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CONCERNING THE HYGIENIC ASPECTS OF LEAD IN THE HUMAN ENVIRONMENT

by

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1. INTRODUCTION

It is the purpose of this statement to present and, so far as possible, to document the salient facts concerning the hygienic aspects of the occurrence and distribution of lead in the environment of citizens of the United States of America, with particular reference to the contribution made by the use of leaded gasoline.

The impression has existed in certain circles that little information is available on this subject, especially as to certain matters that relate to the safety of the public. This impression has been reinforced, to some extent, by the strict limitation, hitherto, of publications concerning it, to relevant scientific and professional journals, and by the unhurried pace of the preparation and the modest extent of the distribution of such publications. The fact is, however, that no other hygienic problem in the field of air pollution has been investigated so intensively, over such a prolonged period of time, and with such definitive results. This is not to claim that there no significant voids in the available information, nor that all of the ultimate answers are at hand. Nevertheless, it is clear that this specific set of problems has been brought to such a point of understanding, in relation to the public health, as to remove it from the realm of urgency and to consign it into that group of hygienic problems on which a watchful and effective surveillance should be kept. A considerable measure of assurance for the future may also be derived from the fact that methods of surveillance have been developed, over the years of investigation, which are characterized by a high degree of technical precision and physiological relevance. Attention will be called to these methods and to the criteria of public safety involved therein at appropriate points in this statement. The methods may be refined and extended by further physiological investigations. The criteria of safety advanced herein are believed to be sound in principle and applicable in practice.

The bulk of the investigative work which bears on lead in the environment of man has been carried out, under the financial sponsorship of the manufacturers and distributors of lead-containing anti-knock compounds in the United States, in the Kettering Laboratory (and in the Eichberg Laboratory of Physiology, of which the Kettering Laboratory was an offshoot), now in the Department of Environmental Health, in the College of Medicine of the University of Cincinnati.

It may be of somewhat more than historical interest to those who inquire into the facts relating to this and certain other early problems of occupational and environmental health in the United States, to know that in the nineteen-hundred-twenties and until the middle thirties, there was an appalling lack of facilities for research in these fields in the United States, in universities, in governmental circles, and in industry. The only laboratories of any size in or available to the Public Health Service were the Bureau of Mines Experimental Station, Pittsburgh, Pennsylvania, and the modest but productive Stream Pollution Investigation Station in Cincinnati, which had been founded in 1913. The former of these two was accessible (at that time, but not now), on a limited scale, to industrial organizations that would provide financial sponsorship for work (of comparatively limited scope) to be designed and conducted by the staff of the Station. In this extremity, certain industries, including the anti-knock industry, which had developed an awareness of their urgent need for toxicological information and medical advice on which to design hygienic measures in the complex and rapidly expanding technology of industry in the United States, provided the initial financial support that led to the establishment of the Kettering Laboratory, through agreements, with primary respect to the policies of the University of Cincinnati, between the officers of such companies and the Board of Directors of the University. This Laboratory has since grown to maturity physically and professionally, has been of service, at the cost of such services, to several hundred industrial organizations in this and other countries, and has been supported, directly, in the acquisition of further physical facilities, by some fifty major industrial organizations. The Laboratory has thrived and is known internationally through its contributions to industrial hygiene and public health, and through its guidance of industry in certain matters related to the health and well being of employees, customers, and the public generally. Since 1947, it has made significant contributions to the specialized training of professional personnel in many parts of the world, in industrial medicine and hygiene, thereby rounding out its academic role.

There have been and are yet, no doubt, those who consider such financial and academic relationships as have existed between industry and the University of Cincinnati, in this instance, to be prejudicial to scientific objectivity and professional integrity. Indeed, it may turn out that the faith of our people in ethical and professional standards will be so slight, and their cynicism so pervasive, with respect to scientific men and their motivation, as to condemn such relationships and to terminate their usefulness. This would be singularly unfortunate, for practical, professional and academic reasons.

From the practical viewpoint, the majority of the hygienic problems created by modern industrial technology are properly the responsibility of industry to solve. Moreover, they can best be examined in the initial period of industrial research, and, later, in stepwise coordination with the further programs of research and development whereby a desirable product is prepared for entrance into the national market. This is to say that the properties of a product for inducing deleterious effects among those who develop, manufacture, distribute, and use it, are as necessary for its proper commercial exploitation as are the physical and chemical properties that relate to its usefulness. Similarly, the cost of providing such information, which ultimately must be passed on to the consumer, is a proper charge against industry in the specific instance, one which, often, can best be handled within industry, and one which carries with it a substantial deterrent to social irresponsibility. From the professional and academic viewpoint, there is urgent need in the entire American community, North, Central, and South, and specifically in industry, for the cultivation and the broadening of the truly professional services of the specially trained physician and hygienically trained engineer. This need can be met most effectively through the intelligent and responsible collaboration of industry in the development, utilization, and support of facilities for research and professional training within the institutions best equipped for such research and training. On the basis of current experience, there is not the slightest reason for doubt that such collaboration is advantageous to all concerned, as well as highly effective in the promotion of a high quality and a broad scope of professional services in industrial and environmental health in their time of need.

