2. THE DISTRIBUTION OF LEAD IN THE EARTH, ITS WATERS, AND ITS ATMOSPHERE

2.1. LEAD IN SURFACE SOIL IN DEEPER STRATA

The quantities of lead found in the surface layers of the earth are generally small, averaging about 16 ppm (Goldschmidt, 1954). There is considerable variation, however, and from place to place outcroppings of mineral deposits ordinarily found in deep strata have come to the surface through the buckling or severe erosion of the earth's crust, and have introduced relatively large quantities of lead into certain surface *soils* (Warren *et al.*, 1960; de Treville, 1964). The full extent of the variability of the *natural* content of lead in the soil of various parts of the earth is of course unknown, since sampling and analysis have not been sufficiently comprehensive, and also because many changes have occurred over the years without satisfactory explanations of their origins.

Through mining and manufacturing, lead and its compounds have been scattered upon the surface of the earth in such profusion as to render difficult a realistic estimation of its natural pattern of distribution. However, there are reasons for believing that the order of magnitude of the contamination of most of the uninhabited and sparsely inhabited lands of the earth with airborne lead has undergone little change recently. The deposition of airborne lead on the soil in rural areas of the United States well removed from industrial operations and heavily travelled highways has been estimated as being of the order of about 1.2 μg per cm^2 per year equivalent to 48 μg per cm^2 in the 40 years since lead antiknock preparations were first introduced into use in the United States (Ter Haar *et al.*, 1967). In contrast, evidence of contamination can readily be found by systematic sampling and analysis of soil (de Treville, 1964; Motto *et al.*, 1970), of flat surfaces, such as the copings, ledges and roofs of buildings, streets, pavements, and the like structures (Willis *et al.*, 1928) and of vegetation in the immediate vicinity of the production or usage of lead-containing commodities (Hammond and Aronson, 1964). Likewise, samples of soil obtained where lead is used in cities (de Treville, 1964), in rural areas near mines and lead industries (Hammond and Aronson, 1964), and adjacent to well travelled highways (Motto *et al.*, 1970), yield quantities of lead which clearly are related to methods of handling or usage of the metal. Few significantly high findings are obtained by the analysis of rural soils elsewhere.

Based mainly upon industrial experience lead compounds are but poorly differentiated with regard to their absorption by living organisms. A number of physical and physiological facts, as well as certain significant voids in our understanding of the physiology of plants and animals, are responsible for this situation. It seems reasonably clear that the physical structure of certain lead-containing minerals, as well as the nearly absolute insolubility of certain compounds of lead, are important obscuring factors. As to the latter factor, lead silicate is a case in point, in that ancient as well as modern practices in glazing ceramic ware are found to be attended by only minute amounts of contamination of food or drink with lead if the composition of the glaze is satisfactory, and if the temperature of the firing of the ware is sufficiently high and prolonged to convert all of the lead to the silicate.

Another example illustrates this point further. In the mining of lead, experience had shown that lead poisoning among miners occurred with great frequency and severity during the early periods of the operations, followed later by a seemingly spontaneous and abrupt cessation. This striking phenomenon coincided with the penetration of the mining operations through the overlying stratum of oxidized ore (much of it lead carbonate) into deeper strata in which the lead was primarily crystalline galena. The incidence of lead poisoning among the workmen reasserted itself with the removal of the galena from the mine and its smelting to obtain the molten metal. Thus, at an early date, certain differences in the various physical states of lead, its ores and its compounds, came to be recognized in relation to the risk of the occurrence of lead

Pharmac. Ther. A, Vol. 1, pp. 161–188, 1976. Pergamon Press. Printed in Great Britain

Specialist Subject Editor: W. G. LEVINE

PHARMACOLOGY AND TOXICOLOGY OF HEAVY METALS: LEAD

ROBERT A. KEHOE

University of Cincinnati Medical Center, Kettering Laboratory, 3223 Eden Avenue, Cincinnati, Ohio 45267, USA

1. INTRODUCTION

Any historical account of the earliest recognition by man of the existence of lead as a natural resource as well as a material possessed of potentially harmful qualities, would be redundant, repetitious, and, in all probability, inaccurate. It suffices here to say that the antiquity of various types of information about this metal have been remarked upon by many previous writers, and that the metal and certain of its preparations were being used for a variety of purposes, in all likelihood, before historical time. As the experience and inventiveness of man progressed, and as his knowledge of minerals increased, he found this metal to be procurable with relative ease through the application of heat to stones of a certain character and source, as well as remarkably useful because of its relative softness and maleability. With the development of lead-containing alloys, other important properties of these metallic combinations have been realized and cultivated. In due course it was appreciated that during the production of lead fumes and lead-bearing airborne particles men who worked with the metal became ill. The onset and course of lead poisoning were no doubt described first by word of mouth. Although lead compounds may have been employed for medicinal purposes in the early days of civilization, they have no place as therapeutic agents for man today. In this industrial and technological era, the utilization of lead must be restricted to those purposes which can be regulated and subjected to sufficient control to prevent toxicological effects upon animals and man, and their environment. This responsibility can be fulfilled only by a comprehensive understanding of the place of lead in the environment of man, and its behavior in the internal media of his body.

Lead is widely represented in the composition of the earth's crust; it has been found in all soils, bodies of water and living things thus far examined, and it seems likely that it is present in all vegetation and animal life. It does not follow, however, that this element is essential to life. Nevertheless, the seeming natural universality of lead in the environment and the comparative uniformity of its concentration in tissues and organs bespeaks the existence of effective physiological mechanisms for its maintenance within certain low limits therein, and suggests that it may have some usefulness in the processes of life. The virtual flood of investigations of the trace metals, and especially of lead, in recent years has made available much information concerning the biological effects of lead and has raised a series of highly challenging questions concerning the behavior of this element within the animal organism, and the mechanisms concerned therewith. The extent to which lead combines with nuclear constituents, enters into a large number of metabolic processes in the body, and influences the behavior of many enzymes only emphasizes the likelihood of a biological role. No further reference will be made to this aspect of the matter, but it is well to remind ourselves that our goal in biological study and research is to seek an understanding of nature, rather than to justify traditional impressions as to the significance of her manifestations. This is especially pertinent in the field of toxicology, for the poisonous property is only rarely a function of a substance itself, but rather depends upon the concentration of the substance within the organism or within specific tissues. Since the toxicology of lead is now a theme which runs through much of our discussion it is desirable to follow it as closely as possible.

into the atmosphere from the equipment in which they are produced, from unenclosed piles of processed, incompletely reacted materials, and from accumulations of dross. The combustion of such solid fuels as wood and coal also yield smoke and fly ash containing low concentrations of lead. The particles may become airborne and remain so over variable distances and periods of time, dependent upon the velocity imparted to them in their production, the air currents, and their own characteristics (size, electrical charges, or hygroscopic capacity). Thus it is that large, heavy particles of lead or lead-containing materials fall out of the air quickly and are deposited within a roughly circular area around the point of origin, or in a strip along a highway. Variable quantities have been found in polar layers of snow (ice) especially in the northern polar area, where as annual layers, like the rings of trees, they bear mute testimony to the relative annual quantities removed from the air (Murozumi *et al.*, 1965; Jaworowski, 1968).

The distribution of lead in the atmosphere prior to its contamination by man, is a matter of speculation. Less than half a century ago, highly sensitive and accurate methods were developed for sampling and analysing the atmospheric envelope of the earth. A few analytical data, obtained in the early years of the twentieth century by inferior methods of sampling and analysis suggest that lead occurred in considerable concentrations in the atmosphere of certain parts of the United States prior to the use of lead-containing gasoline (Bloomfield and Dalla Valle, 1938). However, there are no data, comparable in either geographic scope or quantitative character, to those obtained during the past three decades, to reveal the ranges or the variability of the concentrations in the atmosphere of different geographical areas. The best evidence of an overall pattern in the spread of minute particles of lead within the atmosphere of this planet apparently is that afforded by recent analyses of layers of fallen snow which have been converted into ice in the permanently frozen northern polar region. The concentration of lead in layers corresponding to specific periods of time, in the northern polar region, range from less than 0.001 μg/kg of ice, in 800 BC to more than 0.2 μg/kg in AD 1965 (Murozumi *et al.*, 1965). Considerable increases occurred prior to the twentieth century, in association with the development of industrial activities involving obvious growth in the usage of lead in Europe. The largest increases occurred after 1940 in apparent coincidence with the increasing use of lead alkyls as antiknock agents in gasoline. Jaworowski (1968) has reported similar data from his investigations. His earliest layers of ice, dating from about 1861–66, contained lead in the mean concentration of about 5 μg/l. (of melted ice) as compared with that of 75 μg/l. in ice deposited in the period 1960–65. Only on a much smaller and somewhat ambiguous scale have such variations occurred in the layers of ice in Antarctica, as shown by Picciotto *et al.* (1968). This, presumably, is because of the behavior of the upper air currents, and also because in areas of the earth from which these deposits are believed to have come relatively little corresponding usage of lead-containing products has occurred.

The available evidence which has been cited, when coupled with that provided by Tatsumoto and Patterson (1963) concerning the concentration of lead in the superficial layers of the ocean bordering on the North American continent, has indicated clearly that at the present time the air overlying this land mass contains lead in concentrations which exceed those of previous periods in the same areas. Systematic analysis of the air in certain areas of the United States by Cholak (1964) and by the Public Health Service (1965), as well as determinations of lead in rain and snow (Tatsumoto and Patterson, 1963) and in glacial deposits (Murozumi *et al.*, 1965) have revealed some of the sources of airborne lead, some of the variations in its concentration, and suggested a type of pattern for the overall behavior of particulate lead compounds (and certain comparable aerosols) in the atmosphere.

It seems desirable to consider specific factors which are responsible for serious, localized contamination of the atmosphere with lead on the one hand, and for the more common levels of concentration of the ambient atmosphere with lead, on the other. Within industrial work areas the concentration of lead in the atmosphere may well be of the order of many mg/m^3 of air, and, depending upon raw materials and products

poisoning among workmen. However, despite the body of information and misinformation which has accumulated for centuries concerning the harmful effects of lead, men have dared to develop a great variety of uses for this extremely valuable and versatile metal.

2.2. Lead in Streams, Lakes and Oceans and in Human Supplies of Water

The presence of lead in all bodies of water is inevitable, even in primitive areas, in view of the lead in soils. Not only are water soluble compounds of lead leached out of the soil by rainfall and melting snow, but the run-off into the streams carries with it suspended soil, which soon becomes silt. Some, or perhaps most of the soluble lead in streams is also precipitated by various anions in the water, and is deposited eventually in the bed of some body of water. Because of relative insolubility, most compounds of lead found in water are in the form of suspended particles which tend to agglomerate and settle out eventually. Thus, the silt at the bottom of streams and other bodies of water is likely to be higher in its content of lead than is the water itself, and after filtration or settling of natural waters little lead may be found therein. Nevertheless, a stream or body of water may be heavily contaminated by the incoming flow of process or waste water from an industrial plant or mine, and appropriate steps must then be taken to free the water from excessive concentrations of lead. Official specifications are applied in certain areas of the country for the concentration of lead which may be released into a stream, lake or ocean. Comprehensive governmental requirements in this respect should be established and enforced. In the United States the water available in urban distributing systems is usually considerably lower in lead (Kehoe, 1960) than the official specification of the United States Public Health Service (0.05 mg Pb/l.). However, in areas in which water is obtained at individual homes, institutions and industries from wells or cisterns, or is collected in receptacles or conveyed in pipe lines, the lead content of the water is not always satisfactory because of failure to install lead-free pipes, containers and collecting and distributing equipment, or to avoid the extensive use of solder in making repairs. The roof of a building which collects water for a cistern may be of a lead-containing material or covered with lead-containing paint. Cases of lead poisoning are of infrequent occurrence in connection with such potentially hazardous situations, but they do occur. It must also be recognized that a brook, stream or lake badly contaminated with lead by the discharges of local industry may be sources of drinking water and hence a hazard to domestic or wild animals, whereas people in communities or dwellings in which the water from these same streams has been filtered and treated may be fully protected against any harmful effects of lead. Even in the modern household, however, both water and food may be contaminated significantly and even dangerously with lead, through the use of kitchen equipment or tableware containing unusual amounts of lead leached from antique pewter or improperly glazed, coated or soldered surfaces.

