any recognizable type, is irrelevant, otherwise, for the purposes of this discussion. The lethal dose, while very large (grams), in the one instance in our experience, could not be ascertained. Oral dosages of several hundred milligrams are capable of inducing

acute but not fatal illness in the adult.

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