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COLLEGE OF MEDICINE
DEPARTMENT OF ENVIRONMENTAL HEALTH

KETTERING LABORATORY
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September 11, 1968

Mr. Carl Thompson, Senior Vice President
Hall and Knowlton, Inc.
150 East Forty-Second Street
New York, New York 10017

Dear Mr. Thompson:

Pursuant to the promise in my letter of July 5th, in responding to yours of the first, I am citing some references to pertinent literature, and am sending you certain reprints.

I send also a copy of the monograph of Aub, Fairhall, Minot and Reznikoff, which, published in 1926, was the gospel according to Harvard and, in the minds of many, few of whom have read it at any time or recently, continues to be regarded as a monumental piece of work. Let me say that it represents a very stimulating bit of interpretation, despite the incorrectness of the principal thesis concerning the "mobilization of lead," so that there is some justification for its acceptance aside from its origin in the Harvard Medical School. I think you should examine this as completely as may be necessary to learn the state of the analytical methodology of the time, and to perceive the comparison of the knowledge of the time with that now available. This may be a chore for you, and if I am posing an unreasonably difficult task, you will, I am sure, appreciate my purpose. I think it would be difficult to obtain a copy of this book at present. It belongs to the library of the Laboratory and should be returned.

I am also sending you a volume which I put together many years ago for consultants of Ethyl Corporation, comprised of a series of published articles from the Kettering Laboratory, together with the "Regulations" relating to mixing operations. Reprints of the publications are now out of print. Moreover, the copies of this that were distributed, have disappeared into limbo for the most part. I had four volumes a little while ago (several years), but this is my last copy. Please be careful of it and return it as soon as it has served your purpose. I call attention to certain parts of it that will probably be of interest to you in connection with various aspects of the matter about which you inquired, as follows:

Page 289. Note the protest of Fairhall as to criticism of his analytical methods, despite the fact that the time these data were published, the methods had been found wanting by several investigators. He did not admit his error until many years later, and then only partially. I mention this only because this high-handed tenacity was a factor in the persistence of the thesis about "mobilization." The comments in the preceding articles with respect to the analytical method were not unduly critical, so that Fairhall's reaction to them was indeed an over-reaction. This note of his was published because the Journal in which we published was edited at Harvard by Phil Drinker. Fairhall literally badgered him into the insertion of this note, within the articles, at the time of their publication - a procedure which was certainly very unusual. He even undertook to prevent their publication in J.I.H. to which Drinker would not agree. The real issue, of course, was the matter of finding lead in virtually everything and everybody, against the statements and the discussion in the monographs of Aub et al. See pages 55 and 56.

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Page 320. This article gives the early graphic evidence of the continued excretion of lead in the urine of persons without unusual exposure to lead, and the greater excretion in the urine of persons who had been exposed but now under observation were eliminating that which had accumulated. It is obvious, considering the distribution of lead in the body (90 percent or more in the skeleton) that most of the excreted lead was being released from the skeleton of the previously and severely exposed persons. The meaning of this, of course, is that the skeletal lead is not "locked up" or so bound chemically as to be inert, but is participating actively in the metabolic process whereby it is being lost from the body, after the exposure which induced its absorption came to an end. This was the first concrete evidence submitted to demonstr that lead in the bone "mobilizes" itself - that is, is metabolized physiologically. The question thus arises - can this process be speeded up by chemical means? We attempted to do this by the methods proposed by Aub et al. (see Chapter IX, page 98 of monograph). Especially the summary. Note that the experimental evidence in support of the hypothesis of "deleading" was obtained not from analysis of the urine (for which the analytical methods were insufficiently sensitive), but by analysis of the feces in which the lead found is due to the ingestion of lead in food and beverage The liver, fed as a part of the low-calcium diet, is higher in lead than any other tissu in the animal organism with the exception of the skeleton.

Now for the examination of the therapy for mobilizing lead, as advocated by Aub et al. The trials applied to patients have not been published, and I see no reason for publishing them, in view of the information available from observations made experimen ally on human subjects. In the latter connection, I am sending you two other publications. The one is the smaller of two blue paper-back publications, entitled "Lead Poisoning Symposium," in the last article of which there are recorded, briefly, the results of a series of observations on the intake and output of lead on the part of an experimental subject in whose case a series of dietary changes were introduced in our effort to promote singificant changes in the loss of retained lead from the body. You will note the text beginning with the last (incomplete) paragraph on page 76, and extending on through page 77 down to the last (incomplete) paragraph.