From the earliest period of the exploitation of tetraethyllead as an anti-knock agent, it was recognized that the discharge of lead from the tail pipes of motor vehicles might turn out to be the most serious hygienic problem with which this industry would be confronted. On this account, an investigation of the hazard of airborne lead from this source was initiated in 1923, in the United States Bureau of Mines Experimental Station (1) by means of experiments on animals. About two years later, the first of a series of field investigations of the environmental conditions and their impact on the personnel involved therein, was designed and carried out by investigators in the University of Cincinnati (2), to appraise the individual and combined occupational hazards associated with the handling of concentrated anti-knock compounds, and the handling of gasoline containing such compounds. Later in 1925, a more elaborate investigation was made by a group in the United States Public Health Service (3). Others followed in 1927 (4), 1928 (5), 1932 (6, 7), 1950 (8), and 1955-56 (9), through the efforts of the group in the University of Cincinnati. Through these, the observations were extended to include men engaged in the repair and maintenance of motor vehicles in the shops and garages of motor fleets and individually owned motor cars, (also those of a major airline), as well as the employees of certain car parks and parking garages, traffic officers, and taxicab and delivery truck drivers, who are believed to have been subjected to maximum (or near maximum) exposure to the exhausted effluents of motor vehicles.

Various surveys concerned only with the concentration of lead in the atmosphere of Cincinnati, Los Angeles and Pasadena were carried out in 1945, 1950, 1952, 1955, and 1961, by technical members of the staff of the Kettering Laboratory in the University of Cincinnati (10, 11, 12, 13, 14).

Outside the United States, other investigations have been made, in response, as a rule, to questions raised by local health authorities. Thus, in Great Britain in 1928-29, a Departmental Committee of the British Ministry of Health made an inquiry (and a formal report (15) in 1930) which, among other observations, checked and confirmed the adequacy (for their time*) of the methods of previous investigations at points believed to be crucial in relation to their reliability. More recently, over the period beginning in 1947 and extending through 1960, a comprehensive investigation was conducted

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* The sampling and analytical procedures have undergone significant improvements and are now in a very different state of precision than they were in the first two decades of these investigations.

in Switzerland by a Leaded Gasoline Commission composed of expert professional personnel, appointed by the National Department of the Interior under orders of the Federal Council of the Government. Their report (16) was published in 1961. (Governmental inquiries of lesser scope have been made in certain other countries. These have contributed little of significance to the issues involved.)

The latest field survey of the extent of the contamination of the air with lead in large urban centers in the United States was initiated in 1961, in Philadelphia, Cincinnati, and Los Angeles, by a composite group of investigators from the United States Public Health Service, the Philadelphia Health Department, the California State Department of Health, and the Kettering Laboratory of the University of Cincinnati, under the general guidance of a Working Group on Lead Contamination, made up of representatives of the American Petroleum Institute, the Automobile Manufacturers Association, the California State Department of Health, E.I. duPont de Nemours and Company, Incorporated, Ethyl Corporation, Kettering Laboratory, and the Public Health Service. This group interviewed over two thousand persons in the three cities, and secured and analysed specimens of the blood (and in many instances specimens of the urine) of these persons. It completed its work and issued its report, as a publication of the Public Health Service (17), in January of 1965.

In the period beginning in the early nineteen-hundred-thirties, the group of investigators of this general subject in the Kettering Laboratory concluded that the existing occupational hazards of the lead-using industries, as well as the potential hazards to the general public posed by the presence of lead, from a variety of sources, in their environment, including the contribution made by lead in the exhausts of motor vehicles, could not be visualized or appraised by anything short of comprehensive information concerning the sources of lead in the general environment, and the reaction of men thereto. Accordingly, they began a series of investigations, under the financial sponsorship of the manufacturers and distributors of antiknock compounds in the United States, which, after some years of fact-finding, summarized in certain publications (18, 19, 20, 21, 22, 23), culminated in two series of "balance experiments," of which the first, in 1937, involved human subjects to whom lead, in aqueous solution, was administered, by mouth, in carefully graded dosages, over periods ranging from several months to four years. In 1950, these experiments concerned with the ingestion (swallowing) of lead, gave way to corresponding systematic observations as to the behavior of finely divided inorganic compounds of lead dispersed in the air breathed by human subjects under well-controlled conditions in the laboratory. The experiments concerned with the inhalation of lead are still in progress, and are being conducted at this time in such a manner as to demonstrate the maximum level of the concentration of respirable lead which is compatible with the safety of normal healthy persons in the general population under conditions comparable to those in the general environment of the United States. While these were financed, until 1962, solely by the anti-knock industry in the United States, they are now continuing with the financial support of these and other industrial organizations, (Lead Industries Association, American Petroleum Institute), together with the Division of Air Pollution of the U. S. Public Health Service. The general methods of both series of experiments have been described in the literature, and certain of the details and the results have been reported, somewhat briefly, from time to time

(24, 25, 26, 27, 28). By reason of the long periods of time involved in individual experiments, and on account of the voluminous data resulting therefrom, the publication of the results, in their entirety, has been delayed until these data can be examined minutely in all of their physiological and biometrical relationships, and interpreted, along with other older and current reports in the literature. Such an examination will absorb many months of continuous study, and will hardly find an outlet in current scientific journals, but is expected to appear, in due course, in an extensive monograph. A greatly abbreviated "monograph" was issued in 1961, in the form of the combined (bound) reprints of a series of three published lectures, the Harben Lectures of the Royal Society of Public Health and Hygiene, given in London in 1960 (28), which contained brief, graphic and tabulated summaries and discussions of selected items of the clinical and experimental work of the Kettering Laboratory under the title, The Metabolism of Lead in Health and Disease.

