

Dr. Kehoe

January 7, 1936

Mr. P. C. Phillips, Secretary
International Apple Association
1102 Mercantile Building
Rochester, New York

Dear Mr. Phillips:

Professor Pickett has asked me to write to you about the lead toxicity experiment that we hope to start at the Kettering Laboratory of Applied Physiology at the University of Cincinnati. You and Professor Pickett and I talked this experiment over in Washington, and I spoke about it to Dr. Campbell in your presence. It is described, although not at all in detail, in the paper that I gave at Hartford, two copies of which I sent you. You therefore know the purpose of the experiment and Dr. Campbell's attitude, which is that he is anxious to have sound scientific evidence, including evidence from the source that we propose. He made that reply, you will recall, when I told him that we wanted his preliminary blessing on this experiment. I will, of course, be glad to send you more detailed information about the experiment itself if you want it.

In the first place, I should explain the reason for physiological experimentation. You might ask me why the consumption, by millions of people, of millions of apples carrying lead arsenate in amounts above the tolerance without observed ill effect was not physiological experimentation on a magnificent scale, and I would not be able to give you a very good answer. However, I am going to make the attempt. It is because it is thought by certain physiologists that there may be chronic effects which may not be recognized, and the fact that there may be is sufficient. The courts have ruled that the possibility is enough (in the bleached flour case cited on page 2 of my paper) and physiologists have testified that there is such a possibility. The sale and use of tetra-ethyl lead in gasoline is permitted by the Federal Government, however, after an extensive laboratory and field investigation under the direction of the United States Public Health Service had failed to find actual instances of injury. To quote from the report of the study, published in Public Health Bulletin 163, Treasury Department, United States Public Health Service, no. 109, 110, 1926, "In the regions in which ethyl gasoline has been used to the greatest extent for a period of between two and three years no definite cases have been discovered of recognizable lead poisoning or other diseases resulting from the use of ethyl gasoline. In view of these conclusions (which include the result of a study of automobile users and garage employees) your committee begs to

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report that in their opinion there are at present no good grounds for prohibiting the use of ethyl gasoline of the composition specified as motor fuel, provided that its distribution and use is controlled by proper regulations." (The regulations apply to plants which manufacture tetra-ethyl lead and blend it with gasoline.) The best reason for a physiological investigation is the fact that the physiologists and toxicologists who have been, in the final analysis, responsible for the lead tolerance, recognize only controlled laboratory work, of a physiological nature. The experiments must be on humans. Physiological facts can be developed from work with animals, but such facts cannot be used to set a definite tolerance because animals can be expected to have a different susceptibility, although they may react the same qualitatively. Also, an effort should be made by a field study to find out whether or not chronic effects ever appear among people who eat lead arsenate covered apples in amounts considerably above the tolerance. In that way, we ought to be able to make use of an opportunity that is now neglected and to use it in a thorough scientific way. Such a study would be a part of the experiment, and would require a physiologist.

A great deal of physiological and biochemical work has been done on lead in very recent years. Of 38 scientific articles referred to in a recent paper by Sub, of Harvard University, on the biochemical behavior of lead in the body, nine appeared in 1931, six in 1932, and eight in 1933. The subject is therefore very live and physiologically. Current conceptions depend to a large extent on work done at Harvard, and at the Kettering Laboratory. A summary of some of the important facts follows: Lead is present in minute amounts in the normal diet and excreted in quantities which are, in the long run, equivalent. Under normal circumstances, lead is not cumulative except that very small amounts are normally stored in the bones with increasing age. A large part of the lead in the diet probably passes through the body unabsorbed; inhaled lead is much more dangerous. When comparatively large amounts of lead are ingested or inhaled, which is likely to happen in certain industries, accumulation takes place. Storage is in the bones, along with calcium. After removal from exposure, (for example, when a factory worker exposed to white lead dust leaves the factory) stored lead is normally slowly excreted, also along with calcium. If a metabolic upset results in the rapid liberation of large amounts of stored lead, very deleterious effects may result. The rate of liberation of lead from the bones can be regulated, however, by regulating the supply of calcium in the diet or blood, which is the basis of medical treatment. The amount of lead arsenate or, as a matter of fact, of any other form of lead, that can be ingested before storage takes place is unknown. Several factors probably enter, one of which is the chemical and physical nature of the lead compound itself.

