April 13, 1936

Dr. L. Edward Gaul
100 West 59th Street
New York City
New York

Dear Dr. Gaul:

I have taken the time and trouble to criticize in detail the outline you sent me. I have done this because I wished to put my experience and judgment at your disposal for this purpose, so far as possible. You will recognize that my criticisms are somewhat pointed in their implications, but actually my opinion is even more unfavorable than my comments on the outline indicate. At the risk of giving offence (which I do not intend) I wish to say in this letter what it hardly seemed proper to say in connection with the outline if I were to comply with your request. I realize also that the type of advice I am about to offer is but rarely taken, but I offer it because the occasion seems to justify it.

The scope of the work proposed in the outline implies that you and your associates have at your disposal a great deal of time and a considerable sum of money. Presumably, also, you have able talent within your group. It appears from the character of the outline that you are not sufficiently familiar with what has been done, and with what is known on the subject; that, in fact, you are not quite aware of the character of the problems which await solution. It would be most unfortunate if for this reason the expenditure of your time, funds and talent were to accomplish little or nothing beyond the confirmation of what is already known, for that would be largely a waste of your resources. As one fairly familiar with the literature of this subject and somewhat experienced in both the clinical and experimental aspects of the field, I feel quite sure that the problems which need investigation - and these are numerous and important - do not lie in the direction indicated by your proposed program. May I suggest, therefore, that a careful and adequate study of the literature be made before you embark upon the investigative work. You will then be prepared to plan your observations in such a way as to obtain some of the information of which we are greatly in need.

KE 0001435

Dr. L. E. Gaul

If the above suggestion sounds to you like an indirect means of administering a sharp rebuke, I beg of you to consider whether it is probable that I would have gone to so much trouble for such a purpose.

Very truly yours,

RAK:is

Robert A. Kehoe, M.D.

KE 0001436

Comments on a Tentative Outline for a Study on Lead

I Purpose of the Investigation

1. The expressed purpose is somewhat more ambitious than seems feasible, since it is highly improbable that any one test can prove the responsibility of lead for the production of symptoms. It has been shown that extensive lead absorption may be unproductive of symptoms. All one can prove by abnormal lead findings (analytical means) is that lead has been absorbed in such quantities as to be a plausible factor in the production of illness. The characteristics of the illness, and the satisfactory elimination of other etiological factors, constitute the means of proof.

On the other hand, negative lead findings must be interpreted in relation to the history of exposure i.e. the interval elapsing between the cessation of exposure and the collection of materials for analysis.

(a) This point can be answered without resort to further experimentation. We have recently carried out some check analyses with various laboratories in this country and abroad, which show that there are several modifications of chemical and colorimetric methods which will check each other in dealing with known quantities of lead with a very minute, and clinically insignificant variation. The details of these procedures are available in the current literature. The method of choice depends upon the material which is to be analysed and the quantity of such material which is to be dealt with. The latter, in turn, depends upon the circumstances. Thus large samples of urine can be obtained but always with some risk of contamination except under the most favorable circumstances. Small samples can be obtained without such risk, and in fact, under the eye of the examiner. Blood samples must of necessity be small in most cases. Fecal samples are not homogenous. Therefore it is better to obtain them on a time basis, as for example, a 24 hour sample all of which is ashed and dissolved, the aliquot depending in quantity upon the sensitivity of the analytical method employed.

(b) In my opinion, the answer to this is already in the literature, but there is some room for doubt, here, largely because most of the available information is either non-quantitative or has been obtained by numerous variable methods.

(c) There are several variations of spectrographic technique described in the literature. The method employed in this laboratory has been described in detail together with its sensitivity and accuracy. This method has been employed in parallel determinations on standard samples of known lead content, as carried out by three recognizedly competent groups, two in this country and one in England. The accuracy is equivalent to that of the best known microchemical methods, and it is more than adequate for the differentiation of normal and abnormal lead values in biological material. In fact the accuracy of method is far beyond the precision which can be applied in the interpretation of the results from a

physiologic-pathologic point of view.

II Anamnesis and Physical Examination

The anamesis should contain more specific information as to the nature of the occupation than is indicated in the outline. Some estimate of the severity of the exposure should be made or should be possible from the information supplied here.