2. THE USE OF THE ALKYL COMPOUNDS OF LEAD IN GASOLINE, AND THEIR FATE IN THE ENGINE AND EXHAUST SYSTEMS OF AUTOMOBILES

The lead alkyls in certain formulations of anti-knock compounds are added to gasoline at oil refineries to improve specific qualities of the gasoline, and thereby to improve the performance of the internal combustion engine in which it is used as a fuel. Tetraethyllead has been so used since 1923, while tetramethyllead and certain other alkyls (intermediate in their chemical structure between tetraethyllead and tetramethyllead) came into use in 1960. The average concentration of lead (Pb) in gasoline in the United States during 1965 was 2.43 grams per gallon. The maximum concentration of lead (Pb) used in any gasoline in any part of the United States is 4.23 grams per gallon.

The maximum concentration of tetramethyllead in current use in this country is 2.74 milliliters per gallon of gasoline, this being the concentration of this compound which corresponds in its content of elemental lead with 4 milliliters of tetraethyllead.

These compounds of lead are burned with the gasoline in the engine, and their combustion products appear in the exhaust gas as inorganic compounds of lead, chiefly the chlorobromide, but also as sulfate, carbonate, phosphate, etc., according to the presence and the concentration in the exhaust gas of these and other anions (29). Only minute amounts of the lead alkyls, in the absolute sense, escape combustion in the engine so as to be discharged into the atmosphere. While these compounds can be detected in traces in the air in the immediate vicinity of open containers of gasoline, at refinery loading racks, at service stations during the fueling of cars, and at the tail pipe of automobiles when the engine is started (17), their concentration in the air is too low for precise determination, and is insignificant from the aspect of a toxic hazard.

Only a portion, ranging from 25 per cent. upward to 75 per cent. or more of the lead which enters the engine in the fuel, is discharged from the tailpipe of the automobile under the varying conditions of city driving (29), (the average may be considerably less than 75 per cent. but is difficult to ascertain in a reliable or representative manner). Of the lead which condenses out in the exhaust system of the engine at low speeds of operation, much is discharged in some later period of accelerated operation, in flakes and chunks too large to become airborne (29). These may be raised by the tires of subsequent vehicles to some extent, as dust, which may be borne to the roadside by currents of air, but they can hardly become airborne for more than brief periods of time because of the size and mass of the particles.

3. LEAD IN THE ATMOSPHERE OF CITIES IN THE UNITED STATES

The concentration of lead in the atmosphere of cities in the United States varies from city to city, from one area to another in any one city, and from time to time during the day, week, month or year, according to the activities and patterns of activity of city life, and according to topography and the weather. In Cincinnati, where information about this matter has been obtained over a comparatively long period of time (from 1946 through 1962), the concentration ranges from 0.001 milligram to somewhat more than 0.006 milligram per cubic meter of air, increasing as one goes from rural zones to suburban, business, and industrial areas. The values are lower in warm weather than in cold; the highest results are found in the industrial areas of the city. Significant differences have also been found at individual sampling sites along urban arterial highways, in correlation with the varying density of traffic at different times during the day (10, 11, 12, 17). It is of some importance to note that there has been a downward trend in the concentrations of lead in the atmosphere in Cincinnati over a period of years since the middle forties (12), in association with successful efforts in the abatement of coal smoke and fly-ash, as well as changes in housing and traffic patterns. This has occurred despite a progressive increase in general motor traffic. It is unlikely that meteorological factors have been responsible for this consistent trend.

The results of surveys carried out by ourselves and others in several eastern and middle western cities, and in Los Angeles and Pasadena (13, 14, 30) have been in general harmony with those in Cincinnati, except that the average concentration of lead in the ambient atmosphere of the latter two cities has been higher than that in Cincinnati by a factor of about two. However, only in the "Survey of Lead in the Atmosphere of Three Urban Communities" (17) referred to above, have the observations been extended by the same method over the same period of time in different parts of the country, so as to portray, on a broad base, the general characteristics of the contamination of the atmosphere of our cities with lead, and to confirm the reliability of results that have been obtained over the period of the past twenty years. The expanded information of this survey has demonstrated, among other important items, that the average annual concentration of lead in the ambient atmosphere of all parts of the city of Philadelphia is 0.0016 milligram per cubic meter; that of Cincinnati is 0.0014 per cubic meter; and that of Los Angeles is 0.0025 milligram per cubic meter. The combined experience of investigators of this matter has demonstrated clearly that the sampling and analysis of the atmosphere of cities generally, or of any city in particular, with respect to lead, must be carried out widely and systematically under all kinds of conditions, in order to provide comprehensive information. The composite picture with respect to any one or the several sources of lead, and the rate and direction of their spread and dissipation are by no means simple, and, therefore, assumptions made from scattered and sporadic data are likely to be grossly in error. A few widely aberrant results, for example, have been obtained from place to place and from time to time, and excessive significance has been attached to them. Extra-ordinarily high values may be the result, occasionally, of the concurrence of unusual conditions, but they are more likely to be the result of error, through some chance fault in one or more of the procedures of sampling or analysis. Of much greater significance, both statistically and physiologically, is the prevalence of results of a low order of magnitude, and of average results over prolonged periods of time. (Actually all of the observed high results have been far below the range that is capable of causing lead intoxication in any individual even after many months of exposure. Their fleeting occurrence, therefore, even if factual rather than artificial, is of negligible physiological significance, being but minor deviations from the prevalent environmental conditions.) Under such circumstances, apprehension concerning the unexpected occurrence of a truly dangerous situation is wholly unwarranted.

