Katharine R. Boucot, M.D.
Chief Editor, Archives of Environmental Health
Woman's Medical College of Pennsylvania
3300 Henry Avenue
Philadelphia, Pennsylvania 19129

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Dear Doctor Boucot,

I am reluctant, as a matter of principle, to deprecate the efforts of a physical scientist to cast new light on biological phenomena so as to contribute to the clarification of environmental factors that influence, or appear to be capable of influencing, human health and well being. At this time, especially, the contributions of investigators in a broad range of scientific disciplines are sorely needed in aid of a more comprehensive understanding of the current, complex, human environment, as it is affected by modern technology. However, the article by Clair C. Patterson, Ph.D. in the September issue of the Archives of Environmental Health (11:344-60, 1965), entitled "Contaminated and Natural Lead Environments of Man", calls for critical comment in the interest of a somewhat more balanced judgment concerning this significant issue of environmental health.

In presenting an interpretation of certain geochemical observations made by himself and his associates, with respect to the abundance of lead in certain oceanic strata, as a clue to the artificial dissemination of lead in the present environment of man, this author is within his own field and is entitled to a respectful hearing, subject to the criticisms of colleagues in comparable fields. His subsequent discussion of various general and specific means by which lead, removed from the depths of the earth, has been subjected by ancient and modern man to a variety of processes and uses, and so has been scattered about in unnatural profusion upon the earth's surface, has the authentic flavor of the geologist's view of such matters, and speaks of an imaginative approach to the phenomena of his chosen field. His somewhat disingenuous implication that medical investigators have ignored artificial contributions to the natural content of lead in the human environment, and that the term "normal" has been regarded as synonymous with "natural" in this relationship, is belied by medical literature, in which many artificial sources of lead in the environment have been identified in some detail, and listed collectively by myself (J.I.H. 15:— 1933), among other investigators, while "normal" in medical parlance has been defined repeatedly, and often set in quotation marks to indicate the usual, current state of the environment or of certain responses thereto. This, however, is a matter of minor semantic importance and may be taken lightly.

Unfortunately, there are other matters in the article which may not be glossed over, for Dr. Patterson has ventured, without caution, humility or appropiate critique, into what is clearly, for him, an alien area of biology, has developed his own iconoclastic theses, and has raised certain questions in order to answer them with the boldness, passion and disregard for troublesome facts that more befit zeal in the advocacy of a cause than the attitude of the serious investigator. If proof is needed of his unfamiliarity with the field,

attention is called, in passing, to the naiveté which characterizes his acceptance of certain items of data with which to illuminate his statements, and to his translation of certain dubious statistical correlations into factual evidence. As an example of the latter type, the highly questionable issue of one's absorption of significant quantities (measureable by any acceptable means) of lead while smoking, which is based solely upon thin, inferential statistical correlations (US Public Health Service Publication No.999-AP-12, 1965), in the face of the fact that the great bulk of the lead in and on tobacco remains in the discarded ash of the cigarette (J. Roy. Inst. Public Health and Hyg. 24: 76-77, 1961, and Tobacco 144: 24, 1957), is settled for Dr. Patterson, who even gives it quantitative expression. Further, as only one instance of an unhappy choice of evidence, is his reliance upon a statement in the literature (Schweiz Med Wschr. 87: 1171, 1957), that the potentially harmful threshold of concentration of lead in the blood may be as low as 0.05 mg. per 100 grams (given in the text as 0.5 parts per million). The credulity that is represented in this choice is excusable, in view of the experimental and clinical variables that must be taken into account in the quantitative appraisal of even recent series of analytical data, but is so demonstrated, nevertheless.

