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Dear John:

I appreciate very much your having sent me a copy of the report of the Department of Public Health entitled, "Lead in the Environment and Its Effects on Humans." I have been very busy, as you may well expect, in undertaking to fulfill certain obligations, among them the APHA "Guide," and I have not completed my review of the report. I shall do so as soon as I can find the time. There are, however, certain statements and conceptions in certain of the Sections (Chapters?) which I have covered that seem to me to be open to comment or criticisms, and I pass some of the latter along at this time for what they may be worth. The principal Section to which I take certain exceptions is VII - Health Effects of Atmospheric Lead In California. I would suppose that John Goldsmith is responsible for this Section (and several others), but since no specific author is indicated and the report came from you, I direct my reply to you with a carbon copy, for such use as you may think desirable.

I would start out by suggesting that the title of this section is "loaded," although I would not suppose that this was intended to be. However, since any harmful effects are purely speculative, and the observed effects are in the realm of the physiological differentiation, to some extent, of the behavior of inhaled lead from that of ingested lead, I would regard this title as a bit less than realistic. However, this is of little moment.

It is not of small moment, however, that the first statement in A - Introduction, is a flat acceptance, as fact, that "lead is thoroughly implicated as a causative agent (without regard to quantity) in - - - liver and kidney damage (and in) mental retardation in children. The statements in the literature that these things are true, do not "thoroughly implicate" lead in those matters, and unless one qualifies the statement with the description of the nature of the lesions and the conditions under which they occur, the indication here is that the whole fabric of thiscontroversy has been fully digested and settled. Such is not the case. In the course of an acute intoxication, certainly the liver and kidney show evidence of reversible toxic change, but this is a far cry from the chronic effects that are the burden of the controversy, with particular respect to nephrit: I know of no pathogenic process that is regarded more dubiously by more competent clinical and pathological observers than that which relates to the production of chronic nephritis by lead.

It is true, without doubt, that children who have survived, after a bout of lead encephalopathy that has resulted in a greatly increased and persistent (for days) intracranial pressure, have suffered gross or focal brain damage and have given evidence thereafter of severe central nervous impairment. However, there is no

documentary evidence with which I am familiar that children who have had the milder forms of lead poisoning, including the lesser severe types of encephalopathy and have been found to be mentally retarded, were not mentally retarded before becoming ill from the ingestion of lead. Indeed, there is a distinct impression that the very young children that are afflicted with pica are abnormal mentally. I was inclined, as a pathologist, to the belief that the absorption of lead in the brain, within appropriate limits of concentration, would cause actual cellular damage. No one, however, has succeeded in finding evidence of damage in the brain that can be attributed to the specific effects of lead. It is of interest, in this connection, that the encephalopathy of tetraethyllead poisoning either results fatally or in complete recovery without sequelae. I do not maintain that, either here or in encephalopathy due to the absorption of inorganic lead, no damage occurs. I say, simply, that as of now there is no such evidence. We are dealing here with a post hoc, ergo propter hoc type of reasoning, both for and against this hypothesis. (Incidentally, Scheper's article in the Archives is cited as an authoritative reference as to the pathologic response to the absorption of tetraethyllead. I can think of no more unreliable source of information. He appeared in this Symposium as an uninvited substitute for John Zapf, and since he came as the spokesman for the Haskell Laboratory, I had to show him and John professional courtesy. The paper he submitted was an atrocious botch, which I had to edit very carefully in order to make it acceptable at all. I did so rather than stage a row in which I would have appeared to be an utter boor. I am sorry now that I didn't stage the row, and ask John Zapf to have the report prepared by others of his staff, since the article has been cited by several serious investigators, because of its setting. I consider the pathological descriptions which were his primary contribution to this experimental work, to be essentially worthless. The analytical work, done by others is reliable.)