On page 78, first complete paragraph, beginning with the words "During the fifty-seventh month," is a brief description of an attempt to promote the "mobilization" of the approximately 110 milligrams of lead that had been retained during the entire period of the oral administration of lead, by the use of the method advised by Aub, namely - the administration of ammonium chloride (to produce a shift in the acid-base equilibrium of the subject) in large dosage over the period of two weeks during which both calcium and phosphorous were held at a low level in the diet. You will note that a slight increase in the urinary output of lead occurred at this time - that is, within this 30 day period, without increase in the concentration of lead in the urine. This occurred during September running into October, when the cooler weather in Cincinnati yielded an increase in the volume of the urine. The response to the "therapy" was utterly negligible.

Note also the marked passages on page 79, which, at that time, were made conservativel Later, more significant observations were made on "leaded" industrial employees with similarly negligible results. (This is very nearly the last copy available, of this reprint. Please return it).

The other "blue book," is a copy of the Harben Lectures in which further reference is made to these same experiments. See top of page 37 et seq. Other evidence of the stabile character of the lead metabolism is presented and discussed. I commend this publication (which you may keep) to you in evidence of the predictable pattern of the

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handling of lead in the human body.

There is an additional unpublished experience relating to groups of workmen in the tetraethyllead plants in Baton Rouge and in Deepwater, New Jersey. In one of the years during which we had a severe epidemic of influenza (I have not bothered to look up the year in my records), we had a degree of concern lest this acute, highly toxic illness should be accentuated by the men who were running relatively high in their urinary lead. Many of the men were ill and unable to work. Their urinary excretion of lead was watched, and good contact was maintained by the respective medical personnel with the employees. There were no fatalities, no complications, no really dangerous cases of illness and do evidence whatever of significant changes in the urinary excretion of lead. (This, of course, is not the same situation as that of men exposed only to the inorganic compounds of lead. However, among those employees were men who worked in the production of alloy where they were exposed to metallic lead and inorganic compounds of lead, and in the furnace area, where much, if not the greater part, of the exposure to lead is of inorganic type.) I have had no hesitation since this experience, in advising all who consulted me, that they need have no special fear of infectious disease processes as factors in the mobilization of lead. I have never had to retract or apolize for this advice.

The references to the public acknowledgment, by Fairhall and Aub, of their inability to reproduce in animals or in patients or other human beings, the "mobilization" of lead, as referred to in their experiments, will be found in the following comments. You can obtain these articles readily in the libraries available to you in New York.

Aub and some of his associates published two articles in the A.M.A. Archives of Industrial Hygiene and Occupational Medicine, Volume 9, 1954. The first of these can be found in pages 9-22, while the second is on pages 113-121. The respective titles are "Comparative Exchange of Calcium Lead and Radioactive Lead in Dogs" and "Migration of Inorganic Salts in Bone as Measured by Radioactive Lead and by Alizarin." This work was done in 1937, but the publication of the articles was delayed until 1954, partly, at least, because Aub found it difficult to explain why the lack of effects of the "deleading" procedure in these experiments was so different from that of the earlier experiments. The reason (which he never admitted in print) was that he and his group were using methods for following the radioactive lead that yielded accurate and readily interpreted results, while his prior work was based on the poor analytical methods then employed and also upon a physiological misconception of the avenues for the excretion of lead from the body. This misconception had existed for many many years and in many minds, so that it is excusable until suitable physiological and analytical methods had been applied to the problem. The error is now readily visible and explainable, but unfortunately, few would-be investigators go back to find and understand the errors of past experimentation and interpretation.

You will find the first of these articles to be worth examining in connection with your question of documentation. Note the data, the "Comment" on page 18, and the "Conclusio especially the second and third paragraphs. The lame attempt at the explanation, seventeen years after the finding of the discrepancy, by which time our balance experiments had demonstrated the facts, is an important feature of the doubts that exist in the minds of many people who have not followed the experimental work in any detail.

The second article may not appear to be of much interest to you, but it is important in demonstrating that the radioactive lead (aside from the effects of radiation on the

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animals) behaved in the body of the animals just like the inert lead. There is not a leg to stand on, therefore, in attributing unusual metabolic behavior to it, in relation to a response to the administration of the parathyroid hormone as a deleading agent. Here is where the work of Aub and Hunter, done years earlier and still referred to by persons who are not familiar with the sequence of events, went down the drain.

