The Diagnosis of Lead Poisoning in the Light of Recent Information

by

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The large number of recently published articles on lead poisoning testifies to a greatly heightened interest in what must be listed as one of our oldest clinical problems. Unfortunately, the amount of light which has been shed upon the problem does not correlate closely with the volume of the literary output. Indeed, it would seem that an attempt on the part of the practitioner of medicine to examine and interpret the current literature would result almost inevitably in such discouragement and confusion as to cause him to return to time-honored concepts and procedures. Even the casual reader will note that many of the articles published recently deal primarily with laboratory methods of diagnosis on the apparent assumption that the underlying pathological physiology of lead intoxication has been completely elucidated and may, therefore, be taken for granted, or that it need not be taken into account in the interpretation of findings. One might be led to believe that laboratory procedures may be substituted for clinical study. In fact there is an insistent demand, not only in medico-legal but in general practice, for a laboratory test which, standing alone, will have a positive diagnostic significance. There is good reason, therefore, to

concerns laboratory diagnosis, and to appraise in a somewhat cautious and critical manner the extent to which laboratory observations and the interpretations which are derived from them may be accepted as trustworthy In view of the impossibility of reviewing the literature even in a cursory manner, or even of mentioning many matters which are of physiological importance, in the short time available, I shall attempt to clarify a few points which seem to be of immediate practical importance to the problem of diagnosis.

Normal Lead Metabolism

The ingestion (and probably the inhalation), absorption, and excretion of lead have been shown to be normal phenomena of human life. (1a,b,c,d).* The limits of the normal values for lead ingestion and for lead excretion in the feces and urine of persons in the United States may be defined in substantially absolute terms.(2). The values for the blood, spinal fluid and tissues are not so satisfactorily established, in that the full range of normal variability is inadequately defined.(1c,2). (This is particularly true in the case of the skin, and unfortunately so, since unwarranted clinical significance has recently been attributed to apparent variations in the lead content of this tissue.(3).) The evidence indicates that within the somewhat incompletely defined physiological limits, a state of dynamic equilibrium is maintained in which little or no progressive lead accumulation in the tissues occurs, but, rather, intake and output come into approximate balance after a certain level of absorption into the tissues has been reached. (1 b). Such data as have appeared to indicate that there is a tendency toward progressive accumulation in the tissues, chiefly the skeleton, show that the actual concentration difference between youth and old age are slight, - so slight, indeed as to require further proof that they exceed the limits of chance variation. (4). No evidence has been developed to show that unusual amounts of lead accumulate in the tissues or are retained in the tissues except as the result of an

abnormal intake. There are, to be sure, significant variations in absorption and excretion from day to day, but when compared with the metabolism of the more common metallic constituents of living material, the normal metabolism of lead is remarkably stabile. Whether or not lead is physiologically useful is a matter for conjecture, but regardless of the eventual answer to this question the concept of lead as an accumulative poison, without reference to quantity, has received a rude shock. Obviously, hereafter, when we refer to the poisonous properties of lead in animal or human metabolism, we shall have to make use of quantitative terms.

This point of view necessarily alters the significance of what has long been regarded as an important element in the diagnosis of plumbism namely, the history of exposure. The discovery of a potential source of exposure, without reference to its intensity, has often been a signal for the cessation of further clinical study of a patient. Such lapses of judgement have been encouraged on the one hand by the fact that the clinical manifestations of lead intoxication are many, varied, and largely non-specific, and on the other by the belief that the absorption of any quantity of lead, however small, might cause illness if exposure were prolonged or if an unusual susceptibility existed. There can be little excuse for such reasoning in the future. The history of lead exposure, if it is to be taken seriously, musthave some quantitative meaning. It is not enough to know the trade or occupation of the patient. Industrial conditions change rapidly. Lead hazards exist in trades supposedly free of exposure, and conversely, some potentially dangerous occupations are so safeguarded as to be free of significant exposure. The clinical history of exposure, to be useful, must therefore be precise and specific in developing a basis for an estimation of the extent of exposure either in relation to other exposure conditions which are well known to the examiner, or in terms of the effects of the exposure upon other persons similarly

occupied.