The foregoing criticisms might well be regarded as trivial, were they not indicative of the quality of the author's judgment of the worth of evidence taken from unfamiliar sources. But a much sharper attention must be focused upon the validity of the two principal arguments in Dr. Patterson's thesis, for these are crucial. The first of these is his estimate of the natural body burden of lead "which prevailed (in man) during the creation and evolution of (his) physiological responses to lead". The second is concerned with the "definite indications that residents in the United States today are undergoing chronic lead insult". As he develops these two points, and as they are interwoven in his text, they seem to derive increasing weight from the complexity of the inferences and interpolations on which they are based. The latter, particularly those concerned with a deft handling of various selected elements from the periodic table, may be viewed with scepticism, if not distrust. (Why, for example have lithium, magnesium and aluminium, which hardly fit the patterns of the argument, been excluded from certain tabular comparisons of the elements? And by what magic have the natural body burdens of germanium and thallium been calculated, when these elements have not been found in the human body under ordinary circumstances?). However, in any critical appraisal of the major issues, these superficially impressive and abstruse arguments fail dismally, not so much because of their intrinsic faults, which are difficult to assess, but because of the solid weight of evidence which is opposed to them. Only a portion of such evidence, presented preferentially here because of this critic's first-hand assurance of its reliability, as won by years of increasingly critical experience, is required for this purpose.

In estimating the body burden of lead in primitive man, as a basis for the appraisal of the relative magnitude and significance of the contribution made to their environment by artful and technical men through the centuries, Dr. Patterson has mentioned, only to dismiss, the relevant data obtained by the direct analysis of materials collected in the course of two expeditions into primitive areas of the earth. The first of these, planned and carried out in the field in 1930, by myself in person, involved the investigation of native

people and their environment on the Mexican plateau. The second, only a little later, was concerned with the collection, by proxy, of vegetation, primarily, (a number of samples of soil were obtained), from jungle areas in the Yucatan Peninsula and in the Far East, in containers and in strict accordance with instructions supplied by myself and certain analytical associates in the staff of the Kettering Laboratory in the Medical Center of the University of Cincinnati. (Certain other specimens of vegetation were obtained from such widely separated parts of the earth as Trinidad, Sarawac and Ceylon, among others, that were judged to be free of contamination from industrial or other artificial sources. These data have been assembled recently, out of several articles, for republication collectively (J.Roy. Inst. Public Health and Hyg. 24: 81-97, 1961) No further mention will be made of them here, since more definitive information in scope and significance was obtained in the investigation of the Mexican Indians.

Dr. Patterson's rejection of the results of the Mexican survey was based, it seems, on the relative unreliability of the procedures employed at that time for the analysis of the materials obtained (these are described in detail in association with this and other articles published with it), and on the "discovery" that these subjects made use of lead-glazed pottery (this was no later discovery, but was, rather, one of the matters duly observed and reported fully, together with analyses of the pottery, as a part of the appraisal of the environment of the Indians (J. Ind. Hyg. 15: 257-72, 1933). However, these findings cannot be disposed of so lightly, for reasons which must be made clear.

A preliminary survey of the experimental sites (chosen from several others withing the broad plateau) had brought to light only one artificial factor, of ancient origin, represented in the use of local, native pottery, some of which, including the flat platter (16-18 inches in diameter) on which tortillas and certain other articles, mostly meats, were cooked, had been coated thinly with a lead-containing glaze. These (one to the household), and a very few other earthenware utensils, were generally used for a long time, for the possessions of the Indians were meager, and since these had been subjected to slow heat and animal fat, they had acquired a patina with time and use. Observations of glass and glazed surfaces that have been fired by traditional methods, have shown that when, as in cooking, they are left undisturbed by scouring or by contact with corrosive substances, to prevent "sticking", they yield up only minute, almost negligible amounts of lead. It should also be made known to those without familiarity with isolated Mexican Indians, that they were unaccustomed to the use of dining tables or table ware. They ate much of their food in its natural state, out of doors, or indoors while seated on the earthen floor, or on the mat of woven vegetable fibers which served as table, chair or bed. They employed rolled or folded tortillas as plates, knives, forks and spoons in handling liquid or cooked foods. Hence, it is highly probable that the extraneous portion of their ingested lead came more from the inevitable contamination of their food and beverages (and fingers) with pulverized earth, than from their limited use of pottery. It is evident that neither of these factors can be ignored in obtaining an estimate of the minimum quantity of lead that might have been ingested daily by the adult, male Indians from purely natural sources, that is, from the natural ocurrence of lead in the substance of the edible vegetation

and in the flesh of animals that fed on vegetation and other animals. It is equally evident, however, that earthy contamination has been an inescapable factor in the lead content of the food of the most primitive of men.