2.3. Lead in the Atmosphere

Metallic lead is discharged into the atmosphere as vapor (probably short-lived as such), and more importantly is emitted into the air as fumes, mists and dusts. Operations concerned with the processing of lead-containing products, especially when they involve high temperatures, result in the vaporization of lead or in the formation of fume and dust. Molten lead vaporizes appreciably above 800°C, while its compounds and alloys volatilize at various high temperatures in and above this range and produce finely divided fume which is spread by local heating and often carried afar in natural currents of air. Mists are distributed into the air as aqueous sprays of lead compounds, as finely divided compounds discharged with water vapor (automobile exhausts), and as minute airborne particles washed out of the air in falling rain or snow (Burton and Steward, 1960; Ter Haar *et al.*, 1967; Lazrus *et al.*, 1970). Dusts of lead compounds are produced by crushing, grinding, stirring and collecting operations. They are distributed

TABLE 1. *The Lead Content of Vegetation*

Article	Source	Number of samples	Range of lead content (mg/kg)
Tea leaves, hand picked (dry)	Ceylon	1	0.02
Foliage of tree (wet)	Forest, Yucatan	1	0.25
Root of tree (dry)	Forest, Yucatan	1	0.05
Bark of tree (dry)	Forest, Yucatan	112	0.04–0.40*
Latex of tree (wet)	Forest, Yucatan	36	0.04–0.08*
Latex of tree (wet)	Forest, Sarawac	2	0.02–0.04
Cocoa pod (inner, dry)	Trinidad	2	0.17–0.23
Cocoa bean (husks, on nibs, dry)	Trinidad	3	1.38–1.60
Cocoa beans (nibs, dry)	Trinidad	1	0.03
Peas (green)	Mexico (primitive area)	1	0.03
Beans (green)	Mexico (primitive area)	2	0.15–0.26*
Bean pods	Mexico (primitive area)	1	0.04
Corn (maize, green grain)	Mexico (primitive area)	3	0.03–0.31*
Corn (green husks, wet)	Mexico (primitive area)	1	0.26
Corn (green stalk, wet)	Mexico (primitive area)	3	0.05–0.11

*Even here, carefully gathered samples seem occasionally to be contaminated.

human environment. The lead content of the human diet which derives from this source depends partially upon the extent of absorption of lead by various species but even more upon the distribution in the tissues used as food by man and other animals. Briefly, it may be pointed out that the distribution of lead in herbivora, both domestic and wild, is generally similar to that in man, and that lead, a 'bone-seeker', is found preponderantly in the skeleton, and in low concentrations in muscles, and in only slightly larger concentrations in other organs. Some of these data are illustrated in Table 2. With the exception of the contamination of meat and meat products in

TABLE 2. *Comparative Distribution of Lead in Certain Tissues of Cattle (Illustration)*

Material	Western range steer (normal healthy animal) (mg/100 g)	Dairy cow fed upon forage contaminated with lead (mild signs of illness some weeks before slaughter) (mg/100 g)
Bone of Leg	0.36	1.21
Brain	0.013	0.12
Liver	0.004	0.40
Kidney	0.038	1.10
Spleen	0.003	Not available
Muscle	Not available	0.01
Blood	Not available	0.05
Urine	Not available	0.09

butchering and processing only small quantities enter into the human diet; yet these are somewhat greater than those in uncontaminated vegetable products. Little environmental lead has entered the food chain of man, beyond that existing naturally. The possible consequences of the wide dissemination of lead in the general environment are of a different order of severity, however, for herbivorous animals in that forage, which is their principal food, may be contaminated by the fall-out of lead from industrial establishments, and mines, and also, from land along heavily travelled highways. Even in such instances, the musculature of poisoned animals, which is the principal source of meat for man, is low in its lead content, and is not unsuitable for human consumption. It should be emphasized that the avoidance of a significant degree of contamination of all food, including that of animal origin, continues to depend upon surveillance of the handling and processing of articles which enter the market place, the restaurant and the home. The opportunities for such contamination are numerous, and only the broad dissemination of information concerning containers and additives, as well as processing

involved, the lead-containing particles in the air may vary greatly in their composition from one industrial establishment to another, and from one operation to another therein. The size of the particles also may vary individually and in their proportional representation in the atmosphere over a very wide range. In those working areas where measures of control have been employed for the maintenance of safe working conditions, the concentrations of lead will rarely exceed 200 $\mu g/m^3$ of air for more than brief periods. Furthermore, in an area immediately adjacent to, but not actually in the stream of traffic on a heavily travelled highway the concentration of lead may range somewhat above 10 $\mu g/m^3$ of air, decreasing to 1 or 2 $\mu g/m^3$ of air at a distance of 30–50 *m* to the windward side of the roadway.

We can consider lead to undergo a cyclic migration whereby most of the lead in the air is dispersed widely by prevailing air currents, is washed out by rain and snow, and is removed from the land by rainfall and streams which ultimately reach the oceans. The quantitative relationships in this cycle may vary, but evidence has been provided by Cholak (1954) to suggest that the concentration of lead in the air of Cincinnati has reached a nearly steady state, despite the progressive increase in the number of automobiles and their utilization of leaded gasoline. One would suspect that the fact that the consumption of lead for all purposes in this country has been fairly constant for almost two decades (U.S. Bureau of Census, 1969) would be a factor in this matter. Of greater importance, most of the lead exhausted from motor cars exists in the form of minute particles which have a mass median equivalent diameter of about 0.25 μm (Robinson and Ludwig, 1967). Thus they remain airborne for a long time and migrate rapidly in air currents. Local topographic and meteorological factors in a specific region may be expected to exercise an influence upon the average concentration of airborne lead found in specific cities. The duration of lead in the atmosphere in a number of areas of North America has been estimated by Burton and Steward (1960) to be of the order of 7–30 days (the precise figure depends upon prevalent environmental conditions), on the basis of the behavior of particles of ^{210}Pb. It may be, therefore, that the present cycle of the introduction of lead into the air and its removal therefrom has essentially brought about a steady state with respect to the general level of the concentration of lead in the air.

2.4. Lead Within and On Vegetation

The occurrence of lead in vegetation and hence in food for animals and humans, generally is the result of the growth of vegetation in lead-bearing soil. The quantity of lead derived thereby is generally low, being of the order of a few hundredths of 1 ppm (Kehoe, 1961). It varies among different species, with the characteristics of the soil, and with the chemical and physical state of the lead in the soil. The concentration of lead in various parts of the plant is also variable, but because information is insufficient, it is difficult to make generalizations concerning this, although the concentration tends to be low in the fruit, with the exception of the seeds and their intimately covering tissue, and in the roots (Kehoe, 1961; Ter Haar, 1970). The information currently available, some of which may be seen in Table 1, indicates that the consumption of lead by herbivorous animals from this source is small when it is limited to that derived from the soil. It assumes a very different significance when lead from some external source is deposited upon forage crops used by these animals (Hammond and Aronson, 1964).

The spraying of vegetables with insecticides containing lead is unusual in most areas of North America, so that food contaminated in this manner is encountered infrequently. This, however, is not universally true, especially in view of the present controversy associated with the use of chlorinated hydrocarbons as insecticides, which may result in some degree of return to other sprays including those containing lead.

2.5. Lead in Animals

In this section, an important consideration is the extent to which the organs and tissues of animals constitute food for mankind, and are thereby a part of the effective

portal circulation, whence it is redistributed, some being returned to the intestine in the bile and some being tranported into other tissues, including the erythrocytes and the urine. Some of the lead which passes into the bile undergoes enterohepatic circulation while the remainder is evacuated in the feces. The proportions here are subject to variation depending upon the composition of the alimentary contents and upon the time required for the traversal of the alimentary tract (Kehoe, 1961). Moreover, all of the digestive fluids, which amount to a very considerable volume of liquid, contain lead derived from the secretory membranes and glands.

The processes concerned with the alimentary absorption, secretion, resorption, excretion, and evacuation of inorganic lead compounds, including the amounts derived from the respiratory absorption of lead constitute a varied series of physiological activities which, in the case of normal persons living in the United States, operate according to a remarkably uniform pattern (Table 3). These data were obtained during

TABLE 3. *Intake of Lead Into Alimentary Tract, Output in Feces and Urine, and Concentration in Blood–Normal Human Subject–Normal Period of Observation**

Successive periods of 28 days	Intake of lead in food and beverages (mg)	Output of lead in feces (mg)	Output of lead in urine (mg)	Average lead in blood (mg/100 g)
First	5.22	2.60	0.85	0.029
Second	4.41	2.56	1.24	0.023
Third	3.81	3.24	0.99	0.020
Fourth	5.37	4.19	0.93	0.022
Fifth	5.87	4.13	1.20	0.023
Sixth	3.84	3.97	1.28	0.022
	28.52	20.69	6.49	0.023 + (Av.)

*Data derived from Kehoe (1961).

the conduct of balance experiments described elsewhere (Kehoe, 1961) in which the intake of lead by adult human subjects in their food and beverages came primarily from markets and other retail outlets in Cincinnati. (Certain other articles entered into the diets of subjects who had access to food from the countryside in the general vicinity of Cincinnati.) Precise duplicates of the food and beverages consumed were composited into daily samples for analysis. Likewise, all fecal evacuations were collected and dated individually, and all urine voided each day was obtained for analysis. It is of interest to compare quantities of lead in the daily diets of these subjects, with those calculated by Monier-Williams (1949) on the basis of data obtained through analysis of food materials in Great Britain, when considered against their proportional representation in the national diet. The two sets of findings tend to supplement each other; the latter provides the benefit of being derived from a large number of people and a wide variety of food products in another nation. It may be noted that the quantities of lead found in the food and beverages of the individual subjects were of the same order as those found in their feces. Indeed, but for the fact that the urine of both subjects contained lead at all times, it might have been suspected initially that no lead had been absorbed from the alimentary tract. The relationship between the amount of lead ingested and the amount evacuated in the feces is so uniform in people of regular habits as to justify the use of the fecal lead as a means of estimating the amount consumed (Kehoe *et al.*, 1940).

When the rate of introduction of lead into the alimentary tract of a healthy man increases, there follows promptly an increase in the rate of the elimination of lead in the urine and feces; some portion of the latter is the result of an increase in the rate of the true excretion (as differentiated from the quantity evacuated) of lead from the alimentary tract. The rate of increase in excretion of lead from the alimentary tract reflects the elevated rate of introduction of lead into it. This relationship is maintained so long as there is a continued increase in the quantity of lead available for absorption. Figure 1 illustrates the response of urinary lead excretion to the daily ingestion of

and household equipment, is a practical means of preventing errors of judgment and performance.

3. ABSORPTION, EXCRETION, DISTRIBUTION AND ACCUMULATION OF LEAD BY MAN

Inorganic lead is absorbed into the human body almost entirely through the alimentary and respiratory tracts; the rate of absorption of inorganic lead through the skin is negligible under ordinary circumstances. The transcutaneous, subcutaneous, intramuscular and intraosseous absorption of lead is worthy of discussion only because of the comparative frequency of imbedding of lead-containing bullets or pellets from firearms in or beneath the skin. The absorption and dissemination of lead from such sources is small, and is negligible after clean subcutaneous or intracutaneous encapsulation. However, lead may be absorbed in detectable and occasionally toxic amounts if there is tissue reaction with lead, especially in infected joints in which the combination of being ground in the presence of an exudate induces the solution and absorption of lead into the circulation (Machle, 1940). The minute rate of absorption from a single bullet or shot may be multiplied significantly by a sufficient number of shots distributed into or under the skin.

The lead soaps which are components of certain more or less specialized lubricants are salts of fatty acids. In the absence of adequate information to the contrary, some of them may be presumed capable of undergoing significant percutaneous absorption.

The alkyl lead compounds are fat soluble and are absorbed rapidly through the skin into liver, kidney, muscle, and central nervous system in highly toxic quantities (Kehoe, 1931). Tetraethyllead is absorbed more readily than is tetramethyllead (Springman *et al.*, 1963). Both compounds are absorbed at a more rapid rate from the respiratory than from the alimentary tract (Davis *et al.*, 1963), and in the latter more rapidly than through the skin. The volatility of tetramethyllead (B.P. near 100°C.) is much greater than that of tetraethyllead (B.P. 202°C.), and, therefore, it yields more vapor at ordinary temperatures. The saturated vapor of tetraethyllead at 25°C. contains approximately 5 mg Pb/l. (Kehoe, 1927), and the inhalation of such concentrated vapor for about 15 min by experimental animals will result in their death (though not by lead intoxication) some hours later (Kehoe, 1927). Since these compounds are available only to informed workers who are properly equipped with clothing, impervious gloves and effective respirators, cases of poisoning by these compounds are exceedingly rare. Lead antiknock compounds in gasoline are ordinarily not sources of danger from percutaneous or respiratory absorption for the handlers and users of leaded gasoline because of their high dilution (Kehoe, 1934, 1936), but under conditions that permit complete evaporation of large volumes of gasoline in enclosed places, the concentration of vaporized tetraethyllead in the air may reach highly dangerous levels.