The facts concerning the sources of lead in the atmosphere require some consideration. It is often assumed that the great preponderance of the lead in the atmosphere, especially that of cities and specific zones of cities, is derived from the combustion of leaded gasoline, but the matter is not that simple. Such may well be the case in some instances, but it definitely is not in others. The facts are that there are many sources from which lead is distributed into the atmosphere, and while most of these result from the activities of men which are concentrated in or near urban areas, some are to be found in relatively isolated and sparsely populated places. There were very few recorded determinations of lead in the air prior to the introduction of leaded gasoline into general use in the United States in 1926, and accordingly there are no satisfactory data for comparison with those available now. Of further importance, in connection with the few existing early data, is the fact that prior to 1938 or thereabouts, methods of sampling and analysis had not been developed satisfactorily. Moreover, current investigation has failed to determine the relative magnitude of the contributions made in any community by the combustion of coal, wood, and other vegetation, by dust from the surface of the earth, by the stacks and burning grounds of industry, and by the incineration of waste materials in the community. The novice tends to make assumptions on the basis of the gross weights of lead bearing materials that seem to be subject to distribution in the atmosphere, locally or generally, without taking strict account of the multiple sources and the factors that influence the persistent dispersion of air-borne solids and contribute to their dilution on the one hand, and their conveyance in air currents far beyond their sources, on the other. Fortunately, the hygienic issue, at this time, relates to the total concentration of lead in the ambient atmosphere from all sources, in conjunction with that which is in the food and beverages and in any other material that may be swallowed. This issue may be restated in direct and simple terms as follows:- Any threat posed to the people of the United States by lead in the air which they breathe, is dependent not so much upon the abundance of lead in their entire environment, as upon the extent to which such lead gains entrance to the internal medium of their tissues, - not that which enters the respiratory tract, for much of this is carried out again in the exhaled air and by other mechanisms of pulmonary clearance, and not that which enters the stomach and intestines, but that which is absorbed therefrom. The mere abundance of lead in the human environment is not, of itself, a threat to mankind, nor, in the final analysis, is the mere presence or alleged abundance of lead in their bodies. Abundance is a relative and non-quantitative term, and the outcome of the absorption of lead into the human body depends upon its rate and extent, and upon the physiological mechanisms which are involved in its systemic and cellular distribution, and in the metabolic processes therein, including also, the elimination of absorbed lead from the body, and the extent of the accumulation, if any, in the body with time. These are matters which must be known and understood before one speaks of danger.

4. LEAD IN THE ENVIRONMENT OF THE POPULATION OF THE UNITED STATES, AND ITS ABSORPTION AND METABOLISM

The natural environment of mankind is such that lead is taken into the human body in virtually all food and beverages (18), and in the respired air. The many usages to which lead is put in modern industrial society, one of which is involved in the present discussion, have increased the amounts ingested and inhaled by the "average" modern man, with the result that more than natural quantities of lead enter into the metabolic processes of his body. The quantities are small but not insignificant. The food consumed by an adult in the United States contains lead in amounts which range from less than 0.1 mg. to 4.0 mg. (occasionally more) per day. The higher and lower values mentioned occur infrequently, the larger proportion of the daily quantities grouping themselves regularly and closely around the mean value of approximately 0.3 mg. per day.

The quantities taken in daily with the inspired air are not so well defined, since they must always be the calculated product of the average concentration of lead in a volumetric unit of the air breathed in by the individual during each period of 24 hours, multiplied by the total number of the volumetric units of such air breathed in during that period. On this basis, these quantities range between 0.015 to 0.09 mg. per day, when expressed in the same manner as the lead ingested in food and beverages), and, as in the case of the intake in food, the average in any situation is probably much nearer the low value than the high, for reasons which will appear later.

The maximum quantities of lead absorbed into the body from that taken into the alimentary and respiratory tracts of the average man may be estimated with a reasonable degree of accuracy on the experimental evidence which shows that somewhat less than 10 per cent. of that ingested (swallowed), and somewhat less than 50 per cent. of that inhaled, are absorbed. (These percentages may be twice too high, but it is preferable to err, if at all, on the high side.) Calculations based on these percentages indicate that about 0.03 mg. may be absorbed daily from the alimentary tract, while quantities ranging from 0.007 to 0.045 mg. and averaging between 0.02 to 0.03 mg. may be absorbed daily from the respiratory tract.