Suffice it here to say that this experimental survey was designed to provide an answer to the question of the abundance of lead in a primitive environment of man, as compared with that in the complex industrial and technological environment of modern man in the United States. It is also pertinent to call attention to the fact that the distribution of the degradation products of tetraethyl lead on the earth's crust, at this time, was of small proportions in a relatively restricted area, and that it was not a factor in the analytical findings of this survey. Moreover, careful inquiry, confirmed by the records in the Federal District of Mexico, demonstrated that no mining operations had been carried out in the general region of the investigation. Ordinary observation served to show also, that there were no factories, no industrial operations, and no water pipes of any kind, in the area.

As to the actual investigation, having judged the sites to be satisfactory, I arranged for the shipment, from the Kettering Laboratory, of suitable containers for samples, and accompanied them to the sites, where I collected, in person, samples of suitable size, in relation to the sensitivity of the analytical methods (see later), of the items of the food that entered into the diet of the Indians, from the fields in which many of them were growing or living (animals), and from the stream, households and the few places of storage. A number of samples of soil were collected also. From the people, representative specimens of feces (one evacuation), urine (large volumes of two or more liters), and blood (40 to 50 ml) were collected. (For reasons that need not be discussed here, the results of the analyses of specimens of blood, as given in the original publication cited previously, may well be disregarded, in favor of those obtained some years later and analysed by present highly sensitive methods. Specimens of urine were also obtained for analysis, at that later time, by methods of sampling that have found to be satisfactory. (The mean values of the series of results, of very low variability, were of the order of 0.02 mg of lead per 100 grams of blood, and 0.02 mg. of lead per liter of urine, both of which are in the lower third of the range of the results obtained in the United States). It was not possible, under the conditions that existed in the field, to follow the alimentary intake and output of lead by individuals, nor was it feasible to obtain satisfactory data as to the lead content of the ambient atmosphere.

The specimens of food (and water) were viewed critically from the aspect of their freedom from contamination. Those that had been cooked or stored, and those which had been exposed to dust in the fields, because of their manner of growth, were regarded as contaminated. Notes were made from which the results of analyses of the latter types of growing vegetation were marked in the published data to indicate that likelihood. Other results could safely be attributed to the natural lead in the specimens, since these had been shielded effectively from external contamination until they were enclosed in the containers. An estimate of the total quantity of lead in a composite daily diet made up solely of such uncontaminated articles could be made with a reasonable approximative to the actual facts. A further estimate of the daily alimentary intake of lead, for comparative purposes, could be made from the results of the analyses of the

feces of the subjects, since such findings have been found to yield a sound portrayal of the quantities of lead ingested during the period corresponding physiologically to that involved in the accumulation of feces for evacuation. Such estimates, which will be given later, are admittedly rough in the strictly quantitative sense, but they are clearly indicative of the order of magnitude of the values under discussion.

