U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE CENTER FOR DISEASE CONTROL
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

HEALTH EFFECTS OF *OCCUPATIONAL LEAD and ARSENIC EXPOSURE* A SYMPOSIUM

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A SYMPOSIUM

Edited By

Bertram W. Carnow, M.D.
University of Illinois School of Public Health
Contract Number 210-75-0026

Chicago, Illinois
February 24-25, 1975

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health
Division of Surveillance, Hazard Evaluations and Field Studies

February 1976

For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

SPONSORED BY: Society for Occupational and Environmental Health
National Institute for Occupational Safety and Health
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SUPPORTED BY: National Institute for Occupational Safety and Health
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HEW PUBLICATION NO. (NIOSH) 76-134

The Editor or his staff prepared abstracts of the presentation when they did not accompany the author's manuscript.

PREFACE

The National Conference on Health Effects of Occupational Lead and Arsenic Exposure was convened to consider the impact of these metals on the health of workers. It brought together researchers, workers, union representatives, medical and engineering specialists, industrial hygienists, representatives from industry, and others in the field of occupational and environmental medicine to evaluate studies that have been carried out and to review the state of knowledge regarding the health impact of industrial lead and arsenic exposure. A primary purpose of the conference was to assist the National Institute for Occupational Safety and Health in establishing levels for these materials which will help to provide a safe work environment.

While the intent of the conveners was to consider the acute, subacute, and chronic effects of lead and arsenic, it was hoped that similar approaches for examining safe levels of other toxic substances in the workplace would be discussed and that the question of what constitutes a safe level for carcinogens, such as arsenic, would also be considered. It was anticipated that a consensus regarding solutions to some of these problems might emerge during the proceedings.

ACKNOWLEDGMENTS

Recognition must be given for the participation of Edward J. Calabrese, Ph.D., D. Ed., who acted as Assistant Coordinator of the Conference, and to Badi Boulos, M.D., Ph.D., Binyamin Lebovits, Ph.D., Alvin Miller, Ph.D., Sally Jansen, MPH, Rodney Musselman, MPH, William Kojola, M.S., Alfred Sorenson, M.S., Janine Roumain, B.A., and Edward Diersen, B.S., members of the faculty in Occupational and Environmental Medicine at the University of Illinois School of Public Health, for their assistance with the planning, coordination, and development of program for the Conference.

Acknowledgment for their advice and assistance in carrying out details of the Conference is also given to Judy Padour, R.N., Respiratory Disease Specialist, and Allan Shaw, A.R.R.T., Executive Officer of the Department of Medical and Professional Research, of the Chicago Lung Association, Victoria Bor, Associate Executive Director of the Society for Occupational and Environmental Health, and Mildred Evans, Administrative Aide, of the University of Illinois School of Public Health.

Special acknowledgment must also be made for the efforts of Patricia Schaffner, who assumed the major responsibility for gathering together and organizing the material for the proceedings, and to Olivette Wright, Vicki Roth, and Ruth Dawe for their assistance in typing, proofing, and assembling this material.

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WELCOMING ADDRESS

Dr. Paul Peterson, Dean
University of Illinois School of Public Health

I did not expect to see so many of my old friends and acquanitances in the audience. It is a great pleasure that you have all seen fit to take time from your busy schedules in order to join with us in this conference. As Dr. Carnow has indicated, we in Chicago try to welcome all of our guests with things that make their stay interesting. We had rain for you last night, we understand snow is coming today, we have a lesson in civics that is going on with the last day of the mayoral campaign, and tomorrow the election.

I think it is particularly fitting that this conference is attacking the problems of arsenic and lead, two chemicals in our environment that have been known, abused, and used for many, many generations. We are still struggling with the problems that they present to us. I am sure that this conference will add a dimension of understanding and provide new material for decision makers in health affairs that will be helpful in the decisions that must be made, as we face tomorrow's problems of health.

The School of Public Health is honored to have the privilege of participating with the other sponsors of this conference, and if there is anything we can do to make your stay more pleasant, we certainly will be anxious to do so. I know you are going to have a great conference, it is a great privilege and pleasure for us to participate in this with you.

CONFERENCE CHAIRMAN - Dr. Carnow

Thank you, Dr. Peterson, and now we will have a few words from Dr. Samuel Epstein, who is President of the Society for Occupational and Environmental Health.

CONFERENCE PREVIEW

Dr. Samuel Epstein, President
Society for Occupational and Environmental Health

Dr. Carnow, Dr. Peterson, ladies and gentlemen, I would like to welcome you, on behalf of the Society for Occupational and Environemental Health, which has sponsored this "National Conference on the Health Effects of Occupational Exposure to Lead and Arsenic."

I first of all would like to acknowledge the much appreciated co-sponsorship of the National Institute for Occupational Safety and Health (NIOSH), the Industrial Union Department of AFL-CIO, The United Church Board of Homeland Ministries, and the Chicago Lung Association. Some of you may know that we plan to publish the proceedings of the conference. Our planning and publication of the proceedings of this conference have been made possible by generous financial support from NIOSH, which should again be acknowledged. I should also like to acknowledge the generous and warm assistance of the University of Illinois School of Public Health for acting as the host and planning organization for the administration and program arrangements.

Dr. Peterson was too modest to talk about this new school, but I might mention that the school is only about two years old and in the course of two years, has developed a very important role in the field of Occupational Health and Safety.

The conference planning committee, under the leadership of Dr. Bertram Carnow, has performed superlatively, and is composed of Dr. Edward Calabrese and his staff, Mr. Richard Lemen from NIOSH, Dr. Vaun Newill from Exxon Corporation, and Mr. John Zalusky from the Allied Industrial Workers of AFL-CIO. Those of you who are familiar with the policy of the Society for Occupational and Environmental Health, know that, in general, we attempt to insure balanced representation from management, labor, academia, and government in every conference planning committee. The planning committee for this particular conference was no exception to this requirement for balanced representation.

Preliminary discussions relating to the critical need to establish a National Conference on Occupational Exposure to Lead and Arsenic, which formed the basis for this conference, started about July of last year between Dr. Carnow and various officers of the Society. However, we were unable to proceed with definitive planning for the conference until early December, when Dr. Joseph Wagoner advised that NIOSH was able to fund the meeting; so actual details for planning the meeting started about mid-December. From mid-December to the present date is basically all the time that Dr. Carnow and his committee have had to organize this meeting, and I think that without the enthusiasm of Dr. Carnow's planning committee,

in particular the assistance of his secretary, Mrs. Patricia Schaffner, and Miss Victoria Bor, the Assistant to the Executive Director of the Society, Dr. Henry Heimann, this conference would not have been possible.

You will see from the program that we have scheduled a full, two-day meeting. The first day is devoted to lead and the second day to arsenic. There is a certain symmetry to the program on both of these days, insofar as the first set of each sessions deals with sources and monitoring, followed by sessions on toxicology, and a final session on epidemiology. In addition to this symmetrical distribution of themes, there are three major sub-themes, which I think will be repeatedly raised in the course of the next two days. These themes are: low level lead toxicity, with particular reference to neuro-behavioral effects; epidemiological studies on chronic lead toxicity; and epidemiological studies on the carcinogenicity of arsenic.

Now, over and above the fact that it has been apparent for sometime that a meeting of this kind was cri' 'cally needed, there have been certain recent events in the last two months that have underlined its topicality. These events relate not only to the occupational aspects of lead and arsenic exposures, but also the environmental aspects.

As far as lead is concerned, there are two events, which I think are noteworthy and on which, perhaps, we may enter into some discussion at an appropriate time in this meeting. First, the regrettable decision by the Consumer Product Safety Commission to maintain lead levels in paint at 0.5 percent, based on recommendations by an advisory panel of the National Academy of Sciences (NAS). Second, the recent decision in the Ethyl case, in which the courts, in my mind unreasonably, ruled that the Environmental Protection Agency (EPA) acted capriciously and arbitrarily in promulgating the "phase-out regulations" of lead in gasoline, clearly implying that the burden of proof for demonstrating hazard rests on the agency and not on industry.

As far as arsenic is concerned, the debate on the appropriateness of the proposed new occupational standards on carcinogenicity of arsenic is being vigorously debated at the moment. Another reason for the topicality of the arsenic theme is the recent disclosures on the carcinogenicity of arsenic in the Yellow Knife Community exposure.

So, I think we have, in the consideration of lead and arsenic, two themes that are of critical scientific and regulatory interest, and I hope that the conference will shed some illumination on both of these themes.

At this stage I would like to turn the meeting over to Dr. Bert Carnow, who, I believe, wants to develop some guidelines for the speakers. Thank you.

OPENING REMARKS-Dr. Bertram Carnow, Conference Chairman

Thank you Dr. Epstein.

As you know, this conference was brief in the making and consequently there have been some changes which you should note in the program. The first session on Sources of Lead will be moderated by Dr. Vaun Newill, who, I am sure, will be able to deliver a prepared speech, since he has had approximately ten minutes since being notified that he is to chair the session.

Participants will have an opportunity to get to know each other during luncheon today, since there will be no speaker. Tomorrow, however, we are fortunate in having Mr. Timothy Cleary, Chairman of the Occupational Health and Safety Review Commission. He replaces Mr. Sheldon Samuels who was not able to be here. Dr. Stephen Krop was also unable to attend and he has asked permission to send a replacement for the Panel Discussion on the Problems of Application scheduled for 3:45 pm today.

Tomorrow, Mr. Richard Lemen of the Division of Field Studies and Investigations at NIOSH will chair the first session on Sources of Arsenic, Monitoring the Workplace and Problems Involved. Dr. John Goldsmith of the National Cancer Institute of the National Institute of Health will present the final summation, Conference in Perspective, since Dr. Irving Selikoff will not be able to be here.

Now regarding the discussions, speakers have been limited to ten to twelve minutes in most cases. This may seem like a short time but it will permit speakers to synthesize their thinking on these important questions, and this is what we have asked them to do. We are interested in obtaining a concensus, if possible, at least a review, of the ideas of leaders in the field who all are represented here in the group of speakers.

This light is to assist speakers. It is green for ten minutes, then becomes yellow for two minutes, and then the red light goes on. The speaker should stop then or there is an iron claw that comes out and attacks you. This was planned because we want to encourage participation from the audience. This is a working conference and everyone is here to participate. We are, however, limiting questions or statements to one minute. If you have additional questions or statements, you may write them out and present them to us and if they are reasonable in length they will be included in the proceedings.

I think with this beginning we can move on to our first group of panelists, so here is Dr. Vaun Newill, who is moderator of this panel.

SESSION I SOURCES OF LEAD IN INDUSTRY, MONITORING OF WORKPLACE, AND PROBLEMS INVOLVED

Dr. Vaun Newill, Moderator
Exxon Corporation

As you heard from Dr. Carnow, I was given a long time to prepare introductory remarks for this panel. We all know that lead is an extremely ubiquitous element; particularly those of you who work in the laboratory are aware of this as manifested by the easy contamination of samples during analysis for lead content.

Lead has been in commercial and industrial use since near the beginnings of civilization, and still enjoys rather wide usage within present day industry. Thus, it is extremely appropriate that we address ourselves to the health effects of lead and lead compounds exposures. However, rather than take time from the panelists with my unprepared remarks, I would like to get on to their presentations.

The first speaker is Mr. Kenneth Nelson, Vice President of Environmental Affairs of the American Smelting and Refining Company. Mr. Nelson.

INDUSTRIAL HYGIENE OF LEAD PRODUCTION
A BRIEF REVIEW

Kenneth Nelson*
American Smelting and Refining Company

A B S T R A C T

Lead is mined as a sulfide compound and recovered as the impure element by pyrometallurgical methods. Lead intoxication has not been a problem in the mining, milling, and concentration of sulfides; however, smelting generates dust and fumes which must be controlled. While monitoring airborne lead is useful to measure the potential exposures and efficiency of exhaust ventilation equipment, biological monitoring of exposed workers is essential for early detection of excessive absorption.

It is astonishing that there is such tremendous interest in lead and this has continued to increase. It might be useful for just a couple of minutes to tell you how we get our lead. It occurs in the Midwest, in the lead belt of Missouri and Kansas, and in the mountains west of there in underground mines. Concentrations of lead in ores are about 6 to 7 percent and usually zinc is also present. The ores are mined, crushed, milled, and upgraded to a concentrate of about 60 percent lead content as a sulfide. Then these concentrations are shipped off to a smelter where the lead is separated from the sulphur by a series of chemical reactions. Crude lead, which contains some dissolved metals, is further treated in a refinery by various procedures and the end product is a rather pure lead. Pure lead forms beautiful crystals on cooling and it has some attraction as a metal.

Having been refined, the lead is delivered to various industries for ultimate use. The major use of lead is in the production of storage batteries. Another use is as lead additives for gasoline. Other uses include type metal, cable sheathing, solders, and in brasses, which ordinarily contain 5 percent or more of lead. Lead is used primarily as the oxide in batteries and in other formulations. Red lead paints use lead oxides and these paints have enjoyed great popularity over the years because they give excellent protection to steel against corrosion.

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**Mr. Nelson has been interested in lead for 35 years and has been associated with a company producing lead for the last 30 years.*

Concerning occupational exposure of workers in the mines, this lead is a sulfide, and so far as we have been able to determine, this lead is not absorbed. To my knowledge there have been no cases of lead intoxication or excessive lead absorption among sulfide lead miners. During the old days, when lead deposits were found near the surface of the ground, the lead occurred as oxide and carbonate. These compounds are readily absorbed and the dust generated in mining, crushing, and milling of this material did cause lead intoxication in great numbers of lead miners in the early years of this century.

A story told to me by a physician who was practicing medicine in the Utah area in the early 1900's related that at one time, because of oxide-carbonate lead mining and the number of lead smelters in which there were no controls for dust and fumes, there were literally hundreds, even thousands, of disabling lead intoxication cases each year. This physician spoke of beds having been placed in the corridors of hospitals to accommodate the excessive number of patients who were ill from lead intoxication. That was a long time ago, of course, and conditions have changed markedly. Such things do not exist any more.

