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Dear David:

I must ask you to forgive me for being so tardy in my reply to your letter of August 27. This was not neglect, but rather the result of my being out of my office on a series of jobs that couldn't be sidestepped.

Your interest in the behavior of tetraethyl lead is quite enough to excite a response, and I'll give you as much information as I can. Unfortunately, little of the work we have done on this compound has been published, and the supply of reprints of our published articles has been exhausted long since, because of the concern of a good many people, mostly health authorities and medical men connected with the petroleum industry in various parts of the world. I'll send you what I can, and refer you to a few other articles which you will have no difficulty in consulting.

Actually the intermediary metabolism of tetraethyl lead has been worked out only meagerly. Our efforts have been exerted in other directions, those of determining, by appropriately coordinated clinical and analytical work (on blood and urine, and on the tissues of deceased victims of intoxication), diagnostic and prognostic criteria, and, more importantly, criteria for differentiating safe from dangerous exposure in terms of the excretory rates of individuals exposed to known levels of concentration over varying periods of time. These tasks having been accomplished, we have now turned to the problems of therapy and intermediary metabolism. The latter aspects of the matter are under study from the viewpoint of their vulnerability to attack by the methods of radioactive tracing. I hope we shall be able to find the means of determining what happens.

At present what we know may be stated rather briefly. Tetraethyl lead is readily absorbed as vapor via the lung, and as liquid via the skin. Obviously it can be swallowed and partially (poorly) absorbed in the alimentary tract. The lethal dosages for certain experimental animals are known, but these are of little interest. Men also have

been poisoned, some fatally, via each of these avenues of absorption, and by the combination of them.

The pattern of the distribution of lead in the tissues of animals and men initially and subsequently is known in a sufficiently descriptive manner, and the accompanying pathology (which is not at all specific) is fairly clear. Excretion of lead occurs rapidly after absorption, some via the alimentary tract, but chiefly via the urine, the rate of excretion being very much greater than that which occurs following the absorption of more or less corresponding quantities of lead in inorganic form. The metabolic decomposition of the compound occurs, but the course and the nature of the products are unknown except by conjecture based on the decomposition of the compound in vitro. That is, the compound goes through a series of steps, illustrated simply below, ending in an inorganic lead compound, while the reaction is readily reversible in all steps except the last, under suitable conditions, for example, during steam distillation; -

$$Pb(Et)_4 + R\begin{pmatrix}(OH)\\(Cl)\\(etc.)\end{pmatrix} \rightleftarrows Pb(Et)_3R \rightleftarrows Pb(Et)_2R_2 \rightleftarrows Pb(Et)R_3 \rightarrow PbR_2.$$

Initially tetraethyl lead distributes itself in the tissues after the manner of a fat-soluble material, but by the end of about 14 days in the rabbit, the residue, after considerable loss by excretion from the body, is distributed largely as it would be if it were water soluble. This might well occur if the principal metabolite were tri-, di- or mono-ethyl compounds, these being relatively soluble in water as contrasted with tetraethyl lead, and being crystalline solids rather than the oily liquid which is tetraethyl lead. The main decomposition product, however, is not an inorganic compound of lead, since it is evident that when the source of absorbed lead is tetraethyl lead the quantitative relationship between the concentration of lead in the blood and that in the urine are of a totally different order of magnitude than they are when the source of absorption is inorganic lead.

In this connection I am not sure what you mean when you say that the rapid breakdown of tetraethyl lead results in some combination of lead and phosphorus. If you are speaking of organic breakdown and regrouping in the laboratory, using tetraethyl lead as a reagent, I can follow you, but if you are talking of a biochemical phenomenon, I know of no evidence of such a reaction. This does not insure that I have not missed something in the literature, but I am not familiar with any evidence from any source which indicates that lead compounds exist in the body in combination with phosphorus, except perhaps (by implication) in the skeleton, when lead, like uranium,

probably competes with calcium in forming a phosphate.

Under ordinary circumstances the lead in the circulation is within (or perhaps on the surface of, but this I doubt) the erythrocyte to the extent of 95 to 98% of that available. The amount in the plasma is minute, so minute indeed as to be beyond the present limits of analytical precision in its variability from time to time under varying degrees of absorption of lead. The nature of the compound in the erythrocyte is purely conjectural, but it is capable of being removed slowly from the erythrocytes of shed blood, by repeated washing with saline, and precipitously, in vivo, by the administration of BAL, in which case the urinary lead concentration sky-rockets, while the plasma concentration remains unchanged (within the limits of analytical error). Some of our data are available in an article I am sending. Other data are unpublished.

Your statement that the source of the lead in the circulation is indeterminable is essentially incorrect, although it is not possible to define the source of any specific molecule, and your suggestion that any part of that found in the body under ordinary circumstances might be tetraethyl lead (or am I incorrect in interpreting your comment?) is unrealistic. Only a very few persons in the population are, or have ever been, exposed to tetraethyl lead, in other than an highly theoretical sense, and the synthesis of tetraethyl lead in the body can be dismissed as most unlikely. The balance experiments which we have carried out here demonstrated that the lead in the blood is being derived constantly from three general sources, the relative representation from each source depending upon the relative quantities involved under different circumstances - i.e. the stream of absorption from the alimentary tract, the minute stream being absorbed from the lungs of the ordinary individual (this being greater under conditions of occupational exposure), and the stream from the tissues, including the skeleton. The lead in the blood is being lost constantly to the tissues and to the urine, there being a state of continually disturbed but approximately balanced equilibrium, because of the very great uniformity (within a range of recognized variability) in the order of magnitude of the casual exposure to lead on the part of the ordinary (average or normal) individual (the food and drink provide about 0.3 mg. of lead per day, and the air breathed daily contains 0.03 to 0.05 mg., of which an undeterminate amount, possibly a third, is absorbed).

