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LEAD ABSORPTION AND LEAD POISONING

by

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Despite the availability of sound and well established methods for recognizing and preventing dangerous industrial lead exposure, there is still an unnecessarily high incidence of lead poisoning among industrial workers. Furthermore, despite the existence of generally reliable diagnostic criteria, confusion and uncertainty often enters into the consideration of a suspected case of plumbism, whether the question at issue is the proper care of a sick man, the hygienic status of a plant, the granting of compensation, or the outcome of litigation. For these reasons, one may be justified in restating certain facts which seem to require emphasis, as a background for a discussion of the hygienic and diagnostic problems that arise from the use of lead compounds in industry.

Normal Lead Metabolism

The general character of the lead metabolism of the average normal healthy American adult may be described with considerable accuracy. He ingests with his food and drink quanti-

ties of lead varying from 0.05 mgm. to somewhat more than 2.00 mgm. per day, the mean daily quantity over a period of months being approximately 0.30 mgm. (1,2,3,4). He inhales air containing a small quantity, which probably rarely exceeds 0.10 mgm. per 24 hours, and of which only a portion - doubtless a variable but otherwise unpredictable portion -, is retained by the respiratory membranes and eventually absorbed into the tissues, the remainder being either exhaled, or trapped in the upper respiratory tract and subsequently swallowed. (The quantity absorbed is so small as not to be apparent in prolonged studies in which the total lead output is balanced against lead intake by ingestion only, and is, therefore, generally insignificant.) Little ingested lead is actually absorbed into the body. A very large proportion of it traverses the alimentary tract unabsorbed and appears in the feces (1,4). Some small portion is absorbed and distributed into the tissues of the body, including the liver, from which it is partially secreted back into the alimentary tract with the bile. The effect of poor alimentary absorption together with the biliary secretion, (and perhaps other lead-containing secretions into the alimentary tract), is to make the daily fecal lead output almost equivalent to the total intake by ingestion. The small quantity that escapes elimination in the feces finds its way into the tissues, the blood, the body fluids and secretions.

The concentration of lead in the blood at any particular time depends upon two main factors, viz - the rate of absorption from the intestine or other avenue of entry, and the quantity of lead in the body as a whole (4). Thus the whole blood of normal healthy American adults usually contains from 0.01 mgm. to 0.05 mgm. per 100 grams, with a mean concentration of approximately 0.03 mgm. per 100 grams (3,5,6,7) . (Concentrations as high as 0.06 mgm. per 100 grams are occasionally found.) Very little of this is in the plasma, 95 percent or more being found in the erythrocytes (3,5,7). Lead is found normally in the urine in quantities varying from 0.01 mgm. to 0.08 mgm. per liter with a mean concentration slightly in excess of 0.03 mgm. per liter (3,6,8), and in the sweat in concentrations of the same order of magnitude (4,15). The lead in the tissues is distributed in accordance with a definite pattern. The major portion is found in the skeleton (9), the long bones such as the femur containing higher concentrations than the flat (1,3,10). Measurable and fairly constant quantities are found in the other tissues (1,3,6). The average gross quantity of lead present in the body of the normal human adult is somewhat in doubt, but it is probably not less than 100 mgm. nor more than three to four times this quantity, with due regard to variations in body weight (1). Barth (11) believed his data on the skeletal lead pointed to a progressive increase in the concentrations with age, but the differences between youth and old age

were too slight and too irregular to be convincing. Tompsett's (10) results also suggest the occurrence of progressive accumulation throughout life, in that they show a statistically significant positive correlation between age and the lead concentration in certain bones. (The results of a statistical analysis of Tompsett's data, combined with certain others, have been reported by Morris (12).) However, the variations within narrow age groups were almost as large as those between extremes of age, and the individual results were frequently beyond the range of the normal values given by other workers. These facts cast doubt upon the validity of conclusions with respect to the time factor, and they certainly limit the application of conclusions to any other than the locale of the observations. A personal communication from Tompsett, on the lead content of certain water supplies in Glasgow, has confirmed our tentative conclusion that there were sources of unusual lead exposure in the community from which most of his cases were drawn. Lead does accumulate, at least for some years, when lead is ingested in quantities several times in excess of those present in the normal American diet (4,15), but there is little or no accumulation under normal or average conditions of lead intake (15). The indirect evidence against the indefinitely progressive accumulation of lead in the tissues of persons exposed to fairly constant and essentially normal environmental conditions is much too great to be ignored. It has been demonstrated that the urinary lead excretion of individuals and of groups of persons (cf. Table 6) varies with the magnitude of their current lead absorption (1,4,13,14), and that an abrupt change of even slight proportions in the level of lead intake, results in