The matter of analytical precision is obviously pertinent. The data, as reported, err systematically on the low side, for the reason that the methods used at that time, while yielding reproducible and specific (for the metal concerned) results, were of a lower order of sensitivity [illegible] those which were developed later and used in the Kettering Laboratory since 1937-38. For this reason they failed to detect lead in the material analysed, when the total quantity was less than 0.08 ± 0.008 mg., and always gave a low value, by this much, when lead was present in the sample, as analysed, in measureable quantity. This was counteracted to some extent, but never fully, in view of the low order of magnitude of the quantities of lead dealt with, by the collection of specimens of large volume or weight. The analytical data have been reported, as obtained, without any correction, since, in view of the approximations represented in the estimates of the alimentary intake of natural lead on the one hand, and of total lead on the other, such corrections would have implied a false degree of precision in such estimates. It is sufficient for comparative purposes to indicate that the daily intake of lead in the two categories (natural and total) by the adult males (no women were included) among these Indians was not less than 0.10 or more than 0.15 mg. per day. Such an alimentary intake can be estimated, indirectly, but with a high degree of probability based on extensive metabolic data, to be consistent with a body burden of lead of the order of 40 to 60 milligrams.

2. The more important feature of Dr. Patterson's paper is his conclusion that the present level of the contamination, by lead, of the general environment in the United States, especially its atmospheric component, poses a serious threat to the health of the general population. This conclusion flies in the face of a solid body of reliable evidence to the contrary. It should be pointed out, at once, that the lead in the food and beverages of citizens of the United States is a larger and more variable factor than that in the air. No one can deny that the exposure of modern man to lead is considerably greater that that of primitive man, nor can one be assured, at this point in time, that such exposure may not, without appropriate surveillance and adequate precautionary measures, reach dangerous proportions at some future time. It is precisely because of the latter possibility that our systematic investigations of the past thirty years have been undertaken and continued, to establish facts, hygienic criteria, and methods of monitoring both environmental conditions and people, whereby the hygienic status of our population, in this regard, can be determined well in advance of any threat. These ends have now been accomplished in large part. Criteria of safety, with respect to the lead content of food and beverages, have been set, on physiological grounds, under conditions in which the lead content of the air is maintained at a constant level. Similar criteria for the lead content of the air, when that of food and beverages is maintained within its present limits of variability, are far along in the making. The principle on which these criteria are based is that

of the determination of the combined quantities of lead from food, beverages and air, which can be taken into the healthy human body from day to day and year to year, without a measureable degree of accumulation of lead in the body. The evidence of balance experiments, carried out with healthy men in the Laboratory, partially reported (J. Roy. Inst. Pub. Health and Hyg. 24:81-97, 1961), has indicated clearly that, under present environmental conditions in the United States, individuals take in variable quantities of lead regularly, and that they eliminate lead from their bodies, regularly, in substantially equivalent quantities (within well defined limits of experimental deviation), maintaining theselves in substantial equilibrium with their environment throughout all but the early years of life, during which the mixed components of the adult diet are being added to the infant diet and equilibrium with the environment is being achieved.

There has been no demonstrable increase in the intake and output of lead of individuals in the general population of the United States, or in the lead content of the urine and blood of representative groups of persons in the United States during the past thirty years. On the contrary, there is highly suggestive (but inconclusive) evidence that the total intake of lead by such persons is lower in the present decade than it was in the two preceding decades. It is also likely, on the basis of indirect evidence, that this level is lower in the United States than in certain other countries. Be the latter indications as they may, the hygienic problem, with respect to lead in the environment of man, is not whether there is more or less lead, per se, but whether the quantities are within limits that do not tax, unduly, the physiological mechanisms of the human organism for coping with them. The physiological responses to lead in the general environment (excluding occupational and other unusual types of exposure) of ordinary citizens of the United States are adequate, and the only valid question to be raised and answered, is whether the level of concentration of lead in the body, incident to the stream of lead in and out and through the tissues, is actually or potentially harmful. Simple apprehension, because lead has so long been known to be dangerous under various poorly assessed conditions, may give rise to the belief that it may be, and therefore probably is, harmful in any quantity. The facts of physiological research and clinical medicine speak otherwise. The toxic effects of the absorption of sufficiently large quantities of lead, in certain of their more obscure manifestations, are appreciated more fully, in biochemical terms, than they have ever been previously, and the conditions of dosage and time, under which lead poisoning occurs in the infant or adult, have been clarified to such a point that gross differences are now discernible between the quantities associated with toxic effects, and those which gain entrance to the individual from the sources in the general or common environment. There are, at present, clinically and statistically valid expressions of a dangerous degree of absorption of lead in the individual. (There is more than one, but I choose the most precise). I have never seen a case of lead poisoning from the absorption of the inorganic compounds of lead, in an untreated child or adult, at the onset of illness, i.e. in immediate temporal relationship to the period of absorption, whose whole blood contained less than 0.08 mg. of lead, when analysed by methods (in parallel) of a sensitivity and accuracy equivalent to those employed in the Kettering Laboratory since 1938. (It should be taken into account that the body burden of lead, as represented by this