There is at least one type of potential lead exposure to which the above reservations should not apply in practice, despite their validity in principle. There is every reason for suspecting the existence of significant and dangerous lead exposure in the case of children with a history of pica. The occurrence of lead-containing commodities and the use of lead paints on furniture, toys, and other objects, within the reach of small children is much too common to ignore. The existence of symptoms even slightly suggestive of plumbism should result in prompt investigation of the child and his surroundings.

Abnormal Lead Metabolism

The limits beyond which human lead absorption comes to be associated with injurious effects cannot be defined precisely at present, and until certain details of the behavior of lead are understood more clearly it is not likely that the question will be answered satisfactorily. Certain criteria, which are in line with sound clinical practice in other fields, may be adopted. Industry provides many and varied examples of group exposure to lead compounds. Careful study of representative groups of exposed persons will eventually give a clear indication of the quantitative relationships which exist between exposure, absorption, distribution within the tissues, excretion, and intoxication. It is probable that long before we have learned the details of the physiological mechanisms which are responsible for lead intoxication in any individual, we shall have a clear idea of the types and degrees of lead exposure and absorption which are associated with the production of intoxication within the group. Moreover we shall know the range of the concentrations of lead, in excreta, blood, spinal fluid, and tissues, which are associated with the occurrence of illness among a definite proportion of human beings. Doubtless, also, in the process of obtaining these practically useful data, much will have been learned of the nature of the mechanisms involved.

It is not to be supposed that we are entirely lacking in information of the type described above. A very great amount of work has been done in this direction. What must be realized is that only a beginning has been made, and that we are almost though not quite in the dark as to the actual mechaniems of lead intoxication. It is also true, unfortunately, that the various methods which have been used in obtaining the available data have been so lacking in uniformity, and so variable in their sensitivity, that the respective sets of results cannot be put on an absolute basis for comparison or clinical use. Ambiguities of this type are being eliminated in some of the more recent studies but they are still a source of confusion. Therefore the clinician may well be somewhat cautious in his interpretation of the information which he receives from the laboratory.

For present purposes, we must regard findings beyond the range of normal values as abnormal in the sense that they indicate the occurrence of an unusual and therefore pragmatically abnormal lead metabolism. No clean-cut correlation has been shown to exist between the occurrence of clinical symptoms, and the occurrence of a specific concentration of lead in the excreta, or in any tissue or body fluid.

Litzner and Heyrauch (5) believe they have demonstrated a constant relationship between the level of lead concentration in blood and the presence of symptoms. However, they have not determined adequately the range of variability of the lead concentration in the blood of normal individuals, and their dictum cannot, therefore, be accepted as established. However it has been shown that lead absorption, as evidenced by the lead content of the blood and certain other tissues, as well as alimentary and urinary lead excretion vary measureably in accordance with the severity of exposure to lead compounds. (6). Abnormally high findings may thus be regarded only as evidence of abnormal lead exposure. On the other hand, despite the fact of variable individual response to lead absorption, there

is a threshold of absorption (evidenced by excretion) above which some proportion of exposed persons become ill, the clinical severity of the illness, as well as the proportion so affected, increasing with increase in absorption. (6). Therefore, although there is no clinical justification for the assumption that abnormal analytical results prove the existence of lead intoxication, the demonstration of abnormal findings within the range of values which have been shown to occur among exposed persons some of whom have developed lead intoxication establishes the potential clinical significance of the exposure; the higher the level of lead absorption and excretion, the more certain is its potential significance. There is no certainty, however, that symptoms shown by the person in question are due to lead. Indeed, the diagnosis of lead intoxication can be made with reasonable certainty only on the basis of symptoms and signs of illness which coincide with the known clinical picture of lead intoxication.