a fairly prompt change in the rate of the urinary lead excretion (1,4). Prolonged observations on persons maintained on considerable increases in daily lead intake have shown that the excretory response to a constant abnormal level is not maximal immediately, but it gradually builds up at a rate which is dependent upon the size of the increased daily dosage (4). Persons on the normal daily intake of 0.30 mgm. Pb or less, on the contrary, show no progressive increase in their urinary lead concentration (4,15). Moreover, studies on groups of workmen with prolonged exposure to fairly constant and apparently safe occupational conditions have shown that the group levels of urinary lead excretion do not increase progressively but remain substantially constant over long periods of time (years) if little or no change occurs in plant conditions (15). Such facts can hardly be explained except on the basis that the rate of urinary lead excretion is determined in large part by the gross lead content of the body as an organic whole, and that the maintenance of a constant or nearly constant rate of urinary lead excretion is evidence of an essentially constant concentration of lead in the body. There is sound basis, therefore, for the concept that <u>within certain limits of lead intake</u>, a state of dynamic equilibrium is maintained within the human body whereby lead intake and output are balanced over long periods of time, and progressive accumulation in the tissues does not occur.

The importance of the considerations outlined in the foregoing paragraphs cannot be overemphasized in their relation to

the problems of public and industrial hygiene that arise from the use of lead compounds. Since lead is an inevitable constituent of human tissues and excretions, it is quite obvious that there are certain normal and physiological mechanisms into which this element enters, whether incidentally or usefully. There can be no doubt that lead can be introduced into the human body without prejudice to the normal health and development of the organism, and that a toxic effect on the part of this element as well as of many others is a matter of concentration. The degree of control of public and industrial lead exposure which is necessary to avoid human hazard, therefore, should be based on precise information as to the limits of lead exposure and absorption which are unattended by any toxic manifestations.

The Evidences of Occupational Lead Absorption

The existence of occupational lead exposure can usually be recognized by a survey of the materials and activities in an industrial plant. The general order of magnitude of the exposure can be estimated by the determination of the lead content of the atmosphere of working spaces, by the use of standard methods (16,17). By such means it is usually possible to determine the degree of the occupational hazard and the extent of the need for preventive and precautionary measures. Indeed if the lead content of the atmosphere of workrooms in the lead trades were maintained generally within the limits now recognized as safe, occupational saturnism,

cause
from any other/than accidents and the unforeseen effects of changes in plant operations, would cease to occur. However, so as the hazards of many plants are not under such control, and so long as opportunities for accidental and inadvertent lead exposu exist in industry, it will be necessary to provide medical super vision which will be on the alert for the signs of potentially dangerous lead absorption. The physiological evidences of lead absorption above the normal level should be clearly understood, therefore, for their importance not only in industrial hygiene bu also in general medical and medico-legal practice.

The earlies[illegible] elevated lead absorption, and one which fortunately, is specific for lead alone, is found in an increased rate of urinary lead excretion (4). The demonstration of a small increase requires careful procedures for the collection of samples and detailed knowledge of the physiological factors concerned with the urinary excretion of lead. Various published statements have appeared to the effect that the urinary lead fails frequently to reveal the extent of lead absorption, that the results obtained on urine samples are too variable, and that the blood, more constant as to its lead content, should be used for obtaining analytical information. Those conclusions have sprung from inexperience or from the use of inadequate methods for the collection and analysis of samples. It is true that urinary samples of small volume obtained at random are subject to considerable

variation in their lead content. In individual cases, the latter varies chiefly with the urinary volume during the period of collection, i.e. if the urine is concentrated the lead concentration is relatively high, if dilute from high water intake or diuresis, the lead concentration is relatively low. This factor can be controlled, in the case of small volumes, by proper selection of the time of sampling so as to avoid extremes of water intake and output; it can be eliminated altogether by collecting one or more liters of urine, making sure that no unusual quantities of liquid are taken to speed up the collection of the sample. Equally important is the avoidance of contamination of urinary samples, and the smaller the sample the greater must be the care in this respect. Urine samples collected in the usual type of washrooms or medical quarters in manufacturing plants, or obtained by customary hospital procedures, or, in fact, secured by any other than by precise methods controlled by the examiner, are not only valueless but grossly misleading as to their lead content. Lead is ubiquitous, and it is difficult under the most favorable circumstances to avoid all sources of contamination. Numerous case reports in current journals include analytical data on the urine which by mere inspection can be discarded as erroneous. In some instances the quantities found bear no relation to the conditions of exposure known or believed to have existed, and in others they are entirely beyond the maximal limits of urinary lead excretion. In this connection it should be pointed

out that a urinary lead concentration in excess of 0.5 mgm. per liter is a rarity, that concentrations higher than 0.3 mgm. per liter are associated only with grossly dangerous conditions of lead exposure and absorption, while values exceeding 0.20 mgm. per liter do not occur in any other than highly concentrated urines without a definite and significant exposure to lead such as is associated with the admittedly hazardous lead trades.