In smelting and refining lead, of course, there are exposure and there are also opportunities for dust and fume generation. Lead is readily voltaile and the various operations must be well controlled or exposures to lead could be excessive.

The casual melting of lead poses no problem. I have often observed inspector's worrying about lead concentrations around kettles containing molten lead, or pots in which solder, babbit, or type metal is melting. However, unless the lead in these pots are over heated and begin to volatilize, there is really no problem. We have verified this again and again through sampling. However, should the lead reach a temperature where there is a significant amount of surface oxidation, drossers will be formed and in the periodic skimming of these drossers, dust will be generated, and dust control precautions must be taken.

In handling dry battery oxides, or any dry inorganic lead compounds, there are of course opportunities for exposure. One of the most common exposures, and perhaps one that is often overlooked, is caused by welding or burning lead painted or lead coated steel, lead painted surfaces, or lead alloys. There are leaded steels which contain appreciable percentages of lead, and welding or burning this material will cause voltilization and potentially dangerous exposure.

Concerning air monitoring; when I first started monitoring lead we used the ancient and honorable Mine Safety Appliance Company's electrostatic precipitator, the ancient and honorable Greenburg-Smith, or the midget impinger. After World War II, we began to use a filter paper type samplers. This sampler consisted of an ordinary laboratory filter paper between two halves of a device to hold it secure, with air pulled

through the filter paper by means of a small Westinghouse vacuum cleaner, which measured the air flow by an orifice at the entrance to the apparatus. Using this awkward but worthwhile piece of equipment, we measured air concentrations of lead all around our smelters and refineries and, as much as possible, in the breathing zone of workmen. However, it was a hard job and one could only get limited data in any given day. Nevertheless, we carried on this type of activity over the years in industrial hygiene surveys.

About the mid-50's, Hemeon developed a tape sampler which we quickly adapted to measuring lead concentrations in smelters and refineries. This was very useful equipment, because it gave hour-by-hour concentrations of lead over 24-48 hour periods, or for any length of time we wished to operate the sampler. Now, of course, we have personal samplers which are more useful. Indeed, we get a much better estimation of individual exposure, although we do not measure actual intake, as I'm sure you're aware, because of particle size problems, solubility problems, etc. Still the personal sampler is a giant step forward in obtaining accurate estimations of exposure.

My time is limited so I must merely say that air monitoring has its uses, of course, in identification of areas where lead concentrations are excessive, how well ventilation equipment is working, and many other aspects of the work environment. It does not, however, in my opinion, compare with biological monitoring in protection of the lead worker. There will be a full discussion on this so I won't go into the details. I must add that during the past 30 years of the formal industrial hygiene program in my company, we have come to the inevitable conclusion that biological monitoring is the way to be certain that lead absorption among workers is not excessive. Air sampling can be very misleading. Indeed for some jobs, in our operations at least, air samplings would show safe lead levels one day and hazardous lead levels the next. Some men move all over large areas doing maintenance work and it is very difficult to establish and maintain clean air in all of these circumstances. Hence, we must measure the absorption of the individual by biological monitoring to make certain that his lead absorption is not excessive. I know there will be much debate about this later on, so I won't go further into it. I'm sorry but due to a shortage of time my slides shall remain unshown. Thank you.

MODERATOR-Dr. Vaun Newill

Thank you Mr. Nelson. We will have to see your slides later. Let us proceed with the second speaker on our panel. Dr. Paul Caplan, Deputy Director of the Division of Technical Services at NIOSH. Dr. Caplan.

MONITORING OF WORKPLACES FOR LEAD AND PROBLEMS INVOLVED

Dr. Paul E. Caplan*
National Institute for Occupational Safety and Health

A B S T R A C T

Biological and environmental monitoring of occupational exposures to lead have been well evaluated and documented for more than 30 years. The safe level of exposure for lead dust and fumes has been firmly established to be of the order of 0.15 mg/cu m. Recent studies by NIOSH have shown high exposures, up to 34 mg/cu m and average 3-hour exposures up to 25 mg/cu m, in police firing ranges. Studies of basic lead production, sintering of lead alloys, and spraying of lead chromate paints found high levels of lead both environmentally and by whole blood bioassay. It is reiterated, as Dr. Robert Kehoe stated 28 years ago, that the hazard of lead poisoning is not controlled by the physician, not by prophylactic medical therapy, but substantially by controlling the environment to known safe levels.

It is a pleasure to meet with you this morning to discuss the environmental and medical aspects of exposures to lead in the workplace and some basic industrial hygiene and engineering control considerations. In preparing for this presentation, many reports, papers, and articles on the subject of lead exposure, evaluation, and control have been reviewed and an unfortunate conclusion was evolved. In all the regular journals that industrial hygienists review, there are many articles on recognition of the disease entity, lead poisoning, the biological indices, or the relative merits of blood and urine lead levels, ALA levels, coproporphyrin, etc. Equally as many articles on evaluation of the work environment techniques, relative value of personal samplers *versus* area samplers, respirable lead or total airborne lead, as well as many articles on analytical techniques, such as atomic absorption, activation analysis, dithizone, or polarography, plus the statistics of sampling strategies. Yet, very little has been said or written on the engineering control of this known hazard, and I would like to direct some of my remarks to this subject.

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**As a member of the TLV Committee of the American Conference of Governmental Industrial Hygienists, Dr. Caplan was given the assignment to collaborate with Dr. Hector Blejer in preparation of the documentation for the presently recommended TLV of .15 mg/cu m for lead. One of Dr. Caplan's first assignments as an industrial hygiene engineer for the California Bureau of Occupational Health 25-years ago was to evaluate lead exposures at a major battery plant in Southern California and to recommend a satisfactory ventilation system to control lead dust and fumes. Dr. Caplan is a registered chemical engineer in California.*

First, however, I shall briefly present some environmental and medical data that the Division of Technical Services of NIOSH has found in our investigations of the past several years. Our Industrial Hygiene Services Branch and Medical Services Branch have conducted investigations of five police indoor firing ranges in various locations around the country. Basically, these surveys were intended to determine the magnitude of exposures to firing range officers and police officers, who are required to qualify, usually every two months, in small arms proficiency.

Second, an attempt was made to evaluate the efficiency of existing ventilation systems in these firing ranges. Sequential samples, area samples, and breathing zone samples (using personal samplers) were collected during normal firing schedules. The reported levels ranged from lows of about 0.2 mg/cu m to highs of 34 mg/cu m for extended periods of time. In one range an exposure of 25 mg/cu m persisted for almost 3 hours and 8-hour average exposure of approximately 11 mg/cu m was reported. Low ventilation rates and short circuiting of fresh air intakes and exhausts were common, which resulted in very high exposures in most cases. Also, long periods were required for flushing out the contaminated air. Figures 1 through 5 illustrate and summarize the exposures found in these surveys. Some blood lead levels were obtained showing high exposures in range officers and lower exposures in police officers, because of the less frequent exposure of the latter.

At the same time these studies were conducted, our Hazards Evaluation Services and Medical Services Branch were conducting about 11 hazard evaluations, mostly at the request of concerned employees, involving exposures to lead dust and fume. Operations included spray painting of heavy mobile equipment and bridge girders; manufacture and machining of sintered lead alloys; manufacture of braided garden hoses, floor tile and printed circuits; and production of basic lead shot, rolled sheet lead, lead oxide, etc. At four of these eleven work situations, toxic exposures to lead were observed, based on environmental and medical findings, with some conditions radically out of control. In one study the vast majority of all air samples were found to contain excessive atmospheric lead concentrations; nine of 27 employees demonstrated blood lead values in excess of 80 µg/100 g of blood where respirators were required in most plant areas. Even where respirators were used, excessive absorption of lead occurred. So we know that high exposures to lead do exist in American industry.

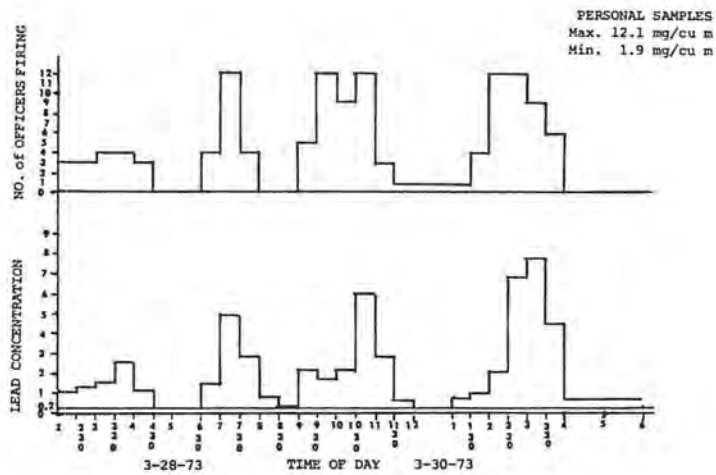

Figure 1 Number of officers firing and lead concentrations vs time, Orlando Police Firing Range, Orlando, Florida, March, 1973

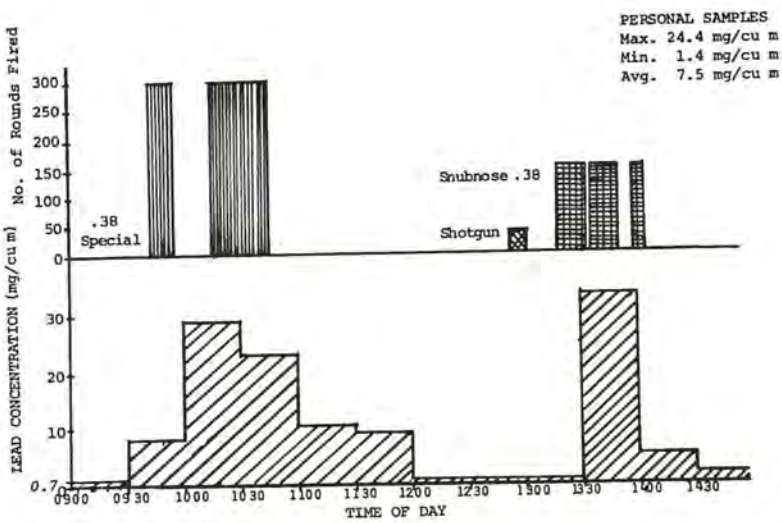

Figure 2. Number of rounds fired and resulting general area lead concentrations in the range, Kansas City Police Department Firing Range, Kansas City, Kansas, January 10, 1974

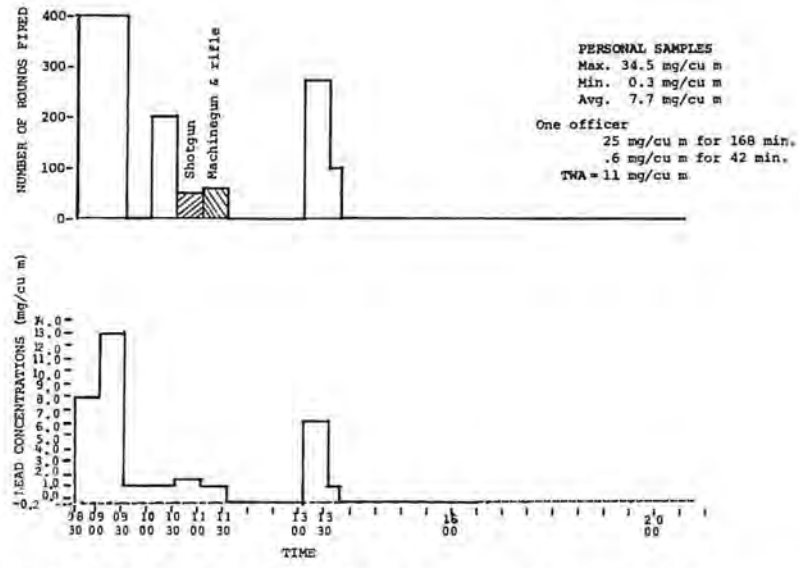

Figure 3 Number of rounds fired and general area lead concentrations vs time of day, Kansas City, Missouri Federal Reserve Bank, January 10, 1974

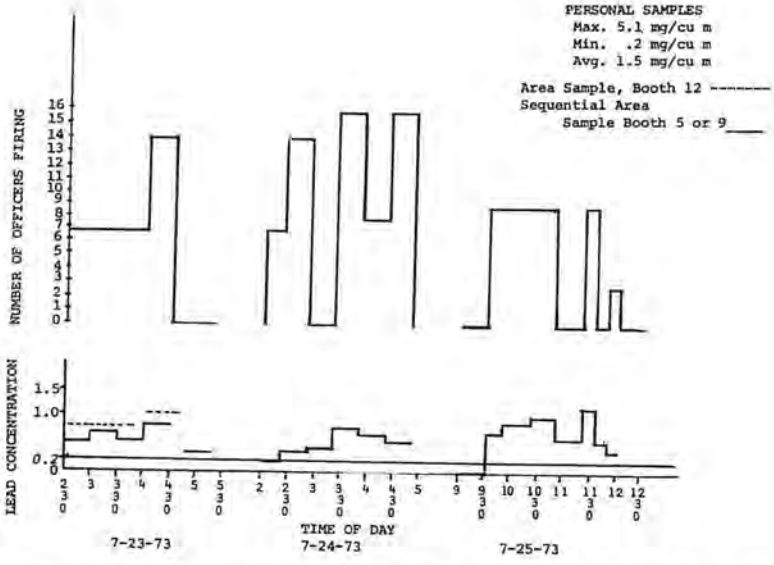

Figure 4 Number of officers firing and lead concentrations vs time, International Police Academy Firing Range, Georgetown, July, 1973

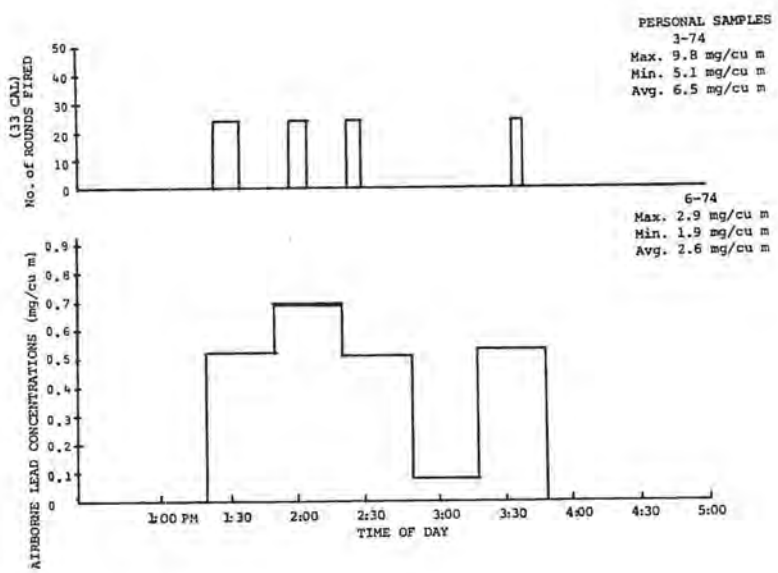

Figure 5 Number or Rounds fired and resultant Lead Concentration of ambient air, Federal Reserve Bank, Omaha, Nebraska, June 13, 1974.