concentration of lead in the whole blood of persons who have not been subjected to chelation therapy, and who have not been poisoned by a very brief period of extraordinarily high dosage, ranges from 4 to 20 times that of persons in the general population). The differences, then, between the quantities of lead, in terms of dosage or of body burden, that are associated with lead poisoning, and those that are represented in the general environment or in the bodies of persons in the latter environment, are not small (in relation to the methods of measurement), nor do they overlap, nor are they likely to be confused by knowledgeable persons.

Dr. Patterson would have done well to have examined the available information more carefully, before making the astonishingly dogmatic (and absurd) statement that "the threshold for damage concept as it applies to lead, is an ill-defined opinion unsupported by any (italics mine) evidence". The facts, set forth clearly in medical literature, are that the periodic investigation of the content of lead in the industrial environment, hand in hand with a meticulous search for clinical evidence of frank or vague illness attributable to the absorption of lead, in association with periodic investigations of the lead content of the feces, urine and blood of workmen, has disclosed definitive relationships between the chemical findings and the incidence of lead poisoning in any detectable form. The "Threshold for damage concept" in action, on the basis of many years of experience in many industries that make use of lead, predicts that no case, not even an occasional mild case, of lead poisoning will occur, unless the physiological threshold value is exceeded. (The threshold value for lead in the air of industrial establishments is not dependable to this extent, for the reason that it does not apply to the total environmental hazard but only to its respiratory component).

The threshold value of lead in the ambient air of a community has a different basis in time than that of industry, that is, it is essentially continuous, rather than intermittent, and so it must be worked out by a different experimental method. On the other hand, the composite physiological evidence of the extent and significance of the exposure to lead is the same in the general as in the industrial population, so that danger can be detected and anticipated, by properly designed surveys of representative groups in the population. Such surveys, five of which have been made since 1927, including the last in 1961-62, made jointly by representatives of the United States Public Health Service, the Departments of Health of the City of Philadelphia and the State of California, and the Kettering Laboratory, have found no evidence of any current threat to the health of representative urban populations in the United States. The basic physiological investigations of the past thirty years have given these surveys validity which the data concerning the lead in the atmosphere and the lead in the blood of the subjects, could not, of themselves, have claimed. In their composite weight, they show that there is no present threat to the health of the population of the United States from the quantities of lead which occur (within well documental ranges of concentration or quantity) in the food and beverages and in the ambient atmosphere of [redacted] our communities. They have indicated, further, the wisdom of measures of control that are now being exercised by certain governmental, industrial and professional agencies, and the benefits of the educational efforts that have brought improvements in

the production, handling and processing of foods and beverages in the United States. Experience has shown that there is a continued need, moreover, for a constant alertness in hygienic circles, for the avoidance and control of many of the potential hazards of a technological society.

Finally, let me say, in terminating these unusually lengthy and detailed comments, lest it appear that I am critical of the editorial policy that has presented this paper to a scientific and professional audience, that such is not the case. The substance of Dr. Patterson's paper has been circulated in private communications, and presented to at least one official agency, so that it had more than a little impact, in professional and lay circles, before its formal publication. It was essential, I believe, that it be brought into the open for professional appraisal, and it would seem that the Archives of Environmental Health is an appropriate place for its publication.

Faithfully yours,

Robert A. Kehoe, M.D.