In practice, one must depend upon results expressed in terms of urinary lead concentration rather than on the basis of lead output per unit of time. The urinary lead concentration can always be determined, but measurement of the excretory rate on a time base is not always feasible, and over short periods of time it has no advantage over random sampling. Moreover, the extensive data on the urinary concentration of lead under a wid variety of conditions, have given it a practical significance which is more certain than is that of the lead output per day. For comparative purposes, therefore, analytical results should always be expressed in terms of concentration, and when possible, on a time basis as well.

The greater stability of the blood, with respect to its lead concentration, from hour to hour, as compared to the urine, is unquestioned. On the other hand the change in the blood concentration as a response to lead absorption is proportionately less than that of the urine, the result being that the effects of exposure are more easily demonstrated by the urinary

lead concentration than by that of the blood. The chief advantage of the analysis of the blood, ~~for diagnostic purposes,~~ lies in the fact that it requires no manipulation on the part of the person examined. If proper precautions are taken by the examiner, therefore, no factor of contamination need by considered. Blood samples, however, must be taken with the utmost precaution in a dust-free room, by means of specially fabricated needles, into specially cleaned containers. The minutest details of handling are of the same importance, though of different type, as those used in the maintenance of aseptic technique in surgery. Lead, like minute living organisms, enters into samples through the air by means of contact with any save the most meticulously purified water, reagents, glassware and other equipment.

The value of the analysis of the feces of groups of exposed workmen as a means of determining the relative magnitude of their lead exposure by ingestion and inhalation has been pointed out by Hunter (15). By this ~~means~~ we know that a considerable proportion of dust in the respired air is caught in the upper respiratory tract and subsequently swallowed, the quantity of lead appearing in the feces provides a somewhat crude but highly useful measure of the exposure for the period represented by the fecal sample. The lead in the feces is predominantly and, indeed, almost wholly ingested or inhaled (subsequently swallowed) lead under any other than the most unusual circumstances. It is probable that considerable quantities of lead may be secreted into

the alimentary tract for a short period following the absorption of very large amounts of lead, but, in the main, the true alimentary excretion of lead is quite small. It is probably of little greater magnitude per day than that excreted in the urine, and it may be even less under certain circumstances (4,15). This true alimentary lead excretion is completely masked by the much larger quantity of unabsorbed lead that is ingested with the food under ordinary conditions. It is quite impossible to determine its magnitude or even its occurrence when lead exposure occurs through inhalation of dusts, for under these conditions it is an exceedingly minute fraction of the fecal lead. For these reasons the fecal lead, as such, bears no significant relation to the lead content of the body of an individual, and indicates nothing with respect to absorbed lead. As a means of estimating the lead absorption of either groups or individuals for diagnostic purposes it is wholly worthless.

Other signs of lead absorption above normal levels are, (1) changes in the quantity and distribution of basophilic material within the erythrocytes, and (2) the appearance of punctate deposits of lead sulphide in certain mucous membranes, especially in the margin of the gum tissue. Neither of these signs is indicative of lead intoxication. Both occur in entirely healthy persons, except that the gingival lead line occurs only where sulphide is present in the gum tissue, and, therefore, it is usually associated with a low-grade gingivitis. It is rarely seen in the gums

of children, for example, among whom chronic gingivitis is uncommon.

Punctate basophilia, or "stippling" of the erythrocytes, within certain limits, is of normal occurrence in the human blood. In examining the blood of some thousands of apparently normal healthy adults free of occupational lead exposure, my associates have found such erythrocytes in numbers ranging from one or two up to as high as six thousand per million erythrocytes. Some 6 percent of the group showed one thousand or more per million erythrocytes, while the mean figure for 784 persons was 339.18 $\pm$ 9.72 per million erythrocytes (18). The number of such stippled erythrocytes in the blood shows little or no change with small increments of increased lead intake, but at higher levels of exposure and absorption their number in the circulating blood tends to increase. Considerable variation in the degree of individual response is observed, and fairly wide variations occur from day to day, but with increasingly severe conditions of lead exposure there is a definite trend toward increasing numbers of stippled erythrocytes in the blood of exposed workmen, if comparisons are based on groups rather than individuals (14). These facts are responsible both for the usefulness of regular microscopic examinations of the blood of workmen as a means of estimating the severity of occupational lead exposure, and for the inadequacies of such measures for diagnostic purposes in individual cases.

Suffice it, for present purposes, to point out that hazardous exposure to lead compounds is associated with the appearance of definitely abnormal numbers of basophilic erythrocytes in the blood of a considerable proportion of exposed workmen.