At one plant, for more than a decade, it has been the medical policy to administer oral CaEDTA to numerous employees as a routine prophylactic method to control potential effects of over exposure to lead.

I would like to comment on one of the areas of controversy; namely, the relative value of different approaches to control of this hazard. As you know, there are three general methods of control of such a known hazard, administrative control, medical control, and engineering environmental control. Last year, in an OSHA Review Board decision, on an appeal by a major lead producer, the original judgment was upheld that administrative control is not an acceptable alternative to reducing environmental exposures to a safe level.[1] That is, moving people in and out of a hazardous area, on the basis of medical and biological testing, is not an acceptable alternative to reducing atmospheric exposures to the TLV for lead. Nor is the use of respirators acceptable as an alternative control method, except in unusual, or temporary circumstances. As we have often seen, respirators are not accepted by workers nor do they keep exposure down. I spent all last week wearing one under a coke oven, so I speak with personal bias.

This argument involving the relative merits of medical administrative control *versus* environmental control is not new. It is at least as old as a statement by Dr. Robert Kehoe in November, 1947 (28 years ago) to the Association of American Battery Manufacturers,[2] and it is as recent as a position paper by the Lead Industries Association in November, 1972, entitled "Industrial Inorganic Lead Poisoning-A Program for Prevention."[3]

In 1972, the Lead Industries Association said, "It is the position of the Lead Industries Association that a biological standard, based on blood lead determinations, provides the best means of protecting the worker and determining compliance under the Occupational Safety and Health Act of 1970. Biochemical indices provide a much more accurate assessment of possible hazard to lead exposure than do air concentrations. It is recommended that air sampling be used only to indicate the necessity to institute biological monitoring and to evaluate engineering controls." Presumably the biological monitoring will measure the degree of absorption, intoxication, or poisoning after the exposure has occurred, rather than prevent or limit the exposure in the first place.

On the other hand, in 1947, Dr. Kehoe told the battery manufactrers, "We are presented with the necessity of making the lead trades safe, not only for a few weeks or years, but for a lifetime of work. Until we have done that, we have not solved our problem, either hygienically, economically or in terms of human relations ... It would be very easy to say that this is a problem for the doctors, but I would like to say and to emphasize that this is not the case. The hazard of lead poisoning is not controlled by the physician. It is not controlled by medical practice. It is controlled substantially in controlling the environment, and in principle, what the industrial physician does is to act as the policeman in determining the extent to which environmental conditions are satisfactorily controlled. If he acts in any other capacity, he is missing the point of his efforts. At the present time (1947) medical and

hygienic information are available to enable us to specify what are safe occupational conditions (in 1947 the MAC for lead was 0.15 mg/cu m) and those specifications, if they are to be met, have to be met by the management. They have to be met by spending money and the technical skill required to control the environmental condition and the operations so that they are intrinsically safe."

A few years later, in 1962, Dr. Kehoe reiterated his thoughts by saying, "The causes for the presently unnecessarily high incidence of industrial lead poisoning are numerous, but certain outstanding factors should be understood by those who would attempt to eliminate this disease from an industry. Certain confused and confusing ideas have persisted for a long time in connection with the lead trades, such as alleged wide variation in the susceptibility of individuals. These have given rise to the erroneous belief that there are no dependable means by which wholly safe occupational conditions of exposure to lead can be differentiated from those that are dangerous. Conversely, the comparative mildness of lead intoxication, as it is seen commonly in American industry ... contributes to the persistence of the irresponsible or illiterate view that there is no need to achieve complete control of the hazard. This view, it seems is especially prevalent in some of the long-established lead trades in which conditions are much better than they used to be while failing to meet adequate hygienic standards ... What is required is a sound understanding of the problem that is to be solved, and a genuine determination to solve it, not by prophylactic medical therapy, but by the application of orthodox engineering principles and equipment coupled with satisfactory medical supervision."[4]

The methods of monitoring exposures to lead, both environmentally and biologically, have been well developed and are essentially reproducible. In the environmental monitoring area, 8-hour exposure levels can be accurately measured with either personal samplers attached to the worker, or by a series of breathing zone and area samples with known analytical and sampling efficiencies. The environmental standard has been well documented to be in the order of 0.15 mg/cu m. We can argue that it should be perhaps 0.10 or 0.20 mg/cu m, but we all agree on the order of magnitude. The exposures that we have observed are, in some cases, an order, or even two orders of magnitude higher levels which all will agree are toxic. The methods of control are known by proper engineering and ventilation design.

The Industrial Ventilation Manual of the American Conference of Governmental Industrial Hygienists describes only two operational designs for the control of atmospheric lead, namely, such as localization of hazardous operations in specific areas, proper design of ventilation systems, taking into account high lead densities, melting points and feet per minute of air, and short circuiting. There is need for dissemination of proper designs in other lead using operations. To fill

this need, NIOSH is preparing manuals of good practice in several areas where lead is found, such as autobody repair, lead acid battery manufacuring, spray painting, and soldering and brazing. Other operations are also being considered.

Although my subject is aimed at monitoring of the lead in the environment, this talk is a plea for the direction of corporate expertise and funding to the design and installation of adequate control systems. The lead disease problem is well recognized; the techniques for valid identification and quantitative evaluation of the environment are well known. Let us complete the industrial hygiene trilogy, the final step of eliminating the hazard by designing and installing good engineering control systems.

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MODERATOR-Dr. Vaun Newill

The third speaker on our panel is Mr. George Becker, Representative of the United Steel Workers of America, Department of Safety and Health, who will primarily discuss the union aspects of the problems involved.

LEAD CONTAMINATION AS VIEWED BY THE WORKER

Mr. George Becker
United Steelworkers of America

A B S T R A C T

Concerns of the United Steelworkers of America for workers' welfare in the lead industry cannot be overemphasized. For years companies and management have weighted the cost of safety devices installation and elimination of health hazards in lead industry work environments against the costs of possible disability or death of workers. Even this calloused industrial attitude pales when compared with the long-standing practice in certain companies of administering on-the-job oral chelating medication, a practice condemned by knowledgeable industrial physicians. This practice tends to convince employees that there is no contamination of the work area and allows continued work in unsafe environments.

I was introduced as a safety and health representative of the United Steelworkers of America. I would like to add to that introduction. During the past ten years I have been assigned to and worked as a field staff representative for the Steelworkers Union. In this capacity I have been in daily contact with people who work in smelters, lead processing plants, dye cast shops, rolling mills, junk yards, battery breaking operations, and cable stripping plants and have developed a very keen sense of feeling for the problems, which in time, became my problems.

It is important that we understand the problems of lead contamination as viewed from the eyes of people who actually work in these types of operations. Most of the doctors in industrial hygiene whom I have met do not really understand or have first-hand knowledge of how workers feel or their fears concerning their daily work environment-- the nagging fear that perhaps something could be poisoning them, in spite of the company's reassurance that they have nothing to worry about. They bury their fears that the stomach cramps, aching joints, and headaches they suffer are connected with their work. They have the company's assurance as their fathers and other workers before them, that there is no real health problem in the lead industry. I have heard many company representatives insist emphatically that they have never had a "leaded employee" in their plant.

Where then do these workers turn for help? They must work to survive, to support their families, so they eagerly grasp whatever assurance is offered to them. They routinely visit the company doctor who examines them and runs periodic blood tests. Maybe the lead level is just a little bit high, but does the employee know about it? More often, he does not.

The very most he may be told is that he should watch his personal hygiene. Many companies give employees a bottle of pills, to be taken, two of them, after each meal, six pills each day, as a "safeguard." They really have nothing to worry about, just take the pills. We have had people in our union who have been taking these pills, not knowing what they are or how they may affect their health, six pills a day, seven days a week, year after year after year. One major lead producer in the United States has given pills in this manner to some lead contaminated employees for as long as nineteen or twenty years, apparently having no concern as to possible long term health effects the pills have on the employees; and, certainly it does have an effect.

You may wonder why an employee would submit to this. Very often people who work in the lead industry have limited education. They have families to raise and children to educate. They have many years service with the company, and cannot afford to switch jobs. In desperation they grasp at whatever straws are offered to them. They eagerly accept the position that lead exposure is not harmful and that they are not ill. The company doctors have told them they are not sick, and would appear to be no reason for rejecting the word of a company doctor since he is a man of integrity, well educated, and pledged to treat ill and sick people. Certainly, his assurances are acceptable; though deep down inside workers fear that maybe they are selling the company more than an hour of labor for an hour's pay; maybe they are selling years off of their lives. However, they still accept the company doctor's opinion. I think it is important that you understand why these workers continue to work in a contaminated environment and recognize the concern and fears of these workers in the lead industry.

Concerning the standard itself, it has been established as .2 mg/cm of air. The question is does this standard adequately protect the health of these workers. The fact is that it does not. Even if the standard was adequate to protect the employees' health, most companies in the lead industry do not meet the standard. They have no apparent intention of meeting it. It is possible to meet the standard if companies give attention to the problems involved.

You may then ask why many companies are not meeting the present standard for lead of .2 mg of air. I suggest it is more economical not to do so. It is cheaper to contaminate employees and replace them when they can no longer work. It is cheaper to appeal OSHA citations to protest proposed abatement schedules and drag the whole mess through future appeals and courts, it is cheaper to do this than to make the necessary corrections at the job site. Putting it another way many companies weigh the cost of installing new equipment or making the corrective changes in existing equipment which would be required to protect the health of workers, against the possible cost of some type of workmen's compensation, or other penalties should they be found liable for workers illness or in violation of the laws at some later date. Certainly

engineering and technical knowledge in this country is sufficient today for industry to clean up this work environment. It comes down to a matter of money and priority. I submit to you that the reason this has not been done in the lead industry, where known hazards have existed for hundreds of years, is it is cheaper to replace people.

One last point that needs to be covered is the use of oral Versenate. Our union strongly opposed to this practice. I mentioned before that some employees have taken this drug for years on end. This condition is still in existence today. Dr. Kehoe's views and opinions do not agree with those of our union as closely as they parallel those of industry; however, I do agree with one thing that he said, "that any physician who would prescribe the use of oral Versenate as an on-the-job medication, while permitting an employee to continue working in a contaminated environment, is unworthy of the name physician." I agree with this philosophy. How can you have accurate blood-lead samples reflecting the medical condition of employees within the lead industry if the samples have been taken from employees who, as a result of taking oral Versenate, are being constantly chelated and what effect does the Versenate have on the health of these employees? This certainly must be considered in the evaluation process.

I would like to close with one last thought. I know that I have not offered any solutions to these problems today. I am, however, making a humanitarian appeal on behalf of workers in the lead industry. It may be cheaper to contaminate employees and replace them when they no longer are able to work; however, it is far more civilized to create a safe environment that will sustain productive workers. I would like to thank you for the opportunity to address this conference today and for your kind attention.

MODERATOR-Dr. Vaun Newill

Thank you, Mr. Becker. We have just a few minutes for questions. Are there some quick questions from the floor?

SOURCES OF LEAD IN INDUSTRY
MONITORING OF WORKPLACE AND PROBLEMS INVOLVED

QUESTIONS, ANSWERS, COMMENTS

QUESTION-Dr. Michael Utidjian

I was curious as to where all this lead comes from in these firing ranges. Is this from the bullet or is it from the lead azide cap?

ANSWER-Dr. Paul Caplan

It was probably from the lead styphnate in the bullet primer itself.

QUESTION-Dr. Hector Blejer

My question deals with the physiological solubility of forms of lead such as lead sulfide. Mr. Nelson said it was insoluble. It may be outside of the body, but is it so in the lungs? I have seen cases in which so-called insoluble forms of lead which upon inhalation do produce increased lead absorption and even lead poisoning. Physiological solubility is not the same thing as physical solubility. Would you comment on this, please?

ANSWER-Mr. Kenneth Nelson

Yes, of course, solubility is a relative term. The question was, is lead sulfide really insoluble? Dr. Blejer said that most things considered insolubles are soluble to some degree, at least in the lungs and other body fluids. I merely want to explain that solubility is a relative term and perhaps nothing is absolutely insoluble. When I said that lead sulfide is insoluble and seems to cause no problems, this is based on the fact that so far as we have been able to determine in the lead mining industry, there have been no cases of excessive lead absorption or lead intoxication among lead sulfide miners. There is one published paper reporting the results of a study done in the lead mines in Missouri which came to this conclusion.

Perhaps we should re-examine this question, but, I repeat, we just have no basis for assuming the existence of any hazard in lead mining now. Certainly lead sulfide is soluble in the stomach. I did an experiment on that about 1941, feeding lead sulfide to rats and the lead content increased in the rat tissues and bones. Perhaps in humans the inhaled and swallowed lead sulfide is dissolved in the gastric juices. Apparently, overall intake and absorption are not great enough to cause excessive absorption or lead intoxication.

