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THE METABOLISM OF LEAD IN MAN IN HEALTH AND DISEASE

by

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LECTURE III

PRESENT HYGIENIC PROBLEMS RELATING TO THE ABSORPTION OF LEAD

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The natural environment of this planet is such that the occurrence of lead in the tissues, body fluids and excreta of its human inhabitants is inevitable. On the other hand, the artifacts introduced into the environment by the past and current activities of mankind have provided numerous unanticipated and often unrecognized opportunities for human absorption of a wide variety of lead compounds. Most of these contributions to the alimentary or respiratory intake of lead are small, but sometimes single or multiple factors produce dangerous conditions. This occurs most frequently in connection with the occupations of individuals and groups. In the United States of America, for example, occupational lead poisoning, although reduced in severity now, in comparison with earlier periods, occurs more frequently, according to somewhat untrustworthy statistics, than any other occupational disease. The large proportion of cases of lead poisoning are occupational in origin, but cases occur from time to time in the adult population as the result of a variety of conditions in the household. Moreover, permanently disabling and fatal cases of lead intoxication occur among children between the ages

of 1 and 3 years with distressing frequency and regularity, in many North American cities.

From the broader aspect of the public health, the contamination of the atmosphere with lead from a number of sources may increase under the influences of modern technology, especially in industrial and urban centres, and therefore, this potential source of public exposure to lead requires periodic investigation. More importantly, the opportunities afforded for the contamination of food with lead, in a country in which the processing of food materials is a complex industry of very large and widespread proportions, must be kept under constant surveillance. The variety and volume of the beverages consumed by the public must also be considered in this relationship, and not even the drinking water of a nation can be ignored, despite the comparative ease with which the lead content of urban water supplies can be controlled. The general exposure of the population to lead from these combined sources must be kept within appropriate limits, and, therefore, no standard promulgated for the safety of the public, with respect to the concentration

of lead in individual items of food or beverages, or in the air, has independent validity.

Of the many medical and hygienic problems that arise out of the matters mentioned above, as well as those which stem from other sources, four have been singled out for consideration on the background of the facts concerning the metabolism of lead, which have been the burden of the two preceding lectures.

1. THE DIAGNOSIS OF LEAD INTOXICATION.

Lead poisoning, in a variety of forms, has been known to physicians for centuries, and like many another matter that is "common knowledge", there have been many false ideas and many more hazy concepts of its nature and significance. This is neither the time nor the place to deal with the manifold facets of this situation, which has been further obscured and complicated by the socio-economic and legalistic aspects of workmen's compensation laws and procedures. Suffice it here to consider the contributions to the clarification of these problems which derive from the establishment of sound physiological criteria by which the magnitude and significance of the absorption of lead by an individual patient can be appraised, not by hearsay, nor by the generally inadequate and quantitatively unreliable history of the patient's exposure to lead as recounted by himself, nor even by the appraisal of his environment, but by the determination of the lead content of his urine and blood, or that of his tissues (post-mortem).

Systematic analyses of the lead in the atmosphere of industrial establishments over sufficient periods of time, in concert with clinical examinations and determinations of the lead in the urine and blood of the populations at risk in lead-using industries, have yielded data which have revealed the relationships which exist (a) between exposure to lead and absorption of lead, and (b) between the absorption of lead and the incidence (and to a lesser extent, the severity) of lead poisoning. The extent of the absorption of lead by men in industry is clearly related to the severity and the duration of their occupational exposure to

lead. Under the somewhat variable conditions which exist in a specific industry or series of industries, this relationship, to be sure, is not as well defined, quantitatively, as it has been shown to be in our well-controlled experiments in the laboratory. On the other hand, the greater range of severity in industrial exposure to lead generally, as compared with the modest range which is compatible with the complete safety of experimental subjects in the laboratory, has yielded unmistakable evidence of a correlation between exposure and absorption. This fact is illustrated in Tables 25 and 26, from the aspect of the absorption of lead, by the data obtained in the investigation of five industrial populations (selected more or less at random from many other corresponding series of data which cover the desired range of findings without unnecessary replication). The environmental conditions under which these groups of men worked were such as clearly to differentiate them, in increasing order of severity from left to right in Tables 25 and 26, on the basis both of periodic inspections, and analyses of the air at the breathing zone of the workmen. The gradation of the absorption of lead among the groups, as indicated by the ranges and the distribution of the frequencies of occurrence of various levels of the concentration of lead in the urine (Table 25), requires little comment, despite the overlapping of the findings in the higher rubrics in the four columns to the right. The mean values show the order of severity satisfactorily, except for the fact that the exposure associated with one of the occupations of the group listed under the sub-heading "Slight and Severe" was considerably greater and more difficult to control than that of the others. As we shall see later, certain individuals in this group (those employed in the job referred to above) were in danger, while the majority of the group was not. This situation exists in many industries. In the absence of quantitative measurements of the severity of the exposure associated with specific jobs or areas within an industrial plant, it has often produced unexpected cases of poisoning and has contributed greatly to the unwarranted belief that the "susceptibility"

TABLE 25
Comparison of Various Occupational Groups with Respect to the Concentration of Lead in Their Urine, in Association with Varying Degrees of Severity of Exposure to Lead Below and Above the Threshold of Danger.

<i>Lead in Urine</i>	<i>Frequencies in Ascending Order of Severity of Exposure to Lead—Left to Right</i>				
<i>mg. per litre</i>	<i>Demonstrable</i>	<i>Slight and Severe</i>	<i>Near Threshold</i>		<i>Very Severe Very Dangerous</i>
			<i>Safe</i>	<i>Unsafe</i>	
0.00 — 0.039 ...	41	35	—	3	2
0.04 — 0.079 ...	156	98	11	7	2
0.08 — 0.119 ...	9	56	22	10	13
0.12 — 0.159 ...	—	35	16	14	14
0.16 — 0.199 ...	—	27	7	11	9
0.20 — 0.239 ...	—	8	2	3	9
0.24 — 0.279 ...	—	7	2	4	6
0.28 — 0.319 ...	—	4	3	3	5
0.32 — and over ...	—	3	—	2	19
Total Number ...	206	273	63	57	79
Mean ...	0.051*	0.102*	0.130*	0.152*	0.238
S.D. ...	±0.014	±0.069	±0.059	±0.024	±0.151

* Calculated from a different arrangement of the frequencies.

TABLE 26
Comparison of Various Occupational Groups with Respect to the Concentration of Lead in Their Blood, in Association with Varying Degrees of Severity of Exposure to Lead Below and Above the Threshold of Danger.

<i>Lead in Blood</i>	<i>Frequencies in Ascending Order of Severity of Exposure to Lead—Left to Right</i>				
<i>mg. per 100 g.</i>	<i>Demonstrable</i>	<i>Slight and Severe</i>	<i>Near Threshold</i>		<i>Very Severe Very Dangerous</i>
			<i>Safe</i>	<i>Unsafe</i>	
0.00 to 0.019 ...	—	—	—	—	—
0.02 — 0.039 ...	11	85	4	1	—
0.04 — 0.059 ...	24	122	30	18	9
0.06 — 0.079 ...	1	50	22	21	12
0.08 — 0.099 ...	—	7	5	6	17
0.10 — 0.119 ...	—	6	1	6	14
0.12 — 0.139 ...	—	2	—	1	5
0.14 — 0.159 ...	—	—	—	—	4
0.16 — 0.179 ...	—	—	—	—	1
0.18 — 0.199 ...	—	—	—	—	1
0.20 — 0.219 ...	—	—	—	—	2
0.22 and over ...	—	—	—	1	10
Total Number ...	36	272	62	54	75
Mean ...	0.042*	0.050	0.060	0.075	0.130*
S.D. ...	0.008	±0.019	±0.016	±0.041	±0.091

* Calculated from a different arrangement of the frequencies.

of individuals to lead poisoning is highly variable.

We shall return to Table 25 later, in considering the relationship between severity of exposure and degree of hazard. Table 26 deals with the analytical findings in the blood of the same individuals and groups (the groups are the same, but certain discrepancies in the frequency of sampling are apparent) represented in Table 25. In keeping with the lesser degree of physiological variability of the concentration of lead in the blood, versus that in the urine, as noted in experimental subjects, as well as with the relatively slighter dependence of the concentration of lead in the blood upon the daily or immediate rate of absorption of lead, the results in Table 26 are more indicative of the true status of these men, with respect to the extent of their body burden of lead at the time of sampling, than are those in Table 25. The distribution of the results within and among the industrial groups is, therefore, more clearly indicative of the relative status of the individuals and groups. Here, there is no doubt as to the gradation of absorption from left to right, except in the "Slight and Severe" group, in which certain individuals in one occupation differ significantly from the main group. (The lack of a bi-modal distribution of the results is due to the small number of persons in this divergent subgroup.)