An article by Lawrence Fairhall (then in the U.S. Public Health Service, formerly the analyst for the Harvard group) and Paul Neal (a good friend of mine who reported these results to me prior to their publication and also his difficulties with Fairhall) appeared in Public Health Reports Vol. 53, Part 2, pages 1231, 1245, 1954. Fairhall had found it very difficult to adapt himself to the use of the dithizone method of analysis (since his own was faultless), and neither of these men had tumbled, at this time, to the fact that the true excretion of lead in the feces (as compared with that which represented lead in transit in the alimentary tract as the result of the ingestion of lead with food and drink and that administered) was not as great, at times, as that in the urine. Therefore, the importance of the response, if any, of the rate of the urinary excretion of lead, to "deleading" therapy, was not emphasized as it should have been. A look at the third section (from the top) of the graph on page 1238 will show, however, that nothing of consequence happened when ammonium chloride (B) was administered during a period of low calcium intake. Note the second paragraph of the text on page 1232. (The idea died hard.)

You may think that I am being a bit hard on the Harvard investigators, especially on Fairhall, in my comments, aside from those of scientific purport. It may be that this is the case, and, if so, perhaps I can be forgiven for some feeling in this matter in connection with my efforts to reveal the truth in those matters during the past forty years. The more important aspect of the matter is not any wish on my part to promote personal bitterness or past controversies, but is rather the necessity of pointing out the errors in methodology and interpretation which have resulted in certain of the present conflicts of opinion. Any one who does this is being unpleasant and combative, by current criteria of behavior. So let it be.

Sincerely yours,

Robert A. Kehoe, M.D.
Professor Emeritus of
Occupational Medicine

RAK:wp

KE 0007464

July 5, 1968

Mr. Carl Thompson
Senior Vice President
Hill and Knowlton, Inc.
150 East Forty-Second Street
New York, N. Y. 10017

Dear Mr. Thompson:

Your letter of July 1st raises an issue to which I shall respond shortly, in the manner of your request, by supplying you with references, and so far as possible, reprints. This will take a little time of which I am in short supply, at the moment, but I'll get to it soon. The trouble is that the documentation of my statement, which has been well known to some of my colleagues, occurred in bits and pieces some fifteen to twenty years ago and now has to be sought out piece by piece. You will be interested, however, in knowing that both Joe Aub and Lawrence Fairhall (Harvard), who were the instigators of the idea of the mobilization of lead from the skeleton through metabolic disturbances, published later and meager accounts of their failure to verify their original hypothesis.

I think you should know the physiological background of the concept, and of the demonstration, later, that the concept, almost in its entirety, was fallacious. I think you should know also, how the false concept came about. These are matters which very few of the would-be experts on this subject have bothered themselves to review and learn about.

In the early twenties, Joseph Aub, M.D., and his associates at Harvard carried out a series of experimental investigations under a grant of funds from Lead Industries Association. This was before the development of analytical methods of sufficient sensitivity to deal with a few micrograms of lead in any specimen. Consequently, they could not, and did not obtain data on the urine or blood of experimental animals and men. (It was not until the middle thirties that a suitable method for the determination of lead in the blood came to be available.) They were able to determine the presence of lead in the tissues and the feces of animals to which lead had been administered (with reasonable accuracy in the skeletal tissues, since most of the lead was to be found there), but they concluded, mistakenly, and so stated, that lead did not occur in human tissues and excreta unless there had been some unusual type and degree of exposure, as, for example, occupational exposure. They concluded further, only partially correctly, that lead absorbed in detectable quantities found its way into the skeleton, where it remained locked up, so to speak, until and unless some disturbance in the metabolic process in the body "mobilized" it. Such mobilization could be induced in experimental animals (cats mainly were used in their experiments) by a variety of procedures, e.g., the administration of ammonium chloride (to induce a shift in the acid-base balance in the body to the acid side), the restriction of calcium (which tended to call upon the store of calcium in the skeleton and with this the release of lead in the skeleton as well). Other disturbances that would cause major shifts in the acid-base equilibrium of the body could be counted on to have the same effect as the administration of acid. (I should explain that the ammonium in ammonium chlorid is readily metabolized in the body, leaving the chloride to attach itself to fixed bases (Na^+, K^+, etc.) with which it is excreted, thus diminishing the basic elements

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in the body.) By inference, and without adequate supporting evidence, physiologic and disease processes that tend to promote an acidic condition in the body, as fatigue, infectious disease, alcoholism, deep anaesthesia, and such stresses as pregnancy, were believed to induce mobilization, and hence to create the threat of the toxic effects of lead.

