

INSTITUTE OF CHILD HEALTH

UNIVERSITY OF LONDON

DIRECTOR & RUPPEL PROFESSOR OF CHILD HEALTH.
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THE HOSPITAL FOR SICK CHILDREN

GREAT ORMOND STREET

LONDON, W.C.1

TELEPHONES:

HOLBORN 2196 & 2122

September 24th, 1964.

Dear Dr. Kehoe,

Many thanks for your further letter, and
I have also seen what you wrote to Dr. Clayton.

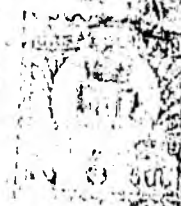
I am also grateful to you for the Harben
Lectures. Curiously enough I have already been
loaned a copy by the Royal Institute of Public
Health because I gave the Lectures for 1963
and they kindly sent me your Lectures to see the
sort of general style and length.

Yours sincerely,


Sir Alan Moncrieff

Dr. Robert A. Kehoe,
University of Cincinnati,
Department of Preventive Medicine and
Industrial Health,
The Kettering Laboratory,
College of Medicine,
Eden Avenue,
Cincinnati 19,
OHIO, U.S.A.

VE 01040



Dr. Robert A. Kehoe.

University of Cincinnati,

The Lettering Laboratory,

College of Medicine,

Eden Avenue,

Cincinnati 19, OHI, U.S.A.

Sender's name and address:

INSTITUTE OF CHILD HEALTH,

GREAT ORMOND STREET,

LONDON, W.C.1.

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IMPERIAL AIR MAIL
AEROGRAMMES

VED 01041

September 4, 1964

Barbara E. Clayton, M.D., Chemical Pathologist
The Hospital for Sick Children
Great Ormond Street
London, W.C. 1, England

Dear Doctor Clayton:

I am pleased to have your letter of August 25, and I hasten to deal with the point of special concern as to the "levels of lead" (in the blood and tissues, associated with) "clinical evidence of toxicity." This is a matter that has continued to give rise to misunderstanding of the specific significance of the analytical findings in the urine, blood, spinal fluid, or other body fluids or tissues, including those obtained at necropsy. The fact, quite clearly, is that the concentration of lead in tissues or body fluids is not indicative of the existence of intoxication, but rather of the general level of the absorption of lead. These findings measure hazard but not illness, in as much as illness never (as so far observed) occurs unless the concentration of lead in the body has reached a certain level, but it does not necessarily occur when the potentially dangerous range has been reached. For one example, we have never seen a case of lead poisoning, at the onset of the illness, in a person whose blood contained less than 80 micrograms of lead per 100 grams (whole blood). On the other hand, we have seen persons without symptoms whose blood contained ten times this concentration. It is evident, from these facts, that there is some mechanism, presently unknown and not capable of being even postulated, whereby lead in the tissues (in the gross sense) in an essentially inert form is activated. I think of this as being chemically bound (un-ionized) and then coming into an ionized state, but there is no evidence that such is the case, and the matter may be quite complex. The phenomena of chelation fail, so far as I am concerned, to shed any very clear light on the problem.

From the point of view of diagnosis, therefore, the analytical results contribute only the conclusion that the lead content of the blood (or indirectly, the soft tissues) is either compatible or incompatible with the diagnosis of plumbism. In practice, it can be said, under appropriate conditions, that this is definitely not lead poisoning, or that it is compatible with the diagnosis of lead poisoning. The tendency of modern physicians and, of course, the non-physicians who are involved in diagnostic problems, is to employ the laboratory to furnish "scientific" proof of the nature of disease. This is at least one example of the fallacy of this type of thinking, for the diagnosis of lead poisoning is made on clinical grounds within the limits of the situation defined by the analytical findings. This is hard for many modern physicians to accept, but in your country, in which clinical medicine has been practiced for so long and so

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Barbara E. Clayton, M.D. - (2) - September 4, 1964

skillfully by so many keen observers, this should not pose too much of a problem.

You will note of course, that there is no difference between your definition of the "normal range" of the findings in the blood, urine or tissues. It is likely, however, that this range, as so defined, differs quantitatively in England and the U.S.A. We know fairly well the contribution made by various environmental factors in the U.S.A., and we have some, but not nearly enough, information about your environment, with respect to food, water and air. It is my tentative opinion that your environment differs significantly from ours, but there may not be enough difference to be of any practical consequence. So long, however, as it does not approach the level of danger, it makes very little difference clinically. I do not suppose, for a moment, that the physiological differences in the human population, will cut much of a figure in the outcome. (I am, of course, unable to appraise the nutritional situation within your juvenile population, and I am by no means certain of the facts within the varied economic levels of this population in the U.S.A. I would consider it likely, however, that this factor may play some part in the incidence of lead poisoning among children.)