As to the influence of lead on the synthesis of hemoglobin, it is hardly proper to refer to this in non-quantitative terms, as though it constituted a function of the absorption of the usual quantities of lead into the body. The evidence is sound, I believe, in indicating that this occurs only when the concentration of lead in the body is within a certain range. One should qualify the statement by including a clause to this effect. This might be regarded as an unduly critical attitude on my part, but it is an astonishing truth that many people who should know better, fail utterly to appreciate the importance of this principle of toxicology. This failure has been noteworthy in the present situation, and therefore it should be combated by suitable care on the part of critical writers.

Statements justifying the third paragraph of the Introduction can be found in the literature, as can very many another that is dubious. I have never found the slightest evidence that this is true, except under circumstances in which workmen have been removed from their primary job involving excessive exposure to lead (whether ill or not), and moved into, or returned back into, a position involving "less or little" exposure, after having suffered a bout of intoxication. Statements of this type have been made loosely in considerable profusion, by investigators who do not have the detailed information about the activities of the person or persons involved. It is rare, in our experience, that the concentration of lead in the soft tissues and in the blood (and bone marrow) remains at a sufficient level to give rise to abnormalities in the porphyrin metabolism after the lapse of 12 to 18 months. The concentration in

the bone, in particular in the dense structure of the shafts of long bones, remains elevated for a long time, because, no doubt, of the very slight vascularity of these structures. But there is no evidence that any type of disease (other than gross osteoporosis) or metabolic disturbance exercises any important influence on the rate of loss of lead therefrom. After the initial period of relatively rapid loss, over the period of a few or many months, dependent on the body burden and the time involved in acquiring it, the curve tapers off to an almost level line above and nearly parallel with the base line.

Perhaps the most serious error in the report, from the aspect of inadvertent misquotation (the reference is to the Harben Lectures) is found in the last paragraph of the Introduction (page 19), in which is the statement that "less than 0.08 milligram of lead per 100 grams of blood, and - - - - less than 0.15 milligram per liter (in the urine), are considered to be within 'normal' limits.[25]" I cannot understand how this statement can have been drawn from the Harben Lectures, in which the "normal" ranges in the blood and urine are defined with care, as is also the abnormal range that is unassociated with illness of any type. The threshold value above which, in our experience, all deviations from normal health and well being occur, is also stated precisely. This does not mean, of course, that the mere exceeding of this threshold results in illness or biochemical abnormality (although the latter is found to be the case not infrequently). Rather it only means that no sign of illness has been found below this level. I cannot accept the parenthetical remark "(even though blood and urine amino-levulinic acid levels may be high)." I do not believe this is true, for while our experience with this phenomenon is not nearly so extensive as that with the porphyrins, we have not seen such findings except in association with values at or above the threshold of danger in the blood. It may be that these phenomena continue for a time after the blood level decreases, following the cessation of exposure. I cannot be sure of this, one way or the other, since we have not followed the amino-levulinic acid long enough to cover the possibilities to my satisfaction. We shall continue, however, to investigate this matter. But my point is, that I would not make such a statement, even parenthetically. And in order to make my position quite clear, let me say that if this were true and it could be ascribed reasonably to the effects of lead, I would be entirely willing to regard it not as the forerunner of lead intoxication but as intoxication. The interference with a recognizably significant physiological function in my book, is intoxication, whether temporary or, so to speak, prodromal. So far as I can see, the establishment of a threshold value for lead in the blood (for physiological reasons, I do not consider the rate of the urinary excretion of lead to be anything like as precise as the concentration of lead in the blood), to which there is no exception, is a very crucial matter, since the blood, as a tissue which participates in the distinct pattern of the distribution of lead in the body, provides an excellent indication of the content of lead in the other soft tissues within reasonable limits of variability, and thereby permits one to estimate, with fair accuracy, the quantity of potentially "effective" lead in the body. I should point out right here that the statement on the next page (page 20, paragraph 2), that "blood - - - levels alone are not adequate criteria on which to base judgments of health effects in adults, and certainly not for children," is indeed a bold statement, in view of the evidence. Certainly the blood level does not signify injury or illness, but rather the danger of illness. It is clear here, however, that the latter is what is meant. It should be so stated, as by changing to some such clause as the following, - "judgments as to the likelihood of the onset of illness." It should have been