QUESTION-Dr. David Parkinson

I've really got three questions, the first one for Mr. Nelson. Does lead in a melting pot have zero vapor pressure? I do know molecules of lead come out of it, in particulate form.

ANSWER-Mr. Kenneth Nelson

Lead indeed may have some vapor pressure in the molten state while quietly reposing in a kettle, but we have actually suspended sampling equipment over such kettles of molten lead and found virtually no measurable lead in the atmosphere; certainly the amounts were well under the TLV. However, if you disturb molten lead when there is surface dross you will disperse some dust; we have not been able to find airborne lead above lead just at the melting temperature.

QUESTION-Dr. David Parkinson

I just wonder what sort of sampler is used in this situation to measure lead in the molecular state?

ANSWER-Mr. Kenneth Nelson

Well, we must assume that our sampling apparatus would catch any particulate lead. If the airborne lead was not particulate, it is questionable if it would be absorbed if it were breathed; that is, if it were a vapor.

QUESTION-Dr. David Parkinson

I would think that a vapor would be more easily inhaled and absorbed.

ANSWER-Mr. Kenneth Nelson

We simply haven't been able to find it.

QUESTION-Dr. David Parkinson

Have any studies been done on the deficiencies in other metals in the body when men are being treated prophylactically with Versenate?

ANSWER-Mr. Kenneth Nelson

So far as the depletion of trace metal from the body by Versenate, indiscriminant Versenate treatment is concerned, you will have to talk to a physician about that. I don't know. Presumably, though, if these men spoken about by Mr. Becker have taken Versenate for many years in fairly significant dosages one would think that trace metal deficiency would have

appeared by this time. I don't know of any such instances; perhaps he does.

ANSWER-Mr. George Becker

I can relate this specific incident concerning Versenate. We had an employee, approximately 55 years of age, who suffered from visible and obvious symptoms of lead poisoning and application was made for Workmen's Compensation and Disability in the State of Illinois. The company responded with medical records concerning the employee's blood samples. Over a period of years these samples had been taken periodically by their medical staff at six month intervals during the latter years of his employment. These records indicated that this worker had never had above .08 on a blood lead examination. Therefore, it was argued that the man had never been contaminated. However, his personal physician diagnosed that he was definitely leaded and suffered the effects of lead poisoning. Still the company medical records showed that he had never had a blood lead level above .08. In discussions with the employee involved, it was found that he had taken Versenate over a long period of years. I certainly believe that this case shows that continued use of chelating agents will keep a blood lead level down for use in company medical records. However, as far as protecting the employee's health, there was no protection, none whatsoever.

COMMENT-Dr. Paul Caplan

At least one study in measuring the depletion of other metallic ions as the result of taking Versenate has been done by NIOSH. I have those results if any of you would like to look at them. However, I do not have the results with me here, but in general, there was some reduction in some of the other metallic ions. The report is available and you can request it from NIOSH.

QUESTION-Dr. David Parkinson

I wondered if anybody apart from myself had ever heard of cases of children getting lead poisoning from eye black which has got lead sulfide in it?

ANSWER-Dr. Paul Caplan

Dr. Barltrop recently reported lead poisoning from this source in one of his reviews of lead poisoning in children.

MODERATOR-Mr. Vaun Newill

In order not to steal time from the rest of the program, we are going to cut off the questions and answers at this point and will turn the program over to Dr. Jaroslav Vostal, Head of the Biomedical Sciences Research Laboratory at General Motors Corporation facilities in Warren, Michigan.

SESSION II TOXICOLOGY OF LEAD

Dr. Jaroslav Vostal, Moderator
General Motors Corporation

I sincerely appreciate the efforts of the first group to keep the time schedule, and I would like to open our session immediately. There is no doubt about the fact that lead is a toxic element or that chronic lead poisoning belongs among the oldest known histories of occupational diseases. Therefore, we are very glad that we can discuss, for some considerable amount of time, some new events in the research on the toxicity of lead.

I have asked Dr. Carnow about the possibility of modifying the procedure for this panel. Since we are presenting some new experimental data, we felt it would be preferable to appeal to the speakers to comply with the ten-minute periods for presentations and then open immediately for a few questions from the audience, following each presentation. This is also preferred, due to the fact that one of our speakers has to leave immediately after his presentation and will not be available for the question and answer period at the end of the session.*

With this in mind, I would like to open immediately and ask Dr. Morris Joselow, Director of the Environmental Toxicological Department of the New Jersey College of Medicine to discuss programs of blood lead levels with us. Dr. Joselow.

**The questions and answers immediately following each presentation will be included in the question and answer section beginning on page* 98 .

BIOLOGICAL MONITORING
PROBLEMS OF BLOOD LEAD LEVELS

Dr. Morris M. Joselow
College of Medicine of New Jersey

A B S T R A C T

Blood lead levels pose problems that involve ethical, technical, toxicological, and societal considerations. Workers may legitimately object to periodic blood sampling to monitor their work environments, and technical problems and inherent errors associated with procedures reduce the accuracy of blood samples in evaluating toxic potential for workers. The inadequacy of blood lead for measurement of occupational exposures was demonstrated in a small population of lead workers in which those with blood lead concentrations below 80 µg/100 ml of blood were found to have unequivocal biochemical effects when a more sensitive testing method was used.* The co-existence of such abnormalities with acceptable blood lead levels casts doubts on the value of the entire blood lead measurement as a reliable index of hazardous exposure to and absorption of lead.

Almost all procedures for the detection and diagnosis of lead poisoning rely heavily, sometimes almost exclusively, on a determination of the concentration of lead in blood. In the criteria document for a recommended standard for occupational exposure to inorganic lead,[1] blood is offered as the better of two acceptable biological monitors; the other is urine analyses. Urinary lead, however, is considered less reliable, less well correlated with either air levels or biochemical indices, and is further confounded by the problems of differing specific gravities, diurnal variations, or the fact that spot samplings are not representative.[2-5]

While blood lead levels are less troubled by these difficulties, there are still some fairly formidable problems associated with their determination and interpretation. In addition to considerations that are essentially technical or toxicological, ethical and societal matters, while not necessarily the major concern of this conference, must be considered, however briefly, when any biological monitoring program is proposed.

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**With two exceptions, all of the 27 employees tested showed blood lead concentrations below 80 µg/100 ml. Yet in this small population, more sensitive tests demonstrated clear and unequivocal biochemical effects; EDTA mobilizations showed inordinately high body burdens of lead; and four cases of lead nephropathy were uncovered, even though only eight workers were adequately examined for renal disease.*

On quite legitimate moral grounds, a worker may object to being sampled periodically to serve, much like a guinea pig, as a monitor of the safety of the work environment provided for him. The Occupational Safety and Health Act guarantees for every work, "safe and healthful working conditions." All the personnel and the extensive apparatus and paraphernalia of OSHA and NIOSH essentially are in business to implement this mandate.

Emphasis on the safety of the work environment is clear, both as written into law, and as demanded by good preventive medical practice. Is it not then an admission of some technical weakness when reliance must be placed on human monitoring to establish safety in a work environment? A worker might well ask, "If biological specimens are needed, why not use real guinea pigs, or rats, or mice? Why me?" How many individuals would agree to being sampled regularly to serve as monitors of the ambient air quality in their residential communities? In viewing the overall record of laboratories performing blood lead analyses, one might well be tempted to suggest that guinea pigs might just as well be used.

Various techniques are now in use for the collection and analysis of lead in blood.[6] These include micro and macro procedures; finger sticking, venepuncture, ear lobe piercing; chemical assays, most notably with dithizone; atomic absorption spectrophotometry; polarography; and emission spectrography, all with various modern refinements and modifications.

Yet the general record for proficiency of laboratories performing blood lead analyses can only be described as dismal. In interlaboratory comparisons for reliability in analyses, undertaken by the American Industrial Hygiene Association in 1968 and 1969, results were disheartening.[7] For almost all the blood specimens submitted, ranges among reports from the laboratories were of the order of several hundred fold. The smallest; (i.e., the best) range reported was from 8 to 50 µg/100 ml for a specimen with an estimated true value of 20 µg/100 ml. Differences of the order of 20 to 300 percent were common. As stated in the AIHA report, only "approximately 50 percent of the laboratories in each of the two studies and 40 percent of those in both years, reported results of acceptable precision." Stated conversely, approximately half of the laboratories in each year and 60 percent for both years were reporting unsatisfactory results.

Those comparative studies are relatively old, about 7 years; and supposedly there has been considerable improvement in analyzing for blood lead since then. The significant point here, though, is that these studies provide a measure of the performance and accuracy of laboratories during the period when much of the background data used for setting concentration limits in criteria documents were being generated; in many cases by laboratories that participated in these AIHA studies. It would be highly unlikely if unreliable data were not included in literature,

enshrined in publications, and cited thereafter as authentic references for use in development of our august criteria documents.

How much improvement has there really been since 1968? The Center for Disease Control (CDC) of the U.S. Public Health Service runs a proficiency testing program to check the performance of laboratories throughout the country which routinely analyze children's blood for lead. Three to four proficiency specimens are submitted monthly. In a quote from a statement made by the CDC, dated September 19, 1974, (only a few months ago): "The number of laboratories," and there are more than 60, nationwide participating in this program, "reporting unacceptable results is over 50 percent of the total." [8]

Is this different from 1968 when almost identical findings were reported? The CDC goes on to state, "If such a large percentage of laboratories, some of which have been performing analyses for many months, are unable to consistently perform on a proficiency test, serious questions are raised about the quality of work done on samples submitted from the field." Serious questions must indeed be raised about the quality and validity of reported blood lead values, values that might well serve to judge the safety of the work environment.

Why there are such problems of reliability in blood lead analyses it is not difficult to understand. The techniques required essentially ultra-micro trace analyses (the lead is present in less than ppm quantities) and very few chemists and still fewer laboratories, are prepared for the scrupulous care, meticulous attention to detail, painstaking avoidance of contamination, and isolation that performance of such work demands.

Leaving questions of accuracy and precision, and assuming that the numbers reported are absolutely correct, how valid is a blood lead level *per se* as an index of the toxic potential of lead and how useful is it as a guide for monitoring excessive exposure to, and absorption of lead? In this country and elsewhere some general diagnostic interpretations have been assigned to certain whole blood concentrations. See Figure 1.

µg/100 ml Pbl	
50	Normal
40-80	Acceptable
80-120	Acceptable
120	Dangerous

Figure 1 Categories of Lead Absorption[9]

These are, of course, quite broad categories. The number 80 µg/100 g whole blood, or 84 g/100 ml, has become widely adopted as an arbitrary cut-off value. Even the criteria document for inorganic lead confers some official sanction to this number;[1] 80 ug/100 ml whole blood is recommended as an upper limit, delineating acceptable from unacceptable lead absorption. Concentrations below 80 ug/100 g are considered, according to the document, as "being indicative of an insignificant risk of lead poisoning."

Recommendations of the Swedish National Board are similar, Figure 2, though a somewhat lower value, 70 µg/100 ml, is recommended as the cut-off or removal-from-work point.

µg/100 ml Pbl	
20	normal for general population
20-38	acceptable - no problems
38-70	warning - watch for changes
70	danger - remove from lead work

Figure 2 Grading Lead Workers

Adapted from Swedish Nat'l. Board of Occupational Safety and Health[10]

Regardless of whether *70 or 80* µg/100 ml is used as the demarcation value, there are at least two reservations that cast doubt on the worth of such numbers:

1. There have been too many reports of symptoms of lead intoxication in workers showing blood lead levels below 80 µg/100 ml.[11-20] These are too numerous to be dismissed or easily explained by faulty analyses, differences in individual susceptibilities, or special circumstances (i.e. a temporary removal from sources of exposure). The inadequacy of blood lead as a monitor of occupational exposure was pointedly demonstrated in our study of a small population of lead workers in New Jersey.[19] With 2 exceptions, all of the 30 employees showed blood lead concentrations below 80 µg/100 ml, Figure 3. Yet, in this small population, more sensitive tests demonstrated clear and unequivocal biochemical effects of lead; and four cases of lead nephropathy were uncovered, even though only eight workers were adequately examined for renal disease. The fact that these abnormalities could co-exist with "acceptable" blood lead levels is sufficient to cast doubt on the value of the whole blood lead measurement as a reliable index of the hazards of exposure to and absorption of lead.

With two exceptions, all of the 30 employees showed blood lead concentrations below 80 µg/100 ml, as listed in Figure 3.

LEAD SCREENING TESTS ON 30 LEAD WORKERS

TEST		B_{Pb}	ALAD	FEP	U_{ALA}	U_{Pb}	24-Hr URINE EXCRETION		
							CONTROL		EDTA
							COPRO	Pb	Pb
UNITS		µg/100 ml	µg/100 ml RBC	µg%	mg/L	µg/L	µg/d	µg/d	µg/d
Subject:	Occ.								
H.Z.	LT	29	66	71	7	138	127	135	976
M.B.	LC	94	43	129	26	---	420	---	2922
J.H.	LC	70	95	147	7	---	350	---	2176
J.P.	LC	64	57	107	3	---	610	---	1794+
J.B.	LC	34	97	4	5	---	48	---	227+
R.V.	LC	47	120	11	4	---	673	---	673
J.Bo.	LB	38	88	73	4	73	---	91	1051
R.A.	LB	48	43	95	5	68	---	81	---
G.B.	LB	68	47	242	--	66	---	145	3375
R.R.	LB	45	44	124	7	82	---	84	1477
S.N.	LB	53	50	125	2	116	---	112	---
M.S.	LB	50	27	51	--	72	---	72	1881+
C.U.	LB	44	45	101	4	44	---	103	1153+
T.G.	LB	32	88	54	4	70	---	---	---
M.A.	LB	38	77	50	5	84	8	65	819
J.Ba.	LB	46	64	45	5	106	---	127	---
S.D.	LB	46	80	71	9	142	---	138	2053
G.H.	LB	54	65	134	4	96	---	102	1988
F.C.	LB	59	52	163	15	180	---	136	2810
C.K.	LB	40	65	59	5	123	---	149	2294
R.F.	LB	52	69	138	5	92	20	43	530
J.Zi.	LB	41	51	63	5	128	---	116	2401
A.B.	LB	40	--	---	5	57	---	58	1776
O.D.	LB	39	74	151	3	84	16	99	2068
J.T.	LB	48	116	63	6	128	---	129	1793
C.E.*	LB	51	82	64	5	80	7	53	1134
R.S.*	LB	66	78	26	6	86	24	99	1590
S.B.	FR	98	67	77	18	334	737	474	4018+
F.C.**	PB	35	88	3	2	70	13	112	990
J.Z.*	SC	48	42	29	70	65	757	305	5200

*Chronic lead nephropathy
**Renal disease and hypertension of uncertain etiology
+Underestimation of 24-hr Pb excretion. Creatinine excretion <1.2 gm/24 hrs.
LT = lead-tin solder worker
LC = lead cutter
LB = lead burner
PR = firing range sweeper
PB = painted steel burner
SC = solder cream worker

Figure 3, Lead screening tests on lead workers.