One other feature of your letter seems to call for some emphasis in my reply. You may not have meant to do so, but your reference to the "possibility of lead poisoning..... in industry" seems to minimize, somewhat, the significance of this matter. It appears (on somewhat unsatisfactory statistical evidence) that lead poisoning is the most frequent type of intoxication that occurs in American industry. In any case, my experience of nearly forty years in relation to a broad spectrum of the lead trades in the U.S.A., enables me to have a fair idea of the situation. The most significant advance in preventive medicine in this series of industries during the past several decades has been the establishment of the threshold of the danger of lead intoxication in terms of the lead content of the blood and (somewhat less effectively) the urine. It is at this point which I had wished to emphasize in my letter to Sir Alan, since there is no question as to the fact that there is a sharp threshold. This is the precise reason that I objected to the statement, in the article, that the significance of the level of lead concentration in the blood is uncertain. There is, of course, the mathematical uncertainty, as between 80 micrograms of lead per 100 grams of whole blood and the analytical error of the analytical method which may be as little as $\pm$ 0.01 microgram, or as much as 0.05 microgram, dependent upon the specific method (among the good methods) employed by a competent analyst. However, there is no doubt as to the physiological fact that there is a well-defined threshold. (There may be, of course, highly unusual persons who do not fit the common pattern, but our thousands of observations over many years, under highly varied conditions, have established, as fact, the essential stability of the metabolism of lead in the human organism.)

I must get on with the mountain of work which has accumulated on my desk during a vacation which has ended just now. This brings me to terminate this discussion. My interest in your efforts, which will be evident to you,

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Barbard E. Clayton - (3) - September 4, 1964

derive, in considerable part, from my hope that you and your associates will extend your work on this dread disease of childhood, so as to visualize clearly the environmental factors which affect it in Great Britain, and the means by which these factors can be brought under adequate control.

Sincerely yours,

RAK:vr

Robert A. Kehoe, M.D.

VE 01044

THE HOSPITAL FOR SICK CHILDREN

GREAT ORMOND STREET, LONDON, W.C.1

CHAIRMAN:

CLAUDE A. LUCAS, ESQ., T.D., M.A., F.C.A.

HOUSE GOVERNOR & SECRETARY

G. J. PILLER, F.H.A.

TELEPHONE HOLBORN 9200

TELEGRAPHIC ADDRESS:

GREAT HOLB. LONDON

25th August, 1964.

Dear Dr. Kehoe,

On my return from holiday Sir Alan Moncrieff has passed your interesting letter to me. It may be that we have not made our point clear. By the "normal range of lead in blood" we mean the levels we found in a series of children exposed to the environmental lead of a city like London but who have not been chewing at all sorts of objects. I would fully appreciate your conclusions about the levels of lead at which clinical evidence of toxicity definitely is apparent. To my mind, much work remains to be done to determine whether there is any evidence of damage as a result of the intake of lead so that the level in the blood lies between that normally found and the higher levels giving clinical toxicity. These borderline cases may be of great significance in the aetiology of mental retardation.

I am of course familiar with your work and already possess reprints of your Harben Lectures. These were kindly given to me by Dr. Camps. They have, of course, been a great source of interest.

I agree with you that the possibility of lead poisoning is an extremely important one in industry and it is certainly of growing importance in paediatrics. I strongly agree that our aim must be to prevent the possibility of children receiving increased intakes of lead.

Thank you very much for the interest you have taken.

Yours sincerely,

Barbara Clayton

Barbara E. Clayton, M.D., M.R.C.P., Ph.D.,
Chemical Pathologist.

Copy to Prof. Sir Alan Moncrieff.

Dr. R.A. Kehoe,
University of Cincinnati,
College of Medicine, Eden Avenue,
Cincinnati 19, Ohio.

LE 01045

September 3, 1964

Professor Sir Alan Moncrieff
Institute of Child Health
The Hospital for Sick Children
Great Ormond Street
London, W.C. 1, England

Dear Sir Alan:

Please accept my thanks for your reply to my letter of some weeks ago, concerning lead poisoning. I have had a letter recently from Dr. Barbara Clayton, to which I have replied at some length, because of my obvious interest in the matter. I trust that she will bring this to your attention, for it concerns itself, among other matters, with issues that are strictly clinical. This, incidentally, aside from general physiological considerations, has been my role in our work, not so much in the detailed performance of clinical practice (which I have engaged in in the past) but rather in the application of preventive medicine to the clinical and toxicological problems of industry. There is much more to this than meets the eye of the analytical chemist or the biochemist. This is why I consider that you depreciate your contribution by suggesting that you are "only the clinician."