3.1. The Alimentary Absorption of the Inorganic Compounds of Lead by Man

Inorganic compounds of lead are absorbed poorly in the alimentary tract of man, whether ingested in aqueous solution or in food (Kehoe, 1961). The rate of absorption is proportional to the concentration within the alimentary tract. However, since the contents of the tract are variable in their composition from day to day, and many of the anions which may react with ionic lead in the alimentary tract, e.g. phosphate, sulfate and sulfide, result in the production of relatively insoluble compounds, it is not surprising that much of ingested lead traverses the alimentary tract unabsorbed. Under ordinary circumstances in eating food and beverages containing customary amounts of lead (0.1–0.4 mg/day), only 5–10 per cent of the lead is absorbed, and the remainder is evacuated in the feces (Kehoe, 1961). This means that lead is always present in the alimentary tract and its absorption is continuous, if somewhat variable.

Most of the lead absorbed from the alimentary tract is conveyed to the liver in the

be accurately determined on a daily basis, but over a year it amounted to about 8 mg, equivalent to 20 μg/day. The graphic representation of this phenomenon is seen in Fig. 2. It is readily understood that the introduction, by any means, of lead into the air breathed by man will induce the same result as that above—that of causing an increase in the body load of lead, demonstrated by the increased excretion—if it is sufficient in quantity.

3.2. THE ALIMENTARY ABSORPTION OF TETRAETHYLLEAD

The principal route of absorption of the vapor of this compound in industry is the respiratory tract. During the preliminary period of limited distribution of the antiknock preparation, tetraethyllead was ingested by certain subjects, by accident or design, with tragic consequences. From these cases it was learned that the toxicity of tetraethyllead ingested by man is manifest initially in the gastroenteric tract, with retching and vomiting followed usually by diarrhea. Soon the central nervous system is affected and there is confusion and disorientation followed by great emotional and muscular excitation and convulsions. In two instances (in adults) after an exceedingly stormy period of illness, during which therapy consisted of barbiturates and supportive treatment, recovery ensued without sequelae. In the case of a small child, death occurred in 36 hr, preceded by progressive cerebral involvement that terminated in coma, with no opportunity to determine the quantity swallowed. The lethal dose for the adult rabbit (up to 3 or 4 kg) has been found to vary under several conditions from approximately 40–120 μg of lead/kg. These animals died only after 2 or more days of illness (Kehoe, 1931). No human case of poisoning with tetramethyllead or its analogues or derivatives has been observed, since these compounds came into use (1960) as antiknock compounds long after satisfactory control measures had been established.

3.3. THE RESPIRATORY ABSORPTION OF LEAD AND ITS INORGANIC COMPOUNDS

The *respiratory absorption of vaporized metallic lead* is effected, presumably, through the partial pressure of the vapor in the inhaled air. Ordinarily, the absorption of metallic lead is probably of little significance, since it may reasonably be expected that oxidation or hydroxylation occurs in the air and also in contact with living tissue.

Some portion of the inhaled, particulate, inorganic compounds is deposited in various parts of the respiratory tract in accordance with their mass and velocity, as well as with the nature of the structures upon which they impinge in the course of their carriage in the air. The aqueous solubility of the particles may well be an important factor in their absorption, but the ultimate significance of this factor cannot be stated with certainty, especially in the case of minute particles (under 0.2 μm in diameter), because such solid particles probably react with substances in animal membranes. The basic mechanisms involved here are uncertain, but some relatively insoluble compounds such as the sesquioxide, when highly dispersed in the air, are readily absorbed in the lung (Kehoe, 1961). Few pure compounds or lead-containing minerals have been investigated quantitatively, or comparatively, from this aspect of their behavior.

The relatively large particles of lead compounds, as dust, ranging from above 10 μm down to somewhat more than 1 μm in diameter will be trapped, for the most part, either in the nares or in the upper respiratory tract. In the latter, the particles will be moved upward by ciliary action into the nasopharynx and swallowed or expectorated; in the former, the particles will be blown out of the nostrils, or will move downward into the nasopharynx. The particles which are swallowed represent the difference between the amounts of lead ingested with food and beverages and the greater quantities evacuated in the feces. The smaller particles will be distributed downward along the respiratory tract to an extent inversely proportional to their size. By no means will all of the particulate material be retained within the tract, but a considerable proportion (in normal respiration, 50–65 per cent, but in rapid, shallow respiration, as much as 70 per

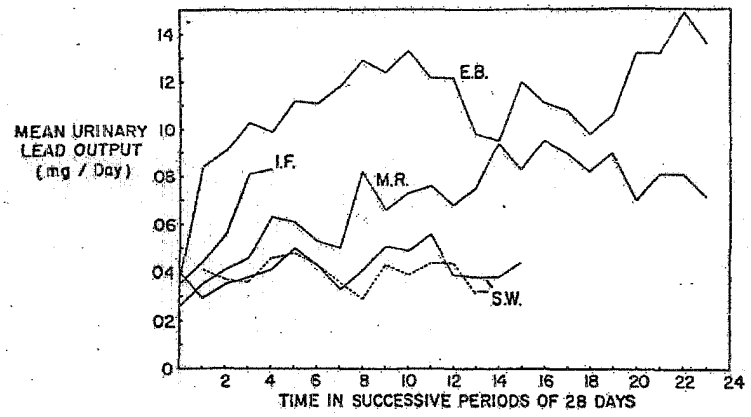

FIG. 1. The influence of a daily oral dose of lead (as soluble salt) upon the mean daily output of lead in the urine, for each 28-day period charted. Each of the four human subjects took the same dose every day, these dosages, from below upward in the chart, being: Subject S.W. (dotted line), no lead, (solid line) 0.3 (3 × 0.1) mg; Subject M.R., 1.00 mg (this subject continued on this regimen for fifty-two periods of 28 days each, but the chart is shortened to correspond to that of Subject E.B.); Subject E.B., 2 mg; Subject I.F., 3 mg (Note that each curve, excepting the short-time curve for I.F., undergoes a decreased slope at intervals. This decrease in the output of lead occurs in the colder months, and resumes its upward trend in the warm months. But for this seasonal variation, the general slope upward remains the same, and in the case of Subject M.R. (see Fig. 2), the obverse phenomenon of progressive accumulation of lead in the body of this subject (in terms of the cumulative difference between intake and output) diminished or disappeared during the period of hot weather of each of the 4 years of the period of administration.)

various amounts of lead by human subjects. The trend of the rate is unmistakeably upward with increased dose. The response of fecal excretion of lead to daily dosage may be assumed to vary similarly, despite the fact that it cannot readily be followed daily, and the increase is not necessarily of the same order of magnitude as that in the urine. Actually, the quantity of lead in the feces and urine of two 'control' subjects for the group exceeded that in the food and beverages, which suggests the possibility that some lead was absorbed from the ambient air through the respiratory tract. The difference between total daily intake and output of lead in these two subjects was too small to

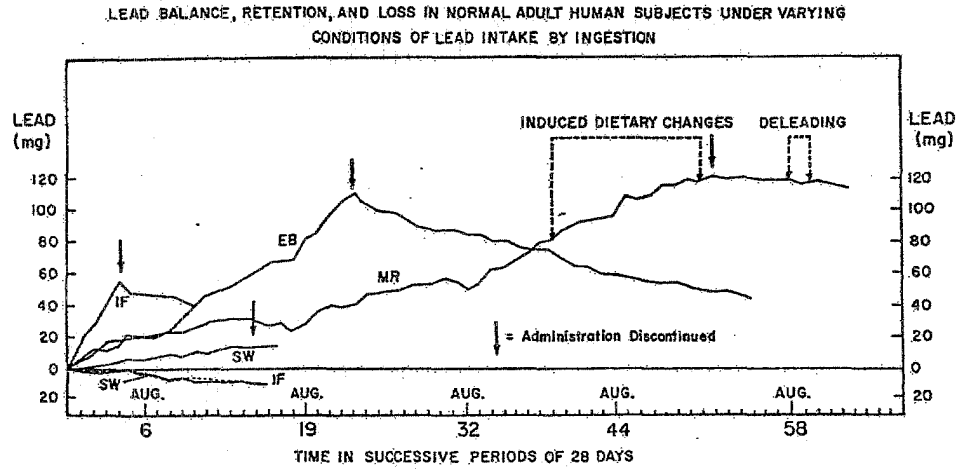

FIG. 2. Lead balance in normal adults under varying conditions of lead intake. Here is shown the cumulative difference between the oral intake of lead and its output in the feces and urine of the four experimental subjects. Each subject took the same oral dosage of lead every day (in addition to that in his diet) in the form of a soluble lead salt over the period of time indicated. The amount of lead taken by the four subjects was: Subject S.W., dotted line, none—solid line, 0.3 mg; Subject M.R., 1 mg; Subject E.B., 2 mg; and Subject I.F., 3 mg. It may be seen that there was no persistent fall-off in the rate of the accumulation of lead in the body of any of these subjects (i.e. no equilibrium was reached) during the period of the administration of lead, even when the latter extended over 4 years, in the case of Subject M.R.

alimentary tract and the kidney. The statistically average adult male in the United States consumes about 300 (range 100–360) μg of lead per day. The adult inhales from 20 to 40 μg of lead per day and retains 30 to 45 per cent. The average turnover in the female is less than that of the male, but the pattern seems to be essentially the same.

The average excretion of lead in the urine is approximately 30 μg per day. The total *output* of lead in the urine and feces averages about 320 μg, which represents the sum of the metal orally ingested (about 300 μg) plus that which has been *absorbed* in the respiratory tract. The intake of lead in man from adventitious or inadvertent sources, and the output in sweat, in all other secretions of the skin, in cutaneous desquamation, falling hair, and the like, can at best be estimated only roughly; however, they may be considered to be usually insignificant. In the long run, they tend to cancel each other. The pattern of lead turnover indicates a nearly steady state of body metabolism, whereby no perceptible progressive change occurs without demonstrable change in the environment (Kehoe, 1961). However, animal experimentation (in progress) indicates that, under conditions in which lead is being absorbed in some quantity, incremental accumulation does occur. This is probably true of man, although normally, it is too slight to be measured with confidence.

3.5. The Excretion of Inorganic Lead Compounds Under Abnormal Conditions of Exposure and Absorption

Following the absorption of lead in quantities that are greater than normal, there is a prompt increase in the rate of the excretion of lead in the urine. This increase depends upon the amount of lead absorbed and, under appropriate conditions, may approach thirty times mean normal values. Such an enhanced urinary lead concentration indicates a dangerous rate of absorption of the metal, although it is not necessarily associated with any known symptoms of lead poisoning.

