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Dear John:

In reply to your questions and criticisms, real or implied, about the report which I sent you, let me say, first, that no attempt is made in this paper to describe the methodology of this piece of the general investigation of the metabolism of lead in the human organism. The same general group of methods has been employed from the first since it has been our intention to make as clean a sweep of the clinical and biological examinations as might seem to be feasible and useful, under "control" and "test" conditions, so as to obtain basic information which is not available otherwise. The results in this instance have been presented briefly and pertinently, that is, in representation of the specific issue or issues under examination.

To answer your specific question with reference to the porphyrins, the answer is "yes." The same is true of delta-amino-levulinic acid, from the time we became convinced of the pertinence of this phenomenon, as being, apparently, the earliest aberration in the hemoglobin cycle to be affected by sufficient quantities of lead.

Of course, in the present experiments, which are being conducted at levels of exposure to lead that are intended to be barely adequate to induce any physiological response, nothing by way of an effect of such types is to be expected, since we have never observed any such effects at considerably higher levels of exposure. However, I repeat that our purpose has been to observe, without modification of our experimental procedures to comply with assumptions. In the current experiments, as I indicated, these results have been scanned and are innocent. They will be dealt with statistically, however, so as to discover and define the types and limits of variability.

Likewise, the data for the control periods of all of the Figures are available and are pertinent, of course, to the extent of their portrayal of the variability under these conditions.

The subjects in the last of these experiments were non smokers. One of those now under investigation - in the extension of the experiment at a higher level - will be followed during a period of smoking following a period (months) of not smoking, just as a side feature of the main issue, (that is, if we decide to test this, after watching the stability of his metabolic pattern for a sufficient period of time). I am frank to say that I consider this a necessary experimental variable to examine, at this time, because the question has been raised and the evidence now available is insufficient to indicate its actual and relative magnitude. I may be wrong, of course, and that is reason enough to put the

question to rigid test, but I do not expect it to turn out to be of any practical significance, when examined on the background of other factors. Perhaps some special experiment will be required to answer this question.

With respect to our other potential disagreement - I speak of it as potential for the reason that we are concerned with an issue which you cannot prove nor can I disprove - that of the significance of the minor differences between Philadelphia and Los Angeles, with respect to the concentration of lead in the blood of the populations investigated. Obviously, if you find a general environmental situation in which such differences are obviously significant, as for example, many explored occupational situations, there is no real doubt as to the facts. However, in view of the magnitude of the factor of ingested lead in the general population, and the unknown elements in this that may be local or regional, it is stretching probability well beyond any valid basis to conclude that the modest variation in the lead content of the air in the regions indicated is responsible. There can be no doubt that the importance of the factor of air-borne lead could be demonstrated if it were the sole variable, but it may well be - and I happen to believe that this is the case - too small to be identified, considering the magnitude and the variability of the ingested lead. You may think, as others have, that there is no reason, ipso facto, for believing that the dietary characteristics of Philadelphia and Los Angeles should differ significantly. I'm afraid that this is no argument at all, and that I may just as well believe the opposite, on a better background of experience. I have not said that those differences are of no moment, but, rather, have said that I am not able to interpret them. Of one thing, I am certain. There were (and are) certain very slight systematic differences between our analytical results and those of the others engaged in this survey, ours being generally somewhat higher. The difference is so slight as to be of significance only for comparative purposes, but here again considerable caution must be exercised in ascribing significance to these differences.

Various persons have believed that I have weighed our own findings and other evidential data in a balance that has been tilted toward the benefit of those who have provided the funds in support of our work. This opinion has been held somewhat covertly in certain circles and has been badly expressed, of late, by certain others. I cannot, of course, defend myself, against those who deprecate in any degree my professional and social sensitivity, but I would ask of all concerned whether the record of my life's work and professional performance has ever, in any way, given evidence of such irresponsibility. If, I speak in this manner to you, as I would not so speak to those who are less cautious in their judgment, it is because, by implication, you have questioned or deplored the absence of certain bits of information, or the trend of certain tentative statements of mine in a brief progress report that was designed not to transmit details, but only to reveal the design of the experiments and to justify their continuation. These specific experiments have followed the general design described in considerable detail years ago, involving the highest precision and scope attainable (by ourselves, on the basis of our knowledge and experience), physiologically and clinically. This Laboratory will, I hope, be able to continue these observations, as designed originally, and improved upon or refined as circumstances require, to the end of elucidating the facts that are most urgently required for human benefit, as these appear to those in charge. It will not be possible to examine all of the minor issues that would result in impeding the general program, since these experiments, from their lengthy and costly nature in pursuit of a major variable must not deviate in such manner as to obscure the primary issue.

You may conclude, from the foregoing remarks, that I react with undue concern to questions or comments such as yours, which have occurred to you, purely out of a direct and natural spirit of inquiry. Perhaps that is the case. If so, I have had ample reason for being sensitized recently. But, I have lived long enough, perhaps, to discount passing irritations, and to feel fairly secure in my own conscience and in the confidence of my most intimate professional associates. I attribute my reaction, to certain of your remarks, perhaps unfairly, to a slightly partisan attitude that would suggest that, as a public servant you must be more careful in matters of human safety and well-being than I. For example, you are quick to deny the existence of the "built in" factor or factors of safety which I consider to be present in all likelihood. That such a factor (or factors exist) is, I think, without question. The question still remains, however, as to their significance and as to whether there are offsetting factors. These questions are subject to further, feasible inquiry. As to my bold statement above, there is evidence that there are particles of lead-containing material in the air that will be captured in current sampling devices and also in the upper respiratory tract. To the extent that this occurs, the lead in the ambient atmosphere, will not be as well retained in the lung and absorbed as will the same quantity of lead in our respiratory chambers. This factor may well be offset by the greater respiratory activity of certain groups of persons in the general population (with exertion), but this possibility remains to be investigated. We have not, as yet, investigated the pulmonary retention of lead by healthy persons at various levels of activity, and one is not privileged to make assumptions about this matter.

Finally, as to your last sentence, I am aware of the public anxiety. I consider it most unfortunate that we are compelled to take this into account in our investigation, of this matter, for it disturbs calm judgment. However, I am not responsible for this situation, nor have I contributed to it. I have been investigating this matter as vigorously and as knowingly as I have been capable of doing, for forty years, and have been reporting our findings, not to the press, but to those officially and professionally responsible for the public health. During this period of time, our group has devoted more careful thought and effort to the means of eliciting the pertinent facts than all other people combined. I have somewhat mixed feelings, therefore, about those who have recognized and been concerned about this problem only very lately, and who seem to believe that they have discovered something new and threatening beyond previous evidence and judgment. I welcome the bona fide and pertinent investigations of others, being reasonably confident that they will verify our own findings, but being quite prepared to learn some new facts arising out of altered conditions or new methods of investigation.

But so much for all of this. I trust that you will not consider it necessary to spare my "delicate" feelings in further correspondence or discussion. I do believe, however, that, by speaking out with frankness, I may have cleared the atmosphere somewhat, while manifesting my confidence that what I have said will be received in good faith.

Sincerely yours,

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