Alike, in Tables 25 and 26, the sub-headings indicate the point at which safe levels of absorption are differentiated from those which are dangerous. The basis for this differentiation is the purely practical criterion of the non-occurrence or the occurrence of cases of lead poisoning within these populations. As the environmental conditions in the industrial plants in which these men were employed were appraised from time to time over periods of years, and as the employees were investigated periodically by clinical and analytical means, a definitive correlation between the levels of lead concentration in the urine and blood, and the non-occurrence or occurrence of lead intoxication, was established. The data listed in these tables, as indicated, are recent examples of the sharpness of the analytical criteria that may now

be applied. Experience and the accumulation of voluminous data have spoken for themselves, in proclaiming that cases of lead poisoning occur only when certain limits of concentration of lead in the urine or blood (or in both) have been exceeded. The critical concentration of lead in the blood of child or adult, below which, in our experience (during the period of exposure, not weeks or months later), no case of even the mildest type of poisoning has been induced by the absorption of inorganic compounds of lead*, is approximately 0.08 mg. (80 micrograms) per 100 grams of whole blood. Due allowance must be made for an analytical error which rarely exceeds 0.01 mg. (10 micrograms) on either the positive or negative side, within the range of concentration of 0.01 to 0.10 mg. per 100 grams (somewhat greater in the higher range), as calculated from the results obtained by the analyses of 10 grams of whole blood. The qualifications, with respect to the known precision of the preparatory and analytical methods, are essential, since the methods and the facilities used by highly competent analysts vary in the type and quality of the equipment, reagents and manipulative procedures, to such an extent that the magnitude of the deviation, although it may be uniform within a specific laboratory, varies from laboratory to laboratory, almost without exception. Aside from carefully controlled procedures for the preparation of samples, two methods of analysis, one essentially chemical and colorimetric, the other physical and densitometric, have been employed in parallel in these investigations, and are applied, as a rule, to duplicate samples of blood, in order by their combined qualities to promote precision, sensitivity and specificity, and also to detect the fortuitous contamination of a sample which occurs from time to time, inevitably. *Parallel* analyses are not readily applicable to the urine because of the difficulty of obtaining duplicate specimens as the urine is being voided. The division of a specimen after single or

* It seems wise to remind physicians and analysts that the determination of lead in the blood in an attempt to appraise the degree of absorption of tetraethyl lead, and, in all probability, other lead alkyls, is futile. Because of the metabolic behaviour of these compounds in the body, the concentration of lead in the blood bears little or no relationship to their absorption and distribution in the tissues.

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multiple voidings is fraught with gross possibilities for error, since, after even slight cooling, the sample, following the precipitation of the phosphates, is no longer homogeneous. The factor of physiological variability, however, renders imperative the analysis of multiple samples of the urine of an individual.

The concentration of lead in the urine, or the output of lead in the urine per unit of time (on the part of individuals without renal damage or impairment of function) which corresponds to the threshold level in the blood, is a range rather than a single value, because of physiological factors (other than the rate of absorption or the body burden of lead) which result in a considerable variability in the rate of the urinary excretion of lead.

The value in the individual case may be as low as 0.15 mg. per litre and as high as 0.24 mg. per litre, dependent upon the number and volume of the urinary samples which have yielded an average result, and also upon the climatic conditions (prevailing temperature) under which the samples were obtained. The objective of the investigation of the urine by analytical means is the determination of the current rate of the urinary excretion of lead. Attention has been directed repeatedly toward this matter in these discussions. Further emphasis on it is justified, however, for despite the absurdity of the performance, a single result obtained from a sample of urine, collected without special precautions and analysed by a nondescript method, is often advanced as definitive diagnostic evidence in case reports and in medico-legal reports and testimony. Such results are likely to be grossly misleading and should be discarded in favour of purely clinical evidence until and unless they have been confirmed conclusively. Unfortunately, their status as numbers, fortified by the semblance of technical precision, catches the poorly disciplined or ill-informed mind, and acquires an authority that can hardly be matched by the superior but non-quantitative judgment of the most competent and experienced clinician.

The significance of the data in Tables 25 and 26 goes beyond their diagnostic

relevance, as we shall see later. They are presented in this relationship, however, for the sole purpose of defining the ranges of the concentration of lead in the blood and urine which are associated with the occurrence of lead intoxication. No such range, in either instance, is indicative of the existence of intoxication. There is, however, a critical level of concentration of lead in the human body, at or above which, under suitable conditions, individuals may develop intoxication. Such a situation, as revealed by the excretion of lead in the urine, or as shown more precisely by the concentration of lead in the blood, when accompanied by symptoms and signs compatible with the known effects of lead, as revealed by clinical investigation of a patient, provides a sound basis for the diagnosis of lead intoxication. The actual existence of intoxication, however, is established on clinical grounds alone, for there are no analytical findings which, of themselves, are indicative of illness. They merely denote the conditions in the background, without which the diagnosis of lead poisoning cannot be made or substantiated.

It is difficult to establish this concept in the minds of physicians and laymen who are unduly impressed by the historic toxicity of lead compounds. The facts, however, are as crystal clear as present physiological knowledge and skill in clinical observation can make them. Lead occurs naturally in the human body; within certain limits of concentration therein, whether useful or not, it is harmless; above a well-defined, critical concentration it is capable of causing lead poisoning; the higher the concentration above the critical point, the more likely it is to cause poisoning in the individual person (higher incidence in groups); even the highest concentration yet found does not, of necessity, cause intoxication, or so it seems, and, therefore, there must be some conditioning, biochemical factor (release of lead ions from chemical bonds?) which initiates a toxic effect. It is obvious that further clinical and physiological investigation may identify toxic effects which are not now recognizable. A phenomenon which may well belong in this category—one, which, in fact, we tend to regard as the first sign of lead intoxica-

tion, is the alteration wherein certain porphyrins, principally coproporphyrin III, occur in the urine in concentrations well above the normal range. This abnormality, as is well known, is not induced by lead alone, but when other causes can be excluded, it seems reasonable to regard it as an early sign of lead intoxication, in the absence of other clinical evidence of illness. The acceptance of this view does not alter the threshold values which are set forth in Tables 25 and 26, for abnormal concentrations of porphyrins have not been found in the urine of men in the safe categories of occupational exposure to lead as defined therein.

In practice, in the clinical investigation of alleged or suspected cases of lead poisoning, it is desirable and feasible to secure analytical data on both the urine and blood of the patient. If the interval of time between the examination of the patient and the termination of highly abnormal exposure to lead, whether occupational or non-occupational in origin, has been sufficient to diminish the concentrations in the urine and blood below threshold levels, the analytical results will have little value. (It may be possible, in some instances, to fit the analytical findings into points on a curve which represents the diminishing rate of excretion of lead in the urine, and the corresponding decrease in the concentration of lead in the blood, with lapse of time after the termination of abnormal absorption, and so to determine the probable status of the individual in this regard at the termination of his exposure. However, this procedure will often involve fruitless speculations.) In such cases, only clinical judgment can yield a tenable diagnosis. When the physician in industry is presented with a diagnostic problem at the onset of the illness of regular workmen, the analytical findings in the urine and blood at that time make their maximum contribution, on the background of results obtained previously at intervals on the same individual. Atypical symptoms or clinical signs lose their potential significance as "unusual" manifestations of lead intoxication, when

considered in relation to insignificant exposure as defined by analytical data, while plausible but non-specific symptoms or signs find a secure basis in concentrations of lead in urine and blood which denote hazardous absorption of lead. Bizarre clinical patterns of illness, in concurrence with dangerous levels of lead absorption, continue to pose diagnostic difficulties and medico-legal controversies, but it is pertinent commentary on the "protean" manifestations of lead intoxication, that they have come to be fewer in number and much more comprehensible, as exposure to lead and the resultant absorption have been given quantitative significance. This simplification and clarification of the clinical pattern of lead poisoning is partially due, in all likelihood, to the fact that some of the more serious effects of this disease are seldom seen in American industry. On the other hand, analytical evidence which is capable of demonstrating the probable insignificance of the absorption of lead as a factor in an illness of obscure etiology, has had a salutary effect in divesting speculative diagnoses of their capacity to become presumptive and then definitive, through authoritarian medical and legal pronouncements. It is obvious that one cannot, without self-deceit or lack of perspicacity, employ the clinical syndrome of lead poisoning as a criterion for defining the level or range of lead concentration in the blood which is required for the induction of illness, and then, simultaneously, use this range as the criterion for defining the clinical pattern of the disease. On the other hand, sound investigative procedure often calls for this very device, when, one after another, individual variables in such an association can be held constant while the manifestations of the others are being observed. Through such a device, probability increases to a point which approaches certainty. During the past twenty-odd years since the present methods of analysis came into use, thousands of observations have been made, and the correlation between analytical results and the clinical features of plumbism has been put on an unassailable basis.