An increase in the true excretion of lead from the alimentary tract is also readily demonstrable, even in an individual who is not suffering significantly from the constipation often associated with lead poisoning. An example of the latter is illustrated in Table 4. The true rate of lead excretion via the alimentary tract and in the urine varies

TABLE 4. *The Urinary and Alimentary Excretion of Lead Following Accumulation of Lead in the Human Body*

Lead turnover in a human subject over the period of 448 days, following the termination of the daily administration, for two years, of dissolved lead at the rate of 2 mg/day, with meals, in addition to that in the diet

Lead ingested in food and beverages	Lead eliminated		
	In feces	In urine	Total
148.20	153.04	35.61	188.65

Excess of lead eliminated over lead ingested: 40.45

In urine:	19.13*
In feces:	21.32
	40.45

*Determined by calculating the amount which would have been excreted normally by this subject in his urine (mean normal, daily concentration in the urine, mg/l., multiplied by the volume of the urine in liters within the period), and subtracting this product from the amount actually excreted during this time. The remainder was excreted in the feces. The values are approximate, but otherwise realistic, in showing a 1:1 (approximate) relationship in this instance, between the two sources of excretion.

with the extent of lead absorption. Alimentary excretion may increase two to three times that of urinary excretion, even when there is no demonstrable impairment of the renal function. A few observations have indicated that at relatively high levels of lead absorption the rate of alimentary excretion of lead is increased when the renal excretion is impaired. Whether this adaptation protects the individual against the

cent) of the inhaled lead in particles of minute diameter (less than 0.2 μm) may be exhaled in the expired air (Kehoe, 1961; Nosaki, 1966). The *quantitative disposition of the particles in the respiratory tract* of a normal person cannot be stated more than approximately, since their fate varies not only with their size and mass, but also with the depth and frequency of respiration, as well as other structural and physiological features. Particles which impinge upon the epithelial membranes in any part of the respiratory tract may remain there and be absorbed, or may be acted upon by other mechanisms. Cells of the respiratory membrane, which are equipped with cilia, will propel some particles toward the upper respiratory tract and the nasopharynx. Movements of the entire lung (as a bellows) may move some of the particles to and fro in the dead air space, thereby enabling some of them, even those in alveoli, to reach more proximal bronchial passages equipped with cilia and so to be removed from the lung. Other mechanisms for removal include the phagocytes which may engulf particles and transport them, and the lymphatics which are involved in the clearance of foreign particles from the lung and the respiratory tract. In the normal individual, they are remarkably effective, but in the debilitated person, especially in the presence of pathology in the respiratory tract, they are probably subject to variable degrees of diminished activity. Seemingly, the most realistic estimates now available on the clearance of particulate materials from the normal respiratory tract are based upon a model developed by the Task Group on Lung Dynamics for Committee II, of the International Commission for Radiation Protection (1966). On the basis of calculations from this model, human subjects who inhale air containing particles of lead sesquioxide, mean diameter 0.05 μm (with but few larger particles up to 0.18 μm) should retain 55 per cent of that inhaled, of which 0.7 per cent would reach the nasopharynx, 0.8 per cent the tracheo-bronchial area, and 40 per cent the lung. Approximately 9.5 per cent of the inhaled lead would be cleared from the respiratory tract into the blood, and 45.5 per cent into the alimentary tract. Assuming that not more than 10 per cent of that cleared into the alimentary tract would be absorbed, the total absorption into the body would approximate 14 per cent of that inhaled. Unfortunately, these calculations are open to question. Retention of lead sesquioxide of mean diameter of 0.05 μm in the entire respiratory apparatus has been found by direct determination to be of the order of 35–50 per cent under conditions of normal respiration. No evidence could be found of any initial deposition of inhaled particles of lead in the upper respiratory tract, which ultimately elevated the lead content of the feces during the months of experiments in which there were 150 μg of lead, as the sesquioxide, in the inhaled air (Kehoe, 1961). Because of this and the fact that no accurate determinations have been made of the actual respiratory clearance of particles of such dimensions, the total absorption of airborne lead in minute particles of this order of magnitude cannot be estimated. Some of the factors involved in the retention of particulate lead compounds in the human respiratory tract as well as the distribution of inhaled lead among the several areas of the tract are well illustrated in the experimental observations of Nosaki (1966). This investigator used seven aerosols, composed of particles ranging from 0.05 to 1.0 μm in diameter, which were inhaled by an experimental subject at rates of ten and thirty respiratory excursions per minute. He observed that the total retention of particulate lead in the entire respiratory tract decreased when the respiratory rate was increased from ten to thirty, and also that the deposition in the lower respiratory tract was less when respiration was rapid and shallow. At the respiratory rate of ten per minute, the deposition of fume diminished gradually from 63 per cent at 1.0 μm particle size to 39 per cent at 0.1 μm, after which it increased to 40 per cent at 0.08 μm and to 42.5 per cent at 0.05 μm. At a respiratory rate of 30/min, the total retention in the respiratory tract decreased steadily from 35.5 per cent at 1.0 μm, to 21 per cent at 0.05 μm.

3.4. The Excretion of Absorbed Inorganic Lead Under 'Normal' Circumstances

The loss of lead from the body of man which occurs normally through the evacuation of unabsorbed lead with the feces, is usually larger than the true excretion of the

TABLE 5. *The Concentration of Lead in the Tissues of Normal Persons*

Tissue	mg Pb/100 g (Wet)		
	Newborn	Child of 6	Adult of 20
Kidney	0.011	0.059	0.07
Liver	0.05	0.051	0.08
Bone (Flat)	0.015	1.022	1.11
Bone (Long)	0.175	1.142	—
Muscle	—	0.009	—
Lung	0.04	0.032	—
Brain	—	0.008	—

has a higher lead content than the kidneys (Kehoe, 1961). The pattern of lead distribution within the tissues resembles that of the adult by the time the child is about 6 years of age. The total quantity of lead in the entire body increases with increase in weight, thereafter, but the concentrations in the respective organs and tissues may remain essentially unchanged (Table 5). As in the normal adult, the concentration of lead in the dense (and less vascular) part of the skeleton of the normal child is higher than that in the trabecular and more vascular part. One can visualize a slow, steady movement of lead from the sites of its absorption into the tissues and still more slowly into the dense shafts of long bones and other areas of comparable composition and structure in the skeleton. A very slight counterstream of released lead, obviously less than that absorbed, flows outward from dense bony tissue, while a greater amount flows out from the trabecular (vascular) bone, so that in time the concentration of lead remains higher in the dense bone than in any other tissue. Only when there is an increased rate of lead absorption, resulting from unusual exposure to lead, does the concentration of lead in the spongy (trabecular, vascular) bony tissue become equivalent to or higher than that in the dense bone. Thus, the child or adult fatally poisoned by lead is found to have this inverted type of distribution of *skeletal lead* and a suspiciously large quantity of lead in the body(Kehoe, 1961). This almost inert lead fraction, accumulating over long periods in the slowly metabolizing dense bone, may represent a protective mechanism for the organism in that a portion of the accumulating lead in a pool from which it is released so slowly as not to affect appreciably metabolic processes. Table 6

TABLE 6. *The Concentration of Lead in the Tissues of a Child Fatally Poisoned by Lead or Suspected of Having Been so Poisoned**

Tissue	mg Pb/100 g (Wet weight)
Brain	0.58
Liver	4.00
Kidney	0.88
Flat Bone	26.80
Long Bone	13.15

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

gives an example of the distribution of lead in a fatally poisoned child and illustrates the relatively high concentration of lead in the flat bone as compared with that in the dense bone, while demonstrating the high lead concentration in various tissues of this child.

Several matters are worthy of comment with respect to the distribution of lead portrayed above. Unless the necropsy is performed almost immediately after death (or, in the case of laboratory animals, blood is taken before death), the condition of the available blood is likely to be such as to yield misleading results on analysis. The importance of this matter lies in the fact that almost all of the inorganic lead in the blood of the living person is found in the erythrocytes. Thus these cells compete favorably with other tissues in the body for the available lead and for this reason, the blood lead

possible effects of an increased rate of absorption of lead is dubious, although it may be inferred that it contributes to the elimination of lead from the body of the individual so affected. However, one of the early manifestations of lead toxicity is an obstinate form of constipation, and when this ensues, elimination of lead from the alimentary tract is greatly impaired. Since lead, which is cleared from the upper respiratory tract into the nasopharynx and then into the alimentary tract, cannot be evacuated rapidly from the alimentary tract at such a time, increased absorption of lead into the tissues would seem to be inevitable.

3.6. The Excretion of Lead Following the Absorption of Alkyl Lead Compounds

The excretory products of the absorption of tetraethyllead are mainly the result of the decomposition of this compound within the organism. In all likelihood, tetramethyllead, and the compounds derived from the mixture of tetraethyllead and tetramethyllead (as in certain antiknock preparations), undergo the same type of decomposition but at different rates, so that the composition of the urine varies with both the compound absorbed and the lapse of time following absorption. The extent and nature of the materials excreted in the feces are not known, but they are probably comparable to those which appear in the urine. Tetraethyllead decomposes (accelerated by ultraviolet light) to triethyllead, which then combines with available anions to form water-soluble salts. As Calingaert and his associates (1939) have shown, this reaction proceeds by stepwise loss of ethyl groups to inorganic lead. Both tetraethyllead and triethyllead compounds have been identified within the body of animals (Stevens *et al.*, 1956; Cremer, 1959; Stevens *et al.*, 1960). Within the animal organism the course of the decomposition of tetramethyllead presumably is similar. Some organic lead occurs in the urine for many weeks.

Following the absorption of tetraethyllead there is a gross increase in the lead in the urine of man (Kitzmiller *et al.*, 1954) which diminishes very slowly during recovery from intoxication. Some of this high rate of excretion is probably due to the fact that the blood lead is not bound to erythrocytes as is inorganic lead. Further evidence of this difference in the behavior of much of the available tetraethyllead (and its decomposition products) is shown by the fact that the concentration of lead in the blood rarely exceeds 0.05 mg/100 ml even when the concentration in the urine is at or above 1 mg/l. (Kitzmiller *et al.*, 1954). This relationship between the low concentration of lead in the blood, and the disproportionately high concentration in the urine, is an important factor in the diagnosis of tetraethyllead poisoning, when the history of exposure cannot be obtained.

In addition to the urinary and fecal loss of lead from animals or men poisoned by tetramethyllead, it may be presumed that there is a loss of tetramethyllead through vaporization from the pulmonary tract. The rate of decomposition of tetramethyllead *in vivo*, is considerably less than that of tetraethyllead (Cremer and Calloway, 1961), while its volatility is much greater than that of tetraethyllead. Slower decomposition and the loss through exhalation may be factors in the lesser toxicity of this compound for rabbits. On the other hand, tetramethyllead is more toxic than tetraethyllead when the two compounds are inhaled in equivalent concentration by dogs (Davis *et al.*, 1963).

3.7. The Distribution of Inorganic Lead in Man

Under normal conditions of pregnancy that exclude maternal employment in lead-using industries or ingestion of illicitly distilled whiskey, the newborn has only a small quantity of lead in the body (Table 5). These low levels are derived no doubt from the maternal blood during intrauterine development and continue until weaning. While the distribution of lead in the tissues of the infant is generally similar to that of the adult, lead found in the underdeveloped skeleton is a much smaller proportion of the total body lead than is that in the adult skeleton (Barry and Mossman, 1970). The liver and kidneys contain more lead than other organs and tissues, while the liver as a rule

TABLE 8. *Immediate Distribution of Lead in Tissues of Rabbit**

Tissue	Lead mg/100 g
Liver (entire)	5.37
Kidney (entire)	2.97
Brain and Cord (entire)	0.38
Muscle (entire)	0.33
Heart (entire)	0.94
Spleen (entire)	2.00
Suprarenals (entire)	3.00
Lung	0.92
Adipose	0.40
Bone (entire skeleton)	0.64

*The rabbit was sacrificed 3 hr after application of 4 ml of tetraethyllead to the abdominal skin.

the body had been excreted. The lead then found in the tissues would not necessarily derive mainly from decomposition products, since the process of absorption of inorganic lead with food had continued. The extent of the process of degradation of either tetraethyllead, or tetramethyllead beyond the stage of triethyllead compounds has not been determined.

4. THE COMPOSITE PATTERNS OF THE METABOLISM OF LEAD IN MAN

4.1. CONTINUOUS EXPOSURE AND ABSORPTION

In preceding sections, the absorption and excretion of lead, and its distribution and accumulation in the tissues of man and laboratory animals, have been dealt with separately, for the most part, in order to present certain features of each of these physiologic processes. It has been difficult to portray the part played by each aspect of the behavior of lead, under certain specific conditions of exposure to and absorption of the metal. It must be emphasized that there are two different patterns of exposure to lead and of the responses thereto, which differ greatly in relation to the hazard of toxicity as well as to the means of avoiding toxic effects. In the general population, exposure to and absorption of lead occur *continuously* at a low level although at somewhat variable rates. This continuous type of exposure in the ordinary environment has been described and interpreted in an earlier part of this discussion, and need not be dealt with further. However, one study will be mentioned in light of the significance of the findings. Four subjects, whose daily lead intake was increased by only 0.3 to 3.0 mg, over environmental exposure, showed over a period of years increases in the rate of urinary excretion of lead and progressive accumulation within the body proportional to the respective dosages of lead. (No suggestion of illness developed during these experiments, but no daily dose, excepting 0.03 mg could be administered indefinitely.) The family of curves representing the respective cumulative differences between the intake and output of lead are shown in Fig. 2. (More complete data for the longest experiment in this group are assembled in Table 9.)

