REPORT OF THE PROGRESS OF AN INVESTIGATION TO DEVELOP A STANDARD FOR THE TOLERABLE CONCENTRATION OF LEAD IN THE AMBIENT AIR

The American Petroleum Institute - Project L-6

Lead Industries Association - Project LH-75

THE FATE OF INHALED PARTICULATE LEAD COMPOUNDS IN THE HUMAN RESPIRATORY TRACT

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INTRODUCTION

In the last extensive report of the progress of this investigation of the fate of an inhaled compound of lead in a finely divided dispersion in the air, some of the previous work of the Kettering Laboratory on this subject was reviewed, and the publications resulting therefrom were cited. Out of this background of information had come a method of approach to the problem at issue, essentially that of determining the role of time in the absorption and retention of lead in the animal - in this instance, the human - organism. For time, as represented in the duration of the lives of people who live and breathe in an atmosphere containing lead continuously, sets a limit on the amount of lead which may be in the respired air throughout the 24-hour day over the period of weeks, months and years of a lifetime. The concentration of lead in the air, apart from localized factors, varies from time to time and from place to place, as in the center or periphery of the community, in the suburban or rural area, in the street or park, and in the office, shop or home (any or all of which may be air-conditioned). Speaking generally, however, there will be an average value which characterizes most of the days of an orderly life as between the hours of waking, working, resting and sleeping, during which the respiration varies in rate or volume or both. If this average value is low enough, what with the functional variability, seasonal and otherwise, of the reasonably healthy, normal individual, in absorbing lead into the body and eliminating it therefrom, the amount which accumulates in the body over a lifetime remains insignificant from the aspect of its potentialities for inducing harmful effects. (Whether or not lead, within certain limits of concentration in the internal environment of the human body, is an essential element, or is even useful at times, is a moot question, and those who would presume to adjudge this matter, at this time, are sadly lacking in appreciation of the complexities of the mineral metabolism, and of the history of the discoveries of the parts played by other

trace elements in animal and human physiology.) It has not been possible, up to the present time, to define the precise limits of the variability of the concentration of lead in the air breathed by individuals or groups of people in any part of the human population. Neither is it feasible to estimate the magnitude of the respiratory intake of lead with satisfactory precision. Moreover, the extent of the absorption of lead, in various chemical and physical forms, from the respiratory tract, is unknown in precise terms, as is also the early and ultimate disposition, within and to the outside of the body, of the lead which is retained in various parts of the respiratory tree. Another difficulty in the elucidation of the facts in these matters lies in the selective absorption of lead by the skeletal tissue of the human body, whereby the bulk of the absorbed lead finds its way, fairly promptly, into this tissue. Its relatively slow and highly variable metabolism (as between the relatively avascular, dense shafts of the long bones, for example, and the highly vascular, spongy medullary tissue of flat bones) tends to remove much of the available lead in the body from the more rapidly moving secretory and excretory streams of the body. And thus, while the lead content of the blood of an individual, because of its participation in the characteristic pattern of the distribution of lead in his "soft" tissue, yields a reasonably satisfactory estimate of the quantities of lead in these soft tissues, it may fail to reveal the status of the skeleton in this regard, in any other than a rough approximation, unless the entire history of the experience of the individual, with respect to his opportunities for exposure to lead, is available and trustworthy. This poses a serious obstacle to the assessment of the body burden of lead within the intact, living person. The nature and the significance of this obstacle seem not to be appreciated by most of those who talk and write about the "body burden" of lead and its importance. For it must be apparent that this same retarded metabolism in the skeletal tissues provides a factor of safety for the entire organism, in precise proportion to its

efficacy in limiting the flow of "accumulated" lead from the skeleton into the stream into (and out of) the "soft" tissues, in which toxic effects may result from the presence of sufficiently high concentrations of lead. The "body burden" is potentially important, no doubt, but the lead which is available to exert physiological or harmful effects is that which is most actively engaged in the metabolic affairs of the organism. The level of this "actively engaged lead" is that which is revealed jointly, in the physiologically intact organism, by the lead content of the blood and the urine. It is in this context that the observations of the past several decades in the potentially or actively hazardous lead-using industries, as well as the results of experiments in the Kettering Laboratory and elsewhere, have been able, in practice, to differentiate between hazardous and non-hazardous types and degrees of exposure to and absorption of lead. There are those who are in great doubt as to the ability of the physicians in our time to detect and interpret the effects of the absorption of minute quantities of lead; who believe, or purport to believe, apprehensively, that there may be "subclinical" effects of the absorption of lead, which, thus far, we have been unable, by any means at hand, to discover. Such may be the case in the future, as indeed it has been found to be in the recent past, in which certain deviations in the synthesis of hemoglobin have come to light and are now demonstrable as elevated levels of the concentration of coproporphyrin III and delta-amino-levulinic acid. While the significance of these biochemical aberrations in relation to incipient plumbism has not been fully elucidated, they seem destined to be regarded as functional pathology, which only a short time ago was indeed "subclinical." The fact is, however, that these evidences of chemical pathology, if they may so be adjudged, do not appear, according to available information, when standards for the safety of workmen in the lead-using industries, such as we have been advocating for the past three decades, have been adhered to consistently. This is to say that the present physiological criteria