The evidence on which this hypothesis was based was that of determining the lead content of the feces of animals to which one or another of the "therapeutic agents" was administered. (It had been believed, up to that time, and actually until our observations had demonstrated the facts in the matter, that lead was excreted solely in the feces, and that there was no necessity for determining the lead content of the urine. Since also there was no grasp of the fact that everything eaten by animals and man contained lead, there was no thought of this as a source of lead in the feces. You can see how easy it is to follow the prevalent view. This tendency was so strong that in the initial field survey of the Public Health Service in 1924-25, no specimens of urine were collected, despite the evidence which Graham Edgar and I had presented in the May Conference. No one believed that these results were valid, because of the prevalent view, and because the Dean of Harvard Medical School ridiculed them /and never had the grace to admit his error/. Thus, the conclusions of the often commended investigation of the USPHS, in 1924-25, which "gave Ethyl a clean bill of health," were based on wholly irrelevant information, except to the extent that their physical examinations confirmed our findings that no of the exposed persons was ill. For obvious reasons, I never pointed out this fact in the literature. I was quite content to accept the "clean bill of health," since I had my own, and much better, reasons for believing it. The fact is that almost no one read the USPHS report, beyond the conclusions and recommendations.)

But to continue from where the parenthesis begins, let me point out that the experimental animals (cats) put on a low calcium diet were fed on liver as their principal dietary component, and that this item was sufficient to yield an appreciable increase in the lead content of the feces. It happens that the liver is relatively high in lead (not so high as the skeleton, but high as compared to other edible tissues). Hence the lead content of the feces of the animals on the experimental regimen (low calcium), as compared to control animals, was appreciably elevated regardless of the other therapeutic agents employed.

There is more to the matter than I have stated above, but this will be enough, I believe, to let you in on the facts. If you are keenly interested, you should read the reports of the investigators. Because this information, published eventually in a monograph, came from Harvard, it made a tremendous impression. Lead poisoning had undergone a monumental clarification. This was indeed, a major effort which deserved due consideration, and you will find that the work is still being commended by people who have no idea how thin the evidence. You may remember how Harriet Hardy defended the Harvard position at the Washington Symposium. There is not a shred of evidence that pregnancy, anaesthetic or infectious disease has ever precipitated a case of lead poisoning, and actually the burden should be on the believer of this hypothesis to adduce proof. Instead, because Harvard has stated the concept forty years ago, the burden has been on the dissenter to disprove the hypothesis. We have done so to the satisfaction of most industrial physicians, and that of all current investigators of the subject, but the idea persists among many clinicians.

As I have said, I'll dig up specific evidence for you in presentable form, but the principal basis for what I've said lies in the physiological facts which have been

emerged from our balance experiments - those tedious, pedestrian observations which have demonstrated the nature of the behavior of lead in the human body over prolonged periods of time. As a physiologist, I found it necessary to do these troublesome and costly experiments in order to find out, once and for all, what happens under the variable conditions of day to day life. Their counterpart, in large groups of persons, young and old, healthy and partially impaired, has been obtained by over more than thirty years of investigation of very large numbers of persons in a wide variety of lead trades. I hope to be able to put this information together within the next few years. It has been too voluminous to handle while I was occupied in directing the activities of the Kettering Laboratory. Therefore, I have put out bits and pieces of "skimmed off cream" in several papers, principally in the Harben Lectures, which I felt compelled to assemble, when the opportunity was presented to do so, by the invitation of the Royal Institute of Health and Hygiene in London in 1960. If other matters would stand still long enough for me to get solidly at this job, it would be much easier for me to answer such questions as yours (and many others) in a documentary manner, rather than in ex cathedra statements. This is by no means a "nasty crack" at you, nor indeed at others who raise questions that require documentation. It is simply an expression of dissatisfaction at the state of many affairs in this troubled and troublesome time in which we live. There is hardly time to ponder, much less to set down in proper form the observations of most of a life time. People who know little, or at least too little for the purpose, continue to speak and to write and to make it necessary to do what reasonably and appropriately can be done to offset their shortcomings.