These observations quite clearly indicate the strictly quantitative difference between the behavior of experimental subjects whose exposure to lead was limited to ordinary environmental conditions and of others whose environmental lead was augmented by additions of lead to their diets. Accumulation of lead under ordinary environmental conditions was too small to be measured, while that which resulted from an augmentation of ingested lead as small as 0.3 mg daily was readily apparent. It is this feature of the continuous type of exposure which poses the risk of a progressive increase in the total body lead, presumably for as long as the level of exposure continues. At issue here is the question of the *quantity* of environmental lead which can

must be considered in the pattern of distribution of lead in the body. This means that the 'effective' quantity of lead in the tissues of the intact living human being can, for practical purposes, be estimated from analysis of the blood, provided that chelating substances have not been previously administered.

The concentration of lead within the *muscles* is remarkably low, while the opposite situation exists in the skeleton. In fact, it is readily possible to determine whether there has been unusual exposure to lead on the part of the deceased person within the past few weeks or months. Since the skeleton can be expected to contain the overwhelming proportion of the lead in the body of man, if the absorption had been fairly gradual, distribution of lead in the body of a deceased person can readily be ascertained through the analysis of suitable skeletal specimens, together with the liver and kidney (especially the cortex of the latter, which is relatively high in its lead content). Since, however, the bones of the skeleton vary considerably in their proportions of dense and trabecular tissue, the entire skeleton would have to be analyzed in order to determine the actual quantity of lead contained therein. Fortunately, there is little reason, as a rule, for such precision.

One other point relates somewhat specifically, to the recognition, *post mortem*, of the likelihood of the occurrence of lead encephalopathy. It has been found (Kehoe, 1961) that the concentration of lead in the brain of a child with this type of lead poisoning is distinctly high. It is by no means certain that such an observation is specific for this variety, but it seems that in the severest form of this disease the brain commonly contains several times as much lead as is found in the normal brain—values of 0.24–0.58 mg/100 g of fresh tissue (Table 6), as compared with the normal maximum of about 0.08 mg/100 g of fresh tissue.

see also p. 185

3.8. The Distribution of Lead in Man, Following the Absorption of Alkyl Lead Compounds

The initial *distribution of alkyl lead* compounds is that of fat-soluble compounds. This is illustrated in Table 7 by the distribution of lead in the tissues of an adult male

TABLE 7. *Lead in Tissues of Man Fatally Poisoned by Tetraethyl Lead* (1943)

Tissue	Lead content (mg/100 g (Wet))
Liver	4.10
Kidney	1.20
Brain (cortex)	1.00
Muscle	0.80
Heart	0.80
Spleen	0.65
Suprarenal	0.46
Prostate	0.13
Testicle	0.23
Lung	0.22
Stomach (washed)	0.10
Ileum (washed)	0.32

who died after the absorption of an unknown quantity of tetraethyllead. In order to visualize, precisely, the initial period, Table 8 illustrates the distribution of lead in the tissues of a rabbit killed only 3 hr after the application of 4.2 ml of this compound upon the shaved belly. The concentration of lead achieved in the bodies of animals treated similarly was sufficiently high to cause death within 72 hr.

As indicated in rabbits killed sequentially following cutaneous application of tetraethyllead, the form of the lead in the tissues appeared to change in about two weeks to that of water-soluble compounds, an indication of the metabolic degradation of the compound to triethyllead. Other decomposition products of tetraethyllead may have influenced the pattern of the distribution later, but by then, most organic lead in

concerning the apparent variability in the toxic properties of lead. Since lead is ubiquitous in nature, this intermittency does not involve the periodic lack of exposure to lead, but lies in the wide variability of intensity of exposure observed from person to person and from one situation to another. It is this variability, often unnoted, and rarely measured in relation to its duration, which has been responsible for the occurrence of lead poisoning in individuals who have been believed free of significant exposure to lead, and conversely, for the absence of intoxication in persons who should, it seemed, have been rendered ill. This is not to say that there is no variability in the human response to the absorption of lead. Rather, the extreme variability often claimed is only a reflection of the failure to observe or interpret the exposure to lead and technical inability to appraise its quantitative significance.

The type of intermittent exposure to lead which is the easiest to recognize is that incurred in the lead industry or in other activity that involves periodic exposure to lead. This results in some accumulation of lead in the body coupled with some increase in elimination. For many individuals there are periods of lead exposure which are not recognized or reported, for example in painting and removal of paint, soldering, repair or fabrication of ceramic ware (glazing), household equipment or automobiles. These may contribute to the body burden of lead, temporarily or permanently, although the contributions cannot be readily assessed. It is also difficult to estimate the body burden over a period of years of any person employed in a lead-using industry since there are always periodic variations in the industrial environmental as well as in the behavior of employees which affects the absorption of lead. In a well operated lead industry, however, the effect of limitation of hours of work and establishment of standards of safety based upon the concentration of lead in the air have led to a situation in which the physiological behavior of the employees can now be understood.

Following initiation of employment in a lead industry, in which exposure to lead has been subject to appropriate control, the rate of urinary excretion of lead increases. After a period of time (usually 4–6 months), it reaches a somewhat irregular plateau and continues so, with daily or other (including seasonal) variations within modest limits, so long as the intensity of the exposure remains substantially unchanged. In the industries which produce or make use of only inorganic lead, the concentration of blood lead also increases and reaches a level which varies much less than that of the urine if the environmental control of lead is satisfactory. The factor which determines the steady state of the urinary and blood lead, under these conditions is the regular degree of intermittency in exposure to lead. During the time that is free from occupational exposure to lead, the output of lead from the body is larger than the intake, although the reverse is true during working hours. At some point, eventually, these two opposite effects neutralize each other. There are, however, two matters which must be considered in the development of this virtually steady state. One is that at any elevated level of absorption and excretion there appears to be some accumulation of lead in the body, judging from unpublished annual data. When lead is absorbed over a long period of time, some of it finds its way into the dense part of the skeleton, the rate of release from which is very slow. The other factor is that respiratory exposure to airborne lead dispersed in large particles (slightly below and well above 1 μm in diameter) results inevitably in the swallowing of lead. In certain uncontrolled and dusty operations, as much as 21 mg of lead per day has been found in the feces of workmen, and with such quantities, the potential absorption of lead from the alimentary tract may be sufficient of itself to induce lead intoxication. Unless the bulk of the airborne lead is composed almost entirely of small particles (under 0.5 μm in diameter), the bulk of the particles lodged in the upper respiratory tract are shifted promptly to the alimentary tract where they contribute to the amount of lead available for absorption. In other words there must not be any large component of alimentary absorption of lead by these individuals above that derived from food and beverage if the intermittency of the respiratory absorption of lead is to be maintained. It is often assumed that respiratory exposure in industry is the only important source of lead absorption. It is generally true that if environmental control in an industrial establishment is sufficient to maintain the lead

TABLE 9. *Lead Intake and Output of Normal Subject During Period of Daily Oral Administration of Lead (1 mg/day)*

Successive periods of 12 weeks	Lead ingested (mg)	Lead eliminated (mg)			Lead (mg) Lost (−) or retained (+)
		Total	In feces	In urine	
1st	112.84	101.48	98.32	3.16	+11.36
2nd	118.74	108.95	103.74	5.21	+9.29
3rd	107.22	105.51	100.15	5.36	+1.71
4th	118.79	111.57	105.57	6.00	+7.22
5th	110.18	111.22	104.66	6.56	−1.04
6th	116.22	121.59	114.15	7.44	−5.37
7th	109.44	93.41	86.57	6.84	+16.03
8th	125.45	118.86	112.47	6.39	+6.59
9th	117.11	114.81	108.97	5.84	+2.30
10th	105.48	98.86	91.22	7.64	+6.62
11th	107.57	109.19	102.25	6.94	−1.62
12th	114.24	102.06	94.03	8.03	+12.18
13th	113.14	100.68	94.02	6.66	+12.46
Total	1,476.42*	1,398.19	1,316.12	82.07	78.73

*Approximately 22.00 mg in drinking water, 372.32 mg in food and other beverages, and 1,082.10 mg administered in solution.

be dealt with by persons in the general population without *any* harm. In the case of the lead in food and beverages (while respiratory intake remains stationary), it appears that if progressive accumulation of lead is to be avoided this quantity should not exceed an average of 0.6 mg per day for the adult; this figure may be adjusted for children in relation to the quantity of food and beverages consumed.

Figure 2 represents for one subject the results of daily ingestion of 1 mg of soluble Pb to that already in the diet over the period of 4 years. It demonstrates a phenomenon long suspected; the rate of accumulation of lead in the body decreased materially and ceased entirely during certain summer months. This was observed, in every one of the 4 years of this experiment in association with an increased output of lead in both feces and urine. It is probable that there is an increase in the elimination of lead, and a corresponding decrease in its retention in normal humans during summer months in the latitude of Cincinnati, and that this phenomenon was the more readily demonstrable because of the quantities of lead involved in this long term experiment. Other experimental subjects exhibited similar behavior, but were not followed for so long a time. It is not possible at this time to explain this phenomenon, but the fact of its occurrence is distinctly worthy of investigation in relation to climatic or other environmental factors.

Exposure to airborne lead must be dealt with so as to establish a level of intake and absorption which is tolerable. An experimental approach to this matter would involve maintenance of the alimentary absorption of lead at a constant level while subjecting respiratory exposure to graduated increases over sufficient periods of time to a point which approached potential risk, or alternatively, to graduated decreases to the vanishing point of risk. The confinement of human subjects, for months or years, under conditions which would enable them to inhale continuously air containing known concentrations of lead in a known state of dispersion, however, presents considerable difficulties, which have not been entirely surmounted. Meanwhile, there is no evidence of impending risk in association with the situation now present in the general environment. Since it is not the purpose of this discussion to deal extensively with this problem, published accounts should be referred to (Public Health Service Publication 999-AP-12, 1965; Kehoe, 1969).

4.2. Intermittent Exposure and Absorption

Intermittent exposure to lead, the results of which are quite different from continuous exposure, has been a source of misunderstanding by physicians and others

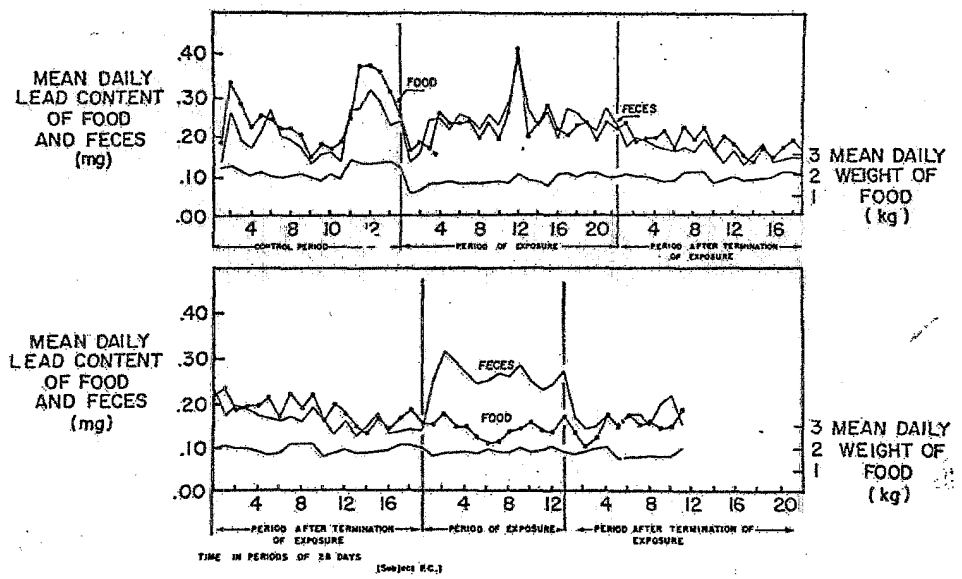

FIG. 3. Influence of particle size of inhaled lead on its fecal excretion. The points of the two upper curves of each chart (above and below) represent the mean lead content of duplicate samples of the food and beverages consumed, and of the feces evacuated, daily, during each consecutive period of 28 days over which the experiment extended. The two sets of values are plotted during a preliminary period of observation, during a further period of exposure to a lead aerosol in a carefully controlled dynamic respiratory chamber, and during a period after the termination of the experimental exposure. In the top experiment, the chamber contained a lead aerosol composed of particles of the mean diameter of 0.05 μm (maximum, 0.18 μm) during the period of exposure; during the corresponding period of the lower experiment, the chamber contained an aerosol composed of particles 90 per cent of which were under 2.0 μm, 50 per cent of which were under 0.4 μm, while the maximum diameter was 4 μm. The bottom line in each chart represents the mean daily weight of the food and beverages, during each consecutive period of 28 days.