A "lead line" may appear in gum margins which are the site of bacterial invasion whenever the lead content of the involved tissues is sufficiently elevated. We have observed the appearance of a faint blue line at the edge of an infected gingival area in one person whose blood contained lead only to the extent of 0.05 mgm. per 100 grams. Easily identified lead lines signify somewhat higher levels of lead absorption, and in general, they are indicative of hazardous lead exposure. Nevertheless, obvious deposits of lead sulphide are seen in the gums of persons with no demonstrable symptoms or signs of intoxication. They must be differentiated from similar deposits resulting from the precipitation of other metallic sulphides, notably of bismuth, and they must not be confused with the normal pigment of negroes and correspondingly dark-skinned peoples. The former differentiation is sometimes provided by the medical history of the person in question, but may require analysis of the blood or urine or both; the latter can usually be made by careful study of the locus and appearance of the pigment. The natural pigment is rarely found in the gum tissue on the lingual side, while a favored site for the first appearance of lead line is in the extreme lingual edge of the gum opposite the bicuspids and molars, especially in the lower jaw.

The bluish purple line of gingival congestion may be taken for lead line by the inexperienced, and especially if examination is made without expression of the blood by means of a transparent applicator (such as a glass slide). More frequently, the stained or discolored surface of a tooth just visible beneath a thin layer of gum tissue is mistaken for a lead line. The differentiation is not always easy and resort must sometimes be had to the use of a hand lens, or even to biopsy followed by microchemical or spectrographic analysis.

The Recognition of Dangerous Lead Exposure

The differentiation of harmless from toxic human lead exposure in any final sense, must be based upon adequate means for detecting the earliest or the slightest toxic effects of lead upon the human organism. So much has been said and believed about the insidious and unpredictable effects of lead absorption, that it is difficult to approach the subject in a realistic manner. Admittedly, in the case of lead, as well as of most elements and compounds whose physiological behavior cannot be defined in complete detail, it is well to maintain openness of mind and acuity of observation, with respect to remote effects upon general health, well being, and length of life, that may accrue to individuals and groups as the result of prolonged exposure. Nevertheless, careful clinical study of workmen under known conditions of lead exposure over periods of years, has pro-

vided convincing evidence of the validity of certain working principles on which modern hygienic practice in the lead trades is based. These principles, stated in general terms, are as follows, (1) that the toxic effects of human lead absorption can be detected and identified as a well defined clinical syndrome despite some variability in details; (2) that persons who do not develop lead poisoning in recognizable form, suffer no demonstrable injury to their health or well being as a consequence of their absorption of lead; and (3) that dangerous lead exposures can be differentiated from safe on a quantitative basis. Each of these points merits careful consideration.

The conviction or the acquittal of lead as the causative factor in the illness of industrial workers is relatively easy if the conditions of exposure to lead are well known and if such illness is subjected to adequate medical study at the time it develops. For this reason the attending industrial physician should have considerable advantage over other physicians who may be consulted. The latter usually lack precise information as to the exposure, and, therefore, must either accept hearsay information on that score, or resort to indirect means for determining the facts, i.e. laboratory evidence of lead absorption. Such indirect evidence can be obtained satisfactorily only if the patient is seen early in the course of his illness. Unfortunately a physician is often con-

sulted some time after the subsidence of the episode of intoxication, and in such case he must depend, for this and all other data, on sources that are likely to be inadequate and are sometimes unreliable. In view of the differences of opinion that arise out of these circumstances it seems advisable to discuss certain major aspects of the diagnosis of lead poisoning from the viewpoint of the general physician, whose knowledge and judgment, as compared with that of the industrial physician on the scene, must be in keeping with the more difficult problem with which he is presented. In this way the scope of the discussion will extend somewhat beyond the toxic effects of lead absorption as an indication of hazardous lead exposure. It [illegible] ~~enhanced thereby~~ and [illegible] ~~thereby~~ and [illegible] its [illegible]

[illegible] diagnosis of plumbism is based upon (a) a history of significant lead exposure, (b) the presence of an illness or injury which is consistent with the known clinical picture of lead intoxication, and (c) certain corroborative laboratory findings. The first and last items of this triad might well be combined into one, in practice, since they lead by different means to the same end, - that of implicating or excluding lead as the specific toxic agent -, and in that role the one supplements and in some instances substitutes for the other. However, they can better be discussed separately.

The history of lead exposure as it is commonly recounted to the physician is likely to be worthless and is often misleading, not so much because it may be intentionally colored, as because it gives an inadequate basis for determining the severity of the exposure. Detailed knowledge of industrial procedures and precise information as to the conditions existing in a specific plant or operation, are absolute essentials for the interpretation of such an history. If the examiner's experience in industry is extensive, he may sometimes elicit the information he requires by careful questioning. Otherwise, he will be well advised to use the history merely as an indication that lead absorption is a possibility in the case, and seek information as to the extent of the exposure through other channels. The assumption that employment in actual or supposed lead trades involves hazardous lead exposure is the most frequent cause of erroneous diagnoses of lead poisoning in industrial workmen. It is one which can be avoided only through the general acceptance among physicians of the fact that lead exposure has no meaning in the hygienic or diagnostic sense unless it results in the absorption of toxic quantities of lead.