Thus far we have spoken of abnormal lead metabolism as though the relationship between absorption, distribution in the tissues, and excretion remained unaltered by an increased level of ingestion or inhalation, i.e. as though it represented the normal type of equilibrium maintained at a higher level. There are certain evidences that this is not the case, but that there is a type of lead metabolism which in itself is pathological. Apparently the urinary lead excretion does not increase proportionally with increased lead exposure, beyond a certain point. (6). Various hypotheses might be advanced in explanation of this phenomenon, as a working basis for further study, but regardless of the explanation it would appear that this is an indication of a change in the metabolic pattern, - a change associated with a progressive accumulation of lead within the organism. There is little adequate evidence that such accumulation is associated with a change in the manner of distribution of lead in the tissues of the body, but further investigation is needed to settle this important question.

Additional evidence of a qualitative change in the character of

the equilibrium between high levels of lead concentration in the tissues and the lead concentration in the excretions is to be found in the fact that the urinary excretory rate drops rapidly for a time after the cessation of severe exposure, and then continues at a much lower but still diminishing rate for a length of time that ~~varies~~ tends to vary with the severity of the previous exposure (7) - apparently until the normal relationship between lead intake, lead content of tissues, and lead output has been re-established. Evidently when the rate of absorption is high, some of the lead is distributed into the tissues in such a way as to be released less readily than that which is involved in a normal or only slightly increased rate of absorption. Aub has provided evidence that a more active calcium and lead metabolism takes place in the fenestrated portion of certain bones as compared with their solid portion.(8). It may be that such differences exert a profound influence upon the manner in which varying concentrations of circulating lead come to be deposited in the skeleton. Whatever may be its cause, the sharp decline in the excretory rate after the cessation of severe exposure must be reckoned with in diagnostic practice. Thus conclusive evidence of abnormal lead absorption in the form of a significantly heightened excretory rate is most readily found within a short time after the cessation of abnormal exposure. The longer the interval between the cessation of exposure and the examination of the excreta, the greater will be the difficulty in interpreting the results. Eventually all evidence will disappear, and not even the analysis of the tissues can be relied upon to show that an abnormal exposure had occurred. (7). On the other hand only a slight increase in lead absorption results in the prompt elevation of the rate of lead excretion (1 b), so that the analytical study of the excreta carried out in close time relation to a suspected exposure will establish the significance or insignificance of the exposure. In our experience, the excretory rate always continues at an elevated level for some time after the sub-

sidence of active symptoms of intoxication.

Radiologic and Microscopic Evidences of Abnormal Lead Absorption.

It is evident from the foregoing paragraphs that analytical procedures are useful as diagnostic measures only to the extent that they are a means of estimating the significance of exposure to lead compounds. They have the advantage over other clinical methods of being entirely specific, and this advantage gives them a unique usefulness. No discussion of the laboratory signs of abnormal lead absorption would be complete, however, without referring to recently discovered radiologic evidence, and to the widely accepted but somewhat ill-defined significance of certain blood changes.

ark, (9) and a little later Vogt, (10) directed attention to a sharply defined line of increased density at the margin of maximal growth in the bones of children, associated with the local deposition of abnormal amounts of lead. Their further observations have provided a means for the prompt detection of abnormal lead absorption in the case of young children. The density produced by lead deposition is not so specific in character as to differentiate it in every instance from those which may result from other pathologic processes, but it may be so striking in an otherwise apparently normal bone as to call attention to previously unsuspected lead absorption. The character of the line changes with the lapse of time, becoming less intense as the lead is given up by the bone after discontinuance of exposure, and also becoming more widely separated from the active growth area as the latter moves progressively forward. No such line is formed in adult bones, so that the usefulness of the procedure is limited to the study of children. Positive findings must be interpreted with the same degree of caution that is required in the case of other indications of abnormal lead absorption. Moreover it is to be doubted if negative findings can be accepted as proof that no recent significant absorption of lead has occurred. This is especially to be

taken into account in view of the occasional case of acute lead intoxication from the accidental ingestion of large amounts of lead.

The numerous blood changes associated with abnormal lead absorpt have been the subject of extensive inquiry and abundant controversy for many years. The greater portion of the present disagreement is concerned with the significance of variations in the numbers of various types of erythrocytes. The reticulocytes have been shown to undergo changes in number under the influence of lead absorption. Likewise basophilic stippli of the erythrocytes has long been known as an accompaniment of lead absorption and intoxication.