It will be noted that the values of the upper curves interdigitate during the entire experimental period of the topmost experiment, while the two diverge promptly during the period of exposure to the lead aerosol in the lower experiment, and resume their interdigitation on the termination of the period of exposure, in indication of the diversion of a considerable and essentially uniform proportion of the particulate lead compound into the alimentary tract of Subject F.C.

industry, over long periods of time. It is important to note that sensitivity to lead may vary both between individuals and in one subject at different times. The present goal of the occupational physician who lacks an understanding of the mechanisms of intoxication is to detect the least concentration of lead in the blood or urine which is associated with toxicity so as to provide an adequate standard for preventive action. Seemingly, the mechanisms which induce clinical signs are often held in abeyance by other mechanisms which render lead innocuous. There appears to be rates of absorption which can be dealt with effectively by the organism. Thus, the slow absorption of lead may result eventually in a relatively large quantity of apparently harmless lead in the body, while rapid absorption is a much more certain means of inducing severe poisoning, despite the fact that the total quantity of lead in the body may be relatively small. This may be explained by the differences in the distribution of lead in the body under different conditions that were discussed previously, or more likely, by considerable variability in the binding of lead within the organism with different rates of absorption. Some such phenomenon would explain the abruptness of the onset of lead poisoning which occasionally occurs in a workman who has had no complaints or clinical signs of illness and who suddenly appears to be suffering from an acute bout of colic. This is not the usual manner of onset of lead colic in unsatisfactorily controlled industries, but this is how it sometimes seems in an otherwise well-regulated industry. It must be recognized, however, that exposure of the average workman to lead during the day's work is often lacking in quantitative relationship to the actual severity of the exposure, sampling devices

concentration in the air at or below the permissible limit (150–200 μg/m^3) no cases of lead poisoning will occur. However, it is not safe to assume that achievement of this standard for airborne lead is all that is necessary to prevent any industrial lead poisoning. The hygienic facilities of the establishment should include facilities for eating in a truly clean, dust-free environment, and for adequate bathing and changing of clothing to prevent the unnecessary carriage of lead compounds by the employee. Workmen in such a potentially dangerous industry should be instructed in the hazards of ingesting lead, and in the personal means of the avoidance of unnecessary exposure. In addition, they should be under the surveillance of a trained and experienced physician who can be counted on to detect the imminence of danger.

The experimental procedures required to limit alimentary exposure to lead and to measure the uncomplicated responses to the respiratory absorption of lead are described elsewhere (Kehoe, 1961). After a preliminary period of observations under the controlled conditions in this laboratory, the subjects of these experiments spent the same length of time per week (approximately 40 hr) for some months within a respiratory chamber into which lead sesquioxide was introduced, as an aerosol containing particles 0.052 μm in mean diameter (maximum diameter was 0.18 μm). A concentration of 150 μg of Pb/m^3 was maintained in the stream of air entering the chamber. Any lead which may have been cleared into the alimentary tracts of these subjects, under these experimental conditions, was too little to be observed daily. The relationship of the intake and output of lead into the alimentary tract of one of these subjects is shown in the upper part of Fig. 3. Whether all of the lead retained in the respiratory tracts of human subjects during these experiments were absorbed into their bodies is uncertain. An example of a different type of situation is shown in the lower part of Fig. 3. The subject inhaled the same quantity of lead as the subject in the upper part for the same length of time per week during which identical observations were carried out. However, this aerosol was composed of larger particles of lead sesquioxide (maximum diameter of 4 μm, while 90 per cent were under 2 μm and 50 per cent were under 0.9 μm). Diversion of the larger inhaled particles into the alimentary tract was shown clearly by the distinctly higher output of lead in the feces during the period of exposure. The extent of the absorption of lead, as revealed by the concentration attained in the blood, while less than that of the subject of the upper experiment (Fig. 3) during the relatively brief period of the experiment, would almost certainly have increased indefinitely if the experiment had been prolonged. Thus the quantities of lead which reach the alimentary tracts of persons who inhale particulate lead appear to depend upon the proportion of relatively large particles dispersed in the air. When the particles are uniformly small, as in the case of most industrial establishments in which dusty operations are enclosed and ventilated, and from which most of the larger particles of lead have been collected, the pattern of the behavior of lead inhaled by workmen will undergo little or no change with time.

On the basis of observations made in numerous industries over a period of many years the concentration of lead in the blood below which the onset of lead intoxication is not believed to occur is 80 μg per 100 ml. This figure applies to the blood of otherwise apparently healthy persons who are being exposed to lead at the time of the analysis rather than to those whose exposure had been terminated days or weeks previously. The concentration of lead in the urine which corresponds to the threshold value in the blood is not so well defined, but it lies between 150 and 200 μg/l. in a properly selected specimen of urine (Kehoe, 1961). Obviously, in American industry as a whole, no such excellence of performance has yet been attained, for, if it had industrial lead poisoning would be a thing of the past, as it certainly is not. The foregoing discussion is not intended to deal with the procedures concerned with the protection of persons employed in the potentially dangerous lead industries. Rather, it is a matter of real concern to any investigator of this subject and to physicians generally to know that there is a limited range in the concentration of lead in the body of man below which no lead-induced illness can be demonstrated. Such a fact could hardly be substantiated by any other means than that of regularly studying the behavior of workmen, under the conditions which exist in

been diagnosed incorrectly as lead poisoning simply because the time and place of their occurrence, as well as other circumstantial evidence, tended to point toward lead as the responsible agent. Multiple neuritis, for example, has often been attributed to lead with no supporting evidence. As a result lead has been credited with the capability of inducing almost any type of illness, including a 'sub-clinical' type of poisoning which bears little or no resemblance to any of the classical forms of lead poisoning. This is an insidious, nonspecific, inferred illness, which has been called a 'lead insult' by Patterson (1965). With the exception of 'sub-clinical' lead poisoning, other types of lead poisoning can be confirmed, while cases suspected of being lead poisoning on unsatisfactory grounds can be excluded as a rule by intelligent investigation. Moreover, the actual existence of such an illness as 'sub-clinical' lead poisoning can be determined through careful investigation of individuals who throughout their lifetimes are under conditions of adequately controlled occupational exposure to lead during which the concentration of lead in their blood may well be twice or thrice that of persons in the general population.

The development of sensitive, accurate methods of analysis of lead in tissues and excreta has decreased the incidence of diagnostic errors. This fact, in combination with partial observance in American industry of hygienic procedures, has led to an imposing reduction in clinical lead poisoning. The occurrence of serious forms of lead poisoning in the adult has been reduced nearly to the vanishing point. More importantly, a number of vague, non-specific illnesses, often unidentified as to their etiology, have been shown not to be lead poisoning as evidenced by negligible exposure to and absorption of lead.

5.2. Clinical Lead Poisoning

Clinical lead poisoning occurs in gastroenteric, neuromuscular, and encephalopathic forms. These types are characterized by the outstanding manifestation of illness which brings a patient to a clinician. In addition, some evidence of hematological abnormality is found: anemia (which is frequent but not inevitable), an increase in the basophilic granulation (stippling) of the erythrocytes in the peripheral circulation, and also of erythrocytic forms in the bone marrow; or an increase of the reticulocytes in the peripheral blood. Other lesions such as hemorrhagic retinitis occur occasionally in clinical plumbism. There are also biochemical changes, an augmented abundance of the precursors of porphyrin and hemoglobin in the urine, for example, which, combined with the anatomical deviations in cellular elements of the blood mentioned above, implicate the bone marrow among the principal target tissues of the body in lead poisoning.

5.3. The Gastroenteric Type of Lead Poisoning

Gastroenteric symptoms in the adult are by far the most frequent characteristics of lead poisoning in American industry. Occupational lead poisoning is usually manifested first, by a loss of appetite, especially for the first meal after sleep or attempted rest. Because of abdominal discomfort, muscular cramps or jactitation, or true insomnia due to irritation of the central nervous system, the disturbance of sleep or rest may be the first complaint of the victim. Minor digestive disturbances are frequent, and constipation of increasing severity is almost always present, although diarrhea occurs in some instances. Colic is likely to become the dominant feature in recurrent episodes which are so frequent and severe as to amount to extremely great distress with but short intervals of relief. This distress may subside spontaneously, although it is much more likely to require therapy. After relief has been obtained spontaneously or therapeutically, and the obstipation has been corrected, the patient usually recovers. Fatigue sometimes persists for a remarkably long time after such an episode.

5.4. The Neuromuscular Type of Lead Poisoning

Occasionally poisoning appears in a form in which the alimentary symptoms are sufficiently mild to be overshadowed by severe neuromuscular disturbances. Frank

attached to individual workmen having revealed astonishing variations in the exposure to lead of individuals working at the same jobs in the same area (Williams *et al.*, 1969).

5. THE EFFECTS OF THE ABSORPTION OF EXCESSIVE QUANTITIES OF INORGANIC LEAD UPON MAN

Aside from the acute toxic manifestations of the administration of large doses of a soluble inorganic lead compound to experimental animals (or accidentally to men) the result of the ingestion or inhalation of these compounds is not predictable. Whereas the least concentration of lead in the blood associated with the *possible* induction of poisoning is now reasonably well established, the onset of toxic symptoms in relation to the quantity of lead absorbed or available for absorption can not be related in time, severity, or actual occurrence. It appears that the onset of illness in relation to a concentration in the blood is dependent upon the rate at which a potentially dangerous concentration is achieved. It appears that no case of poisoning occurs until the concentration of lead in the blood reaches at least 80 μg per 100 ml, and most cases of poisoning occur at a level well above this (100–300 μg/100 ml). Under conditions of prolonged and gradual absorption of lead the time of onset is, however, uncertain. The symptoms and reversible lesions of lead poisoning often persist after the blood concentration has declined well below 80 μg/100 ml so that, if the threshold value at the onset is to be known, the concentration must be determined close to the onset of illness. With these preliminary remarks, the characteristics of lead poisoning may be discussed in a realistic manner.

5.1. The Toxicity of Inorganic Lead Salts for Man

The ingestion of a highly toxic or lethal dose of lead is an unlikely occurrence in an adult, and so need not be discussed beyond the remark that it has occurred. The more likely occurrence is that of the accidental ingestion of a relatively large quantity of lead by a child. A lethal dose of the lead salt for an adult has been reported by Sollman (1948) to have been as small as 10 g, while four or five times that quantity is said to be required to yield a certain fatal result in man. The symptoms produced suggest an acute enteritis, with diarrhea. Death supervenes in about 36 hr. The accidental death of a child has been known to occur within 24 hr following the ingestion of a very large but unknown quantity of an inorganic salt.

Of much greater significance, especially for industrial lead poisoning, is an understanding of the quantitative relationships which exist between the rate of the absorption of lead into the body and the duration of such absorption. The patterns of absorption vary greatly, and as may be expected, the patterns of the resultant disease differ in both the severity of location and of specific manifestations within the body. Lead poisoning, therefore, may be considered not one but several diseases. For example, lead colic is now the most common form of the disease seen in industry and among adults, while lead encephalopathy appears to be the most frequent problem in lead poisoning in children up to 3 or 4 years of age. These are phenomena closely linked to dosage, in relation to time, rather than primarily to age. The neuritis of lead poisoning, which once occurred with fair frequency in industry is now something of a rarity, while the imminence of the threat, rather than the frequency of anemia in lead poisoning, has assumed a new significance with the development of investigations into the biochemistry of this abnormality. On this account, it seems wise to engage in separate discussions of clinical lead poisoning on the one hand, and the biochemical effects of the absorption of lead on the other, until such a time as these two aspects can be related on a rational basis.