2. The dynamics of the interchange of lead among the various components of blood in the body pool, Figure 4, also argues against the primacy of the whole blood lead levels as a valid indicator of the body burden, particularly as a reflection of the lead content of the more vulnerable soft tissues. The most significant component may be the diffusible plasma lead concentration. This component, the metabolically active center of the body lead pool, is but a small percentage of the total plasma lead, which itself is only about 10 percent of blood lead in the body pool. The latter is estimated to be about 2 percent of the total body burden.[5] Thus, the diffusible plasma lead, though the smallest of the lead containing components of blood (and, thus, easily lost in the error factors of whole blood lead assays) may be the most significant for diagnostic purposes. Some support for this concept has been obtained, most notably by the work of McRoberts.[21] In a small number of cases of adult lead poisoning there

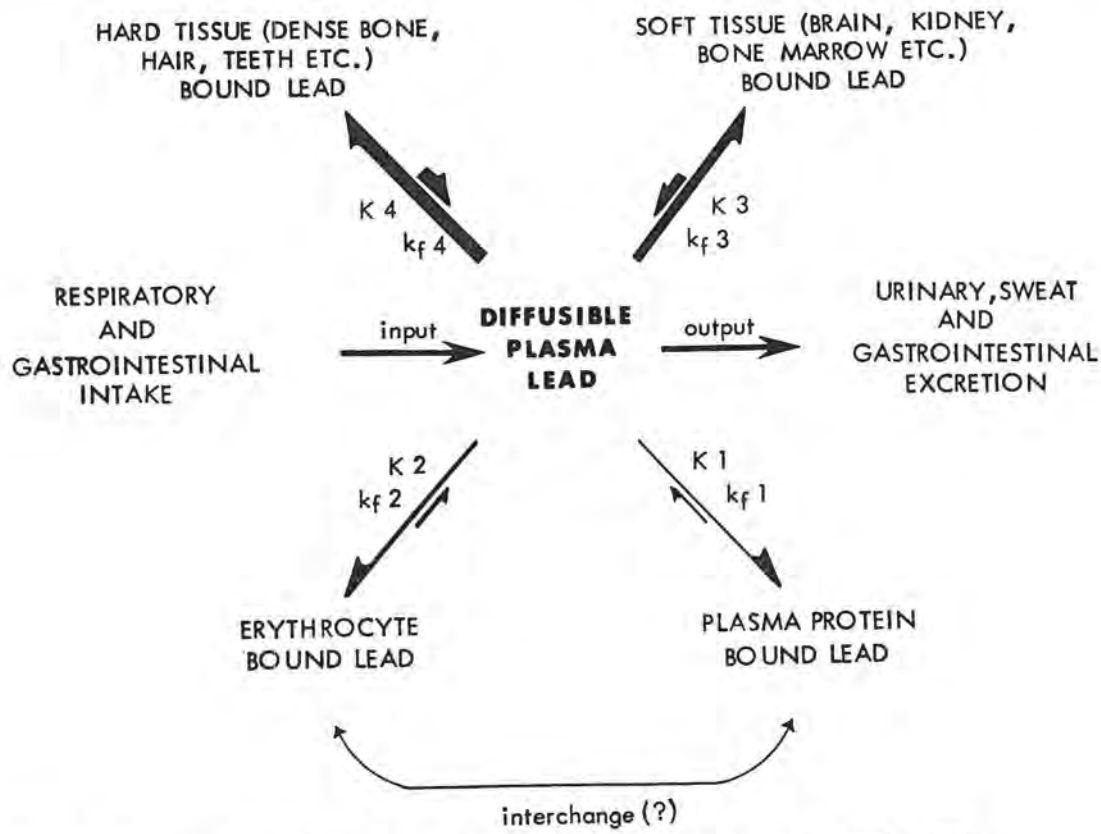

Figure 4 The dynamic interchange of the body lead pool. (5)

Adapted from: Baloh, Arch. Env. Health 27:198-208, 1974

was a shift in the partition of lead from erythrocytes to plasma, with an increase toward the plasma. A concentration of 10 g/100 ml plasma seemed to suggest itself as an upper limit for health monitoring. Determining the lead content in plasma, of course, would be considerably more difficult than for blood, and would almost certainly involve a much greater error; yet, it may prove a better index than whole blood lead.

Because of the dissatisfaction with blood lead levels as monitors of the toxic effects of lead absorption, particularly in response to the diagnostic needs of the massive childhood lead poisoning programs that have been mounted in this country, attention has been focused on measuring the metabolic effects of increased lead absorption as possible substitutes for blood lead analyses. Lead interferes with the synthesis of heme and causes alterations, both quantitatively and qualitatively, in some of the intermediates involved in this synthesis. Among such metabolites are ALA, ALAD, COPRO, and free erythrocyte protoporphyrins (FEP), Figure 5. The latter biological test - the so-called FEP test - has achieved prominence

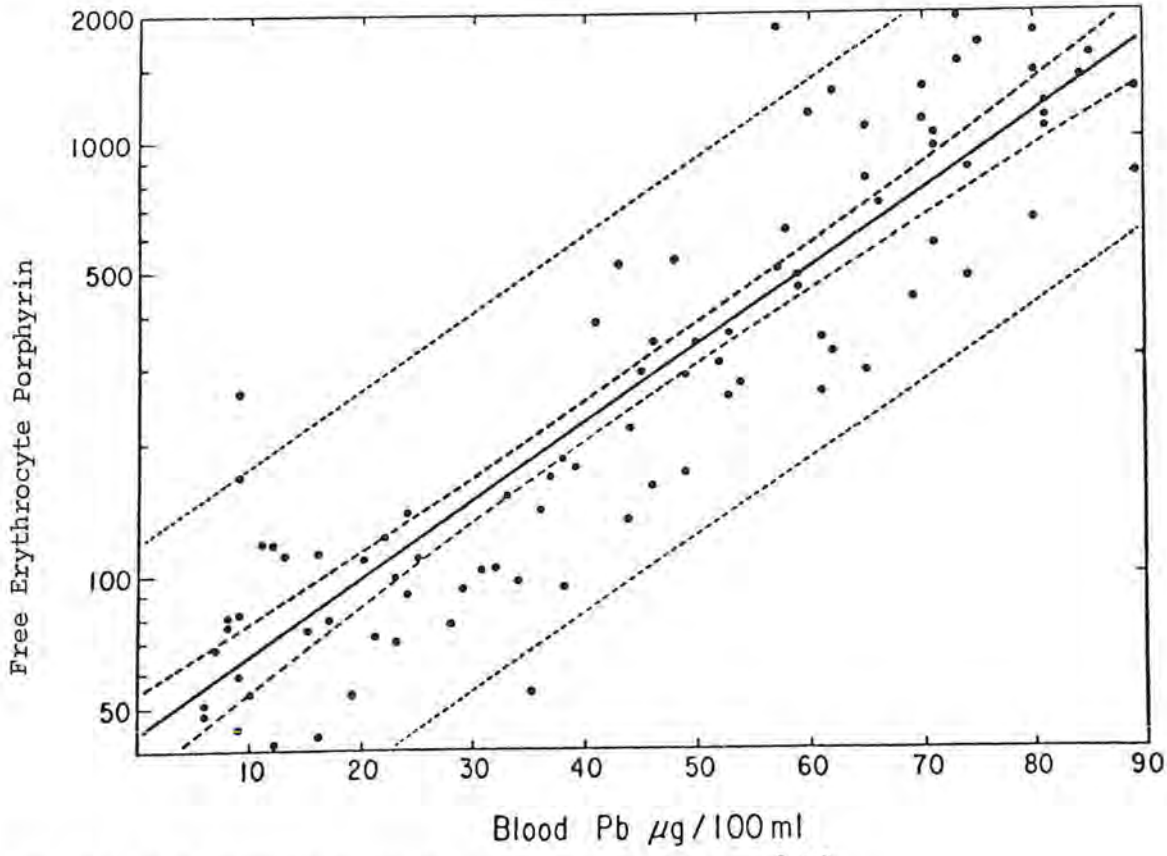

Figure 5 Relationship Between FEP and Blood Lead[22]

Adapted from Piomelli, S., et al, Pediatrics 51:254-257, 1973

with its acceptance by the Public Health Service as an alternative to blood lead testing in screening children for lead poisoning. Protoporphyrins accumulate when the insertion of iron into the protophyrin ring to form heme is blocked by lead. Their build-up in blood is roughly proportional to the blood lead level; but more important, their measurement can serve as a monitor of the toxic effects of lead absorption.

It has recently been discovered,[23] or perhaps rediscovered, that the protoporphyrin in FEP is not really free but is mostly bound with zinc to form zinc protoporphyrin (ZP). The measurement of ZP can be done simply, rapidly, without fear of contamination, directly on a drop of blood, and offers a better and more convenient test for the effects of lead toxicity than FEP. We have demonstrated this persuasively for children; and have also applied the test to adult populations of lead workers, Fig 6.

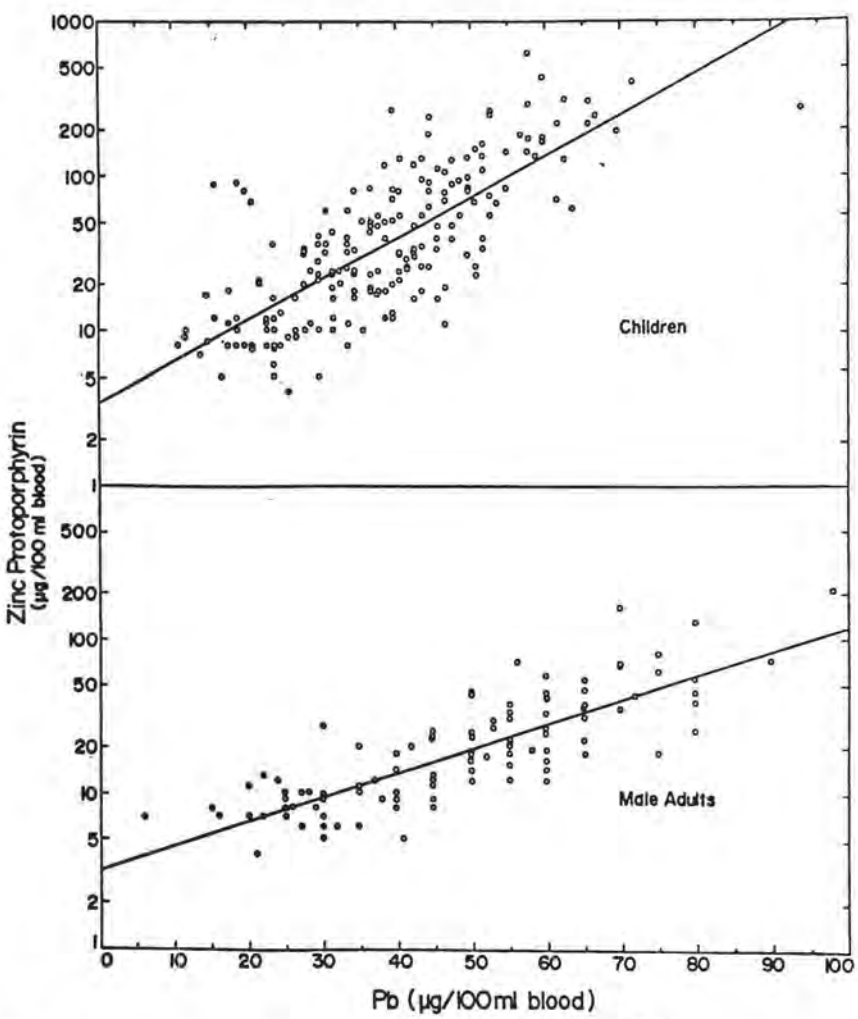

Figure 6 Relationship Between ZP and Blood Pb [23]
Adapted from Lamola, A., Joselow, M., Yamane, T.L., Clin. Chem. 21:92-97, 1973

There is the usual scatter here, characteristic for biological sampling. Children show a comparatively greater response than do adults for the same amount of lead, in keeping with the known greater sensitivity of children to lead intoxication. There is an interesting, intriguing relationship shown in Figure 6. A level of 40 ug/100 ml of blood is generally considered as the safe upper limit for children in the same sense that a level of 80 µg/100 ml has been considered as a safe upper limit for occupationally exposed adults. These lead values for both children and adults, respectively, correspond to the same ZP value of about 50 µg/100 ml.* In ZP we may have a biochemical response to lead that is more basic than any of the other indicators, and ZP may well become the method of choice, supplanting blood lead for monitoring the effects of lead absorption.

The plots in Figures 5 and 6, as well as others relating ALA or ALAD and blood lead concentration, are typical dose-response curves, with lead as the dose and the response of the organism, in terms of a biochemical change, as the ordinate. In making toxicological judgments, these particular curves are especially valuable, since they are based on human data and do not require the always uncertain extrapolation of results from animal experiments. We can apply to these data the safety factors that have become accepted as standard operating procedures in toxicology. In this case, we would apply a factor of ten to the "no-effect" dose to arrive at a judgment of a safe dose or concentration (i.e., the maximum dose of lead that elicits no response, divided by 10, as the maximum concentration that may be safely permitted in blood).