For example, I have just received a journal, SCIENCE AND CITIZEN, published by a Committee for Environmental Information, 5144 Delmar Blvd., St. Louis, Mo. 63108, said to be an official publication of SCIENTISTS INSTITUTE FOR PUBLIC INFORMATION (30 East 68th Street, New York 10021). The present number, Volume 10, No. 3, April 1968, is devoted entirely to lead, and is an excellent presentation of one side of the issue, with some slight attempt to present the other side. It came with a courteous letter from a Staff Writer, Joseph D. Salvia inviting me to comment on it. This, of course, I cannot do for publication. I refuse to be put on the defensive or to be involved in any other than a straightforward scientific discussion with scientists, unless there is an official (governmental) issue which must be met in a manner that is dictated by an agency or representative of government.

But enough of this. I am sure that you are aware of the problem. I am just a bit too sensitized by some aspects of it to sit quietly and patiently for time to work its way.

Sincerely yours,

Robert A. Kehoe, M.D.
Professor Emeritus of
Occupational Medicine

RAK:wp

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CARL THOMPSON
Senior Vice President

ENVIRONMENTAL HEALTH UNIT

July 1, 1968

Robert A. Kehoe, M.D.
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College of Medicine
University of Cincinnati
Cincinnati, Ohio 45219

Dear Dr. Kehoe:

In discussing this problem with Don Fowler at Lead Industries Association, Inc., he suggested I write you directly since you and I have had several conversations and associations relating to the lead problem.

As you undoubtedly know, there has been a resurgence of suggestions of health hazard resulting from alleged accumulation of lead in the bone. As an example, see the attached recent clipping from the Washington Star.

In your comments published in the Journal of Occupational Medicine, February 1968, there is this observation:

> "The author presumes that changes in body pH and/or negative calcium balance shortly before his illness resulted in the outpouring of lead from bone into circulation to cause his acute illness. The hypothesis of the 'mobilization' of lead from the skeleton by such metabolic disturbances has been discredited these many years, and can now safely be said to be entirely fallacious."

I refer particularly to the second sentence and would like to know if you could give me one or two specific references of either your own or someone else's work which relates to the discrediting of the hypothesis of mobilization of lead from the skeleton. It's very possible that a memorandum based on the scientific literature could be very useful if there is continued suggestion that lead accumulation in bones is established as a health hazard.

I hope that you will be able to help us on this without imposing too much on your time.

Sincerely,

Carl Thompson

CT:sdd

cc: Mr. Don G. Fowler

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THE EVENING STAR
Washington, D. C.
May 27, 1968

(front page)

POISON FROM THE AIR

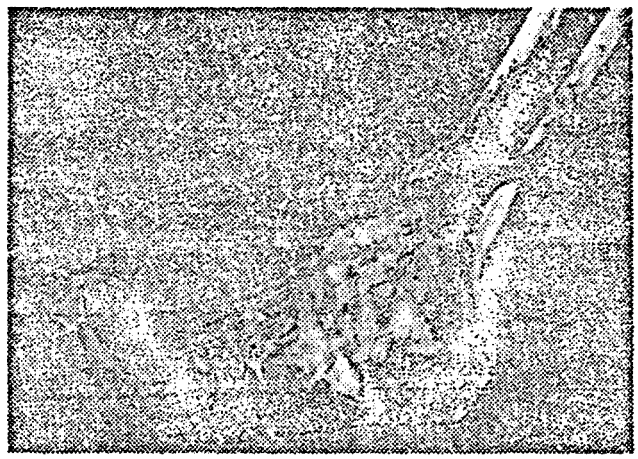
There's More Lead in Us

By JOHN LANNAN
Star Staff Writer

Modern Americans appear to be accumulating up to 10 times as much lead in their bones as some of their primitive forebears.

What it may mean for the future no one can say, but equivalent accumulations in birds and animals are poisonous, according to the experts.

Findings of increased concentrations over the centuries were first reported in the Journal of Bone and Joint Surgery in March. They were based on analysis of bones of modern residents of Syracuse, N.Y., and the mummified remains of ancient Peruvian Indians.



1,000-year-old foot from the sands of Peru.

Other unpublished studies, buried until now amidst reports on other trace metals, indicate that current phenomenally high lead levels are apparently peculiar to Americans. They are based on comparisons with modern human bone samples from the less industrialized Far and Near East.