The previous occupational history should be obtained in some detail, in order to assess the possibility of other hazards, as well as previously unrecognized lead hazards.

In addition to the duration of the exposure, the date at which exposure came to an end either through illness or for other reasons. The analytical results cannot be intelligently interpreted without such information. Under "Past History, item C., notation as to best weight and date, least weight and date, and present weight as judged by patient give useful information. Item K should carry reference to frequency of use of cathartics, and to dietary especially with reference to foods such as milk taken to counteract plumbism.

III Laboratory Data

1. Urine

(a) Routine examination on a fresh sample to determine reaction to methyl Red, specific gravity, albumin by heat and acetic method, sugar by Fehling's or Benedict's. Microscopic.

(b) and (c) Samples for analysis are collected separate from samples for routine examination. One of two methods of collection is employed dependent upon the circumstances and the analytical procedure to be used. When the patient is an ambulatory male who can be instructed and relied upon to carry out the instructions he is supplied with, a chemically clean gallon jug such as is used for vinegar etc. with a cork stopper, the jug being enclosed in a stout clean paper bag. He is instructed to put the jug in a clean, dustless place, and to keep it always corked and in the paper bag when it is not in use. He is to void directly into it, without using any type of intermediate container until not less than 3 liters have been collected. During the period of collection he is not given medication or permitted to use diuretics (other than coffee and tea as usual), cathartics or unusual quantities of beverages of any kind in order to hasten the collection. Time of collection is not accurately recorded except under hospital conditions, the lead concentration being the important factor clinically. If such a patient is in a hospital, the attendant is instructed to see that the above precautions are carried out, and also to record the beginning and end of the collection period. Such a sample is analysed chemically.

Under other circumstances, and often as a check on the large sample (with its greater opportunity for contamination)

approximately a single spot sample of 100 cc is voided directly into a chemically clean glass stoppered pyrex bottle (125 cc capacity), under the eye of the examiner. Such a sample is examined spectrographically.

In the case of small children and infants, urine samples may be collected periodically (with some difficulty) into chemically clean pyrex test tubes (male) or into chemically clean pyrex dishes (female) until the desired quantity has been obtained. With this technique it is safer to obtain a small sample for spectrographic study.

Samples may be obtained by catheter into a chemically clean pyrex bottle only if the catheter has been ascertained to be of lead-free composition. Most catheters contain significant quantities of lead.

The number and type of samples must be made to vary with the circumstances. Spot samples of urine vary considerably in lead content with the time of day, with the quantity of water excreted in unit time etc. If they are sufficiently high or low to be definitely abnormal or definitely normal, and if the blood lead corresponds in import to the urinary result, it is generally useless to repeat the observation. If they are on the borderline, repetition is necessary in the individual case. It may be necessary to make several determinations to determine the trend of the lead excretion. In general, the large urine sample if collected free of possible contamination is more useful in diagnosis since it gives the mean lead excretion over a period of many hours. If it gives results above the known range of normal values for the analytical method employed, one may be reasonably certain that the lead content of the tissues is above the normal level, and that the patient has had abnormal lea exposure.within the recent past.

(d) The chemical analytical method employed by us is published in full detail in the Journal of Industrial Hygiene, 15: 261, (1933). (We are now using a dithizone method also, but we are not entirely convinced as to a satisfactory adaptation of this method to the urine.) The spectrographic method used in this laboratory has been detailed in Industrial and Engineering Chemistry (Anal. Edition) 7: 287, (1935) as modified from an initial method published in J. Am. Chem. Soc. 57: 104, (1935).

2. Feces

(b) The entire fecal evaduation is collected directly into a chemically clean glass-top mason jar, or (in the hospital) into a chemically clean glass-top pyrex dish (set into the bed pan). No intermediate container is permitted. (There are many factors which make the fecal sample of little value for diagnosis except in the case of children with pica (within 24 to 48 hours after indulging their false appetite), and in the case of adults within 24 or 48 hours after the cessation of exposure.) The same precautions applied to the collection of the urine sample apply here. Especially is the use of a cathartic to be avoided. Samples collected in the usual

type of bed pan are entirely valueless and misleading. When collecting 24 hour fecal samples a fresh container is supplied for each evacuation.