TABLE 27
The Concentration of Lead in the Tissues of Children Fatally Poisoned by Lead,
or Suspected of Having Been So Poisoned.**

Tissue	Milligrams of Lead per 100 Grams of Fresh, Unfixed Tissue						
	Case Identification						
	A.J.	S.J.	D.S.	V.W.	L.D.	C.B.	D.E.M.
Brain ...	0.29	0.58	0.24	0.42	0.50	0.09***	0.14****
Liver ...	3.27	4.00	3.91	4.40	2.96	1.80	8.00
Kidney ...	0.61	0.88	—	2.59	1.74	1.10	5.5
Flat Bone ...	10.65	26.80	17.00	17.90	—	9.80	8.0
Long Bone ...	—	13.15	—	—	—	5.60	—
Blood ...	—	—	—	—	—	0.46*	—

* Obtained during life.

** Illustrative data from case material so selected as to exclude results that may have been influenced by chelation therapy.

*** Not characteristic of encephalopathic plumbism.

**** Poliomyelitis.

The problem of post-mortem diagnosis is presented not infrequently, in connection with a belated or neglected history of exposure to lead, when the cause of death, especially in an infant, is left in doubt, in the absence of definitive pathologic processes or in the presence of a non-specific form of encephalopathy. The analytical evidence at such a time may exclude lead as an etiological factor in the fatal illness, or it may demonstrate *not that lead was the cause of death, but that lead had been absorbed to an extent compatible* with such a diagnosis if, in afterthought, the type and course of the terminal illness of the child was such as to justify it.

An illustrative series of results obtained by the analysis of tissues taken from the bodies of children, post-mortem, are given in Table 27. In all but one of these cases, the diagnosis of lead poisoning had been arrived at before death occurred, and the analytical findings had demonstrated clearly that each child had absorbed grossly abnormal quantities of lead within a period not too far removed from that of his terminal illness. In scanning these data, it is enlightening to compare the levels of the concentration of lead in the skeleton with those in the soft tissues, and to reflect that the deposition of lead in the skeleton is the product of the rate of absorption and the

time over which such absorption occurred, whereas the concentration of lead in a soft tissue, such as the liver, reflects the summation of the effect of the stream of lead being absorbed currently (shortly before death) from the environment, with that of the stream flowing from the skeleton, into which relatively large amounts had been absorbed previously. When the lead content of the skeleton is found to be high and that in the soft tissues is relatively low, the time involved in the absorptive process was relatively long, while the rate of absorption shortly before death was relatively low. Attention is called to the fact that the concentration of lead in the flat bone, in these cases, is higher than that in the long bone, this relationship being the reverse of that which obtains in the normal skeleton (cf. Table 15, Lecture I).

In one case, that of L.D. in Table 27, no data relative to the skeleton are available. This is an example of the uselessness of even scanty data. It is always desirable to have information concerning the skeleton, but skeletal tissues are not always obtained by the pathologist in the absence of a toxicological consultant. In this instance, the high concentrations of lead in the liver and kidney are sufficient proof of a potentially dangerous degree of absorption of lead,

while that in the brain is quite high, only one in the series being higher.

The coincidence of the relatively high concentrations of lead in the brain, in five of the seven cases illustrated in Table 27, with the common encephalopathic character of the clinical pattern of lead poisoning in children, is not, it seems, fortuitous. It had been our experience, until the recent appearance of the two exceptions recorded in Table 27, that the concentration of lead in the brain, in encephalopathy due to lead, was always equivalent to, and usually greater than, 0.20 mg. per 100 grams of fresh brain tissue (there is a moderate degree of variability in the concentration in different areas of the brain). In case C.B. the finding of 0.09 mg. per 100 grams of brain was a surprise, for this represents only twice the mean normal concentration and is barely beyond the normal range. This child, in life, was convulsing and otherwise dangerously ill, when first seen, and the concentration of 0.46 mg. per 100 grams of whole blood was indicative of a rapid and highly dangerous rate of absorption of lead. The relatively low concentrations of lead ranging from 0.20 to 0.60 tissue are evidence of the relative brevity of the child's severe exposure, and, therefore, it is reasonable to assume that the shortness of this period of absorption was responsible for the unusually low level of absorption into the brain. It is likely, we believe, that the symptoms were more intimately associated with circulatory dynamics than with the direct effects of lead in the brain. In any case, because of the frequency of the occurrence of concentrations of lead ranging from 0.20 to 0.60 mg. per 100 grams in the brains of children that have died with encephalopathic plumbism, we have come to consider this to be an important diagnostic criterion. In one instance, that of the case designated as D.E.M., this criterion led us to suggest that the diagnosis of lead encephalopathy was in doubt, and that further investigation of the case was indicated. A thorough examination of the brain resulted in the demonstration of characteristic lesions of poliomyelitis. Certainly this child had absorbed abnormal quantities of lead, and the two diseases may have developed con-

currently, but the symptomatology cannot be attributed solely to the effects of lead.

The use in Table 27 of data derived exclusively from cases of lead poisoning in childhood should not be construed to indicate that the diagnostic significance of analytical results differs in any respect in fatal cases of lead poisoning among adults. As it happens, however, fatal cases of lead poisoning are seen but rarely among adults, and the facts could be illustrated much more satisfactorily by the more numerous cases that occur among children. These data serve, moreover, to introduce the subject of lead poisoning in early childhood, and to call attention to the frequently tragic outcome of such cases.

2. LEAD POISONING AMONG CHILDREN

To those who are familiar with the history of lead poisoning among children in Queensland, Australia, in the first three decades of this century (1, 2), it may not be surprising that similar cases occur as the result of somewhat similar environmental conditions in the United States. In Queensland, principally in Brisbane, large numbers of children were poisoned by the ingestion of lead in paint applied on the exterior surfaces of homes built of wood. The most commonly accessible painted surfaces were those of the side walls and railings of the verandas, from which, after the weathering which resulted rapidly in the tropical climate of this city, lead carbonate came off as a powder on the hands and fingers of small children who were confined, for their greater physical safety, during their daily sojourn out of doors, on these verandas.

In older sections of many North American cities, children of the same age group as those in Queensland (largely 1.5 to 3 years), and characterized by some of the same habits of eating, or putting fingers, thumbs and other objects in their mouths, ingest the crumbling and flaking paint from surfaces that had been painted repeatedly in earlier periods of better maintenance. The interior paints of an earlier day contained much larger quantities of lead pigments than those which are marketed and used at present, and this problem,

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therefore, while not entirely eliminated in modern homes by changes in paint technology, is not increasing greatly in its scope with the further growth of cities. The circumstances of life conspire to make this a serious problem of public health, however, in that young children, in the poorer areas or slums of our cities, live under unsatisfactory conditions of housing, and in addition are likely to be left too much to their own devices; some of them are unwanted and unloved, while the mothers of others are compelled to leave them in the care of children but little older than themselves, while they (the mothers) engage in employment outside the home. The children develop aberrant appetites, interests and habit of eating (pica), and tend to deviate psychologically in other respects from those with more favourable social and physical environments.

In Cincinnati, in the period extending from 1928 through 1949, when interest in this subject, and the alertness of the house staffs of the two principal hospitals with which we were associated, were relatively undercultivated and somewhat intermittent, 45 cases of lead poisoning among children, 12 of whom died, were brought to the attention of the Kettering Laboratory. These were verified, with respect to the clinical significance of their absorption of lead, by analytical means, and confirmed by adequate clinical investigation in three local hospitals. They were also investigated in a somewhat desultory manner, from the aspect of the social and environmental conditions out of which they had arisen. Paint from toys, furniture, and the interior woodwork of houses, was implicated as the source of lead in most of these cases; old storage battery casings, used for fuel, were responsible for several cases; toys of lead-containing alloys were involved in a few instances, one of which, in an infant, was fatal; and a nipple shield made of lead was convicted in one case.

In 1950 and afterward, with an increasingly intense and concerted diagnostic effort on the part of the staffs of two hospitals, the recorded cases of lead poisoning among children in Cincinnati increased in number. There were 12 in 1950, 18 in 1951 and

variable numbers of that order of magnitude in the years since, culminating in 28 cases in 1959, of which 6 were fatal. (Of 128 cases entered into the records of the Kettering Laboratory, mostly from Cincinnati, several from neighbouring cities, and two from distant cities, in the period from 1928 through 1955, there were 35 fatalities.) Sanitary inspectors in the Department of Health of Cincinnati collaborated in the investigation of the homes from which these children had come, and an aroused professional and official concern led to the enactment, in 1960, of local legislation, which, with appropriate official and legal action and the intelligent co-operation of the manufacturers and distributors of paints, can be expected to eliminate the large proportion of these cases in the not too distant future among the children of Cincinnati. The problem is widespread, however, within the country, as is attested especially strikingly by the evidence adduced in Baltimore and New York. So long as present conditions, with respect to housing and maintenance of the interiors of houses, persist in the poorer districts of Cincinnati and other North American cities, cases will continue to occur with tragic consequences.