The Peruvian study was the work of Dr. Robert O. Becker, director of research at the Syracuse Veterans Administration Hospital, graduate student Joseph Spadaro and Dr. Edward M. Berg.

In an interview, Dr. Becker said he believes the Syracuse bone content "is no doubt derived from the lead content of the air.

"Lead is a cumulative poison," he added, "and there is no doubt in my mind that since we feel lead atoms in the bone occupy a functional position that the increase will, if it has not done so already, lead to disease."

The lead showed up in a routine study of trace elements — those elements found only in mere traces — of bone. Dr.

See LEAD, Page A-6

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LEAD

The Poison From the Air

Continued From Page A-1

Becker and his associates are involved in long-term study of the mechanisms of growth and healing and were looking primarily for traces of copper in modern bone.

Mummies Unearthed

In the course of their investigation, Dr. Berg came up with the 1,000 year old mummified remains of several Chancay Indians. Their bodies had been buried on Peruvian sands where it has not rained in the memory of man.

Extreme dryness prevented the bones from leaching their minerals into the soil and also forestalled the reverse process.

Spectrographic analysis of the bones showed the ancients had fewer than five parts per million of lead in their solid tissue.

Modern Syracusans had anywhere from five to 110 ppm.

The analyses correlate with an earlier series done by Dr. Isabel Tipton and Jane P. Shafer. Dr. Tipton is a professor of physics at the University of Tennessee. Their findings had been part of an undistributed Atomic Energy Commission report, overlooked since 1964.

Multiplied Intake

Their spectrographic analyses showed that American males have a mean of 50 parts per million while comparable adults from the Far East (Japan and Taiwan) had fewer than 30. Those in the Near East (Bombay, Delhi and Beirut) had fewer than 10.

Dr. Tipton's research on lead and 25 to 30 other trace elements also disclosed that men have more lead in their bones than women, 30 parts per million versus 50 for males.

"It's a function of their exposure," she said yesterday. "Men are outside, driving. They breathe more of it."

Lead has been a big issue in air pollution circles since 1955 when Dr. Clair Patterson of California Institute of Technology published a report showing lead, presumably airborne and the product of modern engine fuels, was present in Antarctic glacial deposits.

Under a subsequent change in the Air Quality Act of 1967, all fuel additives, such as lead, must now be registered with the government as federal investigators attempt to determine the extent of their use and potential effects.

Industry Reports

No one is either willing or equipped to say what effect lead has on humans at present levels. The Lead Industries Assn. Inc., in a current publication called "Facts About Lead And The Atmosphere," says:

"All studies conducted by government, university and other research groups have shown that the levels of lead in the general or ambient air are low and no not constitute a health hazard."

However, these same studies do not prove that it is not a health hazard either, say the trace element experts.

Dr. Henry A. Schroeder of the Dartmouth Medical School Department of Physiology has shown that lead concentrations equivalent to those found in humans do affect small animals.

Animals Tested

He has established that rats and mice die younger, age earlier and are more susceptible to infection if their tissues are lead permeated.

However, animal experiments are not alwas directly applicable to men, even the animals show no specific clinical effects, except for ducks who absorb lead from spent shot.

Dr. Schroeder, on of the country's leading researchers in the trace element field, feels that there is only one major source of lead intake for humans — the air.

He is also about to publish a paper refuting the idea that lead does not accumulate in the body.

Others, particularly those involved with lead blood level studies at the University of Cincinnati's Kettering Laboratory, have long felt that lead reached a certain limit then went into "a lead balance" in which further intake is balanced by excretion.

Of the Syracuse historical study, he said: "it's extremely interesting. I've been waiting for someone to do it. I was going to try it myself ... with bones from the Catacombs or someplace."

Source Defined

Dr. Schroeder says that at current production and distribution rates that "two pounds of lead for every man, woman and chld in the country go into motor fuel every year. One pound apiece comes out the tailpipe and falls on the ground or goes into the atmosphere. This is the obvious source of ncreased lead uptake by the body."

He also argues that 5 to 10 percent of the element eaten with food, beverages etc. is absorbed. Some 50 percent of that breathed in through the lungs is also retained.

In congested cities, at least half that retained comes through the lungs he insists.

Of all the lead ingested, 91 percent lodges in the bones, Dr. Schroeder says, "and if it stayed there, it wouldn't be toxic to the rest of the body. But we don't know what mechanism mobilizes lead into the blood or what it does once it gets there."

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