qualified, at least, by indicating that not all persons agree on this matter. The discussion of this matter, in the report, as well as the discussion of the "susceptibility of children" in relation to the concentration of lead in the blood, is not a well-balanced presentation of the issues. It is much too decisive and, so to speak "authoritative." It is based on acceptance of bits and pieces of data, and an insufficiently critical consideration of clinical and analytical procedures, rather than careful weighing of the evidence obtained in prolonged investigations. (I do not expect your people to take the publications of the Kettering Laboratory as the gospel, but I do have some right to expect that they be given appropriate weight in matters of this type. It is to be remembered that one point after another which has issued out of this source for the past thirty-odd years, has been confirmed subsequently, the reason being that we have never published prematurely or without making a clear differentiation between established fact and opinion. After a wealth of experience with lead poisoning in adults and infants, before and since the development and application of methods of analysis of high accuracy (so that comparable and precise results could be obtained over the period of years since about 1938), I have stated that we have not seen a case of lead poisoning in adults or infants, in our practice as a group, and in Cincinnati Hospitals, in which the concentration of lead in the blood, at the onset of illness, was less than 0.08 mg. per 100 grams. (We have given a satisfactory range to this same situation in the urine, but for various physiological reasons this must remain as a range, rather than a point.) I don't think this statement should be ignored in this discussion, for it represents the longest and almost certainly the most precise critique of this matter that is available. If and when we find exceptions to this, we shall be the first to publish them, but I shall continue to maintain that the "exceptions" found elsewhere must be examined critically, on analytical grounds, and on the further crucial issue of whether the blood was obtained and analysed at the right time or at some time appreciably later than the onset of the illness.

I might continue my critique of the report, with reference to various statements that relate to the physiological facts and their interpretation, through the several other sub-sections. I do not wish to do this, since by so doing I would convey the idea, which is not intended, that I consider the report to be more than slightly misleading. Actually, I recognize that a great deal of effort and concern for the truth has gone into the preparation of this part of the report. It is not surprising, nor in any sense reprehensible, that certain points which I consider to be crucial, scientifically and hygienically, have escaped the reviewer, or have been looked at with less concern or with a different viewpoint. Another example of this is the statement on page 21, paragraph 2, that, "nevertheless, the evidence suggests that when there is increased respiratory exposure over sufficiently long periods, there is increased lead storage." This is simply untrue* and it is a most unfortunate statement. One may suspect that this is true - namely, that under the conditions of intermittent exposure to lead, such as during the simulation of the duration of the ordinary occupational exposure, some increment of that absorbed finds its way into the skeleton, when the metabolic processes are slow, and that this does not get out of the skeleton and the body within the same general period of time, but the experimental evidence gives no clue to such an occurrence. On the other hand, when the exposure is continuous, and sufficient in quantity, there is direct and valid evidence of accumulation of lead in the body. It is in matters of this sort, which from the physiological (and also practical) point of view are vital to our understanding of the behavior of lead,

* as it has been stated,

that the data have not been examined with sufficient care, and statements have been made somewhat loosely. In other words, there has not been a clear distinction between the presentation of the facts derived from the data, and their interpretation into opinion. One cannot properly object to the opinions, whether he agrees or disagrees, but he must object to the distortion, so to speak, although unwitting, of the facts supported by data. The other feature of this same situation is the critical acceptance or rejection of data. One recognizes, of course, that it is virtually impossible to do this accurately without direct and precise inside information.

I shall not continue the detailed critique which I began, since, I believe, I have illustrated my attitude sufficiently. This is a difficult pathway to tread without appearing to be unduly opinionated and carpingly critical. I seem to have gained something of a reputation of the latter type in certain circles recently, and it is not of the type that I would choose to cultivate. Consequently, it is time for me to get back to my own contributions to the literature of this field, and to the balance and care that are required to have them stand the test of time. I am indeed impressed with the necessity of assembling, studying, appraising and publishing a much greater volume and variety of information than has yet been done.

Sincerely yours,

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Occupational Medicine

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