For a linear response, such as appears to be the case here, this presents something of a dilemma. Can any dose be set that will not have some measurable deleterious effect? This is a difficult question, about which there is not likely to be universal agreement among toxicologists, any more than there is agreement about the problems of setting safe limits for radiation or carcinogenic agents. However, for the moment, for blood lead concentrations, we can agree with the widespread acceptance that levels of 80 µg/100 ml whole blood should not be exceeded, since such a "dose" may be associated with overt symptoms of lead poisoning.

This, of course, is not quite the "no-effect" level we seek in toxicology. If one applies to this the safety factor of 10, the maximum allowable blood concentration of lead in the blood of adults should be 8 µg/100 ml, and about half that for children. These concentrations are, of course, beyond attainment now, and in the foreseeable future. All of us carry from birth, lead burdens considerably in excess of these levels.

When 80 µg/100 ml is offered as an acceptable concentration of whole blood lead, we are in effect ignoring the demands of toxicological protocol. We are also accepting (really asking workers to accept) some finite, though indeterminate, risk of some damage for the sake of practical expediency, or, in the euphemism of business, economic feasibility. This is, in truth, another version of the inexorable benefit/risk equation

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* Based on zinc protoporphyrin-apohemoglobin standard.

imposed by society, and raises issues of dimensions that supersede all other associated with the problems of blood lead levels.

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MODERATOR-Dr. Jaroslav Vostal

Thank you Dr. Joselow for such an excellent review in a short time, which is an almost impossible thing to do.

Whenever we are discussing the toxicity of any element in the environment we would like to identify if there are other affected groups. This is the topic of the next presentation by Dr. Badi Boulos, Associate Professor of Occupational and Environmental Medicine at the University of Illinois School of Public Health. Dr. Boulos's presentation is entitled, Special Problems of Lead in Women Workers. Dr. Boulos.

SPECIAL PROBLEMS OF LEAD IN WOMEN WORKERS

Dr. Badi M. Boulos
University of Illinois School of Public Health

A B S T R A C T

Women workers may be more susceptible to lead toxicity than men, and they developed more central nervous system manifestations than men. The incidence percentage for convulsions and blindness was greater among women than men.* Also, lead may affect the reproductive capacities in women since incidence of miscarriage is greater among occupationally exposed women workers.# Lead was found to cross the placenta in experimental animals and may affect developmental growth and behavior of newborns. Compounds used in therapy may have potentiating toxic effects. In experimental studies, lead was found to potentiate the toxic effects of lithium on the fetal liver, as well as Chang human liver cell cultures.

The major symptoms of lead poisoning have been described many years ago. These symptoms include loss of appetite, metallic taste in the mouth, constipation, anemia, and pallor. Weakness, insomnia, headache, and nervous irritability have been described as other manifestations in lead toxicity. There also could be muscle and joint pain, fine tremors, encephalopathy, and abdominal colic. The muscle weakness may progress to palsy, often observed as "wrist-drop" or "foot-drop."[1-2-3-4]

The exposure of the worker to lead could occur through several routes, namely ingestion, inhalation, or through the skin. In women workers this hazard could be increased, since long hair can become contaminated with lead dust.[5]

When absorbed lead reaches the blood, it is predominately associated with the erythrocytes.[6] However, the manner in which the lead is associated with the erythrocytes is not well understood. It has been postulated that lead in erythrocytes cannot be removed by dialysis. The lead remains in the cells and is only slowly exchanged with lead in the plasma.[7] The concentration of lead in blood is considered more useful for toxicological evaluation than lead in the urine because of the dilution fluctuation which occurs in urine lead.

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**Percentages: Convulsions, men 15.0, women 34.9; blindness, men 2.3, women 7.7.*
#Three times as great in pre-maritally exposed women workers.

There are no data which correlate the concentration of lead in blood and that in other tissues of the same person.[3] The difficulties in this type of approach are due to the distribution of the body burden of lead in exchangeable pools. There have been studies which correlate the level of blood lead to the lead in the air. Goldsmith and Hexter[8] were able to show a linear correlation between the amount of lead in the air and the concentration of lead in the blood of people exposed to environmental lead pollution.

Lead interferes with heme synthesis and disturbs the formation of hemoglobin.[2,4,9] This might produce anemia and deposition of lead in the bone marrow of the fetus where depression of heme synthesis in the mother's cells could also contribute to the production of anemia. The intermediate substrate, delta-aminolevulinic acid (ALA), has been found to increase with increased lead exposure. As lead interferes with delta-aminolevulinic acid dehydratase (ALAD), the enzyme necessary for heme synthesis, the inhibition of such an enzyme is accompanied by an increase of the substrate, ALA. Both ALAD and the substrate, ALA, have been used as parameters in determination of exposure to lead. Blood levels of the enzyme and substrate, or urine levels of the substrate, are sometimes utilized in determining the amount of exposure to lead.

The cardiovascular system could be affected indirectly by increased levels of lead due to interference with blood hemoglobin levels and eventually diminished capacity for oxygen saturation. It has been shown that hypertension among workers in the lead industry correlates with lead exposure. These hypertensive crises could lead to rupture of cerebral vessels and eventually to brain damage and paralysis.

The oxidative enzymes in the retina could be inhibited by lead, leading to cases of total or incomplete blindness. As lead is deposited in different organs, the end result of toxic manifestation is dependent upon the damage to such target organs.

The approach to discussion of the problem of lead in women workers can be considered from the following points:

1. Are women more sensitive to lead than men?
2. Does lead affect their reproductive capacity?
3. Does lead cross the placenta and affect the fetus?
4. Is there any synergistic effect of lead with other therapeutic drugs?

To discuss the first question, there are no current data which can show six differences in sensitivity to lead. However, as was mentioned above, blood lead levels have been used to correlate exposure to airborne lead and the rate of uptake. Table I shows blood lead levels of several selected populations. This table shows the mean of blood lead level in µg/100 ml of blood was 26 µg. Most of these analyses have been done by less sensitive techniques than are available in testing today.

TABLE I

BLOOD LEAD LEVELS OF SELECTED POPULATIONS

Type of population	Mean Blood Lead µg/100 ml
Cincinnati Policemen	25
Cincinnati Traffic Officers	30
Cincinnati Automobile Test Lane Inspectors	31
Cincinnati Garage Workers	31
Los Angeles Traffic Policemen	31
Boston Summer Tunnel Employees	30

Adapted from Publication #999-Ap02, January, 1965
United States Department of Health

Table II shows blood lead levels of selected populations exposed to the same environmental conditions, but categorized as mean blood levels for women and men in µg/100 ml of blood. It is shown that women in any of the types of occupations studied had a much lower blood lead level than men having the same environmental exposures. This observation has been noted by several workers, however, no proper explanation for the differences has been given.

In the University of Illinois Medical Center Hospital, such differences between men and women have been shown to exist with regard to

lead levels.* In these two studies, there was no correlation between air levels of lead exposure to that of blood lead levels.

TABLE II

BLOOD LEAD LEVELS OF SELECTED POPULATIONS

Type of Population	Mean Blood Lead µg/100 ml	
	Men	Women
Remote California - Mountain	12	9
Composite Rural United States	16	10
Suburban Philadelphia	13	13
Composite Urban United States	21	16
Los Angeles Aircraft Workers	19	17
Pasadena City Employees	19	12
Downtown Philadelphia	24	18

Adapted from Publication #999-AP02, January, 1965
United States Department of Health

It has been shown that a linear correlation exists between exposure to lead in air and the rate of uptake as manifested by blood lead levels.

Comparisons of the blood lead content among men and women with correlation to an environmental lead level. These data suggest that there is greater accumulation of lead in target organs among women

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**Information obtained from a personal communication.*

than among men. Urine lead can be used to evaluate the rate of excretion of lead from the blood.

Men and women workers have been divided into three groups, those having a low exposure, intermediate exposure, or high exposure to lead, see Table III.

TABLE III

COMPARISON OF URINE AND BLOOD LEAD CONTENT AMONG MEN AND WOMEN UNDER SAME EXPOSURE

GROUP EXPOSURES	Urine Lead Content		Blood Lead Content	
	Number Analyses	Average µg/liter±S.D.	Number Analyses	Average µg/100±S.D.
LOW				
Men	146	35 ± 21	148	26 ± 11
Women	123	28 ± 19	124	26 ± 10
INTERMEDIATE				
Men	102	43 ± 30	108	30 ± 11
Women	25	27 ± 15	27	22 ± 10
HIGH				
Men	386	88 ± 60	329	44 ± 16
Women	61	46 ± 25	58	34 ± 13

Adapted from Neal, P. A., et al, Public Health Bulletin 267, Washington, D.C., GPO, 1941

At any of these levels of exposure the mean blood lead level among women was much lower than the mean among men similarly exposed. Also, the urine content was lower in women than men. This suggests that, although women were exposed to the same lead levels as men, their rate of excretion of lead was lower and their blood lead levels were lower than those found in men. By this comparison, it can be further suggested that lead in women has a different distribution pattern than in men and that lead in women may be stored in organs at higher concentrations than in men, when both are exposed to the same environmental conditions.

If one accepts this hypothesis, one might expect some target organs to show different stages of injury among women that do not correspond to what happens in men. Table IV lists some incidences of clinical lead toxicity among men and women.[10] These data date back to several years ago, at which time a recent study was not available. The fact is, women were not allowed to work in lead industries prior to 100 years ago. However, the trend today is for women to work in the same occupational areas as men, which might tend to produce more nearly identical exposures in

women and men who have been exposed to the same environmental conditions.

TABLE IV

INCIDENCE OF SOME CLINICAL PICTURES OF LEAD TOXICITY AMONG MEN AND WOMEN

TOXIC MANIFESTATIONS	INCIDENCE PERCENT	
	Men	Women
COLIC	77.6	69.8
PARALYSIS	57.0	30.0
CONVULSIONS	15.0	34.9
BLINDNESS - TOTAL	2.3	7.7
BLINDNESS - PARTIAL	3.5	10.2

Adapted from Pendergast, W. D., British Medical Journal, 1:1164, 1910[10]

From the limited data listed above, we can deduce that women workers are more sensitive to lead exposure than men because of the amount of lead in the blood in women exposed to the same level of environmental lead is much lower than that found in men. Also, the excretory rate of lead among women is lower than the rate in men exposed to the same level of environmental lead.

In dealing with the second question, "Does lead affect the reproductive capacity in women?" Lund,[11] has shown that there is an effect of lead on the reproductive capacity of women. In this research, it was found that the number of productive pregnancies were abnormally small among women previously exposed to lead in their occupations. This has been commented on by Hamilton, Oliver, Lane, Cantarow, and Trumper.[12-5-3] On the other hand, the Wentachee Study in 1941,[13] had shown that exposure to low lead levels in the air had no effect on fertility, either in men or women. However, women workers are exposed to higher lead levels than environmental lead. Several studies have shown that lead affects the reproductive organs in animals.[14-15-16]

From the above presentation, it is desirable to suggest that women at the stage of reproduction should not be exposed to high levels of lead.

The third problem facing us is the effect of lead on the unborn fetus. There have been several animal studies which show that the lead can cross the placenta.[14-15-17] Table V lists some lead levels in fetal or newborn blood of different animal species, as well as in humans exposed to ambient levels of lead.

TABLE V

MATERNAL-FETAL "STEADY STATES" FOR LEAD

MATERNAL DOSE OR CONCENTRATION OF LEAD			SPECIES	CONCENTRATION OF LEAD IN FETUS OR NEWBORN
Diet	µg/g		Rat	µg/g
	0.61			0.56
	64.0			4.2
	512.0			23.4
I.V.	µg/ml	time	Rat	µg/g
	705.0	1 hour		6.0
	1080.0			53.0
I.V.	µg/ml		Rat	µg/g
	50.0	6 hours		0.3
I.V.	µg/ml		Mouse	µg/g
	30.0	6 hours		0.02
I.V.	µg/100ml	20 min.	Goat	µg/g
	26.0			25.0
Ambient	µg percent		Human	µg/100 ml
	14.0			11.0*
				µg/g
	(6-26)			100.0#

* *Cord Blood (4-24)*

\# *Rib at Term*

During pregnancy, exposure of pregnant animals to a high level of lead was accompanied by abortion. This has also been shown in several clinical observations, among women workers in the lead industry. In the battery industry, among pregnant women workers having blood lead levels ranging from 30 to 80 µg/100 ml of blood, several cases of abortion were reported. The effects of lead on the fetus may be due to the necrotic effect and disturbance in the fetal blood supply which results in abortion.

If the placental membrane is of the lipoid nature with high levels of phospholipids, as in the brain, one may expect a one-way movement of lead from the maternal to the fetal side.

In some of our studies,[17-18-19-20] concentrations of lead injected into pregnant animals were accompanied by concentrations of lead in the fetus up to 10 times higher than the maternal blood levels. This may represent a selective transport of lead from maternal to the fetal side. However, with exposure of pregnant animals to higher lead concentrations, abortions occurred with only 60 percent of lead in fetal blood, compared to the maternal blood level. The protein binding capacity of lead may play a role in such cases of high blood lead levels.

Exposures of pregnant mice to different low levels of lead chloride were accompanied by complete development of the litters and normal delivery.[20] However, the litters did not show normal growth rate over a 35-day period, as expressed in weight gain in grams. See Fig 1.

