LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE
INCORPORATING THE ROSS INSTITUTE
(UNIVERSITY OF LONDON)

Cables :
Hygower London W.C.1

KEPPEL STREET,
(GOWER STREET),
LONDON, W.C.1.

MKW/JD

March 4th, 1966.

Professor R.A. Kehoe, M.D.,
The Kettering Laboratory,
University of Cincinnati,
College of Medicine,
Eden Ave,
Cincinnati 45219.

Dear Professor Kehoe,

Thank you very much for your letter of January 26th. I find it most interesting, but would like to make just one comment - I do feel that when one is controlling lead absorption in industry it is useful to have a term to describe those men whose lead absorption is higher than is safe, but who are not yet suffering from lead poisoning. This I call excessive lead absorption which I do not feel is semantic hair-splitting; ~~but~~ it requires that action should be taken to reduce their lead absorption in some way.

I would very much like to discuss at length your other points with you, but perhaps this would be better kept for a meeting rather than a letter.

Yours sincerely,

M.K. Williams

M.K. Williams

January 26, 1966

Dr. M. K. Williams
London School of Hygiene and
Tropical Medicine
Keppel Street
LONDON, W.C.1.

Dear Doctor Williams:

I am impelled to comment on certain of the further queries and views in your letter of January 7; I shall take them in the order of their occurrence in your letter.

First, with reference to the significance of the concentration of lead in the blood, I shall have to say that I cannot accept your statement that it is the best index of the exposure to lead(which I shall speak of as the current level of exposure to lead). The rate of the urinary excretion from day to day is by far the best indication. The concentration in the blood, on the other hand, is the best available evidence of the extent of the absorption that has occurred - that is, of the body burden of lead, or the result of the exposure to lead over some considerable period of time. It is clearly not indicative of the existence of lead poisoning, which, as I have indicated previously, is manifested by a characteristic illness, or a specific interference with a specific interference with function - as, for example a lead-induced disturbance of the porphyrin-hemoglobin metabolism. I wonder why it is that you are loath to label the latter phenomenon as a feature of lead poisoning. I agree that it is not always possible to determine the cause of this phenomenon, or the cause of anemia. However, these are situations in which I would be quite willing, on the probabilities (without actual proof), to ascribe one or the other, or both of these, to the effects of lead. Under such circumstances, it is intoxication. Why split semantic hairs? "Excessive lead absorption" has no meaning in clinical medicine, except to indicate that the individual so involved, is in a state of risk. He is not, necessarily, in a state of illness. I abhor confusing words, and this phrase is not only obscure, but has been a shield to hide behind, medically speaking. On the other hand, the man with lead-caused anemia or lead-induced porphyrinuria is ill. He may not be aware of it, but his physician may be. I think here you are bandying words when you say this is not clinical poisoning, because there is no awareness on the part of the patient, of exceeding the symptomatic threshold.

You are in error, in my experience, in saying that a "little" lead causes an increase in porphyrinuria. If one determines the concentration of porphyrins in the urine (this, of course, requires the use of a good quantitative procedure), he will find a sharp cut-off between the results which occur under ordinary conditions and those which are associated with dangerous levels of lead absorption. This, in my view, when other causes of an abnormal concentration of coproporphyrins in the urine can be excluded, is the first clinical (in the sense of a functional disturbance) sign of lead poisoning, and one which should be heeded promptly, lest a more serious form of poisoning should appear. I am prescribing, here, of course, a conservative medical procedure in handling the workmen in a dangerous lead-using industry. This is a bit different, admittedly, from the making of a diagnosis for

medico-legal purposes, on a basis that is acceptable, generally, among medical men. However, this is the way a new diagnostic position is achieved, and this is something quite different from compensable disability due to lead poisoning. But so, for that matter, is the recognition of impending danger because of a degree of absorption of lead - a danger which requires action on the part of a physician in removing a man from further exposure. We have no mechanism in this country for dealing in compensation law with such cases. Consequently, the employer will make every effort to find a job for the workmen that is free of lead hazard. In any case, I see no reason for not expecting a knowledgeable physician from exercising judgment in such cases, as to whether the probabilities are in favor of abnormal effect due to lead. I really don't care whether or not he labels the condition as "lead poisoning," or "incipient lead poisoning," or "threatened lead poisoning," but I don't take kindly to the term, lead absorption (by itself or modified by an adjective) since this term relates to a general physiological process. It suggests that lead absorption implies some potentially harmful effect of lead, whereas this is basically untrue, and it is high time that we recognize this fact in our speech.