I believe you will find the Harben Lectures (1960), of which I am sending a bound copy, to be a combination of physiological information and its direct application to hygiene and clinical problems. I trust that I have some understanding and appreciation of academic life, since I have been in this environment most of my life. However, for a physician, with a physician's view of life, it is far from being the protected life in the ivory tower, or a retirement from the world into the realms of pure science. I do not scorn the latter, but it has never been my cup of tea.

Sincerely yours,

RAK:vr

Robert A. Kehoe, M.D.

Encl. - Harben Lectures of 1960

LE 01046

INSTITUTE OF CHILD HEALTH
UNIVERSITY OF LONDON

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D. A. REDSTON, B.A., F.C.A.

THE HOSPITAL FOR SICK CHILDREN
GREAT ORMOND STREET,
LONDON, W.C.1.

TELEPHONES:
HOLBORN 2198 & 2122

July 29th, 1964.

Dear Dr. Kehoe,

Thank you for your very interesting letter about lead poisoning. I am afraid that I am only the clinician in the team and my colleague, Dr. Barbara Clayton who is head of our Biochemistry Department, is on leave until the end of August. I will certainly have your letter waiting for her on return.

I am sure that we should find your Harben Lectures most interesting, although I was shown them briefly a little while ago when I was asked to give the Lectures for 1963 and wanted to get some idea of the length and style. It was very kind of you indeed to take all the trouble to write to us in so much detail.

Yours sincerely,



Professor Sir Alan Moncrieff

Dr. R. A. Kehoe,
University of Cincinnati,
Department of Preventive Medicine and Industrial Health,
The Kettering Laboratory,
College of Medicine - Eden Avenue,
Cincinnati 19,
Ohio.

KE 01047



Dr. R.A. Kehoe,

University of Cincinnati,

Department of Preventive
Medicine and Industrial Health,
The Kettering Laboratory,

College of Medicine -

Eden Avenue, Cincinnati 19.
OHIO, U.S.A.

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IMPERIAL AIR MAIL
AEROGRAMMES

VB 01048

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July 15, 1964

A. A. Moncrieff
Department of Chemical Pathology
The Hospital for Sick Children, and the Institute
of Child Health
Great Ormond Street
London, England

Dear Sir:

My unfamiliarity with Paediatrics and Paediatricians in your country denies me the privilege of addressing you with a proper salutation, for which, I trust, I may be forgiven. The occasion for this communication is an article by yourself and your associates in British Archives of Disease in Childhood, 1964, 39, 1.

This otherwise splendid article has in it one highly significant conclusion which I believe to be incorrect, and since the point involved is crucial in relation to diagnosis, and even more so in relation to industrial hygiene, I cannot refrain from commenting on it. I have considered it wiser, as well as more courteous, to write to you directly, rather than through a letter to the editor, for my purpose is not to raise an objection as a matter of record, but to invite your comments and more particularly, your search for evidence in support of your expressed view or mine. I shall not subtract anything from my emphasis on this one point, by commenting on any of the other aspects of the physiological and clinical information assembled in this excellent paper. I should say, however, that it is necessary to examine, skeptically, the statements of a number of American authors, with respect to the significance of the analytical findings in the urine, blood and solid tissues, for exactly the same reason that I give in criticising your interpretation of the same data. There is no substitute for direct experience in these matters, and there are very few persons in the United States or elsewhere, who have had such experience.

My point of departure from your position, which is also that of Byers and others cited in the very beginning of your article, relates to (1) the "normal" range of lead in the blood (of both adults and children), and (2) the variability of the levels of the concentration of lead in the blood which are indicative of lead poisoning. The first of these requires little comment, perhaps, although the environmental background of the term "normal" in our day, as in former times, is of more than a little significance, considering the natural opportunities for the absorption of lead, and the ubiquity and variety of the artificial factors in the environment. Concerning the second point, it seems evident that the variations in the concentration of lead in the blood of both adults and children have so impressed themselves upon most of the interpreters of these phenomena as to have obscured almost utterly the facts which emerge when the variability is examined critically in relation to the clinical entity of lead poisoning, and the factor of time. I shall explain in some detail what is meant by the latter part of the last sentence.

There can be no doubt, whatever, that there is a high degree of variability

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in the concentration of lead in the blood. There is also, as the counterpart of this variability, a high degree of variability in the rate of the absorption of lead by persons in our society. These relationships have been investigated in some detail in this Laboratory over the period of many years, and it is important to recognize, in this connection, an extremely important matter. The analytical data so obtained have been furnished by the same persons, employing the same two methods of analysis, in parallel, which have been in use essentially unchanged since 1938. The error associated with the application of each of these two methods has been well defined, so that the data can be given essentially absolute significance in positive and negative terms. The importance of this fact, in relation to the concentration of lead in the blood, is fundamental to the consideration of many of the analytical data which have found their way into the literature from certain other sources, especially those concerned with case reports.