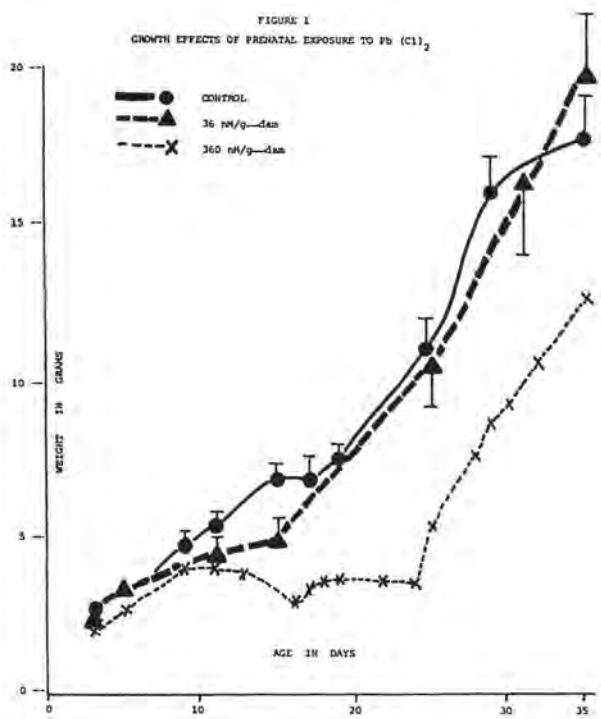

Figure 1 Growth Effects of Prenatal Exposure to Pb $(Cl)_2$

Another study was conducted on the litters with regard to motor activity development in post natal life. Figure 2 represents the effect of low concentrations of lead on the motor activity of litters born from

mothers injected with different lead levels, as well as that of controls. As is shown at the end of a 10-day period, the experimental group were very close to the controls; however, as litters developed in age, motor activity was more affected. Litters from mothers exposed to 360 nm of lead had much lower motor activity than those of control mothers or mothers injected with 36 nm of lead.

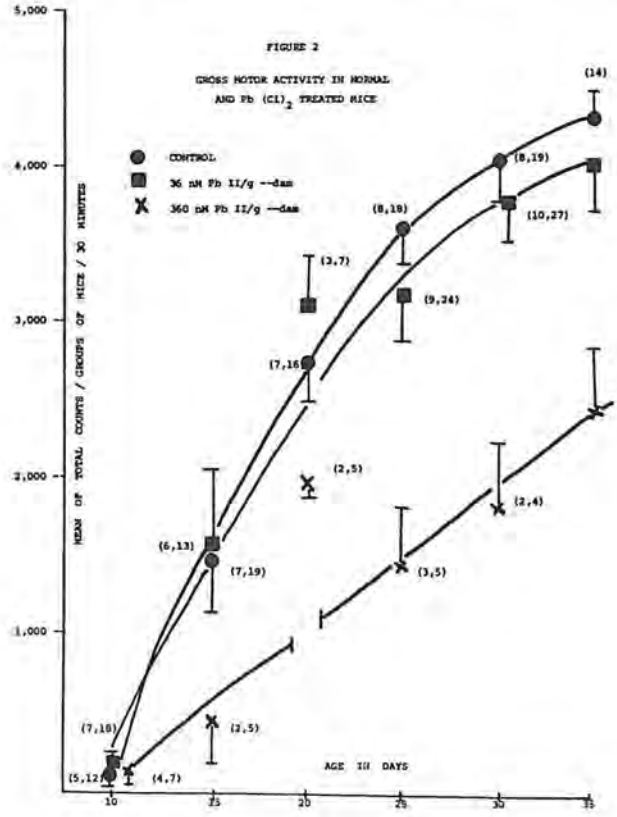

Figure 2 Gross Motor Activity in Normal and Pb $(Cl)_2$ Treated Mice

So the hazardous effects of lead on the fetus could be summarized as the occurrence of abortion with high exposures and, when litters were not aborted, a much lower rate of growth as well as diminished motor activity developed.[20]

The last point to be considered in this presentation will be the question of exposure of women workers to drugs, in addition to their exposure to lead. The synergistic effect of lead has been studied in animals and in *in vitro studies*.[17-21] The combined injection of lead and lithium in pregnant animals were accompanied by much higher damage to fetal liver than exposure to either compound alone. Tissue cluture of human liver cells (Chang cells) were used to determine such an effect. The determination of some leakage of lysosomal enzymes as β-glucoronidase and lactic dehydrogenase were determined for cultures

where lead alone, boron alone, lithium alone, or any of the combinations were added. The levels of β-glucoronidase and lactic dehydrogenase were higher in cultures exposed to any of the three elements than the control where no element was added. The increase was more than double in combinations of lead and lithium, the increase in the enzymes were mainly additive. As lithium is used a a psychotherapeutic agent, women workers exposed to lead while undergoing such therapy, may experience increased toxic effects. Also, both lithium and lead cross the placental membrane and more hazardous effects on the fetus could be expected[17,21].

In conclusion, more research is needed to determine safe levels of lead which will not result in harmful health effects in women of child bearing age. Pregnant women are at high risk to lead exposure which can also affect fetal development. Recent studies indicate that men working in the lead industry have a higher rate of abnormal children, which suggests that the reproductive system in males is affected by lead. It is important to establish a low safe level for lead in the industrial environment which will protect both men and women in the work place during their reproductive years.

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MODERATOR-Dr. Jaroslav Vostal

Thank you, Dr. Boulos, especially for keeping note of the time.

As Dr. Epstein indicated in his opening remarks, there are some questions which are of deep interest to us, especially the low level of lead toxicity as it is reflected in behavioral changes. Dr. Robert Baloh, Assistant Professor in the Department of Neurology at the University of California, Los Angeles, will be the first speaker on the topic of neurological and behavioral exposure of lead toxicology. Dr. Baloh.

NEUROLOGICAL AND BEHAVIORAL TOXICOLOGY OF INCREASED LEAD ABSORPTION

Dr. Robert Baloh
University of California, Los Angeles

A B S T R A C T

Neurologic symptoms play a prominent part in acute lead poisoning and growing evidence suggests an etiologic role of chronic increased lead absorption in several chronic neurologic diseases. A type of motor neuron disease characterized by symmetrical distal muscle wasting, slow progression, and a history of extensive exposure to lead was reported. Although response to chelation therapy was inconclusive, a therapeutic trial of chelation in any patient with motor neuron disease and history of major lead exposure was recommended. Delayed nerve conduction was demonstrated in guinea pigs slowly poisoned with lead acetate, and subsequently, electrophysiologic abnormalities were found in asymtomatic lead workers. Because of these and other similar findings, neurologists and behavioralists are questioning the adequacy of present standards of safe lead absorption.

A good way to demonstrate the spectrum of neurologic disease seen with increased lead absorption and to illustrate the problems that neurologists face when dealing with such patients is to present a few clinical case reports.

The first case concerns a man, aged fifty-one years, who worked in a secondary lead smelter for three and one-half years before developing headache, constipation, abdominal pain, metallic taste in his mouth, nausea, vomiting, and bleeding from the gums. He was treated with two five-day courses of Calcium Edthamil Disodium (CaEDTA) with relief of the acute gastrointestinal symptoms on each occasion; but he continued to complain of dizziness, headache, irritability, insomnia, decreased memory and decreased sexual drive. Six months after the onset of symptoms he had an acute onset of right sided paralyses, diagnosed as a stroke in a community hospital. He had a slow, progressive improvement over a twenty-six day hospitalization which left him with only mild residual right sided weakness.

Six months after the stroke, he had not returned to work and was admitted to the University of California, Los Angeles (UCLA) Medical Center for evaluation of persistent headaches, irritability, decreased memory and insomnia. On neurologic examination the only positive finding was mild right sided weakness. Laboratory examination revealed the following:

Blood lead: 34 µg/100 ml

Urine: 24-hr Coproporphyrin (COPRO) - 75 µg total volume (T.V.) 1411 ml

24-hr ALA - 1.4 mg T.V. 700 ml

24-hr lead - 35 µg T.V. 1070 ml

24-hr post chelation lead - 400 µg liter

EMG: Decreased voluntary motor units on right side consistent with right sided stroke; denervation potentials in small hand muscles. Nerve conduction studies within normal limits.

Other studies were within normal limits.

The second case is a forty-one year old man who worked in a secondary lead smelter for one year before developing constipation, abdominal pain, dizziness, nausea, and vomiting. These symptoms were relieved with a course of CaEDTA; but, after returning to work, he began complaining of generalized weakness, incoordination, intermittent dizziness, personality change and impaired mental functioning. During this period of time his blood lead ranged from 70 to 100 µg/100 ml. He quit work and was treated by a private physician with 10 iv infusions of 1g CaEDTA over the next five months. The 24-hour urine lead after the first CaEDTA infusion was 2631 µg and after the last 390 µg.

Because of persistent symptoms despite treatment, he was referred to UCLA Medical Center for further evaluation five months after quitting work. The only positive finding on neurologic examination was mild diffuse weakness most prominent in wrist extensors. Laboratory data were as follows:

Blood lead: 23 µg/100 ml

Urine: 24-hr COPRO - 190 g T.V. 3740 ml

24-hr ALA - 1.0 mg T.V. 1910 ml

24-hr lead - 12 µg liter

EMG: Radial nerves could not be stimulated on either side. Decreased motor units in hand muscles bilaterally.

Other studies were within normal limits.

The final case is a 26-year old man who worked in a secondary lead smelter for 1-1/2 years before developing fatigue, generalized weakness, constipation, crampy abdominal pain, nausea, headache, irritability and insomnia. During this period of time his blood lead ranged 100 to 190 µg/100 ml. He received two courses of treatment with CaEDTA (dose not known) with prompt relief of acute symptoms on each occasion. He did not return to work after the second course, however, because of persistent headaches,

fatigue, irritability and insomnia.

Three months later he was referred to UCLA Medical Center for evaluation of these chronic symptoms and additional complaints of personality change, impaired memory, decreased sex interest and intermittent chest pain. Neurologic examination was entirely within normal limits. His laboratory data were as follows:

Blood lead: 51 µg/100 ml

Urine: 24-hr COPRO - 95 µg T.V. 1580 ml

24-hr ALA - 1.0 mg T.V. 1580 ml

24-hr lead - 63 µg liter

24-hr post chelation lead - 674 µg liter

Complete Physical Examination: 3x upper normal

EKG: Nonspecific T and ST changes

Other studies were within normal limits.

These cases have several common features that deserve comment. Each patient had at least one bout of typical acute lead poisoning, manifested by severe gastrointestinal symptoms and milder nonspecific nervous system symptoms. In each case, the gastrointestinal symptoms promptly responded to chelation therapy, but the nervous system symptoms persisted and ultimately resulted in referral to the Medical Center. At the time of hospitalization, each patient had been removed from exposure for several months and there was little remaining laboratory evidence of increased lead absorption, including 24-hour post chelation lead excretion.

Unlike children, adults rarely develop prominent central nervous system symptoms as part of the acute lead poisoning syndrome.[1] However, as in these three cases reported, chronic complaints such as irritability, personality change, headache and insomnia are common. There are at least two reasons for this difference between adult and childhood lead poisoning; differing susceptability and differing rates of exposure.

The difference between acute and chronic exposure was demonstrated by Fullerton[2] when she produced death from cerebral edema in guinea pigs given a single massive dose of lead salt whereas, larger amounts spread out over weeks produced chronic wasting and weakness with wide spread motor nerve demyelination. In general, children with lead based paint ingestion have a much more acute exposure than adult lead workers.[3] A single paint chip can contain 1000 times the maximum daily permissable intake for a two-year old child.[4] A comparable degree of exposure in adults would be rare.

The developing nervous system is more sensitive to the damaging effects of lead than the mature nervous system.[5-6] This point is clearly demonstrated by the difficulty research pathologists have had in producing lead encephalopathy in adult animals.[7] Large doses of lead salts can be given to adult females of several species producing severe encephalopathy in their weaning young with little observable effects on the mother. In a recent report of brain uptake of radioactive labeled lead in adult and suckling rats, Goldstein, Asbury, and Diamond[8] found that brain uptake of lead in adults peaked after a week of chronic lead ingestion, whereas, the infants had a steady increase in brain lead concentration until they developed a fatal lead encephalopathy at four weeks of age. They also observed that CaEDTA could not remove lead that has already entered the nervous system of adults or infants. Similar results were obtained *in vitro* where the addition of CaEDTA did not remove lead bound to brain mitochondria.

Patient 1 had an apparent cerebral vascular thrombosis at age 50, without a previous history of hypertension or vascular disease. Although strokes are not a reported feature of either acute or chronic adult lead poisoning, there have been epidemiologic studies suggesting an increased incidence of strokes in lead workers compared to age-matched controls.[9] These studies were based on analyses of death certificates of former lead workers, most of whom had been heavily exposed during the early part of this century. A more recent study reported by Malcolm[10] of lead workers who died between 1963-1967, could find no increased incidence of cerebral vascular disease, suggesting that improved hygienic procedures beginning in the 1930's had paid off in improved worker survival. Because of the usual difficulties involved in retrospective studies of this type, however, the relationship between increased lead absorption and cerebral vascular disease is not settled.

The impaired nerve conduction and EMG findings in the second patient suggested chronic peripheral nerve damage consistent with his complaint of generalized weakness and the finding of wrist extensor on neurologic examination. There have been several recent reports suggesting physiologic abnormalities of peripheral nerves are common in lead workers.[11-12-13] Seppalainen and Hernberg[12] compared nerve conduction velocities in 39 lead workers with thirty-nine age-matched controls and found a significantly decreased nerve conduction velocity in the lead workers. In this original study, thirty-one of the thirty-nine lead workers had clinical lead poisoning and most had blood lead levels greater than 80 µg/100 ml.

As a follow-up study, Seppalainen and Hernberg[13] studied twenty-eight employees of a storage battery factory where worker exposure had been carefully monitored with frequent medical check-ups and blood lead determinations. They chose only workers who were asymtomatic and whose blood lead levels never exceeded 70 µg/100 m. These workers, along with an equal number of age and sex matched control subjects, were tested using

several nerve conduction measurements. As in the case of the earlier group with more severe exposure, the second group also showed a statistically significant slowing of the median and ulnar nerve maximum motor nerve conduction velocities. Even more significant were the decreased conduction velocity of slower conducting fibers, a new, apparently more sensitive, test developed by Seppalainen. On questioning, a few of these workers complained of paresthetic feelings and tiredness of the legs but none required sick leave for these symptoms. Of particular concern, in Seppalainen's preliminary observations is the suggestion that these measurable electrophysiologic abnormalities are not reversible. The continued impaired nerve conduction in the second patient, despite multiple injections of CaEDTA and months of removal from lead exposure, would support these observations.

