April 9, 1957

Dr. Samuel B. Nadler
1520 Louisiana Avenue
New Orleans 15, Louisiana

Dear Doctor Nadler:

I shall try to give you the information requested in your telephone call of last Tuesday, although I am not quite sure that I shall cover all of the points to your satisfaction from the medico-legal viewpoint, since some of the things I shall say are not documented by published data. I send such publications as may be pertinent and refer you also to the work edited by Frank Patty in which much that I have to say has been published. Much too much has been written to refer to in any conprehensive manner.

First with reference to the normal limits of the excretion of lead it is quite clear that the normal range in representative samples of large volume collected with adequate care to prevent contamination extends from about 0.01 mg. (10 micrograms) per liter up to and including 0.08 mg. (80 micrograms) per liter. The values for the output per day, as established most clearly by balance experiments on human subjects in this Laboratory, are very close to the same range, since the urinary volume per day is not far from 1 liter. Indeed the observations made on a fairly large number of individuals indicate that it makes little difference, statistically, whether one speaks of the average concentration in milligrams or micrograms per liter or the average output per day in milligrams or micrograms. The range of normal values and the average value in either case are somewhat under 0.10 mg. (100 micrograms) per day.

These values, however, have little to do with the diagnosis of lead poisoning, since considerably greater quantities of lead may be handled without any risk whatever. Under the conditions of experimental or occupational exposure to lead, the range of complete safety is much wider, extending upward to the maximum figure of 0.22 mg. (220 micrograms) per liter, or roughly 0.22 mg. (220 micrograms) per day, occasionally. That is to say that individuals whose excretory rate ranges from 0.03 to 0.22 mg. per liter or per day and averages not more than 0.10 to 0.12 mg. per liter or per day, are in no danger of developing symptoms. The evidence of many years gained from the experience of thousands of persons of all ages and types indicates that the average rate of excretion must be equivalent to or exceed 0.15 mg. (150 micrograms) per liter or day, if symptoms of even the mildest detectable type are to appear. (I am excluding here any form of latent or obscure

intoxication. I mean to say that below the threshold value referred to, the individual is wholly without hematologic or other vague anatomic or symptomatologic abnormality. It is possible that a gingival lead line may appear, if there is sufficient gingivitis to initiate such deposits, but this is not a sign of illness. It simply means that there is lead in the local tissue (just as there is in the urine) which can be precipitated out as the sulfide if enough sulfide is available locally.)

Now the same average values apply to samples of urine of small volume, as distinguished from those of large volume (i.e. spot samples or a single voiding). The difference relates only to the range of values found in samples of small volume. The excretion of lead in the urine is subject to considerable variation from hour to hour, dependent upon the throughput of water and upon a number of other factors which cannot always be determined. Suffice it to say that the shorter the time over which a sample of urine is excreted (and collected) the greater is the variability. Thus, if one obtains samples of about 100 ml. in volume (a tenth, more or less, of the day's output) the range of value extends from somewhat less than 0.01 mg. (10 micrograms) to 0.14 mg. (140 micrograms) per liter. The average value of a large number of samples is about the same as that of the large samples, but any one sample obtained on one occasion from a single individual may be anywhere within the range indicated. This is the problem with which one is presented in a single session of clinical study in office practice. The one result is likely to be all that is available, and as you can see, such a result is woefully inadequate to show the status of the patient.

It is for the reasons given above that we always obtain blood samples. The blood lead is influenced significantly (in the untreated individual) only by the level of lead concentration in the body as a whole (the body burden of lead) and by the current (present) rate of absorption from a portal of entry, such as the alimentary tract or the respiratory system. (One must exclude tetraethyl lead from this discussion and think only of inorganic compounds of lead, since the metabolism of tetraethyl lead poses a somewhat difficult problem, especially from the aspect of the blood values). The blood level then does not vary significantly from hour to hour, except under conditions of extremely rapid lead absorption in response to a very severe type of exposure. This means, in the diagnostic sense, that we can obtain two samples of blood, check one against the other so as to deal with the possibility of chance contamination, and if the two results check within the limits of analytical error, we know, beyond reasonable doubt, the status of the individual from the aspect of his over-all absorption of lead.

So long as the concentration of lead in the blood is below 0.08 mg. (80 micrograms) per 100 grams, the absorption of lead has not reached the critical level at which symptoms begin to appear in occasional individuals. At that

level or above, some individuals develop symptoms, and as one goes upward the frequency of occurrence of intoxication and the severity of the manifestations increase.