The clinical picture of lead poisoning is illustrated in part by the data obtained from a series of thirty proved industrial cases that have come to us before the subsidence of an acute episode of intoxication. Table 1 gives the symptoms as recorded, in the order of decreasing frequency of occurrence, and indicates the number of instances in which the specific symptom was not mentioned

in the record. Table 2 lists the physical signs in similar manner and in addition shows when the sign was recorded as absent. Table 3 shows the chief complaint at the time of the examination. None of those cases was seen at the onset, and several were seen late in the toxic episode, the average time between the onset and our examination being thirty days. The series, therefore, is characteristic of cases of active industrial plumbism as they occur in general or consulting practice in diversified industrial centers.* From these data it is apparent that the physical signs found in lead intoxication, with the exception of the gingival lead line, - which as indicated previously is not a sign of intoxication, but only of absorption -, are rather few in number and are quite non-specific. The subjective complaints, on the other hand, are numerous. They too are non-specific, but case study shows that they group themselves in such a way as to reveal the patterns of the toxic process. Obviously, there is a general intoxication in which weakness, loss of weight, and lassitude are prominent. Associated with these, and producing much the commonest clinical picture, is a disturbance of the gastroenteric tract of which constipation, anorexia, and abdominal discomfort or actual colic are the regular manifestations. There may be additional symptoms arising from neuro-motor abnormalities, and from intoxication of the central nervous system. The variations in the severity of these associated complaints give rise to the three main clinical types of

* Compare the symptoms and signs with those described by Russell and his associates (19) and Dreessen and others (20) in their studies of workmen in the storage battery industry.

saturnism, -the gastro-enteric, neuro-muscular, and cerebral. Physical signs, although meager, accompany these symptoms, and by their type and importance tend to establish the character of the intoxication. Thus, if the only complaints are referable to the gastro-enteric tract, the physical signs are likely to be limited to pallor, malnutrition, loss of weight, and abdominal tenderness on examination, or the visceral signs of acute abdominal pain. If the neuro-motor symptoms are predominant, there will be concomitant signs of motor weakness, paralyses, atrophy or dysfunction of muscles and muscle groups, or at least disturbances in muscle tonus and changes in reflexes. The occurrence of cerebral symptoms, such as insomnia, excessive dreaming, nervous excitation or depression, together with headache, vertigo, nausea and vomiting, (the latter four cannot be assumed to have had cerebral origin), may be seen not to be limited to the encephalopathic type of plumbism, of which there were only two examples in the series. Whether due to the effects of lead upon the brain or to circulatory disturbances, these symptoms indicate that the central nervous system is involved frequently in lead poisoning despite the low incidence of serious cerebral intoxication. This fact is in keeping with other clinical and experimental evidence, too extensive for this discussion, that strongly supports the belief that the degree of cerebral lead intoxication is not a matter of chance variation in individual response to lead absorption, but is rather an expression of the extent of cerebral lead absorption. Further sup-

port for this thesis is given by the occurrence of the two cases of encephalopathy in this series, both having their origin in severe and prolonged exposure to lead dust. It is generally believed that lead encephalopathy in adults is the result of intense lead exposure, and that the comparative infrequency of its occurrence in present-day American industry, in comparison with an earlier period, is due to the elimination, in the main, of unregulated and grossly hazardous lead exposure. Our experience bears out this belief. The clinical evidence likewise supports it, in that when the cerebral symptoms are foremost in the clinical picture, the objective signs of increased intracranial pressure and of profound cerebral and general intoxication develop, culminating not infrequently in convulsions, coma and death.

It is not always recognized that other serious or disabling manifestations of lead poisoning involving the nervous system are associated only with relatively severe types of lead exposure. The instance of bilateral wrist-drop in this series, is a case in point. Our experience indicates that tremor, hyperreflexia, varying degrees of weakness of extensor muscles in the forearm, and minor sensory distrubances are not infrequent in their occurrence among workmen under definitely hazardous conditions of lead exposure, but that full-blown neuritis and paralysis is rare and arises only from severe and usually from prolonged lead exposure. We have not seen paralyses of the lower extremities or trunk in lead poisoning in the adult, nor have we seen optic neuritis and atrophy except in

association with such an obvious etiologic factor as glaucoma.

It is apparent from the foregoing data and discussion that lead poisoning as a clinical syndrome resulting from the less severe, (i.e. partially but incompletely controlled), types of lead exposure that characterize the American lead trades by and large at this time, is essentially a toxic derangement of the gastro-enteric tract, on which are superimposed various functional disturbances of the peripheral and central nervous system, the type and severity of which depend largely upon the severity and duration of the lead exposure. This epitome is lacking in one important respect, in that the effects of lead absorption upon the blood and the bone marrow are not included. This feature of the disease will be covered under the findings of the laboratory.

The laboratory findings occupy an important position in diagnosis of lead poisoning in any case, and are especially valuable, as suggested previously, when the severity of the lead exposure is unknown or open to question. Indeed in many instances they constitute the only objective means for determining whether or not there has been occupational lead exposure, and for establishing its potential significance in relation to a suspected or alleged case of lead poisoning. However, if it is useful and often necessary to obtain laboratory data, it is even more important to recognize their limitations.