A curious phenomenon, in connection with these cases, is their seasonal incidence. They occur sporadically, throughout the year, but, in the Eastern and North Central States, to the extent of the available records, almost all of the cases occur between the months of May and September in accordance with an essentially Gaussian curve of frequencies. This fact has been responsible for much speculation concerning a seasonal factor (or factors), which may coincide with the presence of dangerous quantities of lead in the bodies of children, in the induction of intoxication. There can be no doubt that the temperature (and humidity) of the summer months along or near the 39th parallel of the northern hemisphere provides a significant factor of stress, and the experiments of Baetjer (3), have demonstrated an effect of this factor, in association with lead poisoning. No evidence has been found, however, of a profound disturbance in the metabolism of lead in association with elevated ambient

temperatures. On the contrary, it is clear that these children have been ingesting large quantities of lead up to the very day of the onset of their illness. Roentgenographic examination of the abdominal region of the sick child reveals, frequently, the presence of irregularly shaped, radiopaque objects along the course of the alimentary tract, and the feces, which often contain grossly demonstrable flakes of paint (sometimes painted splinters of wood) yield variable but large quantities of lead on analysis. By the latter means, the nature of the source of the ingested lead is often rendered apparent, and an investigation in the home, and an analysis of paint scraped from a tooth-marked wooden object—a window sill, the railing of a play-pen, the arm of a highchair, the orally accessible part of a toy—complete the record in this respect. It is not always so easy, however, for when no one has been caring for a child and observing its activities, there is no direct source of information, and often there is no physical clue to the source of the ingested lead. Under such circumstances a thorough search of the child's environment may call for numerous analyses, before the source of the absorbed lead shall have been disclosed. As a generalization, it may be said that no great mystery attaches to these cases. The exposure to lead, in immediate temporal relationship to their onset, has been readily demonstrable, and the extent of the absorption of lead has not been slight or dubious but of gross and obviously dangerous proportions. Two questions of major importance arise out of their occurrence. (a) What factor or factors operate to cause the absorption of lead by these children, to reach a critical level in the summer months? (b) Why is it that encephalopathy is so frequently the presenting form of lead poisoning in children up to four years of age?

It is obvious of course, that the accumulation of lead within the tissues of these children will usually have reached a dangerous level some weeks or months before the onset of the convulsive seizure which so frequently is the alarming episode that brings the child to the hospital. Such an occurrence on a specific day, which, in terms of the quantity of lead in the body of

the child, differed little from many a preceding day, had some exciting cause—perhaps a fall, a blow on the head, an unusually hot day or succession of days, or some other added stress. The stage was set, and as is true of lead poisoning in the adult, some necessary 'trigger mechanism' was all that was required to initiate a toxic response. Generally, however, the length of time involved in the period of abnormal absorption of lead is short in the case of the child, as compared to that of the adult whose exposure to lead is occupational in origin. It may be as brief as 30 days, or even less under unusual circumstances, although it may continue, at a much lower rate of absorption, for six months or even a year. (We have seen two cases of lead poisoning in young adults, whose abnormal exposure to lead, by ingestion, was limited to 30 days, and we have also seen several children who continued, probably intermittently, to absorb lead at rates which did not result in actually dangerous levels of accumulation in their bodies for periods of time somewhat shorter or longer than one year.) The usual brevity of the period of absorption, coupled with the unusually high rate of absorption which is common in childhood, means, however, that the child is especially vulnerable to the initiation of the intoxication, for the danger of acute saturnism is the greater, the more rapid the absorption of lead, so long as the quantity absorbed is sufficient to raise the concentration of lead in the body to the necessary level. It means, also, in most instances, that the abnormal absorption began several months, at least, before the onset of illness. It is likely, therefore, that some feature in the lives of many of these children or in the character of their surroundings, leads to a gross increase in their exposure to, and absorption of, lead during the first half of the year. An alternative explanation of the facts may lie in the frequency with which some stimulus, associated with the summer months, operates to bring about the onset of an intoxication for which the way had been prepared weeks or perhaps months previously.

The frequency of the occurrence of encephalopathy in the child is an expression, we believe, of the rapid rate of the

absorption of lead by these children. Saturnine encephalopathy, as we have observed it occasionally in the adult who has been subjected to exposure to inorganic lead, may or may not occur in response to *brief*, as well as highly severe, exposure to lead, but it has not occurred except under the conditions of *severe* exposure. When such exposure has been brief, the adult patient with cerebral symptoms may recover promptly, even abruptly; when the exposure has been prolonged, and associated with multiple episodes of minor severity, recovery is much less likely to follow promptly, and the outlook for eventual, complete recovery is relatively poor. In the case of the child, the facts with respect to the duration of the exposure are often in doubt, but the severity is always great, and, as the data in Table 27 have indicated, the quantity of lead absorbed by the children who die is large. Moreover, the concentration of lead in the brain, in encephalopathic plumbism, is greatly increased over normal levels, and while this may, in a sense, be coincidental, the probability is high that it is an important factor in the character and the outcome of the disease.

In view of the apparent similarity of the conditions of housing in the poorer districts of many cities in North America, and in consideration of the fact that the recorded incidence of lead poisoning among children varies greatly with the quality and accessibility of the diagnostic facilities in these cities, or in any one of them in different periods, the conclusion is virtually unavoidable that the large proportion of such cases escape recognition. It is this fact which justifies this somewhat lengthy discussion, and points to the urgent need for special consideration of the requirements of differential diagnosis of lead poisoning in the small child. The strictly clinical aspects of this problem have been discussed fully in numerous publications, of which only two recent articles (4, 5) have been selected for citation because of their appraisals of certain recent methods of therapy. These and earlier articles demonstrate clearly that the careful application of non-specific clinical methods will usually identify cases of lead poisoning in infants and children, and

will differentiate them from other types of disease. The fact is, however, that the less serious forms of lead poisoning—colic for example—are rarely seen or recognized in the inarticulate and neglected child, and that it is the children with varying degrees of encephalopathic involvement, who are brought to the public clinic or to the pediatric wards of the hospitals. Whether or not lead poisoning is regarded then and there to be a possibility, depends, to a very large extent, upon the clinical experience of the physician. Whether or not a definite diagnosis of lead poisoning is made promptly, and appropriate therapy initiated without delay, will depend, in no small measure, upon the availability of analytical facilities for the determination of the concentration of lead in the blood. Often, the differential diagnosis by other means cannot be made promptly, and in some instances, not at all, with certainty. Time after time, in our association with a completely competent and thoroughly indoctrinated pediatric staff, the prompt exclusion or conviction of lead as an etiological factor in a specific case has rested upon precise information as to the concentration of lead in the blood. It is evident, therefore, that this analytical procedure, in and of itself, when properly carried out on satisfactory specimens of blood, is the most important clue to the existence of this disease in an infant or small child. Even more important, perhaps, is the fact that it is the best of all specific procedures for use in case-finding, or in the exploration of the effects of environmental conditions which pose the threat of lead poisoning to children.

The emphasis on the determination of the concentration of lead in the *blood* for diagnostic purposes in the small child, in contradistinction to the application of this procedure to the *urine*, is entirely intentional. It is not to be denied that satisfactory results may be obtained in many instances by the analytical investigation of the urine. We relied upon it before we had gained sufficient experience with analytical results on blood to be certain of their meaning. There are, however, altogether too many cases in which this cannot be done, and since lead poisoning is often a

fatal disease in the child, such exceptions should not be disregarded. It often happens that a satisfactory sample of urine cannot be obtained, or that obtaining such a sample is too difficult to be practicable, if there is a suitable alternative. The urine of a co-operative or even a semi-conscious male child can usually be obtained without contamination, but this is not true in the case of the female child, for it is advisable to collect the urine from the patient in the container from which it is to be taken for analysis. Any intermediate container, and especially the use of a catheter, in-dwelling or otherwise, is a likely source of a contamination of a type and degree which is rarely appreciated or avoided by anyone who lacks quantitative chemical training or careful indoctrination and supervision. Urine voided by the female child is likely to undergo some degree of contact with the perineum, and if this occurs, the urine will usually have been contaminated appreciably and, sometimes, grossly. An even more serious difficulty exists, however, in that the urine excreted by a very sick child may fail completely to contain lead in any significant relationship to the amounts available in the body. It is not unusual to find a low concentration of lead in the urine of a child that is very ill, at a time when the concentration in the blood is very high. The corresponding situation in the adult is very rare—so rare, indeed, that it scarcely justifies consideration in relation to diagnosis, although there are other reasons, as indicated previously, for obtaining additional information by the analysis of the blood. The nature of the presumed impairment of the kidney that is responsible for this phenomenon has not been investigated, but it is reversible in many, if not most, instances, for, as the child recovers, the rate of the urinary excretion of lead mounts until it reaches its usual relationship (in terms of concentration or daily output) to that in the blood. Meanwhile, of course, the concentration in the blood will have diminished gradually, and the somewhat paradoxical relationship, for a time, will have been that of a progressively decreasing concentration of lead in the blood in association with a progressively increasing

concentration and output of lead in the urine.