Evidence obtained by corresponding means has demonstrated that the quantities of lead eliminated from the body daily by the average man are substantially equivalent, statistically and physiologically, to those taken in. Thus, the lead which is evacuated with the feces, daily, correlates with that in the food and beverages, extending over the same range and yielding the same average, within the limits of individual variability and probable statistical error. That which is excreted in the urine ranges from somewhat less than 0.01 mg. to about 0.08 mg. per day, and averages approximately 0.03 mg. per day. The total output of lead in the feces and urine, over a period of months, usually exceeds, slightly, the intake in the food and beverages, thereby indicating, indirectly, that the approximate order of magnitude of that absorbed in the respiratory tract of persons investigated in Cincinnati may be 0.02 mg. per day.

From these experiments and from field surveys referred to in the INTRODUCTION above, facts have emerged which demonstrate clearly that, under the conditions that exist in the United States at the present time, the quantity of lead which is being absorbed daily by the average adult citizen who is not subjected to occupational or otherwise unusual types of exposure to lead, is balanced for all practical purposes by the excretion of a corresponding quantity of lead. From theoretical considerations, it seems likely that some slight progressive accumulation occurs with time, at least from time to time, but the rate is low and certainly intermittent, and is believed to be physiologically insignificant. The uncertainty as to the facts, in the absolute sense, raises a point of some practical importance, which should not be made the subject of assumptions. This point is concerned with the means of determining, in the intact, living, human organism, the lead content of the entire body or the socalled "body burden" of lead. The principal factor in the uncertainty which characterizes this matter lies in the fact that lead, like certain other mineral elements, is distributed selectively into the skeleton of man, and that the skeleton, although a living, functioning part of the human organism, carries on its metabolic activity at a relatively slow rate. Moreover, the mass of the skeleton, both relative to other tissues of the body, and also to such a minor constituent as lead, would seem to reduce the content of lead, under ordinary circumstances, to almost negligible proportions. Thus the concentration of lead in the skeleton of the average child or man in the United States who has not been subjected to any unusual exposure to lead, appears to be of the order of 1 to 3 milligrams per 100 grams of fresh, untreated bone, and this, when restated in the gross relationships of the total weight of the lead contained in the skeleton to the total weight of the skeleton, comes to the average value of about 20 parts per million, which is not far from the concentration of lead in soil and coal. Thus it is that the overwhelming quantity of the lead in the body of the "ordinary" adult (95 to 98 per cent.) is somewhat sequestered, so to speak, in that part of the body that is least likely to be affected by it, and is, in addition, in low concentration even there. But it is this partial removal of the lead of the body from the more reactive metabolic processes, that tends to conceal its presence, by reducing its concentration in the soft tissues and body fluids. Lead is distributed in the body in accordance with a regular pattern in which all of the tissues share. It might be supposed, therefore, that, if the concentration of lead in the fluid and cellular tissue, the blood, which is accessible to sampling and analysis, were determined at a time when environmental conditions had been fairly stable for a time, it should be possible to project the concentration which is to be found in all other tissues, and, from their weights, to calculate the quantities in these tissues, thereby, through a summation, to arrive at the total quantity in the entire body. And so it would, but for the fact that the skeleton, itself, is physiologically inhomogeneous, in that the hard shafts of the long bones are extremely limited in their blood supply and in their consequent share in time in the bodily metabolism, while their spongy structure is rich in blood and relatively active metabolically. This physiological inhomogeneity poses the obstacle to the precise determination of the body burden of lead in the intact (living) man. The attempt is being made, by extending the information on the metabolism of lead in the human organism under a wide variety of controlled conditions in the laboratory over prolonged periods of time, and by the collection of analytical data from selected human cadavers, to work out the factors in a mathematical equation that will take these variables into account and yield a numerical value for the body burden. It seems fairly certain that this can be done with a reasonable degree of accuracy. Until it has been done, however, the estimation of the body burden of lead in intact man must be made by a "rule of thumb" which will yield only an approximation of the fact. Certainly the best approach to it, at the present time, and one which appears to yield a satisfactory estimate of the "effective body burden" is that of relating it mathematically to the concentration of lead in the blood while making some allowance for the time of the occurrence and the duration of any period of occupational or other unusual exposure to lead. (The term, effective body burden, as used here, is not meant to have any subtle meaning, but is thought of as that quantity of lead which is most readily available in the complex chemical organization of the body, to enter into the more active metabolic processes, including transport and excretion.)

5. THE ABSORPTION AND EXCRETION OF LEAD UNDER "ABNORMAL" CONDITIONS OF EXPOSURE

One could not support the foregoing interpretation of the findings obtained from experimental subjects in the Laboratory and from various groups of persons in the community at large, were it not for additional types of evidence. The most important features of such evidence relate to the demonstrable physiological responses of experimental subjects and occupational groups of persons to the absorption of quantities of lead beyond the range of those which are encountered in ordinary life.

The rate of the urinary excretion of lead is influenced significantly by a number of factors, but under ordinary conditions it varies primarily with the current rate of the absorption of lead (21, 24, 25, 26).