One other point requires some clarification. (Please do not think I enjoy being a carping critic. I am merely trying to talk plainly.) You speak of the "release of lead from cells." That is not what I have in mind when I consider the release of lead from a firm or loose chemical bond. I think rather of its release within cells, and the induction of an effect thereby. There is no evidence for this, any more than there is evidence of an elevation of the lead content of the plasma in acute infections, alcoholic bouts, and disturbances in the acid-base equilibrium of the tissues. But since there is no evidence of the latter group of factors (which you speak of as having been noted in the past), I cannot but suspect that some such subtle biochemical change occurs, without any representation of such change in the peripheral blood.

You may be right, of course, about the occurrence of lead poisoning when the concentration of lead in the blood is low. If so its occurrence is rare, for I have never seen such a case. The erythrocytes have a very great capacity for taking up lead and virtually depriving the plasma of more than traces. Consequently, I cannot think it very likely that their reduction in number, within moderate limits, will have much effect upon their carriage of the lead that is available through the usual metabolic processes of the body.

It is entirely possible that you will react unfavorably to my comments, although I have found British physicians and scientists to be somewhat less reactive in such matters of discussion and controversy than many of my colleagues in this country. I am encouraged, therefore, to express divergent points of view, without fear of seeming to be excessively opinionated or discourteous. Believe me, I should like to talk with you in person.

Cordially yours,

RAK:wp

Robert A. Kehoe, M.D.

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Department of Occupational Health and Applied Physiology:
Professor R.S.F. Schilling.

January 7th 1966.

Professor R. A. Kehoe
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Eden Avenue,
Cincinnati, Ohio.

Dear Professor Kehoe,

Thank you so much for your very detailed and helpful letter; and for the reprints.

I was glad to hear you are continuing experiments with lead inhalation. I am particularly interested in its estimation using personal samplers and would like to prove mathematically that blood lead, say, is the best index of exposure, but not necessarily of poisoning; whereas ALA say might be the best index of tendency to poisoning - but not of exposure. For example, some cases of clinical lead poisoning have blood leads of 110 ugm/100 ml: whereas some workmen without poisoning have 400 ugm/100 ml. (a 300% increase). It would be nice to show that no-one with ALA less than x units has clinical poisoning, but everyone with x + 50%x has clinical poisoning.

I wonder if workers in this field on the whole do not distinguish sufficiently between the use of certain biological indices to estimate exposure, and the use of the same indices to estimate the tendency to poisoning. I wonder if you agree?

I certainly agree with your point (page 2) that lead poisoning is diagnosed clinically and not by analytical means. That is why I am less happy when you say (page 3) that a reduction in haemoglobin due to lead is lead poisoning. For the reduction may only be detectable by analytical means, and not clinically - so I would prefer to call the case "excessive lead absorption" (and grossly excessive to be sure!)

Admittedly, men with lowered haemoglobins, but no symptoms and denying "tiredness", when removed from lead say later that they feel much better, and were tired before. But one would call this poisoning from the symptoms rather than from lowered haemoglobin.

Similarly, I am not happy to call unusual quantities of coproporphyrin in the urine (analytical test), lead poisoning, in the absence of clinical symptoms and signs. A very little lead causes an increase in porphyrinuria - where then can one draw the line and say this is an "unusual quantity" and therefore = lead poisoning? Increased porphyrin in urine is certainly a sign of interference with a physiological process, and an abnormal metabolite appears in the urine. But an abnormal metabolite appears in the urine after drinking a pint of beer - yet again we do not say this is a sign of alcoholic poisoning.

I was very interested to hear your hypothesis that poisoning may be precipitated by the release of lead from cells. I too had imagined that possibly when the red cell becomes "poisoned", it may release some of the large amount of protein bound lead it holds; which in turn, as ionic lead, increases the plasma ionic lead concentration which initiates further stages of poisoning - a sort of trigger mechanism which could be fired earlier by illness, alcohol, dietary deficiency and other factors noted in the past. This incidentally might cause a lowering of the total blood lead, accounting for poisoning with "low blood lead" and non-poisoning with high - I would like to do some animal experiments on that.

I take your point about not adding to unproven hypotheses in the literature, and agree that normally this is a very undesirable approach. But I feel strongly that a lowered red cell volume must reduce the "lead-carrying power" of blood, and therefore there are good grounds for deducing a correction factor for "observed total blood lead" to get the "corrected blood lead" in cases of lowered haemoglobin. So I am publishing the suggestion in a subsidiary paragraph of a paper in Brit. Journ. Industr. Med. next April, very tentatively to stimulate thinking on this line - I hope this meets with your approval. The paper, incidentally, is on blood lead and haemoglobin and demonstrates (yet again!) that haemoglobin is not a good control - though better than nothing, which is why the legislation was introduced in this country.

Again, very many thanks for your letter and reprints. I hope this letter isn't too long - it would be a great privilege to talk sometime instead! I hope that may be possible someday.

Yours sincerely,

M. K. Williams.