Going now to the collection of samples of urine and blood without precautions, the possibilities for error are almost infinite. In general the contamination is likely to be gross, and our experience as well as that of others (literature) is filled with incidents of this type. A twenty-four hour sample of urine, collected in the average hospital by the usual methods (the use of a urinal, emptied into a bottle or other container as the urine is voided), often has ten times as much lead in it as was actually voided in the urine. This situation is utterly impossible, and therefore we never allow 24-hour samples to be collected for us in hospitals. It is practically impossible to avoid contamination unless one has an intelligent and cooperative patient, who, himself, will take care of the details, by keeping a large container at hand and voiding directly into it over the period indicated. To give you some idea of the minute care that must be taken, let me cite an experiment. The collection of samples of blood by the usual technique of using a pyrex syringe and an ordinary needle, after careful cleansing of syringe and needle and sterilization in distilled water, resulted in roughly 20 per cent (average) contamination of the samples. This resulted from the lead-containing brass hub in the ordinary needle. The substitution of an all-steel needle resulted in average values about 20 per cent lower. If this can occur from this cause, how much more contamination can result from lesser factors. We have obviated this difficulty in the collection of samples for diagnosis by working with B and D in their effective attempt to supply suitable equipment for the collection of blood. The problem of the urine still persists as a difficult one, but we consider it impractical under most circumstances to try to collect urine, except as "spot" samples voided directly into a clean container in the presence or under the supervision of the examiner or his instructed agent. Even then unclean workmen in unclean and perhaps dusty clothing can and do contaminate the containers which they handle and the urine which they void. Since one is dealing with micrograms of lead any kind of dust or foreign material introduces a significant error, for lead is ubiquitous A little ash from a cigarette, for example, has much more lead in it than several liters of urine.

Now, as to the results of the use of edathamil-calcium-disodium. It is utterly futile in our experience to attempt to assess the significance of the analytical results on the urine and blood of an individual who is undergoing such therapy. If the response is great, the chances are that the individual had considerable quantities of lead in his soft tissues (those exclusive of the skeleton). But even this is not absolutely certain in relative terms, for the reason that the extent of the response depends in large measure upon the duration, the severity and the recentness of the individual's exposure to lead. In my opinion, one cannot determine the general level of lead absorption of an individual in any reasonably reliable manner, except by determining the general character of the lead

metabolism at a time when it is proceeding normally. That means determining either the general rate of the urinary excretion, or the general level of lead in the blood, or preferably, both of these. The reason for this lies in physiology, that is, in the known behavior of lead in the body. This behavior is distorted greatly by the administration of edathamil, in that the lead in the soft tissues unites with this chelating agent, parts company with these tissues promptly in most instances, and is excreted by the urinary apparatus first at a very rapid rate and then more slowly as time goes on. The blood, (that is, the erythrocytes) gives up its lead somewhat slowly dropping not at once, but only after a bit of delay, but the outpouring in the urine is dramatic. Even the normal individual (with no unusual quantity of lead in his body) loses much of that which is in his soft tissues and responds, therefore, to the administration of this agent. What one finds depends to a considerable extent upon the time of obtaining samples, and therefore it is very difficult to interpret the results unless one follows the process before, during and after the administration of the agent. This is generally impossible of accomplishment in other than metabolic experiments, and then most of the data obtained in a spotty manner are valueless. It is exactly like an attempt to measure rainfall by stepping outside for a moment and collecting the water during that period. The result has only momentary significance and is incapable of providing a basis for exterpolation. Too many people are making such attempts and trying to interpret them without any knowledge of the physiology of the process. The outcome, unfortunately, is confusion.

I should point out that the skeletal lead (which under ordinary circumstances of slow and more or less prolonged absorption of lead constitutes most /but not all, and indeed, not the important part/ of the lead in the body, is essentially unaffected by the administration of edathamil (and, for that matter also, of BAL). However, after the soft tissues (including the blood) have undergone great (proportional) reduction of their lead content, the lead in the skeleton is in a disturbed state of equilibrium, and it begins to restore the normal relationships of the distribution of the lead within the tissues generally. Slowly, then, over a period of some weeks, the lead comes out of the skeleton into the soft tissues (including the blood) and the latter become elevated again to an extent which is proportional to the available lead in the skeleton. The blood of poisoned children, for example, may fall to a normal level during several days of therapy, and then rise slowly during the next two to four weeks to a level very nearly as high as it was originally, i.e. anywhere up to 0.20 or 0.30 mg. per 100 grams. It is for this reason that we follow the blood carefully before and then for some time after therapy. Whenever the blood values go back up to 0.08 mg. per 100 grams or more, another course of edathamil-calcium-disodium is administered (intravenously) until the values remain low and within safe limits. Only by such methods of trial and study can we make any prediction as to the ultimate safety of the child from the recurrence of intoxication.

With the foregoing fairly extensive comments I hope that I have answered your

questions. I hope to get these statements and their supporting evidence published soon, but I've been too busy with the day's work to put the data together. Obviously, I cannot afford the time to answer enquiries like yours very often, but I do my best to help those who come to us for advice and information.

Sincerely yours,

Robert A. Kehoe, M. D.

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A Critical Appraisal of Current Practices in the Clinical Diagnosis of Lead Intoxication - Kehoe
The Plasma-Cell Partition of Blood Lead - Bambach, Kehoe and Logan
Exposure to Lead - Kehoe