Characteristic laboratory findings in lead poisoning are

illustrated in Table 4. A cursory examination of these data reveals a number of important facts.

(1) The erythrocyte count is likely to yield low and perhaps quite low results, but on the other hand it may be entirely normal.

(2) Likewise, the hemoglobin content of the blood may be significantly low, only slightly diminished, or undiminished.

(3) The leucocytes show no characteristic change. (Although more or less specific, progressive changes in certain cell types have been reported under conditions of prolonged occupational lead exposure (21), such changes could have but little significance when only one or a few differential leucocyte counts can be carried out on the individual case.)

(4) There is a significant increase in the number of "stippled" erythrocytes in the peripheral blood in most cases. Occasionally, the numbers are little or no greater than those found in normal healthy persons with no abnormal lead exposure. Without exception, however, stippled erythrocytes were found in the blood of these persons with active lead intoxication, and in most instances definitely abnormal numbers were found. This is in accord with our experience and that of many other workers. Indeed, except in rare instances of sudden overwhelming lead intoxication, the absence of stippled erythrocytes in the blood during the course of an active illness is convincing evidence that lead is not the

cause of the illness.

Additional facts with respect to stippling of the erythrocytes may be summarized briefly. Because of wide variation in the individual response of the blood and the bone marrow to lead exposure and to a variety of other poorly defined factors, it is not possible to determine the severity of the lead exposure, or the extent of lead absorption, in the individual case, by counting these cell forms. There is a decided tendency, however, toward a prompt and progressive increase in the number of such erythrocytes, both in individuals and in groups, when the lead exposure is abruptly increased, and in the absence of proof to the contrary such changes in the blood should be regarded as presumptive evidence of increased lead absorption in workmen in lead trades. Increases in stippling may not be taken as a sign of existing or impending lead intoxication, for large variations occur without symptoms or signs of illness, but they should be considered as danger signals, the urgency of which is roughly proportional to their magnitude and speed of development. The numbers of stippled erythrocytes in the blood diminish with variable rapidity on termination of lead exposure, and it is usual to find them restored to substantially normal levels long before the lead concentration in the blood and urine have shown corresponding decrease. For this reason the results in the cases included in Table 4 were considerably lower than if they had been obtained earlier.

(5) The lead content of the blood was elevated significantly above the normal in all of these cases, despite the time interval between termination of this exposure and the analysis of the sample. No relationship could be established between the lead concentration in the blood and the severity of the toxic episode from its onset or the acuteness of symptoms at the time of the examination. The blood lead concentration may return to substantially normal levels before the urine does so, and for this reason, the urine should always be studied if the case is seen late in the course of the intoxication.

(6) There is an elevation in the lead concentration of the urine in every instance as shown by the analysis of samples of large volume (1 liter or more). The necessity for care in the interpretation of analytical results on spot samples of urine is illustrated by the results obtained on such samples in this series of cases. One of these small samples, obviously dilute, yielded a result of 0.07 mgm. per liter; while another, which was of very small volume and may have been contaminated slightly, gave the almost incredible figure of 0.85 mgm. per liter. Such results would require checking if they stood alone. In these cases, however, the analyses of the blood and the large samples of urine provided all the information required to verify the significance of the lead exposure. It is good practice, therefore, to obtain blood samples along with spot samples of urine in routine diagnostic work. If both the blood and the urine give normal or abnormal results, the interpretation is obvious, but if they are divergent,

further analyses are required to establish the facts.

Considering the laboratory data as a whole, there is nothing in them, except some evidence of anemia, in most instances, to denote intoxication, and since anemia due to lead is not specific in its characteristics, neither this abnormality nor any other gives adequate basis for a diagnosis. On the other hand, the analytical data provide the very significant evidence that hazardous lead exposure had occurred, if the time interval since termination of exposure were taken into account. This, as previously indicated here and elsewhere (22) is the role of lead analyses in the diagnosis of plumbism. They perform this role admirably, but they should not be given weight in any other capacity. We have not been able to verify the conclusion of Smith and his associates (7) that a shift in the partition of lead between cells and plasma in the blood serum is indicative of lead intoxication. We have seen intoxication when the distribution of lead between cells and plasma was entirely normal, and conversely, we have seen high lead values in the blood, with relatively high lead concentrations in the plasma in the complete absence of toxic symptoms. It may be that the lead of the erythrocytes is relatively inert, while that in the plasma is more active chemically and physiologically. This has not been established, however, and the nature of this equilibrium is not understood. Until it is, assumptions should not be made concerning it, except as working hypotheses.

