

December 2, 1947

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Dear Dodds:

I have been slow in replying to your letter of October 20, for I have been hard pressed. I shall do my best, however, to give you all the information I can. Incidentally Davison will be able to tell you a great deal about our set-up, and I shall also explain to him in some detail the manner in which we work so that he may be able to answer any questions that are not contained in this letter.

Our observations on industrial chemicals are rather varied in their methodology and scope. I shall go from the simplest to the more complicated.

1. It sometimes happens that one merely wishes to determine the relative hazards of a series of compounds that are either related chemically or that are being considered for a given purpose. Which is the least dangerous? This resolves itself into a determination of their immediate toxicity, and their potential hazards under the conditions of use. We usually start out by determining the lethal dose administered orally. This relates the compound to many others that we have examined in a similar way. Then we determine whether or not the material is absorbed through the skin at a rate sufficient to produce illness or death. There are various procedures for this purpose, and I shall not go into detail at this time. The matter of solvent, the concentration in solvent, etc., etc., are matters of consequence. In the course of these observations the extent of damage to the skin is observed incidentally. This is also of considerable importance for obvious practical reasons. If the material is volatile, or if it is likely to be vaporized under the conditions of its use, one must determine the acute toxicity, at least in a preliminary way, by this means.

2. Assuming that a selection of a material or materials has been made, and that the material is not harmless, it then becomes necessary to determine whether it tends to accumulate in the body, or whether the injury, if any, tends to be additive. This involves repetitive administration of the material by one of several means, the choice of which depends in large part on practical considerations, both in relation to the use of the material, and to the ease of experimental procedures. In the course of these observations one would usually make some effort to determine the mode of action, the fate of the material in the body, its metabolism, and its distribution in the

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tissues. The extent of this work will depend upon a number of considerations which I need not go into because they are self evident. During such observations the examination of the animals as to their behavior, and as to the gross and microscopic pathology, can best be made, and in general should be made. More and more one will find that his failure to do the things that best promote good experimentation at this time will subsequently be found to be wasteful, in that the work or some of it will have to be repeated in order to fill any gaps in the necessary information.

3. Finally comes the business of determining the conditions of safety. This may involve prolonged feeding experiments during which every effort is made to detect metabolic disturbances, nutritional difficulties, and finally pathologic changes. A sufficient number of animals must be used to provide for statistical handling of the data, and it is quite apparent that enough observations must be made on individual animals to provide the background for such statistical work. I am sure you will appreciate the difficulties here, but I set the example of an experiment in which nothing much is found but retardment of growth. The interpretation of such an outcome can be made properly only if one can exclude chance abnormalities in the behavior of individual animals. Any experiment which extends over 18 to 24 months provides many opportunities for an introduction of variables into one group or another, and therefore rigid control is absolutely necessary. All of this is admittedly costly.

The requirements of safety may necessitate careful inhalation experiments. These are done with smaller numbers of animals than are required in feeding experiments, but there are great difficulties which must be overcome. I believe that the best way for us to illustrate our handling of these problems is by providing you with reprints of a number of articles in which these matters have been dealt with by various means. I hold no brief for perfection and completeness of our work in this regard. Many things could be done beyond what we have done. We always study the gross and microscopic pathology during such observations. Almost always we make a concerted effort to find out something about the metabolism of the material being inhaled. You will realize, of course, that the whole armamentarium of the physiological and pharmacological laboratory can be applied in the study of these animals from time to time. We merely pick the high spots in the hope of keeping our work and our expenditures within finite limits.

In the conduct of this work we try to set up a team composed usually of the principal investigator and one or more assistants to do the routine analyses, to handle the animals and to keep the records straight. We have a pool, so to speak, of special technicians who make observations on the hematology, the pathology, and on special metabolic phenomena. Our group, representing the principals of our different sub-departments, meet together to plan an experiment. We outline in advance what is to be done, and the principal investigator adheres to this plan as closely as possible, but not slavishly. In this way we

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are enabled to assign adequate staff to a given job and to estimate the probable expenditures within reasonable limits. The latter is necessary, since the sponsor knows that he can afford to investigate a given material only to some extent which is determined by the potentialities of the product commercially. Failure to appreciate this situation and to allow for it can result in considerable friction and misunderstanding between sponsors and the Laboratory. From time to time our estimates have not been very accurate, and especially during the war we sometimes allowed a problem to run along without keeping close track of it, with the result that the expenditures went far beyond our estimates. I mention this only because it is of considerable practical importance.

I shall send you under separate cover a number of reprints. They should have come to you anyhow. I should appreciate it very much if you would reciprocate. I am especially interested in knowing whether you have been able to carry out observations on normal British subjects, which would tell us something of the magnitude of the normal intake and output of lead and/or other metals. I have gone over some of the results from the Northwich plant. These indicate that the lead content of the feces of men who are starting in their work is rather unusually high as judged by American standards. This needs looking into, and I wonder if you have any information on it. I think it likely that Davison will want to discuss this matter with you.

My present plans do not suggest that I will be in the United Kingdom in the near future. In fact I am so swamped with work that I hardly see how I could go anywhere, unless it were quite urgent. Needless to say I should be very happy to see you anytime you can arrange to come over. All I can wish for myself is that I have a long undisturbed period right here in Cincinnati. You will be interested in the development of our program for the training of industrial physicians. I am sending you bulletins which briefly outline our program, and would appreciate it if you would see that they get into the hands of a number of my good friends and any of your colleagues whom you may wish to hand them to. Davison can tell you much more about this than appears in the bulletins. Please convey my kindest regards to Mrs. Dodds and to any of my friends whom you may see.

With kindest regards,

Sincerely yours,

Robert A. Kehoe, M. D.

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