Several practical facts have been established by these means.

1. It is entirely certain that there is no level of lead in the blood which is indicative of lead poisoning. Persons with very high levels up to approximately 1000 micrograms of lead per 100 grams of whole blood, may be wholly free of symptoms (not necessarily free of certain biochemical deviations from the apparently normal range).
2. Conversely, there is a range of concentration, which is wholly incompatible with the onset of illness due to lead. In our experience with adults this is utterly incontestable at this time. No case of lead intoxication in industry has ever been found to occur (at the onset), in our experience, except in association with the concentration of lead in the blood equivalent to or in excess of 80 micrograms per 100 grams. (The exact point, if there is a point rather than a narrow range, is difficult to establish, for the reason that there is, inevitably, a small unknown area within the range of the variability of analytical precision. Thus a single finding of 80 micrograms may be 75 to 85 micrograms, at best, or 70 to 90 micrograms, at worst, in terms of analytical error. Only occasionally, however, is this a matter of practical importance, and then it can usually be settled by multiple analyses.)
3. Our observations of "normal" and sick children, made over the period of more than twenty years, in collaboration with our colleagues in the Department of Paediatrics of this Medical Center, have indicated, beyond reasonable doubt, that the relationships of the concentration of lead in the blood to clinical plumbism in childhood are essentially the same as those in adult life. Children with high levels of concentration of lead in their blood (above the threshold) are not necessarily ill. There seems to be somewhat greater threat of the "triggering" of intoxication in the child than in the adult, but there may well be such a simple explanation of this as that the exposure of the child is shorter and more severe, in quantitative terms of absorption, and is this more difficult to handle, than is that of the adult in the industrial environment. (The fact is, of course, that we do not understand the mechanism by which an "excessive" quantity of lead in the body initiates intoxication.)

A. A. Moncrieff - (3) - July 15, 1964

We have never found an exception to the rule that, at the onset of lead intoxication, the blood of the child contains 80 or more micrograms of lead per 100 grams. It is true that certain evidences of plumbism persist (in sufficient intensity to justify the diagnosis on historical grounds), after the concentration in the blood has subsided. It is also true that there are often residual findings induced by organic injury, especially to the central nervous system, which, on the historical basis (and on the fairly unique character of certain neuro-muscular lesions), can be diagnosed as the effects of the absorption of lead in excessive amount. Moreover, certain unpredictable (or so it seems to me) vagaries of the relationships between the concentration of lead in the blood and the "body burden" have resulted from the institution of chelation therapy.

All of the foregoing factors, plus variability in analytical precision in various hands, have entered into reports in the literature in recent years. I have yet to encounter a systematic investigation, in the hands of competent persons whose analytical facilities are above criticism, which has brought out data that are in essential disagreement with any of the statements I have made in the several paragraphs above.

You may suspect, at this point, that I have gone to extravagant lengths in presenting this issue to you. And so I have, if I were concerned only with the problem of diagnosis of lead poisoning. There is, however, a good reason for my concern and this relates to the importance of the concentration of lead in the blood, from the aspect of preventive medicine, in industry, particularly, but also in the general field of environmental medicine and hygiene. If you have examined the data, and the theses in preventive medicine that emerges from the Harben Lectures on "The Metabolism of Lead in Health and Disease," you may realize that this is a very crucial point in the recognition of the danger of plumbism, before any illness or disability appears. The adoption and implementation of this principle in industrial hygiene has served to eliminate, utterly, the occurrence of cases of lead poisoning in a number of industries. Its general application would clean up the "lead trades" in this country. This I have been undertaking to bring about in an appropriate professional manner for many years. At this time considerable progress is being made. This progress could be brought to a standstill, or nearly so, if the principle, itself, were to be regarded, in certain circles as invalid. The application of this principle is costly, initially, in a badly managed (from the aspect of industrial hygiene) industry. It is also troublesome, medically, because it requires understanding, attention to detail, and a thoroughgoing development of professional responsibility, on the part of persons who "do" industrial medicine with their left hands in their "spare time." (I should not like to be quoted in this vein, for reasons which will be evident to you, I believe, and it is for this reason, among others, that I write to you rather than to the editor of the Archives.)

I trust that what I have taken the trouble to say will be of some interest to you and your colleagues in their further investigation of this important and preventable (with some difficulty to be sure) disease of childhood.

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A. A. Moncrieff - (4) - July 15, 1964

Incidentally, if you or others of your associates would like to have bound copies of the reprints of the Harben Lectures referred to above (and in your article), I shall be pleased to supply them.

Cordially yours,

RAK:vr

Robert A. Kehoe, M.D.

cc - Dr. P. S. I. Barry

VE 01052