Experience has shown that when occupational lead exposure is insufficient to cause at least occasional toxic episodes resembling those described as characteristic of plumbism, no evidence is found of vague general disorders or impairment of the health of workers, that differ in frequency or degree from those seen in any comparable group of unexposed industrial employees. To be sure, careful studies must be conducted over long periods of time to determine whether this is strictly true, but there is no presently available evidence which justifies serious doubt on this score. It is possible, however, that the standards now employed to define safe lead exposure may be subject to slight change, both qualitatively and quantitatively. Of the various standards that might be considered, there are two which by reason of their sound practical and theoretical background are most likely to endure.

(1) Expressed in terms of air analyses, the upper limit of safety for industrial lead exposure is taken to be a concentration of 1.5 mgm. Pb per 10 cu. M. of air. One interpretation of this standard holds that "when the air of workrooms regularly contains not more than 1.5 milligrams of lead per 10 cubic meters of air, as measured by standard methods, cases of disabling lead intoxication do not occur among the men who work regularly in such workrooms, and cases of questionable or mild intoxication are rare. In practice, the attempt is made to maintain the lead content of the air within such limits as will yield an average of not more

than 1.5 mgm. Pb per 10 cu. M. throughout the working day, while preventing the occurrence of materially higher concentrations (5 mgm. per 10 cu. M. or more)"(43). Evidence of the validity of this standard has been provided by other investigators (39, 27), and need not be enlarged upon here.

(3) The upper limit of safe lead exposure as defined on the basis of the urinary lead excretion of exposed workmen is represented by a mean value of approximately 0.10 mgm. Pb per liter for samples that do not exceed 0.15 mgm. per liter frequently and rarely exceed 0.20 mgm. per liter. In order that there may be no opportunity for misinterpretation of a standard which includes a range of values as well as a mean, some characteristic illustrations of results obtained on various groups of persons are given in Table 5. It should be pointed out that these data have resulted from the application of analytic methods of high sensitivity and accuracy. Less sensitive methods will yield lower values under corresponding conditions, while less accurate ones may give either higher or lower values.

The line of demarcation between safe and dangerous lead absorption as drawn in Table 5 is indicated by the change in the rubrics under which the data are grouped. The lead exposure that was responsible for the analytical results listed under Plant E was associated with occasional but definite cases of lead intoxication among workmen. The cases seen during a period of several years in which the severity of the lead exposure had undergone little or no apparent change, had been comparatively mild. In contrast, cases

of wrist-drop had been seen among the workmen in Plant G, and one fatal case of lead encephalopathy had occurred. The analytical results grouped under all three of these plants cover a wide range and are irregular in their frequencies in the higher levels. Irregularly occurring high values are open to the suspicion that they have resulted from the contamination of samples, and for that reason they have been ignored in calculating the means. It is also true, however, that excessively high urinary lead concentrations are more prone to occur sporadically, when the lead exposure of a plant is highly variable, whether because of unavoidable technical difficulties or through disregard of hygienic measures.

The several sets of data, beginning with normal individuals from whom samples were obtained under the most favorable conditions of the laboratory, and extending through those from Plant D, are quite regular with respect to the frequencies under the different rubrics. All of the results are credible in the statistical sense, and the range of variability is not excessive. The range increases, however, with increase in the general level of the lead exposure. There is a distinct gap between the results on Plant D and those on Plant E. Despite this gap, the upper level of safety is set definitely at Plant D, for the reason that while no actual cases of lead poisoning have occurred in Plant D in more than 12 years, suggestive clinical evidences of incipient lead intoxication have been seen from time to time in men whose exposure has been increased for short periods by reason of changes or difficulties in plant operations. The workmen in Plant C showed no evidences of lead absorp-

tion other than the elevation of the lead content of their excreta (and also of their blood, which had a mean level of 0.05mgm/gm.) Those in Plant B showed only a slight elevation of the urinary lead concentration. There was no statistically significant increase in their blood lead concentration over that of persons with no occupational lead exposure. No statistically valid increase could be detected in the numbers of stippled erythrocytes over normal levels among the men in Plants A, B, and C, but a well defined increase could be demonstrated in the men in Plant D. (The relative insensitivity of analytical and microscopic changes in the blood in detecting lead exposure can be recognized from the two foregoing statements.)

There is reason to believe that the critical level of safe lead exposure set on the basis of urinary lead excretion does not coincide exactly with that expressed in terms of air analyses, and that it is somewhat on the safe side. Examination of the recent data of Dreesen and co-workers of the U. S. Public Health Service (20) would seem to indicate that exposure to atmospheres containing less than 1.5 mgm. Pb per 10 cu. m. may yield urinary values that average higher than 0.10 mgm. per liter. Their data, while perhaps not comparable to those given above on a strictly quantitative basis, are, nevertheless, in general agreement with what has been said on the subject of the urinary lead excretions in relation to lead exposure, in the foregoing discussion. Time and further work will be required to work out an exact correlation between the two standards.