Only since the fourth decade of this century have highly sensitive and precise methods of study permitted a detailed elaboration of the behavior of lead in man. The association of quantitative chemical findings with characteristic abnormalities has greatly altered the precision of clinical interpretations of this disease. Certainly, many cases of lead poisoning in the past have gone unrecognized, and many illnesses have

5.6. MIXED TYPES OF LEAD POISONING

The three principal types of lead poisoning in the foregoing discussion tend to blend into a single clinical entity in which all of the target tissues may be involved, but with one predominating, as a rule. Thus, gastroenteric toxicity is by far the outstanding feature of most cases of occupational lead poisoning, while encephalopathy, which is frequent in the cases of early childhood, is the dramatic and lethal feature which gives this pattern of plumbism its prominence. In addition, other organs, tissues and physiological processes of the body may be involved in such a manner as to modify the pattern of the disease. Such individual symptoms or signs are: the Burtonian line of blue-black deposits in the gingivae, hypotension, bradycardia, fatigue, facial, circumoral or retinal pallor, peripheral neuritis, convulsions, retinal hemorrhage, proteinuria, aminoaciduria, uricaciduria, abnormal quantities of porphyrins and δ-aminolevulinic acid in the urine or blood, increased stippling of erythrocytes in the peripheral blood, increased reticulocytes in the peripheral blood and bone marrow, anemia, and jaundice. Two tissues may be singled out for brief consideration—the bone marrow, which is stimulated (early) and sometimes seriously damaged by lead, with the production of severe and occasionally persistent anemia, and the kidney. The biochemical phenomena of lead poisoning have recently been reviewed at length by de Bruin (1971) to whose paper students of the subject are referred.

Anemia frequently is an important clinical feature of lead poisoning, and has been one of the most productive areas of investigation because of recent insight into the mechanisms of hemoglobin synthesis and its inhibition by lead. The absorption of excess lead is capable of inducing signs of the inhibition of certain enzymic syntheses in the bone marrow and elsewhere without necessarily causing any evidence of illness, or any demonstrable degree of anemia. One of the most striking effects is an inhibition of the synthesis of heme, resulting in the accumulation of δ-aminolevulinic acid in the body and in the urine. The concentration of δ-aminolevulinic acid in the urine is correlated so closely with the concentration of lead in the blood as to provide an indirect indication of the blood lead concentration. The inhibition of δ-aminolevulinic acid dehydratase becomes apparent when the concentration of lead in the blood exceeds 0.04 mg/100 ml, and the urinary δ-aminolevulinic acid increases rapidly as the blood lead increases. Porphyrins, especially coproporphyrin III, also accumulate in the body and increase in concentration in the blood and urine when lead is absorbed in somewhat greater quantities than normal. Differential diagnosis is complicated by the fact that excessive quantities of porphyrins in the blood and urine occur also in a number of other intoxications, as well as in congenital porphyria. The absorption of lead at sufficient rates results also in concentrations of protoporphyrin in the erythrocytes ten to fifty fold higher than those usually found. This is believed to be a much more specific effect of lead than is the increased accumulation of coproporphyrin III. The effects of lead are indeed so specific in the inhibition of enzymes concerned in hemoglobin production that Gadjos (1971) feels that the following specifically reflect excessive absorption of lead: a urinary δ-aminolevulinic acid level of 20 mg/l., a urinary coproporphyrin level of 400 μg/l., significant increase in erythrocyte protoporphyrin, and possibly a slight increase in uroporphyrin in the urine. Inhibition of δ-aminolevulinic acid dehydratase in the erythrocytes *in vitro* has been shown by Hernberg *et al.* (1970) to occur at concentrations of lead within the range of those found in the blood of normal individuals. This effect cannot be shown *in vivo*, since the method for measuring enzyme activity requires lysis of the erythrocytes. The demonstration of this degree of sensitivity of an enzyme to lead of itself is an interesting phenomenon.

The incidence of chronic nephritis in lead poisoning in Europe, England and Australia, and the investigations made into this problem, convinced a number of highly respected clinicians and investigators of the causal relationship of lead to the induction of chronic nephritis of a gross pathologic type which is seen terminally as small, contracted kidneys. However, despite the fact that such a type of nephritis may result from the prolonged, severe absorption of lead (Goyer *et al.*, 1971), little evidence has

paralyses, involving the extensor muscles of the forearm and sometimes the fingers and hands, are most likely to occur in the muscles used to the greatest extent. Bilateral paralyses were seen in the past, but are infrequent at this time. In fact, paralyses are uncommon, although extensor weakness with some degree of atrophy of the affected muscle is not so rare. In either case, the exposure to lead required to induce either the paralysis or a distinct weakness of muscles or muscle groups, must be severe and usually prolonged. It appears that the victims of paralyses have usually suffered recurrent episodes of non-disabling illness, before succumbing to the muscular disability of a paralytic lesion. If indeed it occurred at all, paralysis in the lower extremities of the adult in the absence of paralysis in the upper extremities was a rare lesion of occupational lead poisoning in the middle decades of the twentieth century in the United States and in the experience of many industrial physicians is nonexistent in the present era. Occasionally, after prolonged severe exposure to lead in association with hard physical effort, there may be greatly increased muscular tonus, spontaneous pain and tenderness in muscles and joints, and hyperreflexia in the extremities, especially in the legs of men who have been engaged in heavy lifting. More frequently, following prolonged hard work and moderate to severe exposure to lead, there is reduced muscular tonus, weakness and a modest degree of atrophy of extensor muscles, in the forearm and, to a lesser extent, in the hand. Fatigue, pronounced in such individuals, seems to be disproportionately great in relation to the severity of the illness.

5.5. The Encephalopathic Type of Lead Poisoning

Under extremely severe conditions of respiratory exposure to lead an encephalopathic type of lead poisoning occurs in the adult. Rarely, this manifestation is seen with other types of exposure. In young children, by contrast, encephalopathy occurs most frequently as the result of the ingestion of large quantities of lead for relatively short periods of time (2 or 3 years at most, but usually months). The metal is ingested as lead-containing flecks of paint from woodwork, furniture, putty, or plaster within housing which dates from the time when the paints employed for interior surfaces contained large amounts of lead pigments. The disease occurs with such frequency and mortality (about 25%) as to represent a serious public health problem in many of the older cities in the United States. Despite the widespread impression that the occurrence of this type of lead poisoning is peculiar to children, encephalopathy occurs in the adult as well. It results from a rapid rate of the absorption of large quantities of lead. In consequence, the introduction of lead into the brain is so facilitated that its concentration therein reaches levels ranging up to more than 0.5 mg/100 g of fresh tissue. Findings of such levels at necropsy, in the absence of other information as to the cause of death, are taken as highly suggestive evidence of the occurrence of fatal lead encephalopathy. Lead encephalopathy due to the absorption of lead from occupational exposure is now an unusual occurrence. In consequence, little opportunity has been afforded for the detailed investigation required to delineate its clinical characteristics. This type of lead poisoning in the young child has occurred, most unfortunately, with such frequency as to provide extensive opportunity for clinical, epidemiologic, pharmacologic, and therapeutic investigation, and it is from this source that the modern concept of the precise nature of this type of lead poisoning must come. It is worthwhile here, however, to point out that lead encephalopathy, in the child, bears so little resemblance to the usual case of lead poisoning in the adult, as to require extensive experience with the disease and trustworthy analytical evidence for its recognition. The disease in many cities of the United States has been an important feature of pediatric practice here where facilities for case finding and diagnosis have been available for nearly 40 years. Despite this fact, many cases elsewhere have been misinterpreted and will continue to be misinterpreted unless adequate diagnostic facilities become available, and the pediatric housestaff of hospitals to which such children are often brought have been alerted and instructed in the nature and origin of this problem.

Certainly, the absorption of the products of the degradation of tetraethyllead into or upon the surface of the erythrocytes, does not occur, at least to the expected extent, in the presence of comparatively large quantities of organic lead in the body. It may be presumed, therefore, that significant conversion to inorganic lead does not occur.

6. THE THERAPY OF LEAD POISONING

The presently employed therapy of lead poisoning, from the aspect of relief of major symptoms and preservation of life is not satisfactory. The use of a chelating agent, such as calcium disodium edetate, serves to release inorganic lead from tissues and organs, but not that in dense bone, and probably only a portion of that in fenestrated osseous tissue, and to eliminate it from the body at a somewhat accelerated rate. It may bring about some improvement in the patient's immediate condition. Excessive quantities of coproporphyrins and δ-aminolevulinic acid in the urine tend to decrease promptly to more nearly normal levels. The precise significance of this phenomenon is not entirely clear, but it is associated with restoration of normal physiological processes, and as such it deserves consideration. The relief of lead colic, however, as well as certain other symptoms must be achieved, as a rule, by other means, e.g., calcium salts, anti-spasmodic drugs, or even strong sedation for colic, supportive and rehabilitative measures for other disabilities or functional abnormalities.

The average adult patient suffering from lead poisoning recovers fairly promptly with or without specific medication if he is removed entirely from exposure to lead and cared for symptomatically, especially if it is his first episode of intoxication. The usual child with encephalopathy, on the other hand, may not do well, even under expert care, and while it is believed that the therapy now available has shortened recovery and reduced disability and mortality, the latter is still little under 25 per cent. (Obviously here, the only effective procedure, as yet, lies in eliminating the sources of exposure to lead in the homes of young children.)

The principal difficulty associated with the medical care of patients with lead poisoning is that of the medical handling of the convalescent or, the seemingly recovered individual. Most of such cases have occurred either among workmen employed in industrial plants in which handling of lead compounds is not satisfactory, or among young children from urban areas of poor housing in which there is uncontrolled access to interior surfaces coated with layers of cracked and scaling paint of high lead content. The frustrating problem in dealing with such adults or children is that of preventing their return to the unchanged conditions which were responsible for their illness. The unhygienic industrial plant is likely to remain unhygienic for precisely the same reasons which made it so initially, i.e. the ignorance, incompetence, or putative economic necessities of owners or managers. It has been possible, for many years, to achieve satisfactory hygienic conditions in the industrial operations concerned with the production or use of lead; the ingredients of a satisfactory hygienic regimen are knowledge, technical competence, and appropriate medical supervision of workmen, in addition of course to social sensitivity in all persons concerned with the production of commodities and the conduct of the hygienic program. To eliminate lead poisoning from modern industry it would seem to be necessary, however, to effect uniform hygienic practices through governmental compulsion, since in the cross currents induced by modern social and economic pressures, the humane impulse cannot always survive within the elastic structure of freedom of individual action. It is also feasible to create and maintain a satisfactory physical environment for children.

The necessity for treating the poisoned industrial employee, or the sick child from the slums, is a clear indication of the role of an unsatisfactory environment in the causation of the illness, and this in neither instance is directly within the power of the physician to correct. The situation, however, whether or not it is recognized and acted upon, is within the province of the physician to consider, and if possible to deal with, whether he be a personal or family physician, or one in the employ of the industry, or of the unit of government involved. This is not necessarily a matter of law, but is one of the

been found in American industry of any undue incidence of chronic nephritis among workmen in the lead industries. Moreover, in this country, chronic nephritis has not been found to occur with any undue frequency in later life following lead poisoning in childhood (Tepper, 1963), as has been the case in Queensland, Australia (Nye, 1933). The situation in the United States may not parallel the Queensland cases. Lane and his associates (1964) in England have reported their investigations of the recorded information concerning pensioned workmen who had been engaged for many years in the manufacture of electric storage batteries, before and after the adoption and full application of measures for the prevention of occupational lead poisoning. They found evidence of an abnormally high incidence of fatal chronic nephritis and of cerebral accidents associated with prolonged and severe exposure to lead. The modest statistical evidence was the more convincing in view of the fact that, with the elimination of such severe exposure to lead and the achievement of acceptable conditions of occupational exposure to lead, the disparity between the incidence of chronic nephritis among these workmen and that in the surrounding population disappeared. The significance of the increase in incidence of cerebral accidents in relation to the absorption of lead, and renal disease, is somewhat uncertain. In view of the lingering concept that absorption of excessive quantities of lead may induce disease of the blood vessels, the question still arises as to the relationship, if any, between vascular disease and chronic nephritis. The pathogenesis of chronic nephritis due to a continuing exposure to fairly large quantities of lead has been investigated in animals. It has been found that nuclear inclusion bodies in kidney tubule cells, mitochrondrial swelling, altered renal tubular function, as well as radial scattering, occur in the kidney of laboratory animals poisoned by lead. The literature of this subject has been reviewed recently by Goyer (1971).

5.7. The Effects of the Absorption of Tetraethyllead by Man

Although the absorption of alkyl lead compounds other than tetraethyllead has not been reported in man, one may presume that the effects would be similar in most respects since the differences in the toxicity in experimental animals are not very great. As regards tetraethyllead, however, sufficient information is available to justify the early suspicion that it induces a clinical syndrome totally different from that associated with inorganic lead. The description of tetraethyllead poisoning by Kehoe (1925) was the result of following the course of the symptoms in a group of workmen, who had been subjected to what may now be designated as a mild degree of exposure to tetraethyllead. Two of their number had died unexpectedly and were not seen by this author, while the others recovered slowly. The latter group were certainly ill, but it is impossible, at this time, to estimate the significance of the persistent fear of these men, as to their ultimate fate, upon the duration of their disability.