A further important fact, with reference to the blood, and one which is true also of the urine, with the exceptions noted above, is that the significance of the concentration of lead therein, in relation to the likelihood of the onset of intoxication, is no different in the child than in the adult. We have not seen a case of lead intoxication in an infant or child, at or within a few days of the time of the onset of illness, in whose blood the concentration of lead was lower than 0.08 mg. (80 micrograms) per 100 grams. The intoxication, once developed, tends to persist after the concentration of the lead in the blood has dropped well below the threshold level, but illness is not initiated at lower levels. This fact, added to the more frequent observation that illness is not always associated with high concentrations of lead in the blood, has misled some investigators into the belief that there is no relationship between illness and the concentration of lead in the blood. It is true that the discovery of significantly high concentrations of lead in the blood, is not, in itself, diagnostic of lead intoxication. On the other hand, there can be no doubt that there is a level of concentration in the blood, below which, lead poisoning does not occur in the child or in the adult. In the light of extensive experience this critical level is very little above or below 80 micrograms of lead per 100 grams of whole blood. The individual who has absorbed lead to that extent is in grave danger of developing lead intoxication, if and when the conditioning state or stimulus comes into being.

3. OCCUPATIONAL HYGIENE IN THE LEAD USING INDUSTRIES

The danger, indicated in the preceding discussion, that intoxication by lead will occur, if the concentration of lead in the blood, or the rate of the excretion of lead in the urine, exceeds threshold levels as defined herein, constitutes one of the basic considerations in the prevention, by medical means, of occupational lead poisoning. The fact that such poisoning will not occur if these threshold levels are not reached or

exceeded, provides the one additional feature of sound preventive medicine that is required to eliminate lead poisoning, as an occupational hazard, from even those industries in which serious obstacles are afforded to wholly and continuously successful environmental control, or in which, from time to time, the hazard incurred by an individual workman or a small group of workmen may differ markedly from that associated with the usual operating conditions. This is not to say that the fortuitous consequences of a highly unusual circumstance, such as a mechanical or human failure or other emergency, can always be avoided. It can be said, however, with full assurance based on many years of experience, that cases of lead poisoning, in connection with all of the regular operations of a highly hazardous industry, can be eliminated utterly, through careful and persistent application of this principle of preventive medicine. What is required is the will to do so, and the economic and administrative backing of managers who believe in the complete protection of their employees against the avoidable hazards of their work. There must also, of course, be a parallel and equally meticulous control of environmental conditions, as these are influenced by the processes and equipment employed in the operations, and by the associated procedures and equipment of environmental hygiene, together with satisfactory maintenance of all equipment, careful housekeeping, and attention to such supervision and indoctrination as may be required to insure against carelessness and disregard of instructions on the part of operating personnel. All of the appropriate armamentarium of industrial hygiene should be put to use for the control of the conditions of work, and for the protection of the workmen. The special virtue, however, of a medical regimen which includes determinations of lead in blood or urine (or both) and the interpretation of the results of such analyses, lies in its direct applicability to the *individuals* who comprise the industrial population, as well as to the specific *groups* of individuals who represent the several occupations in which the industrial population, as a whole, is engaged.

A man can work in freedom from the risk of lead poisoning, so long as the concentration of lead in his blood or the rate of the excretion of lead in his urine remains within the limits defined by the threshold values indicated above. If his work is potentially hazardous, as it may be, at times, under unusual circumstances or during operating stresses within the industry, or if, under ordinary circumstances, his freedom from hazardous absorption of lead is difficult to maintain, he may approach or reach the threshold level. At such a time, he can be transferred to a job in which his exposure to lead is negligible or greatly reduced, and after a period of relative freedom from exposure, sufficient to lower the body burden of lead to the desired point, he may be returned to his former work. Such a man may be paired with another man whose work is substantially free of hazard, and provision may be made thereby for a schedule of rotation which will insure the avoidance of significant hazard by both men.

Such procedures as those indicated above can be carried out satisfactorily, only if arrangements have been made in advance whereby all of the difficulties inherent in such an administrative and employment policy can be surmounted. Admittedly, certain industries are so constituted or organized that such arrangements are extremely difficult to effect; policies and agreements, with respect to wages, promotions, grievances, seniority and similar features of labour relations, may operate as obstacles to such plans; or there may be no jobs which are sufficiently free of exposure to lead. Generally, however, the implementation of such a programme, developed in advance of casualties, and designed in the strictly professional terms of industrial hygiene, will be found to be acceptable to both employers and employees. If the circumstances are such that the regimen of medical supervision cannot be made to include the temporary removal of workmen from hazardous exposure, there remains but one alternative—the operations of the industry must then be so designed as to eliminate truly hazardous conditions, and so to avoid the necessity for such a procedure. This alternative may be the

method of choice in the large proportion of industries in which the hazards of exposure to lead may be controlled by conventional engineering methods at moderate cost, and it is recommended highly as the best and often the most economical manner of dealing with the problem. There are, however, a number of extremely useful products, such as for example, electric storage batteries, in the manufacture of which, large quantities of metallic lead and of lead compounds are so handled as to become significant sources of human exposure. Not all of the plants in which such batteries are made are of the best design, from the aspect of industrial hygiene, and not all of them are operated so as to achieve the best results obtainable by the application of appropriate methods of industrial hygiene. Even the best of them have certain hazardous operations, and the maintenance of safe working conditions for the employees engaged in these operations requires intelligently designed and constantly applied technical and medical measures of industrial hygiene. It is in the medical supervision of such employees that a properly planned programme for the analysis of the blood and urine of employees can have its most effective and salutary application. Indeed, the question may properly be raised as to whether a wholly satisfactory regimen of medical supervision can be maintained in actually hazardous industries without resort to such a programme. Certainly the current status of industrial health in many of the plants engaged in the manufacture of electric storage batteries in the United States is evidence of the need for the consistent application of sounder, more specific, and more stringent standards, with respect to the permissible limits of the absorption of lead.

It may be useful to view the present position of industrial hygiene, generally, in the lead-using industries of the United States, and to consider how this situation has come about. As stated previously, the more severe forms of occupational lead poisoning are encountered infrequently, but the frequency of occurrence of the less severe cases demonstrates clearly that occupational exposure to lead has not been controlled adequately. On the one hand,

there are young industries in the more recently industrialized areas of the country, in which knowledge and experience are lacking, and there are old, well established industries, in which the ideas and practices of the past are entrenched; in neither of these has the science and art of industrial hygiene been developed. On the other hand, some industries have pioneered or shared in the development of measures both of environmental control and of medical supervision, and have eliminated lead poisoning from among their occupational hazards and liabilities. As examples of what to avoid and of what to strive for, these opposite extremes of the present situation are not unimportant, but the more general state of affairs is the more deserving of attention, especially from the aspect of preventive medicine. As one takes stock of this matter, the striking fact is that the role played by the physician has diminished greatly in importance, while that played by the engineer has enlarged. As a corollary to this, the principal techniques of industrial hygiene in the lead-using industries in recent years have been those of analytical chemistry and engineering, and not those of medicine. The abdication of medicine has been nearly complete in many instances, having often reduced itself to the level of the nominal supervision of a laboratory technician who, at arbitrary intervals, examines a series of blood films for "stippling," and of making sober interpretations of these non-specific, non-quantitative and often irrelevant findings, in lieu of the critical observations of environmental conditions and work-a-day practices, and the periodic examinations of the personnel, that would give meaning to medical supervision. In consequence, conditions of work which fall short of adequacy are condoned, and some degree of impairment of the health and well-being of workmen is accepted as the natural consequence of employment in a dangerous occupation. Under such conditions, some workmen have occasional episodes of minor or incipient intoxication or continue in a state often referred to, ambiguously, as "lead absorption," which, apparently, while not being clinical "lead poisoning" is the nearest approximation that can be sustained

by the individual without complaint or disability. From time to time, inevitably, these conditions give rise to frank cases of occupational lead poisoning among "unusually susceptible" persons who are often, if not usually, relatively new employees. This is the state of the science and art of industrial hygiene in the United States, in its medical aspects, that yields an unnecessary incidence of occupational lead poisoning. Clearly it is in need of an infusion of methods of preventive medicine that are in accord with physiologic and toxicologic facts. The medical procedures of an earlier day in the lead trades have been plagued by gross inadequacies based upon their non-specificity, on the one hand, and their lack of quantitative significance, on the other. They have made a poor showing, indeed, in comparison with the specific and quantitatively precise methods of the industrial hygiene engineer. Preventive medicine, in the strict sense of the word, was ineffectual in practice, prior to the development and application of specific and precise methods for determining the magnitude of the absorption and excretion of lead by exposed workmen. Instead, the control of the environment according to specifications was the method of choice, and despite the fact that the adequacy of the specification depended basically upon competent and persistent medical interpretation of the hygienic status of the exposed personnel, the latter, being relatively unsatisfactory and difficult of attainment, was characterized more by default than by its application in the specific instance.