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TABLE 1

FREQUENCY OF OCCURRENCE OF SYMPTOMS IN 30 CASES OF LEAD POISONING STUDIED BEFORE SUBSIDENCE OF AN ACUTE EPISODE

Symptoms	Recorded as Occurring	No Data
Weakness	30	0
Weight loss	27	3
Constipation	25	5
Colic	24	6
Anorexia	23	7
Abdominal pain	23	7
Arthralgia	21	9
Lassitude	17	13
Frequent use of cathartics	17	13
Generalized aching	16	14
Vomiting	16	14
Nausea	15	15
Insomnia	13	17
Headache	12	18
Metallic taste	12	18
Generalized stiffness	10	20
Excessive dreaming	9	21
Excessive salivation	8	22
Localized myalgia	8	22
Vertigo	8	22
Nocturia	5	25
Numbness of extremities	5	25
Muscle cramps	4	26
Impotence	3	27
Visual disturbances	3	27
"Nervousness"	3	27
Convulsions	2	28
Dysphagia	2	28
Ataxia	2	28
Stupor or coma	2	28

TABLE 2

FREQUENCY OF OCCURRENCE OF PHYSICAL SIGNS IN 30 CASES OF LEAD POISONING STUDIED BEFORE SUBSIDENCE OF AN ACUTE EPISODE

Physical Signs	Present	Absent	No Data
Lead line	20	10	0
Pyorrhea	20	5	5
Extensor weakness of wrists	17	9	4
Malnutrition	12	12	6
Abdominal tenderness	11	14	5
Hyperactive biceps reflex	10	12	8
Hyperactive patellar reflex	9	18	3
Tremor	9	12	9
Pallor	8	11	11
Sensory disturbances	7	17	6
Excessive salivation	5	14	11
Myoedema	4	5	21
Joint tenderness	4	20	6
Eyeground changes	3	20	7
Stupor	2	28	
Convulsions	2	28	
Delirium	1	29	
Coma	1	29	
Bilateral wrist-drop	1	29	

TABLE 3

CHIEF COMPLAINT AT TIME OF EXAMINATION IN 30 CASES OF LEAD POISONING STUDIED BEFORE SUBSIDENCE OF AN ACUTE EPISODE

Complaint	Frequency
Abdominal pain, cramps or colic	22
General weakness	4
Joint pain	3
Nausea and vomiting	1

TABLE 4

RANGE OF VALUES AND MEAN VALUES FOR VARIOUS ITEMS OF LABORATORY INFORMATION ON 30 CASES OF LEAD POISONING STUDIED BEFORE SUBSIDENCE OF AN ACUTE EPISODE

Item	Range	Mean and P. E.
Erythrocytes (M/cu mm)	3,440-5,400	4,275 ± 71.0
Hemoglobin (Gm/100cc)	8.47 - 14.9	11.4 ± 0.3
Leucocytes (cu mm)	4,300-11,000	7,750 ± 300.1
Percentage polys.	35 - 88	60.6 ± 1.7
Percentage lymph.	12 - 56	32.7 ± 1.5
Stippled erythrocytes/million	720 - 16,000	5,856 - 688
Lead in blood (Mg/100 gm)	0.07 - 0.35	0.17 ± 0.01
Lead in small sample of urine (Mg/L)	0.07 - 0.85	0.23 ± 0.02
Lead in large sample of urine (Mg/L)	0.12 - 0.33	0.22 ± 0.01

TABLE 5

LEAD CONCENTRATION IN THE URINE OF VARIOUS GROUPS OF PERSONS

Lead in Milligrams per Liter	Frequencies of Occurrence of Values Indicated: 24 Hr. Samples on Unexposed Experimental Subjects	Samples of Large Volume on: Unexposed Persons	Workmen in Plant A	Workmen in Plant B	Workmen in Plant C	Workmen in Plant D
0-0.019	339	42	8	3		
0.02	216	54	8	110	5	3
0.04	17	26	3	239	6	14
0.06	1	3	3	104	11	17
0.08	1		2	15	5	10
0.10					2	9
0.12					4	6
0.14					3	9
0.16						4
0.20						1
0.22						1
No.of Samples	574	125	24	471	36	74
No.of Persons	2	125	24	9	36	74
Mean	0.021	0.028	0.037	0.051	0.079	0.097
P.E.	±0.0003	±0.002	±0.004	±0.0005	±0.004	±0.004
S.D.	±0.009	±0.014	±0.025	±0.016	±0.040	±0.045

* Means calculated on results above dotted line.

Lead in Milligrams per Liter	Frequencies Samples of Large Volume on: Workmen in Plant E	Workmen in Plant F	Workmen in Plant G
0-0.079	11	4	6
0.08	31	27	28
0.16	14	17	20
0.24	8	7	13
0.32	2	1	3
0.40	1	2	5
. . . . .	. . . . .	. . . . .	. . . . .
0.48	1		4
0.56		2	3
0.64			2
0.72 or 0.80 more	3	2	1
	73	62	86
	73	24	86
	0.155*	0.172*	0.194*
	-0.007	-0.008	-0.008
	-0.087	-0.085	-0.102