for freedom from the likelihood of lead intoxication in any form, based on the level of the concentration of lead in the urine and, more precisely, the blood of workmen in the lead-using industries, have stood unchallenged by the tests of time and clinical experience. It is unlikely that they will suffer from serious shortcomings in the foreseeable future. If this be granted, in relation to occupational exposure to lead, then the principle of measuring human freedom from lead intoxication in terms of the content of lead in the urine and blood, as indicators of the relative lead content of the soft tissues of the body, is equally applicable. The objective of our experimentation, therefore, has been to seek out and define a level of environmental exposure to lead which will not result in a progressive increase, on an elongated time base, in the lead content of the urine and blood of the human population. Put in this way, the criterion for human health in relation to lead may seem to be unduly restricted, and would be so were it not for two considerations - namely, (1) that this criterion has withstood the test of time, thus far, and (2) that it is certainly correct in principle and can be corrected quantitatively, should there be any valid reason for so doing in the future.

The preceding discussion arises from the circumstance that the experimental work to which this report relates, has come very near to achieving its specific objective. It seems appropriate therefore to restate its basic physiological and clinical background, and to consolidate the position established thereby. Every effort will be made by ill-informed and apprehensive persons in this country and abroad to set a standard for the lead content of the ambient atmosphere at a number which will provide a factor of safety based on ignorance and apprehension, rather than on a realistic examination of the facts.

THE PRESENT EXPERIMENT

This experiment, as noted previously (full Progress Report made to USPHS

in February 1967; and in brief report to Melvin R. Plancey in a letter dated April 17, 1968), was initiated on October 10, 1966. Two men, Subject [redacted] and Subject [redacted], entered upon a regimen of exposure to airborne lead sesquioxide, within two parallel respiratory chambers, at the level of 20 micrograms in terms of lead, in the same state of subdivision as that used in the last preceding experiment (mean diameter 0.05 micron, with the maximum of 0.18 micron). The initial proportion of the time spent by the subjects within the chambers was 21 hours of the 168 hours of a full week, and the exposure continued so for 20 weeks. The further schedule involved corresponding periods of time (20 or 16 weeks, either of which appeared to be sufficient to elicit the maximum excretory response), in succession, at rates of 31.5, 42.0, 52.5, 63.0, and 73.5 hours per week.

Subject [redacted], as has been reported previously, found it advisable, with our approval, to discontinue his services in August of 1967. On finding out, in advance, that this would occur, the course of the experiment was modified somewhat in order to gain as much information as might be possible in the short time available. The results are being worked up for their contribution to the full account of the experiment, which will be completed by another man, Subject [redacted]. The latter was brought into the experiment as promptly as he could be found, tested, and accepted, and after a preliminary period of 24 weeks (sufficient to cover the two most different seasons of the year), he began his experimental schedule in one of the respiratory chambers, at about the point at which Subject [redacted] had ended, thereby maintaining the continuity of the experiment in a manner which seemed appropriate. Since the experience of Subject [redacted] was incomplete, while that of Subject [redacted], because of the delay occasioned by the preliminary observations, has not been sufficient, as yet, to yield definitive results, no further reference will be made to either in this report.

Subject [redacted] has now completed the schedule of exposure as described above. As of October 6, 1968, he had spent 73.5 hours per week for 16 weeks in the chamber. He will continue until the end of the calendar year, at least, on a regimen similar to that of the successive periods of exposure, except that he will have discontinued the experimental exposure to lead. In this manner, we shall be able to observe such decrease in his urinary output of lead as may occur. (It may be that some suggestion of a decrease will occur in the concentration of lead in his blood. See below.)

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It appeared, as early as the mid-year of 1967, that this subject was responding to the experimental exposure to lead by excreting a somewhat larger quantity of lead in his urine than he had previously. This trend continued throughout the remainder of the experimental exposure. The large volume of results has been but partially examined in detail, and there is a considerable amount of statistical work yet to be done. Nevertheless, by careful inspection, alone, of the grouped and plotted data obtained by the analysis of the urine and blood (along with a cursory glance at those of the food and feces), certain crude facts are evident. There was, indeed, a regular increase in the rate of the excretion of lead in the urine, following an initial significant increase at about the middle of the period during which the exposure was maintained (this time for 20 weeks) for 42 hours out of the 168 hours of the week. As nearly as can be ascertained without examining all of the pertinent data, and subjecting them to statistical analysis, Subject [redacted] failed to yield any demonstrable increase in his urinary excretion of lead during the 20 weeks of his exposure for 21 hours per week (12.5 percent of the time) to 20 micrograms of lead in his respired air. There is dubious evidence of some increase (too slight to be beyond the range of ordinary variability) during the latter half of the period of 16 weeks of exposure for 31.5 hours per week. The trend seems unmistakable from there on to the end of the experiment, despite certain irregularities in the rate of the increase from one period to the next, and so on. Seasonal effects have been observed in all of our experiments in which the magnitude of the exposure to lead has remained nearly constant throughout a year or more, and these have to be taken into account in this experiment, despite the primary trend.