The principle of environmental control is, of course, basic in industrial hygiene. As it was first expressed in relation to occupational exposure to lead by Sir Thomas Legge (6) as the result of his clinical observations and the analytical work of his associate Duckering, it was a profoundly significant contribution to the armamentarium of industrial hygiene. It is a principle, however, which is difficult to apply to many industrial operations, and even in its best application, it leaves something to be desired, in so far as the safety of certain individual workmen is concerned. Moreover, it has not been extended, by the conjoined efforts of the engineer and the

physician, so as to apply broadly to the variety of the compounds of lead or to the various physical forms of these compounds dispersed in the air. It is, in fact, an approximate expression of good practice for the lead-using industries, which, when employed in co-ordination with a sound programme of medical supervision, can be expected to yield a satisfactory control of hazards due to lead. With the development of sound methods for the interpretation of the status of the individual workman, the physician may now resume his former position of professional responsibility, and find security and satisfaction in the precision and efficacy of technical procedures that lie within his own domain.

Some objection has been raised to the technical difficulties and also the expense of establishing and maintaining a medical regimen which includes a programme for the sampling and analysis of the urine or blood (or both urine and blood) of workmen. The difficulties, while real, are far from insurmountable, being more formidable in anticipation than in their vanquishment. The laboratory in which such analyses are carried out must be specially designed, properly equipped, and capably manned; the containers for samples must be selected for the purpose and prepared with an eye to the avoidance of even the most minute contamination with lead; and the procedures for the collection of samples must be carried out by properly trained or carefully supervised persons. Even so, samples will be contaminated with lead occasionally. Attention to minute details, therefore, is mandatory; everyone concerned must know what he is doing and why he is doing it, and the technique must be essentially faultless, for lead is everywhere in the environment, and unless it is excluded by satisfactory technical means, it finds its way into samples in the process of their collection and while they are being analysed. The minuteness of the quantities of lead which are to be determined, and the facilities and techniques required to collect satisfactory samples and to carry out such determinations with adequate precision, contribute to the cost of the entire activity, but they do not render it prohibitively expensive, if reasonable judg-

ment is exercised in the economical employment of the analytical regimen. One may be inclined to ask how it is that a medical procedure which is so important to the safety of many men should be so carefully weighed in economic terms. What is a reasonable cost in such a situation? An acceptable answer would be, that if it is essential it must be borne, but that it should be used only to the extent of its essentiality. A further question is often raised in this relationship, to which attention is given here because it relates to the frequency with which workmen in the lead trades are to be examined in this or in any other manner, whether the periodicity is determined by official or legislative regulation, or as a matter of policy or design within an industrial organization. Nothing is more frustrating to a wise and competent industrial physician, or to a responsible and prudent management, than to find that the procedure in such a matter is dictated by a statute or by an official authority, and that their own knowledge and judgment may not be exercised. It is hard to resist the impulse to condemn utterly, as senseless, the regulation of such matters by official or legislative fiat, for such regulation cannot create the knowledge and judgment without which, the task cannot be done; it can only hope or imply that these exist, on the one hand, or interfere with their application, on the other. The point is, that the periodicity of the application of any specific medical measure of industrial hygiene, if it is to be effective, must be determined by the nature and the degree of the hazard that is being guarded against. With specific reference to the proper utilization of medical information obtained by the analysis of the urine or blood for their content of lead, frequently repeated observations are wholly unnecessary and wasteful of effort and money, unless the hazard of a specific man or group of men in a specific operation or area are such as to result in a rapid increase in their absorption of lead. In some industries in which lead or its compounds are employed, the environmental conditions, with respect to exposure to lead, are stable, uniform and well controlled, and the men are well-trained and indoctrinated

in appropriate performance. In others some processes and areas are much more difficult to control than others. In still others, all or most of the processes are potentially hazardous, and uniformity of both human exposure and performance are difficult of attainment. Periodic medical surveys of the personnel, in co-ordination with careful observation of the conditions under which men work and of their manner of working, will disclose the degrees of hazard to which men are subjected, and will show clearly how the medical procedures must be scheduled so as to provide the necessary information at the proper time. It may be that the status of the workmen in a specific industrial establishment can be determined by the analytical investigation of a representative group of employees once per year or even once in two years. Or it may be that every man in an occupational group will have to be sampled at intervals of one month, if the risk is large and unpredictable. Within these extremes of scheduling, a programme can be adapted to the requirements of safety within an industry. When so designed, it can be counted on to reveal the sites of hazard that require the application of more satisfactory measures of environmental control, and to demonstrate faulty operations, faulty performance on the part of the men, or faulty maintenance of operating equipment or of housekeeping. Inasmuch as the extent of the analytical effort and of its cost will depend upon the severity of the hazard of lead absorption, it can be expected, automatically, to indicate the need for better environmental control, which, if achieved, will reduce the need for analytical information and lower its cost. It is not likely, however, after once having been instituted as a part of the medical regimen of a lead-using industry, that this regimen will ever be abandoned. The security of mind which is afforded to all who are involved in responsibility for the safety of workmen, and the satisfaction of the workmen with a regimen that protects them, are assets which are not lightly to be regarded. With respect to the attitude of the workmen, it has been our experience that, once their natural resistance to inconvenience or

to their initial dread of venipuncture have been overcome, as these so easily are overcome by the ministrations of doctor or nurse, they will offer vigorous resistance to any reduction in the established schedule of sampling and analysis. This is a consideration of sufficient importance to justify some caution in fitting the scope and frequency of these observations to the actual needs of the situation in the beginning.

The sampling of the urine has been something of a problem under certain circumstances. There are two general methods which can be employed satisfactorily, in our experience. Other investigators or industrial physicians have employed other procedures with success. Workmen can be instructed verbally and also in writing, as to the means of avoiding contamination of specimens of urine with lead, and in the collection of physiologically representative samples of large volume. A container with a capacity of four litres can be so prepared as to be chemically clean, sealed in a paper or plastic bag, and given to a workman, after he has bathed and changed his clothing, to take home with him (or, if need be, the container can be delivered to his home). There, he is to keep it in a place which is reasonably secure against accident or tampering, and to void directly into it at intervals until a suitable volume (2 to 3 litres, up to a mark) has been obtained. He is not to collect unusually dilute or unduly concentrated voidings (such as would be associated with the convivial drinking of unusual quantities of beer, ale, or other beverages, or with a period of restricted consumption of liquids), but to obtain a composite sample representative of his ordinary manner of living. This type of sample is likely to be a very good representation of the general rate of the urinary excretion of lead, as the latter is expressed in terms of the concentration of lead therein, rather than on the basis of time. (As ample data have demonstrated, this is as satisfactory a means of expression, for comparative purposes, as is that based on time, and it obviates the necessity for the collection of the time-honoured, but not always practicable, twenty-four or forty-eight-hour specimen.)

A second and alternate method of collecting the urine, and one that has the advantage of being accomplished under the eye of the examiner, is that of obtaining a single voiding of somewhat more or less than 100 ml., in a small container. This can be obtained when the workman has presented himself, after bathing, for an examination (as a normal part of the procedure of examination along with the collection of blood, if desired) or it can be obtained at the bathing and clothes-changing quarters, at the end of the work of the day (or shift), or at its beginning. By such means, contamination of these samples can be avoided, and a further advantage can be gained by the judicious use of the bathing facilities, in that the samples will have a uniform relationship to the day's work and its exposure to lead. These samples of small volume will be somewhat less satisfactory than those of large volume, because of the factor of physiological variability, but this disadvantage can be overcome by the numbers of samples which represent the group or by increasing the frequency of the sampling in the individual instance. The statistical array of data representative of a group of men engaged in comparable work will be entirely satisfactory in portraying the status of the group, while individuals at either extreme of the statistical array can be checked by the collection and analysis of additional samples. Moreover, when an individual who has been exposed to the inorganic compounds of lead is found to be in a dubious state, the necessary facts can be established by an analysis of his blood. The latter procedure, as has been indicated previously, is always desirable when, as in private or medico-legal practice, the patient may not be available later for re-examination.