Various methods for staining and counting one or the other or both of these type cells have been devised and recommended, and a large number of experimentalists and clinicians, working with widely variant methods and groups of patients, have set up standards for the differentiati of normal from abnormal findings. It would be difficult if not impossible to bring any order out of the chaos which has resulted, or to harmonize the diametrically opposed points of view into a generally acceptable statement of the facts. Accordingly I shall mention only a few opinions, and shall confine myself largely to the presentation of the results which have been obtained by L. W. Sanders, of the Kettering Laboratory, through the consistent use of one simple clinical method as applied to the study of the occurrence of stippled erythrocytes in the blood of normal and abnormal individuals.

Lehman (11) believes that stippling of the erythrocytes occurs in what is usually regarded as significant numbers in conditions other than lead poisoning or the well recognized anemias. He believes that he has demonstrated that exposure to humid atmosphere, alcohol, and cement dust results in the production of increased stippling. The majority of experimental workers deny the occurrence of more than a very small number of stippled cells in normal blood. Those who admit their normal occurrence

set up a maximal limit of from 100 to 500 per million. Schwarz (12) maintains that "considerable quantities are never found in the really healthy". Koch (13) regards 100 stippled erythrocytes per million as suspicious of plumbism, and 500 per million as diagnostic. Heim (14) states that stippling is not found in cases other than lead intoxication, severe anemias, and grave intoxications. Schmidt (15) has established a figure of 100 per million as useful confirmatory evidence of lead intoxication and 1000 per million as showing a "deep seated condition".

An incompleted study of our data accumulated over a period of ten years, which is now being made by Dr. Sanders, shows that the presence of stipled erythrocytes is of frequent occurrence in the blood of persons who are apparently normal and healthy, and who are free from abnormal lead absorption. In a series of 784 persons whose carefully taken histories showed no evidence of occupational lead exposure, the mean number of stippl erythrocytes per million was found to be 339.18 with a probable statistical error of 9.72, and a standard deviation of 405.6 (equivalent to about 1 stippled erythrocyte in every 12 fields where each field contains approximately 250 erythrocytes); 6% of these men gave results varying from 1040 to 1440 per million erythrocytes, over 2% ran from 1520 to 1920 per million, and the upper limit was near 6000 per million.

It follows from these observations that the mere occurrence of stipled erythrocytes in the blood is not indicative of abnormal lead absorption and that the mere demonstration of stippling has no diagnostic value. The range of normal values must be established for any method of examination of the blood, and the method itself must be so standardized as to yield consistent and comparable results.

Our data on persons abnormally exposed to lead and to certain other agents have not been so worked up as to justify a complete statement of their significance. Nevertheless certain facts which have a bearing upon diagnosis, have become obvious from the nature of the individual results.

With due regard to the technique which we have employed, the following conclusions are justified. (a) There is a definite overlapping of the normal and abnormal range of stippling, due to wide individual variability, both among normal and abnormal groups. (b) Lead absorption is but one of a number of factors which may cause an increase in the number of stippled erythrocytes without inducing subjective illness. (c) Lead absorption tends in the individual case to cause increased stippling of the erythrocytes. (We have seen as many as 19000 stippled cells per million erythrocytes in subjectively well but leaded persons.) (d) The extent of the increase produced by lead absorption is not necessarily related to the magnitude of the lead exposure, or to the rate and magnitude of the lead absorption. (e) There is no necessary correlation between the number of stippled erythrocytes and the onset or severity of lead intoxication. (In active lead intoxication we have found up to 48,000 per million erythrocytes) (f) In our experience, thus far, lead intoxication is always associated with the presence of some degree of stippling, although in certain cases with abrupt onset following promptly upon a brief massive exposure, it may not appear promptly.

Granting the validity of these conclusions, the examination of the blood for stippling by methods of equivalent sensitivity to those which we have employed, is useful as a means of excluding lead as a factor in suspected cases of lead intoxication, when the results are negative, and as a means of providing confirmatory evidence when positive.

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(Footnote: Extensive reference to the literature of the subject may be found in this series of papers.)

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