In this problem it is necessary to take into consideration the question of whether or not the occasional or prolonged ingestion of lead, even below the point of accumulation, is injurious. This also is physiological. It can be said, however, that the absorption of lead in minute quantities is natural and

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unavoidable, and that it has always occurred even among the animals from which man has evolved. It takes place, as workers in the Kettering Laboratory have shown, even in the most primitive environments. As they have expressed it, it is unavoidable on a lead bearing planet. I suppose that one could argue that the body has become adjusted.

Perhaps I did not explain to you that the Kettering Laboratory was established as a part of the medical college of the University of Cincinnati by General Motors and DuPonts, especially to study lead toxicity physiologically. General Motors makes tetra-ethyl lead, used in ethyl gasoline, and DuPonts make many lead products. They are therefore greatly concerned with the hygienic effects of lead in many forms. (You may be interested to know that an effort is now being made to pass laws requiring paint manufacturers to incorporate a lead antidote in paints. The legislation is pushed by the firms making the supposed antidote, and they have been successful in one legislature, in Canada I believe.)

The Kettering Laboratory has studied lead toxicity with humans for years, has published its results in first class journals, and will undertake our problem, which they consider very important, if we will pay for the cost of the analyses, food, etc. We would not be charged for overhead, e.g. for the use of the building, heat, and light, or for direction. It is remarkable, to say the least, that there is such a laboratory all equipped with apparatus, staff, medical connection, and experience, for this problem, all ready to work on it. Most of the difficulty and expense of conducting the investigation is thereby obviated. It is an opportunity that should not be lost. I am very confident that all of the people who visited the laboratory with me in September agree with me entirely in this statement. These people were: Dr. Bourne Greene; Professor R. H. Freybill, State Chemist of Indiana; Dr. T. H. Rowlett, Associate Horticulturist; Professor W. J. Walbert, Professor of Horticulture. Incidentally, I derived my first information that such an opportunity existed from Professor Roger Adams, Head of the Department of Chemistry here, and President of the American Chemical Society. The laboratory is first class, as you could expect such a laboratory to be. I hope that you will be able to visit it. (If you take a bus or car from downtown Cincinnati, get off at the Jewish Hospital. The laboratory occupies a building just back of the Medical College building which is nearby. The director is Dr. R. A. Kehoe, who will be there until about January 18, when he will leave for a month in Europe.)

I should especially emphasize in this letter the fact that the only way to determine the toxicity of lead arsenate on apples is to work with humans, feeding them lead arsenate on apples. This is the only way that we can hope to secure the facts about this particular material which is what we are all after. By we I mean the fruit growers, the horticulturist, the entomologist, the enforcement official, the manufacturer of insecticides and of other materials that are allied, directly or indirectly, with deciduous fruits and, of course, the consumer. Also, the Kettering Laboratory

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is the only laboratory in the country equipped to handle the experiment on the scale that would be required. The first object would be to see how much lead arsenate could be fed without accumulation or clinical effects. For the purpose, lead arsenate would be fed in amounts in the neighborhood of the tolerance, and in multiples of that amount. Because of the number of things that would have to be studied, such as individual susceptibility, we should count on running the experiment three years. At least \$20,000 a year should be available.

As you know, Professor Pickett, Mr. Fraser and I visited Mr. L. S. Hitchner, President of the Agricultural Insecticide and Fungicide Association. His address is 245 Madison Avenue, New York City. Mr. Hitchner was interested and wanted material to send to members of his organization before their next meeting. I sent him 25 copies of my paper and a brief description of the experiment for him to copy and send around.

Professor Pickett and I also visited Mr. Robert F. Wilson, of the Associated Grocery Manufacturers of America, 205 East 42nd Street, New York. Mr. Wilson says that their industry is greatly interested in lead in general. I promised to send him material for Mr. Willis, who has charge of the organization, and who was out at the time. The organization includes General Foods, etc.

We talked at length to Mr. F. V. Wernser, Secretary of Lead Industries Association, 420 Lexington Avenue, New York. They, of course, are greatly interested.

I think that when you are in New York a visit from you to any of these men would help very materially in securing financial support for the project, but I am wondering if there should not be some preliminary understanding between you and Professor Pickett so that you will not be in the dark about any part of the proposed financial set-up. It may be that he has already written to you about this. You probably have other suggestions also, about financing the work.

Yours very truly,

W. A. R. W.

Chief in Entomological
Physiology

WAR:MH

cc: Kraybill Talbert
Overley Pickett
Greene Kehoe
Howlett Ware

Blair