The foregoing details of procedure may appear to be wholly redundant, in a broad presentation of the physiological principles and facts with which we are here engaged. Experience has shown, however, that attention to these details, which is so necessary in order to obtain valid information, is honoured frequently in the breach. Therefore, at some risk of wearying or even offending those to whom the facts are well-

known, it seems wise to speak of them for the benefit of those who, otherwise, now or later, may waste valuable time and effort in learning, as we have done, by trial and error.

4. EXPOSURE TO LEAD IN THE REALM OF THE PUBLIC HEALTH

The facts concerning the metabolism of lead are of paramount importance in the development of criteria for public safety. Modern technological developments pose certain problems with respect to the composite exposure of men, generally, to lead in the food and beverages which they consume, and in the air which they breathe. No standard of safety in relation to any one of these general sources of exposure has validity, in itself, but each may achieve validity, in practice, when considered in relation to the others.

It is fair to say that, at the present time, in the United States, the absorption of lead on the part of the public, generally, from all sources, is attended by no hazard. This is not to say that there may not be situations productive of danger and of actual cases of lead poisoning within the population. Attention has been called emphatically, herein, to lead poisoning among children. Cases of lead poisoning also occur among adults, as the result of the contamination of food and drinking water, and even of the air in the home (e.g., from the use of battery cases scavenged from dumps or heaps of refuse, as fuel). On the whole, however, the food and beverages of the nation contain but little more lead than that which occurs naturally in them, while the ambient air, even in the more heavily contaminated areas of our cities, is contaminated with lead only to the extent of a few micrograms per cubic metre. The facts in these matters, as they now obtain, have been given in a fairly representative manner in Lecture I, in which, also, the normal metabolism of lead, as we have chosen to speak of it, has been described. We have found no reason to believe or to suspect that the quantities of lead involved in this normal metabolism of lead have increased within the past twenty-odd years. Indeed, if we were to rely upon the available evidence, without some reservation of judgment based upon recognized improve-

ments in the techniques of sampling and analysis (which have reduced the opportunities for contamination of samples at our hands), we should be justified in concluding that the over-all exposure to lead, on the part of the "average" adult citizen of the United States, has decreased in the past decade.

The food and beverages of the country represent the largest source of lead intake, under the ordinary conditions of life, and they are most open to opportunities for artificial contamination. It appears that this source has undergone some decrease in recent years. The data obtained by the analysis of the feces of 453 persons (Table 9, Lecture I) involved in a field survey in 1955 yielded the somewhat surprising mean lead content of 0.23 mg. per sample. (The relationship of these data to the lead in food and beverages has been demonstrated in Lecture I.) The mean value of a corresponding series of results obtained in 1934 in the investigation of a group of 307 persons of comparable type from the same general area of the country (7) was 0.32 milligram. The difference between these two values is barely significant, statistically, and so is not to be taken too seriously, but the frequency with which the mean lead content of the food and feces of various large and small groups of persons had been found to exceed 0.3 mg. per day (8) in the period prior to the year 1950, and the more recent and fairly regular finding of mean quantities appreciably less than 0.3 mg. per day have not gone unnoticed. (Note the mean lead content of the food and feces of the experimental subjects listed in Table 12, Lecture I; the three subjects, E.B., I.F., and S.W., were under study prior to 1945, while the investigations concerned with the last six subjects began in 1950; the last three subjects are now under observation and will continue so through 1961.) These and other similar results provide only the proof of the variability of individuals, in this respect, but the coincidental factor of time is, at least, suggestive. It seems reasonably certain that if any change has occurred it has not been in the direction of an increase.

The lead content of drinking and culinary water, as supplied to town and city

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dweller from a common source, is not a problem in the United States, with the exception of certain of the older communities in the New England area, in which, even now, lead pipes are said to be in use. Throughout the greater part of the country, the methods employed in the treatment, if any, and in the distribution, of water supplies, are such that the concentration of lead therein rarely exceeds 0.03 mg. per litre. There is no present reason, therefore, for the persistence of the standard of 0.10 mg. per litre which was adopted by the United States Public Health Service many years ago, but was reduced to 0.05 mg. per litre in 1960. Obviously, opportunities for the ingestion and absorption of lead from this source should be as few and as insignificant as possible, in view of the ease with which this can be accomplished when the general water supply of a community is subject to control. On the other hand, there is no reason for concern, when, in emergency, the water supply of an entire community, or a sizeable segment of it, contains lead in a concentration approaching 0.10 mg. per litre, for a few weeks or months. This, to our knowledge, has occurred in times of severe drought, when water had to be transported in highway and rail tanks that had not been made chemically clean. The quality of the water made available under such circumstances should be known, however, from this and other aspects, in order that proper steps may be taken to protect the public.

Two related questions arise concerning the ingestion of lead, both of which can be answered in straightforward terms, on the basis of the experimental observations that have been described in Lectures I and II. One of these is concerned with the matter of the average quantity of lead which may be ingested daily, without risk, over the span of life, in the food and beverages including water, if it be assumed that the quantity absorbed from the air remains essentially unchanged or undergoes no significant increase. The other question involves the opposite side of the same coin, namely, the quantity of lead which, when ingested, will result in a dangerous degree of absorption within a definite period of time.

The answer to the first of these questions is based in part on the observation (Lecture II) that the oral administration of 0.3 mg. of lead (as lead acetate, in solution) per day (in addition to that contained in the food and beverages, thus bringing the total quantity ingested per day up to approximately 0.6 mg.) to experimental subject S.W., for a period somewhat longer than a full year, resulted in a barely detectable increase in the rate of the excretion of lead in the urine, but in no demonstrable increase in the concentration of lead in the blood. This is as near as one might expect to get to the least incremental increase in the oral dosage of lead that would yield a detectable response. On the background of the evidence provided by other similar experiments, in which larger dosages of lead were administered orally, the conclusion is fully justified that the quantity of lead which accumulated in the body of subject S.W. was slight indeed, and that such a rate of accumulation could continue for many years, probably for an entire lifetime, without any likelihood of reaching a potentially dangerous level. On the other hand, the ingestion of approximately twice this quantity of lead daily (1.3 mg. per day, by subject M.R., Lecture II) gave rise to a progressive increase in the rate of the excretion of lead in the urine and in the content of lead in the blood and other tissues of the body. The retention of lead in the body of subject M.R., continuing over the period of four years, at an essentially constant rate, resulted in the accumulation of 120 mgs. therein, at the average rate of approximately 30 mgs. per year. One cannot be certain that such a rate of accumulation would continue indefinitely, but since there was no evidence of a gradual diminution in the rate within four years, there are no grounds for the assumption that it would not. As it will be shown later, there is reason to believe that this would be dangerous if it were to continue unabated. It is unlikely that the ingestion of 0.6 mg. of lead daily for many years would be a source of danger to an adult. The accumulation of lead in the body, under these conditions, appeared to be of the approximate order of 8 mgs. per

year, at which rate it would be insignificant for many years and probably for a lifetime. At any rate it may be said, with reasonable assurance, that the quantities of lead in the food and beverages available to a population should be such that individuals may choose what they will in quality and quantity, without running the risk of ingesting more than 0.6 mg. of lead per day, on the average, over any prolonged period (years) of time.

In considering the problem of public health involved in the possible contamination of food and beverages with lead, from the aspect of any type of regulatory action, the conclusion arrived at above would seem at first to be wholly academic and impractical. And so it would be, were it not for the feasibility of ascertaining the facts, as they apply to persons or groups in the population, by the application of methods of investigation that have been described herein. There are, of course, other approaches to the more specific hazards presented by the discovery of the contamination of certain items of food or drink, which occupy established and quantitatively ascertainable places in the dietary habitude of the population. Tolerances may be, and indeed have been, applied to these in accordance with their importance in specific instances. These represent special situations, however, and even they need to be fitted into a general or all-inclusive standard.