The concentration of lead in the blood, also under ordinary conditions, varies to some extent with the current rate of the absorption of lead, but is relatively slow in reflecting this rate (unless the latter is very rapid). Instead, as indicated above, it tends to represent the approximate state of the body generally, with reference to its over-all burden of lead (21, 24, 26). Accordingly, if the current rate of the absorption of lead is sufficiently high, as compared to that which characterizes the usual pattern of persons in the general population under ordinary environmental conditions, there is an accumulation of lead in the tissues of the body, including the blood, and the concentration of lead in the blood mounts slowly to a point at which, with due regard for the complexity of the processes whereby lead is distributed within the tissues under various conditions, it is indicative of the approximate quantity accumulated in the entire body (28).

Under the conditions of occupational exposure to lead, it has been possible to develop criteria for the safety of workmen, individually and collectively, in terms of the rate of the urinary excretion of lead, on the one hand, and the concentration of lead in the blood, on the other. Stated briefly and without the necessary qualifications with respect to the type and duration of exposure to lead, and the methods of sampling and analysis, the threshold values indicative of the dividing line between definitely safe and incipiently dangerous degrees of occupational abosrption of lead are, approximately, the concentration of 0.15 mg. per liter in the urine, and that of 0.08 mg. per 100 grams in the whole blood. If these threshold values are in error they err on the low side.

There is little doubt that the criterion represented by the level of the concentration of lead in the blood of persons of all ages and in most physical states, is adequate to distinguish between those who are threatened with the toxic effects of the absorption of lead, and those that are under no such threat. (The concentration of lead in the urine is not so dependable in this matter, for a number of reasons.) This is, of course, a very crucial point in the questions that have been raised concerning the safety of our population, especially that in our urban communities, from the deleterious effects of lead in the ambient air. Because this is so obviously the case, the matter has been subjected to rigid examination. The fact is, that even in the case of infants and very young children, the onset of lead poisoning has not been found to occur in association with levels of lead concentration under 0.08 mg. per 100 grams of whole blood, with due regard to an analytical deviation of $\pm$0.01 mg. per 100 grams, in the case of samples of the usual weight of 10 grams. (The analytical error can be reduced by special procedures, or neutralized by multiple analyses, in border-line instances.)

Freedom from intoxication by lead does not mean the mere avoidance of disabling lead poisoning. Rather it means that no symptomatic or objective evidence of intoxication can be detected, as such, by a skillful and experienced physician. It may be that some effect not now identifiable as the result of the absorption of lead will be recognized at some future time. Even now, however, there are biochemical phenomena indicative of subtle effects of the absorption of sufficient quantities of lead, such as interferences with the synthesis and metabolism of hemoglobin, which, under appropriate conditions, are considered to be evidences of intoxication by lead. There is no evidence, however, that such toxic effects as these are irreversible, nor is there any mild form of lead intoxication which is known or believed to result in any type of permanent damage.

It has been suggested that such a numerical limit (threshold of harmlessness) as that stated above is most unusual in connection with the toxic action of a chemical. To the contrary, it is a guiding principle of toxicology that a toxic effect is mediated by the concentration of the agent within an organism or at the vulnerable site in the organism. The harmless dose of a chemical or physical agent is that which induces no discoverable toxic effect.

This is not equivalent to saying that a toxic effect is induced in every individual of a susceptible species when this threshold has been exceeded. There is, indeed, a wide range of human variability in the toxic reaction to the absorption of lead. This limit is not, therefore, the point above which cases of lead poisoning occur inevitably, but is, rather, the point below, which, regardless of human susceptibility, no case of lead poisoning, at its onset, has been found to occur, in our long and varied experience.

In view of the nature of lead poisoning, as understood in the light of the cumulative medical knowledge of the centuries and of our time, with respect to the effects of the absorption of very much larger quantities of lead than those which gain access to the tissues of persons in our general population, it would seem that there is, indeed, little justification for apprehension concerning a possible hazard of any presently unknown type. On the other hand, there is justification for the continued examination of an environmental factor as common as lead. It is an extremely versatile and useful metal, both in itself, and in its combination with other substances to produce a wide variety of metallic alloys and chemical compounds. The metal and its uses need to be kept under surveillance, to make certain that such uses are compatible with human safety, as specified by the most meaningful criteria that can be defined by physiology in relation to health. Such criteria are available for use in industry and in respect to food and beverages, and such a criterion is being developed with respect to the ambient atmosphere. It is possible that present criteria will be replaced by simpler and more readily applicable specifications. If so, such action may be part of the expected product of the extensive research which is required now and in the future to enable modern man to understand and to control the environment which he is altering, drastically, to his own ends, so as to preserve and cultivate his health, well-being, and longevity, along with his affluence, comfort, and happiness.

6. CRITERIA OF PUBLIC SAFETY WITH RESPECT TO THE ABSORPTION OF LEAD, AND METHODS OF IDENTIFYING A THREAT TO THE PUBLIC

As indicated previously, the opportunities for the absorption of lead afforded to the average citizen of the United States (who is not subjected to demonstrable occupational or unusual types of exposure to lead) are concerned with his ingestion (swallowing) and inhalation of lead compounds which occur in his general environment. The total quantity of lead that may be absorbed from these combined sources constitutes the total threat, if any, of the environment, with respect to lead. However, since these sources differ in their means and capacity for the penetration of lead into the body, and, to some slight extent at least, in their effect upon the distribution and handling of lead in the body, they must be examined, separately, as to their quantitative significance. Accordingly, the limit of safety, with respect to the absorption of lead from the one, must be established while the other is being held constant, and *vice versa*. This has been done, up to a point, in experiments in the Kettering Laboratory.