You are quite right that lead poisoning is a significant medical problem in industry, because of its frequency. Therapeutically, however, it is only a minor problem among many other medical problems, since (1) it is a wholly preventable disease in industry, and (2) most of the cases are self-limited, and only temporarily disabling. Do not misunderstand me, I am not minimizing the

importance of a disagreeable type of illness, or its therapy, but our lack of adequate therapy is of greatest significance, in view of the ease of the prevention and the relative mildness of the disease as it occurs in industry, in those situations in which there is a high incidence of fatal or seriously disabling cases - namely, the rare case of encephalopathy in the adult, and the much less rare case of encephalopathy in the infant. (I exclude cases of TEL poisoning, since these are rare.) The high incidence of lead poisoning in industry is a disgrace, and is wholly a matterof ignorance and carelessness. We know the limits of safety and danger in well defined physiological terms, and in wise American industrial organizations, the disease does not exist, except as a rare accident. Control then is available, and nothing new is required, except that if there were less expensive procedures, they would find more prompt and widespread acceptance. Diagnosis is also relatively simple. (I enclose an article which was written by request for a special purpose, and which, therefore, is not actually adequate.) On the other hand, the actual mechanism of intoxication is conjectural, and certain aspects of the metabolism of ordinary lead compounds are yet to be clarified, while the intermediary and final steps in the fate of tetraethyl lead within the body are unknown.

I am sending two articles which describe, incompletely, our balance experiments, since these may interest you if you have not seen them. Others are under way at present, specifically those concerned with the fate of a given type of lead compound, in a specified state of subdivision and in known concentration in the atmosphere breathed by the normal human subject. Data are available, but will not be published for some time, on a human subject who has been subjected to the inhalation of lead oxide in the air in particles the median size of which is 0.05 micron (with a narrow range of size) in the concentration of 0.075 mg. per cubic meter, for 7 hours per day on five days per week for nearly 2 years. The data on pulmonary retention, and on the total intake and output of lead during the period, permit one to calculate the quantity absorbed, the quantity excreted, and the quantity retained in the body during this experimental period, with a small margin of error. Experiments planned for the future will be concerned with variations in the condition of exposure with respect to particle size, type of lead compound, and concentration in the atmosphere, each condition being set up and maintained over a long period of time (within the limits of safety) during which the pulmonary retention, the absorption from all sources, and the excretion, will be followed.

So much for all of this. I have made up in volume what I lacked in promptness, and in all probability have only demonstrated to you that the examination of the problem, tetraethyl lead, as so far accomplished, will give you little help in your work.

We visited with your mother and father on Sunday, and since Katy is now at home for some weeks, it was something of a reunion.

I hope that you are finding your new work and surroundings stimulating and satisfying.

It was good to hear from you, and if you write again, I shall try to reply with less lag.

With best regards,

Sincerely yours,

Robert A. Kehoe, M. D.

RAK ef

Enc.

On the Toxicity of Tetraethyl Lead and Inorganic Lead Salts - Kehoe
Tetraethyl Lead Intoxication and Poisoning by Related Compounds of Lead - Machle
An Appraisal of the Lead Hazards Associated with the Distribution and Use of Gasoline Containing Tetraethyl Lead. III The Occupational Lead Exposure of Filling Station Attendants and Garage Mechanics - Kehoe, Thamann and Cholak
The Plasma-Cell Partition of Blood Lead - Bambach, Kehoe and Logan
Experimental Studies on the Ingestion of Lead Compounds - Kehoe, Cholak, Hubbard, Bambach, McNary and Story
Exposure to Lead - Kehoe
A Critical Appraisal of Current Practices in the Clinical Diagnosis of Lead Intoxication - Kehoe
Influence of Dithiopropanol (BAL) on Human Lead Metabolism - Ryder, Cholak and Kehoe

REFERENCES

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Mason, E. C.: The Pharmacologic Action of Lead in Organic Combustion: J. Lab. and Clin. Med.: 6: 427, 1921

Eldridge, W. A.: A Study of the Toxicity of Lead Tetraehtyl: C.W.S., Edgewood Arsenal, Med. Res. Div. Report 29 (1924)

Kehoe, R. A. and Thamann: The Behavior of Lead in the Animal Organism II. Tetraethyl Lead: Am. J. Hyg. 13: 478, 1931* (*)

* No longer available.

None of the above will be of much help in relation to the possible chemical interaction of tetraethyl lead. From the experimental viewpoint they merely point the way to further work. The chemistry of the organic lead compounds is another matter, and if you want references I can supply them. However, they do not advance our biochemical knowledge to any very considerable extent.

(*) Extensive but unpublished data on the lead excretion in TEL poisoning, and on the distribution of lead in the organs of fatally poisoned persons are available if you wish to see them.