The second question raised above, concerning the risk of lead poisoning in relation to the degree of contamination of food with lead, can now be answered with reasonable accuracy. Various statements have been made in the literature concerning the dose of lead which, when ingested, i.e., taken by mouth, daily, can be expected to cause lead poisoning. These estimates have been based on indirect evidence, and they have varied so widely as to have dubious worth. No doubt the conditions out of which they came, as interpretations, were variable and subject to a large margin of error. The carefully controlled conditions of the experiments relating to the ingestion of lead in solution have provided opportunity for much more precise estimates of the relationship between time and dosage,

on the one hand, and a toxic effect, on the other. This is made possible by the establishment of the association between the concentration of lead in the blood (also the rate of the urinary excretion of lead) and the induction of lead intoxication. The fact that this association, in the quantitative sense, has a statistical, rather than a strictly individual basis makes it the more applicable as a general, rather than an individual, human experience. There is a high degree of probability, therefore, that if the experiments involving the ingestion of lead by our experimental subjects could have been continued until the threshold concentration of 0.08 mg. of lead per 100 grams of whole blood had been reached, we should have observed the early clinical evidence of a dangerous degree of absorption of lead, at least to the extent of an abnormal degree of elevation of coproporphyrin III in the urine. Fortunately it is unnecessary to go to such an extreme of experimental zeal, even if it were feasible, since it is possible to extend the curves in which the concentration of lead in the blood has been plotted against time (cf. Fig. 3 and Fig. 10, Lecture II) so as to establish approximately the length of time required to reach the threshold concentration in the blood. The result of this extrapolation, in the case of subject M.R., whose average daily intake of lead in food and beverages, together with that taken in solution, was 1.27 mgs., came to somewhat more than 7.5 and somewhat less than nine years (while the mathematical treatment of the extrapolation would yield a more precise value, such a value, without qualification, would be misleading); the corresponding result in the case of subject E.B., who ingested 2.35 mgs. daily, was approximately four years, while that of subject I.F., who ingested the average quantity of 3.27 mgs. daily, approximately eight months. Whether or not these subjects, or their counterparts in the population, would develop episodes of lead intoxication at or near the time indicated in each instance, is, of course, open to question, but that they would incur such danger is reasonably certain. With respect to the factor of time in association with still larger oral dosages taken regularly, we have had the oppor-

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tunity recently of investigating the illness of two young adults, whose ingestion of unusual quantities of lead began at the same time and terminated in the nearly simultaneous onset of acute intoxication. The entire period of exposure was limited to about one month, during which the dosage of lead, while variable from day to day and from one to the other person, is believed (on the basis of simulated experience) to have averaged between 5 and 10 mgs. per day. It is interesting in this connection to consider the problem of susceptibility, and that of the exciting or enabling feature of lead intoxication to which reference has been made. As these matters have been viewed critically over the years, human susceptibility to lead poisoning has diminished steadily in importance, in favour of the influence of the variability of human experience whereby the quantities of lead being absorbed by individuals were significantly different. Likewise, and as something of a corollary observation, the variability in the time of onset of intoxication among individuals, under seemingly similar environmental conditions, has tended to be greater when the exposure to lead has been fairly uniform at a moderate level of severity. It seems that the onset of intoxication often coincides with the occurrence of a *sharp increase in the rate of the absorption of lead* by an individual. This observation has led us to suspect that the "trigger mechanism" of lead intoxication is that of overburdening the tissues with unbound or ionic lead, whether through an unduly rapid rate of absorption or through the loosening, under appropriate but presently unknown conditions, of chemical bonds within the tissues.

It is of further interest to consider the order of magnitude of the contribution made to the body burden of lead in subjects S.W., M.R., E.B., and I.F., at the time when each of them, by extrapolation, would have reached the concentration of 0.08 mg. of lead per 100 grams in his blood. This can be arrived at by extending the upward sloping curves of Figure 11 (Lecture II), for these subjects, for the lengths of time required in each instance to bring the concentration of lead in the blood to that point. The concentration of

lead in the blood of subject S.W. (total daily oral dose of 0.6 mg. of lead) did not increase demonstrably during the experimental period, but apparently he added approximately 8 mgs. per year to his body burden, under the conditions of the experiment. On the reasonable and modest assumption that his body, prior to the experimental ingestion of lead, contained a quantity of lead of the order of 100 mgs., a period of 12.5 years of continuing ingestion at the same rate would be required to double, and 25 years, to triple, his body burden. His assumption of risk in so doing must certainly be considered to be negligible, in view of the fact that the body burden of lead of ordinary (normal) individuals in the general population is found, from time to time, to be of that order of magnitude (See Table 15, Lecture I).

As judged by similar means, subjects M.R., E.B., and I.F. might be expected to have added quantities of lead of the order of 270, 250, and 110 mgs. respectively to their initial body burden, if each had continued on his experimental regimen until he had reached the threshold level in his blood (i.e., in 9, 4 and 0.64 years, respectively). It will be noted that the total body burden, at the time the blood reaches its critical level, tends to be greater as the daily rate of intake and absorption diminishes, whereas the time factor involved in reaching the critical concentration in the blood, under these circumstances, is disproportionately large. This is in keeping with the relative inaccessibility of the lead which moves slowly into the relatively more dense and less vascular areas of the skeleton. Evidently it is not the body burden of lead, *per se*, which is the primary factor in providing the conditions in the body that are necessary to induce lead intoxication, but, rather, the manner in which the lead is distributed, with specific reference to its immediate metabolic accessibility, is the important factor. That is to say that the concentration of lead must be sufficiently high at the point or points of vulnerability, if intoxication is to be induced.

Notwithstanding the importance of the lead in human food and beverages, as the principal source of that which enters into

the "normal" metabolism of the population of the United States, generally, the finely divided lead in the ambient atmosphere cannot be ignored, as the observations noted in Lectures I and II have indicated. In so far as the quantities in the air are dispersed as particles less than 1 micron in diameter (as the large proportion of these appear, on somewhat scanty evidence, to be, under prevalent atmospheric conditions); and to the extent that the particles are retained within the lungs, rather than deposited in the nasopharynx, trachea and bronchi, or returned to the atmosphere in the expired air (the results of the respiratory experiments indicate that such retention ranges from 35 to 45 per cent); and, further, to the degree that the highly dispersed compounds of lead in the atmosphere are capable of being absorbed (as most of the lead in the general atmosphere seems to be); the air-borne lead in the general human environment has greater significance in the human economy, quantity for quantity, than that in the food and beverages. Whereas less than 10 per cent of the lead which occurs commonly in the food and beverages is absorbed (the absorption is proportionately greater when the quantities (concentrations) of comparably soluble compounds of lead are large), virtually all of that retained in the lungs is absorbed. Therefore, a given quantity of lead drawn into the respiratory tract in inspiration, if it meets the necessary specifications as to particulate dimensions and some degree of solubility, may contribute three to four times as much absorbed lead to the tissues of the body as would the same quantity of lead taken in with food and beverages. Likewise, a given quantity of lead actually *retained* in the lungs may yield ten to twelve times as much absorbed lead as would an equivalent quantity which enters the alimentary tract. On the other hand, it must not be forgotten that when the particles of lead compounds in the atmosphere exceed 1 micron in diameter, few of them reach the finer air passages of the lungs. Most of the particles between 2 and 5 microns in diameter will be captured in the upper respiratory tract and will eventually be deposited in the nasopharynx, to be swallowed or expectorated,

and so absorbed to a much lesser extent than if they had been retained in the respiratory tract.

It seems advisable, in passing, to refer briefly to a potential source of inhaled lead to which undue speculative significance has been ascribed recently. The occurrence of lead in tobacco (along with arsenic and certain other mineral constituents) has given rise to calculations of the amounts of lead that might be absorbed in the respiratory tract, from this source. The calculations have failed to take into account three factors which are highly pertinent, namely: (a) the extent to which the lead in tobacco appears in the smoke which enters the mouth, as differentiated from that which remains in the ash of the burning cigarette, cigar or pipe tobacco; (b) the degree to which the smoker draws the smoke into his lungs; and (c) the actual length of the time, per day, involved in smoking. While the latter two factors cannot be ignored in any strictly quantitative appraisal of the absorption of lead from the smoke, there is no urgent need for their investigation, for the reason that only a small proportion of the available lead is found in the smoke; much the larger proportion of it remains in the ash. When this matter was brought somewhat forcibly to our attention by persistent questions, we were taken aback by the realization that we had no direct information on the subject. It was plain to be seen that there was no such difference between smokers and non-smokers, within the groups of persons whom we had investigated, as to justify the suspicion that this was a significant factor in the absorption of lead. The explanation was supplied by an associate (Cholak) in the Kettering Laboratory, who determined the quantities of lead removed from the smoke of each of several cigarettes by millipore filters, the quantities of lead in the residual ash of each cigarette, and the quantities of lead in individual cigarettes (ashed in the manner of the usual preparatory procedure for analysis, rather than by smoking). The average weight of each of several cigarettes was approximately 1 gram, of which the weight of the ash (obtained by the usual preparatory method) averaged approximately 150 mgs., and the lead content of the ash of the

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