(a) The upper safe limit of the daily intake of absorbable lead into the alimentary tract

In one set of experiments, each of a series of human subjects, after a period of observation of his daily intake of lead in duplicate samples of food and beverages, and his daily output of lead in the feces and urine, (under basic conditions with respect to the inhalation of lead from day to day), was given a measured quantity of lead per day, one-third of it with each meal, in simulation of his ingestion of food contaminated with lead. These experiments have been described in some detail (24, 25, 26). In brief, however, they have set up the criterion for safety, and have yielded the results that meet this criterion. It was evident that, under the conditions of these experiments (in which about the same quantity of lead, the sum of that in the food and beverages and that administered, was ingested each day), each individual, to whom a sufficient quantity of lead was administered daily, gave evidence of the absorption of lead, in proportion to the dose administered, and excreted lead in his urine at a steadily increasing rate during the entire period of the administration (for somewhat more than 4 years in one experiment). He also sustained an increase in the concentration of lead in his blood, at a substantially uniform yearly rate, and accumulated lead in his body (the cumulative difference between intake and output), at a uniform yearly rate. No such effect was observed, however, in the subject to whom the least dose (that of 0.3 mg. per day), in addition to that in his diet (mean value, 0.32 mg. per day), was administered in 3 doses, each of which was 0.1 milligram. In this instance, there was a very slight increase of borderline statistical significance in the output of lead in the urine, no increase in the concentration of lead in the blood, and evidence (of borderline statistical significance) of the accumulation of 12 mg. of lead in his body in the course of 1.5 years. This is believed to be as near the vanishing point of a positive response as one is likely to obtain in an experiment of this type. In consequences, it is altogether probable that a young, healthy adult can be expected to ingest, regularly, an average quantity of lead of the order of 0.5 mg. per day, without any risk of accumulating a significant quantity of lead in a life time.

Now that a criterion is available with respect to the quantity of lead which may be ingested daily, with safety, the question arises as to the means by which the quantities being ingested by people can be determined, at any time or place of necessity. If this question could be answered only by the comprehensive sampling of the food and beverages of the country or of an area, it would be both difficult and costly to obtain the answer. Fortunately, a much better, easier and less costly method of surveying this situation has been provided by the experimental demonstration that the lead content of the food and beverages eaten and drunk during a period of twenty-four hours is indistinguishable, statistically, from the lead content of the evacuated feces that relate to the corresponding period. Translated into practice, this means that suitable specimens of the feces can be provided by healthy, young adults, who have been simply but properly instructed to collect what is for each of them a typical evacuation of the bowel. (For aesthetic reasons, but also for very practical physiological reasons, this method of investigation is best carried out with the cooperation of the younger male members of the adult population, who, as a rule, are the consumers of the most varied and the largest quantities of food. However, it can, and has been, carried out with females.) The procedure acknowledges the principle that representative human subjects are the best of all sampling devices for the purpose of establishing the composite quality and quantity (and the lead content) of that which is taken into the alimentary tract by people, generally. All that is required for the purpose of determining the cross-sectional performance of the population of an area or of the country, in this respect, is to obtain a representative sample of the population as subjects for the observation. This has turned out to be an extremely useful device for this purpose, and when it is employed, with appropriate care, by the investigator, the information so obtained is relevant and sufficiently precise. Moreover, in situations in which certain results are extraordinarily high (in the statistical sense), inquiry, and if necessary, the examination of specific items of the food or drink, will, as a rule, reveal the source of the unusual quantity of lead.

(b) The upper safe limit of the concentration of lead in the ambient air

It will be noted that this subheading is couched in different terms than that above, (a), the reason being that the quantity of lead which is taken into the body with the air breathed, as indicated previously, cannot be determined directly, but is subject to calculation from the weighted average of the concentration in the air and the volume of air breathed during a specified period of time. A number of variables are involved in this calculation, so that it can be carried out with a reasonable degree of accuracy only under well controlled conditions, with respect to the measurements of the lead in the air and of the volume of respired air. Even so, the quantity of lead absorbed in the respiratory tract and lung varies with the rate and depth of the respiration as well as its volume and, to an even greater extent, with the dimensions, shape and solubility of the particles of lead-bearing material that are being inhaled. The most satisfactory physiological criterion, with respect to the rate and significance of the absorption of lead in the respiratory apparatus, lies, therefore, in the response that is afforded by the change in the content of lead in the urine and blood. However, while analyses of the urine and, more effectively, the blood provide definitive evidence of the safety or the potential risk of the individual (and of groups of individuals) at the time of the analyses, they cannot yield information on which to predict the probable extent of the absorption that will occur ultimately, <u>when lead is being absorbed into the body at a constant, significant rate</u>. This is the difference, and it is a fundamental physiological difference, between respiratory exposure to lead according to the occupational schedule, now standardized, generally, in the United States at 8 hours per day on 5 days per week, and that associated with lead in the atmosphere of the community, which, though somewhat variable, from place to place and time to time, is continuous through the 24 hours per day on 7 days per week. In the occupational situation, (and as simulated by our experiments in which men were subjected to the inhalation of a known compound of lead in a known state of subdivision - nearly ideal for both retention in the lungs and for absorption - in the air for approximately 40 hours per week), the output of lead in the urine and its concentration in the blood increase for some months until they reach a plateau the height of which is determined, under uniform conditions, by the concentration of lead in the air. Afterward, it remains essentially unchanged, on the average, so long as the occupational (or experimental) exposure continues unchanged. This plateau is an expression of an equilibrium between the absorption and excretion of lead, which is achieved by reaching a balance between the periods of exposure, when absorption is greater than excretion, and those out of exposure, when the excretion is greater than the absorption. There is no opportunity for the achievement of such a balance when the rate of absorption is sustained, as in our experiments during which lead was administered by mouth in three doses through the day, and as it must be when lead-bearing air, within appropriate limits of concentration, is being breathed throughout the twenty-four hours of the days. These facts make it necessary to approach the criterion of the safety of the public, in relation to lead in the ambient atmosphere, on a different principle than that of the safety of employees in the lead-using industries. It is also necessary to employ a different method of observation from that concerned with the ingestion of lead, although the same principle applies, that of establishing the largest daily dosage of lead derived from the air which, when combined with that derived from food and beverages, will be insufficient to result in a discernible accumulation of lead in the body in the course of a life time.