The description by Machle (1936) of the much more severe cases of tetraethyllead poisoning which he saw is a more complete picture of the toxic potential of tetraethyllead than can be found elsewhere. It is remarkable, therefore, that clinical experience, including Machle's, brought to light no residual effects or dramatic sequelae of tetraethyllead poisoning among the survivors of highly severe states of intoxication. The recovery of persons who at one time had been desperately ill appeared, without exception, to have been complete.

Another characteristic worthy of emphasis is the almost purely mental character of the illness of persons, who at the onset of their illness were not violent or convulsive. The onset of illness was always delayed; in a few instances the delay was as long as 8 days after the cessation of exposure. When the delay was long, it was most apparent that the illness presented was primarily mental aberration, often of an extremely bizarre type.

Still another feature of tetraethyllead poisoning should be mentioned because of our concern to record the incomplete state of the knowledge of the behavior of this and related compounds in man. Mention has been made of the fact that the rate and extent to which this compound is converted to inorganic lead in animals and man is unknown.

29. KEHOE, R. A. (1969) Toxicological appraisal of lead in relation to the tolerable concentration in the ambient air. *J. Air Pollut. Control Ass.* **19**: 690–700.
30. KEHOE, R. A. (1971) A brief account of a conference on standards for the prevention of occupational lead poisoning in the course of exposure to inorganic lead. *Archs envir. Hlth* **23**: 245–248.
31. KEHOE, R. A., CHOLAK, J., HUBBARD, D. M., BAMBACH, K., MCNARY, R. R. and STORY, R. V. (1940) Experimental studies on the ingestion of lead compounds. *Jt. ind. Hyg. Toxicol.* **22**: 381–400.
32. KEHOE, R. A., CHOLAK, J., MCILHENNEY, J. G., LOFQUIST, G. A. and STERLING, T. D. (1963) Potential hazard of exposure to lead. II. Further investigations in the preparation, handling, and use of gasoline containing tetramethyllead. *Archs envir. Hlth* **6**: 255–272.
33. KEHOE, R. A., CHOLAK, J., SPENSE, J. A. and HANCOCK, W. (1963) Potential hazard of exposure to lead. I. Handling and use of gasoline containing tetramethyllead. *Archs envir. Hlth* **6**: 239–254.
34. KEHOE, R. A. and THAMANN, F. (1931) The behavior of lead in the animal organism. II. Tetraethyl lead. *Am. J. Hyg.* **13**: 478–498.
35. KEHOE, R. A., THAMANN, F. and CHOLAK, J. (1934) An appraisal of the lead hazard associated with the distribution and use of gasoline containing tetraethyl lead. Part I. *J. ind. Hyg. Toxicol.* **16**: 100–128.
36. KEHOE, R. A., THAMANN, F. and CHOLAK, J. (1936) An appraisal of the lead hazard associated with the distribution and use of gasoline containing tetraethyl lead. II. The occupational lead exposure of filling station attendants and garage mechanics. *J. ind. Hyg. Toxicol.* **18**: 42–68.
37. KITZMILLER, K. V., CHOLAK, J. and KEHOE, R. A. (1954) Treatment of organic lead (tetraethyl) intoxication with edathamil calcium-disodium. *Arch. ind. Hyg.* **10**: 312–318.
38. LANE, R. E. (1964) Health control in inorganic lead industries. *Archs envir. Hlth.* **8**: 243–250.
39. LAZRUS, A. L., LORANGE, E. and LODGE, J. P. JR. (1970) Lead and other metal ions in the United States precipitation. *Envir. Sci. Technol.* **4**: 55–58.
40. MACHLE, W. F. (1935) Tetra-ethyl lead intoxication and poisoning by related compounds of lead. *J. Am. med. Ass.* **105**: 578–585, 1935.
41. MACHLE, W. F. (1940) Lead absorption from bullets lodged in tissues. *J. Am. med. Ass.* **115**: 1536–1541.
42. MOTTO, H. L., DAINES, R. H., CHILKO, D. M. and MOTTO, C. K. (1970) Lead in soils and plants: Its relationship to traffic volume and proximity to highways. *Envir. Sci. Technol.* **4**: 231–238.
43. NOZAKI, K. (1966) Method for studies on inhaled particles in human respiratory system and retention of lead fume. *Ind. Hlth.* **4**: 118–128.
44. PATTERSON, C. C. (1965) Contaminated and natural lead environments of man. *Archs envir. Hlth* **11**: 344–360.
45. PICCIOTTO, E., CAMERON, R., CROZAZ, G., DEUTSCH, S. and WILGAIN, S. (1968). Determination of rate of snow accumulation at the pole of relative inaccesibility, eastern antarctica: A comparison of glaciological and isotopic methods. *J. Glaciol.* **7**: 273–287.
46. ROBINSON, E. and LUDWIG, F. L. (1967) Particle size distribution of urban lead aerosols. *J. Air Pollut Control Ass.* **17**: 664–669.
47. SPRINGMAN, F., BINGHAM, E. and STEMMER, K. L. (1963). The acute effects of lead alkyls. *Archs envir. Hlth* **6**: 469–472.
48. STEVENS, C. D., FELDHAKE, C. J. and KEHOE, R. A. (1956) Isolation from liver of tetraethyllead after its inhalation. *J. Pharmac. exp. Ther.* **117**: 420–424.
49. STEVENS, C. D., FELDHAKE, C. J. and KEHOE, R. A. (1960). Isolation of triethyllead ion from liver after inhalation of tetraethyllead. *J. Pharmac. exp. Ther.* **128**: 90–94.
50. TASK GROUP ON LUNG DYNAMICS (1966) Deposition and retention models for internal dosimetry of the human respiratory tract. *Hlth Phys.* **12**: 173–207.
51. TEPPER, L. B. (1963) Renal function subsequent to childhood plumbism. *Archs envir. Hlth* **7**: 76–85.
52. TER HAAR, G. L., HOLTZMAN, R. B. and LUCAS, H. F., Jr. (1967) Lead and lead-210 in rainwater. *Nature, Lond.* **216**: 353–355.
53. WARREN, H. V. and DELAVAULT, R. E. (1960) Observations on the biogeochemistry of lead in Canada. *Trans. R. Soc. Can.* **54**, Sec. IV: 11–20.
54. WILLIAMS, M. K., KING, E. and WALFORD, J. (1969) An investigation of lead absorption in an electric accumulator factory, with the use of personal samplers. *Br. J. ind. Med.* **26**: 202–216.

traditional responsibilities of the physician which has not been altered by the structural changes of modern society. The resumption of work with the same or even lesser degree of exposure to lead in an industrial plant with persistent hygienic deficiencies, is to set the stage for the recurrence of intoxication in a shorter time than that required initially because of the heightened body burden of lead. Likewise, the return of children to the home in which they were originally poisoned all but guarantees a high level of mortality, unless appropriate corrective measures have been taken.

REFERENCES

Books, Reviews, and Monographs

1. BLOOMFIELD, J. J. and DALLA VALLE, J. M. (1935) *The Determination and Control of Industrial Dust*, Public Health Bulletin No. 217. Government Printing Office, Washington.
2. GOLDSCHMIDT, V. M. (1954) *Geochemistry*, MUIR, A. (ed.). Clarendon Press, Oxford.
3. GOYER, R. A. (1971) Lead and the kidney. *Curr. Topics Path.* (in press).
4. KEHOE, R. A. (1966) Criteria for human safety from the contamination of the ambient atmosphere with lead. In *Proc. 15th Intern. Congr. Occupational Health*, vol. 3, pp. 83–98. Wiener Medizinischen Akademie, Vienna.
5. MONIER-WILLIAMS, G. W. (1949) *Trace Elements in Food*, pp. 64–106. Wiley, New York.
6. MUROZUMI, M., CHOW, T. J. and PATTERSON, C. (1965) Concentrations of common lead in Greenland snows. In *Marine Geochemistry. Proceedings of a Symposium Held at The University of Rhode Island, October* 29–30, 1964, Aug. 1965, pp. 213–215. U.S. Atomic Energy Commission Document NYO-3450-1.
7. NYE, L. J. J. (1933). *Chronic Nephritis and Lead Poisoning.* Angus & Robertson, Sydney, Australia.
8. TATSUMOTO, M., and PATTERSON, C. C. (1963) The concentration of common lead in sea water. In *Earth Science and Meteoritics*, pp. 74–89, GEISS, J. and GOLDBERG, E. D. (compilers). North-Holland, Amsterdam.
9. U.S. BUREAU OF THE CENSUS (1969) *Statistical Abstract of the United States*, 90th ed., Table 1054, p. 682. Government Printing Office, Washington.
10. WILLIS, F. J. (Chairman) (1930) *Final Report of the Departmental Committee on Ethyl Petrol. Examination of Settled Dusts*, pp. 27–33. H.M. Stationery Office, London.
11. WORKING GROUP ON LEAD CONTAMINATION (1965) *Survey of Lead in the Atmosphere of Three Urban Communities*, Public Health Service Publication No. 999-AP-12. U.S. Department of Health, Education, and Welfare, Cincinnati, Ohio.

Original papers

12. BARRY, P. S. I. and MOSSMAN, D. B. (1970) Lead concentration in human tissues. *Br. J. ind. Med.* 27: 339–351.
13. BURTON, W. M. and STEWARD, N. G. (1960) Use of long-lived natural radioactivity as an atmospheric tracer. *Nature, Lond.* 186: 584–589.
14. CALINGAERT, G. and BEATTY, H. A. (1939) The redistribution reaction. I. The random intermolecular exchange of organic radicals. *J. Am. chem. Soc.* 61: 2748–2754.
15. CHOLAK, J. (1964) Further investigations of atmospheric concentrations of lead. *Archs envir. Hlth* 8: 314–324.
16. CHOLAK, J. and STORY, R. V. (1941). Spectrochemical determination of trace metals in biological material. *J. opt. Soc. Am.* 31: 730–738.
17. CREMER, J. E. (1959) Biochemical studies on the toxicity of tetraethyl lead and other organo-lead compounds. *Br. J. ind. Med.* 16: 191–199.
18. CREMER, J. E. and CALLAWAY, S. (1961) Further studies on the toxicity of some tetra and trialkyl lead compounds. *Br. J. ind. Med.* 18: 277–282.
19. DAVIS, R. K., HORTON, A. W., LARSON, E. E. and STEMMER, K. L. (1963) Inhalation of tetramethyllead and tetraethyllead. *Archs envir. Hlth* 6: 473–479.
20. DE BRUIN, A. (1971) Certain biological effects of lead upon the animal organism. *Archs. envir. Hlth.* 23: 249–264.
21. DE TREVILLE, R. T. P. (1964) Natural occurrence of lead. *Archs envir. Hlth* 8: 212–221.
22. GOYER, R. A., LEONARD, E. L., BREAM, P. R. and IRONS, T. G. (1970) Aminoaciduria in experimental lead poisoning. *Proc. Soc. exp. Biol. Med.* 135: 767–771.
23. HAMMOND, P. B. and ARONSON, A. L. (1964) Lead poisoning in cattle and horses in the vicinity of a smelter. *Ann. N.Y. Acad. Sci.* 111: 595–611.
24. HERNBERG, S. and NIKKANEN, J. (1970) Enzyme inhibition by lead under normal urban conditions. *Lancet* 1: 63–64.
25. JAWOROWSKI, Z. (1968) Stable lead in fossil ice and bones. *Nature, Lond.* 217: 152–153.
26. KEHOE, R. A. (1925) Tetra-ethyl lead poisoning: clinical analysis of a series of nonfatal cases. *J. Am. med. Ass.* 85: 108–110.
27. KEHOE, R. A. (1927) On the toxicity of tetraethyl lead and inorganic lead salts. *J. Lab. clin. Med.* 12: 554–560.
28. KEHOE, R. A. (1961) The harben lectures, 1960. The metabolism of lead in man in health and disease. Lecture 1. The normal metabolism of lead; Lecture 2. The metabolism of lead under abnormal conditions; Lecture 3. Present hygienic problems related to the absorption of lead. *J. R. Inst. publ. Hlth Hyg.* 24: 81–97; 101–120, 129–143; 177–203.