The straight line drawn, by inspection alone, to represent the approximate slope of the incremental increase in the rate of the urinary excretion of lead, has been projected to the point which, hypothetically, is an expression of the effect

of breathing, continuously, ambient air containing 20 micrograms of lead in the form provided in the experiment. This line and its projection have not been determined by calculation, and therefore may not be regarded as precise, but the outcome of the projection, even as an approximation, points to the unacceptability of 20 micrograms as the threshold value for the ambient air. Thus, by extrapolation, it is predicted that, under the experimental conditions, the average lead content of the urine will have reached the high point of its normal range - that is the average output of lead per day in the urine will have shifted from somewhat less than 30 micrograms to approximately 80 micrograms, in about four and one-half years. After that time, the increase in the rate of excretion will continue at an equivalent rate, at least, and will be accompanied by a somewhat more slowly increasing concentration of lead in the blood, as a manifestation of an increase in the body burden of lead.

In contrast with the renal response to the experimental exposure, that represented by the concentration of lead in the blood during the conduct of the experiment is strikingly different. The behavior of the urine and the blood was apparently parallel during the period when the duration of the exposure was 42 hours per week; it continued so during the first half of the (next) period of 52.5 hours per week. But from this time on, after a fairly sharp decrease (actually a drop of only 7 micrograms - about 25 percent - per 100 grams of whole blood), there was no further consistent increase. Evidently the lead content of the "soft tissues" of the body sustained little or no further significant increase within the period of time represented in the experiment. (This phenomenon has been observed previously in connection with elevations of the absorption of lead at rates near the threshold of detection.) It would appear that the factor of the dilution of available lead (a few milligrams distributed into the kilograms of soft tissue) by reason of the excretion of lead in transit, augmented by the selective absorption of lead into the

skeleton, diminished effectively the rate of the accumulation of lead in the soft tissues.

DISCUSSION

The results of this experiment thus far are seemingly clear. Their interpretation in relation to the promulgation of a standard for the lead content of the atmosphere is not quite so simple, for it involves careful consideration of all of the information that can be gleaned from the experiments completed thus far, and from the further observations being made on companion Subject D.H. It is evident that the concentration of 20 micrograms of lead per cubic meter, in the chemical and physical form employed in these experiments, would not be tolerated indefinitely by the human population. Such respiratory exposure to lead, under existing conditions as to the lead content of the food and beverages in the human dietary, may be counted on to result in an increase in the body burden of lead in the average person, as compared with that of the present time. In all likelihood, as judged by earlier experimental results, this increase would be of an indefinitely progressive type, and while the consequences of such a slow accumulation of lead in the body, throughout the lifetime of the individual and that of a human population, are by no means predictable (since no such situation has ever been examined carefully in the course of human history), they can hardly fail to be potentially hazardous. No such hazard would be socially acceptable.

It has been suggested by Stopps, in view of the results of the experiments carried out at the level of 10 micrograms of lead (in the same form), and in the light of other considerations, that this level might well be considered to be the threshold value. This is not far, it seems, from the correct figure, but since, on the one hand, the experimental evidence does not apply to exposure at that level beyond 73.5 hours per week (slightly less than half the full time), one cannot be

certain, at this time, that no response, in the form of an increase in the rate of the urinary output of lead, will occur under the conditions of a more nearly continuous exposure at that level. It may well be feasible, however, to convert all of the degrees of severity of the respiratory exposure of all of the subjects involved in these experiments to a common and absolute basis for comparison, by expressing them as the product of time x concentration. By this means, one can develop a moving standard on a time base, representing freedom from hazard at a certain level of concentration in terms of the proportion of the total period of time. This, in itself, is an highly desirable achievement. Conversely, with time as a constant, at the level of 24 hours per day or 168 hours per week in the case of the ambient air, one can arrive, by calculation, at a level of concentration which is compatible with freedom from the accumulation of lead in the body.

Upon examining the data of all of the relevant experiments in a variety of ways, during the coming months of the continuation of the current experiment, one may be able to establish a satisfactory level on a firm base, or alternatively point the way to a decisive experiment, such as that now under contemplation by A.P.I. The latter should be so designed, in any case, as to serve this purpose, if it turns out to be feasible. It should be examined carefully from the latter viewpoint.

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