It is hardly feasible, within the limits of a reasonable cost, to maintain human subjects, continuously, for months and years, in an experimental atmosphere containing an elevated concentration (above that of the ambient air) of lead of ideal chemical composition and physical dispersion for retention and absorption within the lung. However, a feasible means of determining the facts would appear to be that of establishing ideal conditions of respiratory exposure to lead, at such a level of concentration as to induce a series of increasing responses (on the part of the urine and blood), in experiments in which all of the conditions are held constant except that of time, i.e., the duration of exposure per day, over such periods as will establish the height of the plateau of the urinary excretion associated with each period, so as to arrive, by extrapolation, to the level that would be attained in time, by exposure for 24 hours per day every day.

Preliminary experiments, conducted with two subjects in parallel, under conditions of exposure to a relatively high concentration of lead in the air (150 micrograms per cubic meter) for 3 hours per day on every other day for 4 months, then for 6 hours, 9 hours, and 12 hours per day, on every other day for 4 months, in each instance, demonstrated the feasibility of the method. Whereupon, with two new subjects, two experiments, also in parallel, were initiated at a low level of concentration (10 micrograms per cubic meter), and have now, (May 20, 1966), been under way over the period of 32 months. The subjects are now spending almost half of their time, (12.25 hours per day on 6 days of each week), in the experimental chamber, without having responded as yet, by a demonstrable increase in the concentration of lead in their urine (none would be expected in the blood without some prior change in the urinary output). Since this experiment has very nearly run its course, (with due regard to the comfort and convenience of the subjects) with negative results thus far, it seems necessary to begin again at a higher level of the concentration of lead in the chamber, so as to obtain barely positive results by which to describe, by extrapolation, conditions which are at or slightly above the threshold of danger. This is a painfully slow process, but it seems necessary, at this point, to make sure that any result obtained in these experiments is either barely positive or negative, so as to define the threshold accurately. Through such results, a satisfactory criterion of public safety can be established on a physiological basis, with such margin as may be considered to be prudent.

7. CERTAIN GENERAL OBSERVATIONS AND CONCLUSIONS

Aside from the question of the reliability and accuracy of the experimental work outlined briefly herein, one feature of its outcome that is somewhat disturbing to some of those who have professional responsibility for the safety of some segment of the population of this or other countries, is its quality of negativity. No one, and, strangely enough, this includes men with sound scientific training, is impressed by negative findings, despite the fact that the public health must be described, in practice, in such terms, and that safety must, correspondingly, be defined as the absence of hazard, when a satisfactory search for hazard has been undertaken and carried out. We are seeking, here, not a disability nor a disease, but a threat. No such threat has been found, although the methods for detecting it have been forged and sharpened in their sensitivity for such detection. In terms of present information, which has been sought systematically, the fact is clear. No present hazard to the public health is represented by the lead dispersed in the air in association with the distribution and use of leaded gasoline. No increase in the total intake of lead by persons in the general population of this country has been found to occur during the past three decades. Instead, there seems to have been a sufficient decrease in the average daily intake in food to lower the total intake. Moreover, the methods of investigation available at present are such that a sudden or gradually progressive increase in the lead content of the atmosphere, or, for that matter, in the intake and absorption of lead from any and all sources, can be detected before it reaches dangerous proportions.

In addition to this safeguard, it should be possible, before long, to supply criteria for the promulgation of a reasonable standard of air quality, with respect to lead content, which will take into account the physical and physiological factors that influence the respirability and the absorbability of the compounds of lead found commonly in the atmosphere. Truly, this is a matter which is complex in itself, and one which must be balanced against the other sources of lead absorption, if it is to be valid. A satisfactory procedure, in relation to public safety, and one which, because of its direct pertinence, must be employed, is that of making observations from time to time on representative groups in the population, by methods which will indicate the general sources and the order of magnitude of any significant changes in the exposure of the public to lead, and provide intelligent bases for hygienic control.

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