(c) The entire 24 hour sample is subjected to analysis, so that the lead content can be expressed in terms of output per 24 hours. (This obviously requires a record of the evacuations before and after the day on which the sample was collected, or some other means of determining whether or not the sample obtained is typically a 24 hour sample.) Fecal samples are not homogenous. Thus weighing out a definite quantity of a fecal sample introduces a gross sampling error.

The method employed by this laboratory on fecal samples has been described in step by step detail in the Journal of Industrial Hygiene 15: 263, (1933). Inasmuch as the quantities of lead involved here are usually in excess of 0.20 mgs. per sample (the mean value for normals is approximately 0.25 mgs. per 24 hours) straight analytical procedures are entirely adequate.

3. Spinal Fluid

(b) It is necessary to collect the sample directly into a chemically clean (preferably pyrex or silica) tube, with a fitted glass stopper, using a chemically clean specially made spinal puncture needle free of lead in all parts. ) (The customary needle has a brass hub which seriously contaminates the samples.)

The range of normal values has not been fully worked out so that the diagnostic valueof the lead concentration is not soundly established. However, excessively high values are certainly significant. Five to 20 cc samples can be employed. In any case, only methods of analysis which can be employed are those of extreme sensitivity of which a spectrographic is by far the best. The details of our method have been referred to above.

4. Blood

(a) The routine examination should include a red, white and differential count, a haemoglobin determination by one of the more accurate methods (I prefer the Haden-Hausser instrument), and an approximately quantitative stippled erythrocyte count. There are a number of techniques. I prefer one of the simplest and least variable. This is described precisely in the Journal of Industrial Hygiene 18: 43, (1936). Stippling is easier to determine than to interpret since it can scarcely be proven to correlate in the individual with severity of exposure (i.e. magnitude of absorption) or with intensity of symptoms, in my experience.

(b) Samples of blood must be obtained with the same precautions as spinal fluid. A sample of 10 cc is adequate for spectrographic examination or analysis by a suitable dithizone

method. (Several modifications of the latter have been published. Our own adaptation of the method is in process of preparation for publication, but is not now available.) Our spectrographic method has been referred to above. The range of normal values is not established in an entirely satisfactory manner, but is sufficiently well based for most diagnostic purposes.

The number of samples which are required varies with the case, borderline cases being somewhat difficult. (Most cases can be satisfactorily studied by a single blood analysis together with a single analysis of the urine. When in doubt as to the meaning, the observation must be repeated.)

5. Tissue analysis

In the present state of our knowledge as to distribution of lead in tissues, the only adequate information about them must be obtained at autopsy. The blood tissue is the next best bet, and the skeleton and vital teeth are the next best. The latter will probably be found to be the most practical index to the lead content of the body as a whole in the living subject since the osseous structures are more uniform in their behavior toward lead than are any other tissues of the body. I am not prepared to discuss the methods of removing skin samples since I regard them as probably untrustworthy and as illogical from the point of view of our knowledge of the behavior of lead in the tissues. As to the methods of analysis only a spectrographic method of analysis could be used reliably at present, and of those described in the literature, the only quantitative one which has proven its accuracy as described is that of Cholak to which I have previously referred. The technique of Dingwall and his associates as described in the literature is substantially faultless, and their work antedates ours by some years. However it was not strictly quantitative, nor did they adapt it so as to attempt fine distinctions between normal and abnormal findings.

IV Correlation etc.

I have no detailed comments to make here except to point out that the usefulness of certain of the diagnostic measures which are apparently to be re-studied has already been rather clearly demonstrated, in that clinical and laboratory data have been quite effectively and accurately correlated and published.

Concluding comment. A statement in the letter which accompanied the outline intrigues me considerably. The last sentence states that "the obtaining and transporting of the specimens can be easily arranged". That may be true, but as one who has had to contend with the difficulties of obtaining uncontaminated samples from all parts of the world over a period of some ten years, I beg

leave to doubt it. If I am not mistaken that will be the most difficult and most exasperating part of the work. Unless one has time and facilities which permit him to give porsonal attention to the details of the collecting of samples, many of them will be found to be contaminated and hence misleading.

Signed: _____

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