Although there are isolated reports of significant improvement in lead induced motor neuron disease and peripheral neuropathy after treatment with chelation therapy,[14-15] most studies have not been encouraging, and in the case of motor neuron disease, death has occurred despite adequate chelation treatment.[16]

All of this data reinforces a disturbing clinical impression that nervous system damage from increased lead absorption is only partially, reversible, if at all, with chelation therapy and/or removal from further exposure. This is not particularly surprising, however, since experience with other heavy metal intoxication has been similar. Nervous system damage from arsenic and mercury responds minimally to chelation therapy.[17-18-19] Apparently, irreversible changes occur once the heavy metal is bound by nervous tissue. Although further study is clearly needed, the major point I would like to make this morning is that there is strong evidence to suggest the only reliable way to treat nervous system damage from increased lead absorption is to prevent its occurrence in the first place.

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MODERATOR-Dr. Jaroslav Vostal

Thank you Dr. Baloh for your interesting discussion. We must get on with the session for we still have one presentation before the coffee break.

The behavioral effects of lead intoxication cannot be disassociated from the neurological symptomatology of the central nervous system, and Dr. John Repko, Assistant Professor and Acting Director of the Performance Research Laboratory at the University of Louisville, will address himself to this question. Dr. Repko.

BEHAVIORAL TOXICOLOGY OF INORGANIC LEAD EXPOSURE*

Dr. John Repko
University of Louisville

A B S T R A C T

Behavioral measures of task performance and measures of body burden of lead were obtained from experimental volunteer subjects exposed, during work in three storage battery plants, to inorganic lead and sex, race, age, education, duration of employment, and geographic location matched volunteer controls working in light manufacturing plants, who reported no known exposures to organic lead or other toxic agents. Correlated, multiple-regression analyses of results indicated that measured intellectual functions were not affected but hearing, tremor, eye-hand coordination, muscular strength and endurance, hostility, aggression and general dysphoria functions were influenced by body burden of lead. Strongest relationships were obtained in the neuromuscular or psychomotor functions, and major changes occurred at blood levels between 70 - 79 µg/100 ml of blood.

A great deal of clinical and laboratory research has been concerned with the non-specific symptomatological reactions to lead. Much careful work has been devoted to subclinical monitors of lead and to the identification of underlying mechanisms that initiate and sustain such a response. Yet, and in sharp contrast, the nature and pathogenesis of the psychophysiological and mental impairments and the work performance decrements that appear in workers with elevated lead levels have received very little systematic study. Until recently, there have been no quantitative data from controlled experiments on the behavioral or functional effects of organic lead exposure.

Most of the studies relevant to occupational exposure describe behavior patterns that result from either excessive or dangerous body burdens of lead. Little is known of the behavioral or performance effects of low or "acceptable" body burdens of lead. Moreover, no study has attempted to systematically relate an individual's functional capacity to wide ranges of specific indices of the body burden of lead.

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**This research was conducted by Dr. Repko, John A. Nicholson, Performance Research Laboratory and the Department of Pharmacology, University of Louisville, Louisville, Kentucky, and Ben B. Morgan, Jr., Old Dominion University, Norfolk, Virginia. The program under which this work was completed was supported by NIOSH under Contract No. HSM 99-72-123, "Evaluation of Behavioral Functions in Workers Exposed to Lead."*

From the studies dealing specifically with the evaluation of psychological and behavioral functioning and the data compiled in our laboratory, one is able to identify functional categories in the types of behavior affected. Specifically, these studies have identified psychological and behavioral patterns which demonstrate the effects of lead poisoning on (a) intellectual functions; (b) sensory functions; (c) neuromuscular functions; and (d) psychological functions. A study, which involved the behavioral testing of 316 lead workers with lead levels ranging up to 243 µg/100 ml of blood,* was recently completed at the Performance Research Laboratory (PRL). This presentation will not only provide a summary of some of the more important data cited in the literature but also data obtained from this study. In both cases, remarks will be confined to the functional categories mentioned previously.

Intellectual Functions

Although the impairment of learning and memory has been cited in case descriptions of lead poisoning, experimental investigations of the effects of lead on learning and on memory are sparse. Mentesana[1] and Kiryakov[2] both describe subjective reports of progressive deterioration in learning capacity. In each study the case histories describe individuals with several years of excessive, industrial lead exposure. The data, however, were based on subjective observations made by the patients and their families and leave much to be desired in terms of the quantitative effects of lead.

Nevertheless, cases of intellectual deterioration in adults have been reported. In Hay's Study in 1950[3] a 30-year old man, who worked in a British co-operate firm, developed encephalopathy. A large number of the classical symptoms of lead intoxication were evident and treatment was initiated. About four to seven months later, the Wechsler-Bellevue intelligence test and the Shipley-Hartford test showed intellectual deterioration. Rageth[4] reported the case of a 60-year old man who clearly showed reduced learning ability, retardation, and failing ability to concentrate. These behavioral changes, however, were not evident until 6 years after an injury from metallic lead chips. In both studies the intellectual deterioration was associated with extreme levels of lead intoxication.

In the study at the PRL, significant differences in intellectual functioning or a systematic relationship between body burden and

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**For a full report of this study see Repko, J. D., Morgan, B. B. Jr., and Nicholson, J. A. "Final Report on the Behavioral Effects of Occupational Exposure to Lead." PRL Report No. ITR-74-27, 1974.*

functioning were not obtained. However, this should not be taken to mean that all intellectual functions are unaltered. Re-analysis of our data has indicated that particular attention should be given to the ability of leaded subjects to learn new skills or to improve performance through practice. Although not significant, the data did suggest that performance efficiency on a forced-paced arithmetic computations task did not improve to the same extent for the experimentals as it did for the controls.

Sensory Functions

The second functional category, sensory functions, involved specific behavioral deficits which deal with the visual and auditory systems. Lead apparently affects three areas which specifically support visual functioning.

1. Neuritis may occur within the visual system itself.[5] If this neuritis is intraocular, it is associated with papiloedema; if it is retrobulbar, only the subsequent atrophy and the nerves behind the eye will be seen. Moreover, a scotoma, which may be limited to certain colors, is usually present in optic neuritis and some degree of atrophy usually occurs.[6,7]

2. Within the circulatory system, changes in the character of the red blood cells and supporting fluids and tissue may lead to changes in intraocular tension.[7] According to Mel'nikova,[8] this effect may result from reflex regulation rather than changes in the character of the circulatory system *per se*.

3. Lead apparently affects the intrinsic muscles and oculomotor nerves of the visual system. Interference with the normal functioning of these areas may lead to mydriasis (pupillary dilation) or visual paralysis.[5,6,7] In this study, a test of visual acuity was employed, which, in retrospect, was not sufficiently sensitive to detect systematic differences in functioning. Ryazanov[9] suggests that threshold measures of light and dark adaptation might be used to indicate the existence of lead poisoning.

While some auditory dysfunctions have been attributed to lead intoxication,[4,10,11] the actual effects are unclear. A deficit of up to 30 or 40 dB at the high frequencies has been reported in workers in European battery plants.[12,13,14] For example, Valcie and Manojlovic[11] studied the effects of carbon monoxide, lead, and carbon disulfide on the auditory threshold of workers from several different industries and found deficits in the 4000-8000 hertz range. Similarly, Balzano[14] studied 16 workers who had been exposed to lead fumes or dust for several years, or who showed clinical symptoms of lead poisoning, and found no deficit in hearing low tones (below 512 Hz), mild deficit in the middle tones (512, 1024, and 2044 Hz), and large deficits in the high tones (above 2044 Hz).

The same hearing losses were evident, irrespective of whether the tone was promulgated *via* air or *via* bone conduction, suggesting that the effects of lead on hearing are central rather than peripheral. Koch and Serra[15] found that 12 workers exposed to tetraethyl lead (TEL) experienced impairment but possessed normal audiograms below 200 Hz. On the other hand, Atchabarov, Moshdevich, and Pyataev[16] found that 15 percent of a sample of 21 leaded workers had deficits at the low and high frequency ranges with good sound perception at the medium frequencies. These findings are supported by data obtained from the PRL group. In the PRL Study, loss of hearing, as evidenced by increased auditory threshold, was significantly correlated with decreases in ALAD, thereby suggesting that as the body burden increases there is a commensurate loss of auditory function. Moreover, initial increases in hearing levels were evidenced at blood lead levels between 70 - 79 µg/100 ml for all frequencies tested. In order to look further at auditory functions, a tone decay test was conducted, Figure 1.

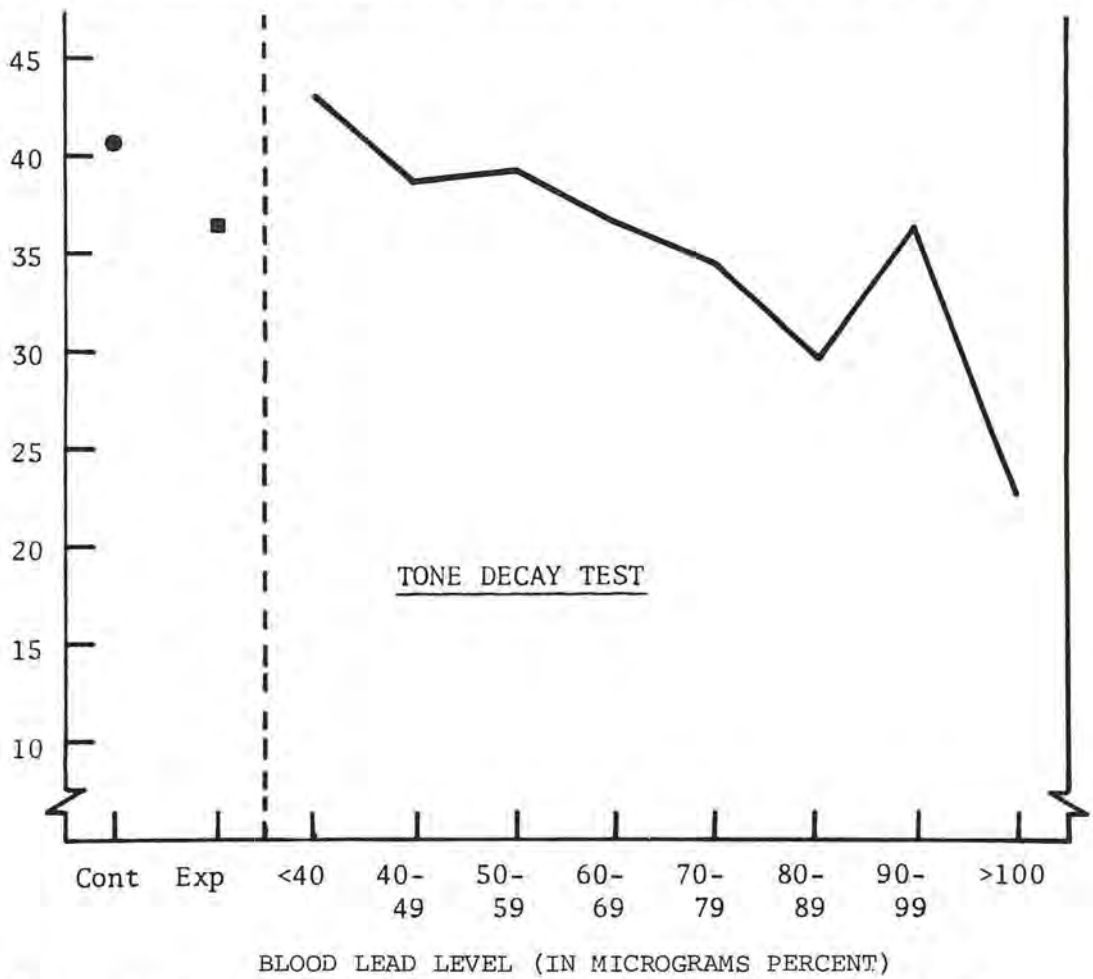

Figure 1 Mean duration of tone decay for the experimental and control groups and as a function of PbB subgroups

The results showed that there was a significant correlation between increases in the audible duration of a tone and increases in blood lead, thereby providing some suggestive evidence of auditory pathology. Data showing the relationship between body burden levels and the audible duration of a tone are shown in Figure 1.

Neuromuscular Functions

The impairment of neuromuscular function is one of the classical signs of severe lead intoxication.[17-18-19] Impairment has been reported most commonly in four groups of muscles: (1) the extensors of the wrist and fingers (radial nerve); (2) the extensors of the toes and foot (peroneal nerve); (3) the small muscles of the hand; and (4) the deltoid, biceps, brachialis anticus, and long supinator.[19] Early signs of neuromuscular dysfunction include muscle weakness,[3-16-20-21-22] easy fatigue,[19-23] tremor,[24-25] and lack of muscular coordination.[3-24-26] The observed weakness generally occurs after muscular exertion and on the preferred side.[19] If intoxication is substantial, paralysis may result.[18-27]

Behavioral effects have been measured in tasks that require rapid motor responses. Reaction times of lead intoxicated workers have been compared to those of non-exposed workers by various Soviet and Eastern European scientists.[28] Increased reaction times have been reported in leaded workers in response to spoken words or other auditory stimuli,[29-30] to visual stimuli,[30] and to electrical stimuli.[29-31]

In our study, three tasks assessing muscular activity were employed; namely, tremor, eye-hand coordination, and muscular strength. The data in Figure 2 show increases in tremor for the non-preferred hand with increases in body burden and these increases correlated significantly with decreases in ALAD. You can see from these data that groups above 70 µg/100 ml of blood (especially on the pre-test) showed a great deal more tremor than groups below that level. Moreover, in our test of eye-hand coordination there was also a significant negative correlation between blood ALAD and response variability and a similar negative correlation with increase in response latency. The specific relationship between blood-lead groups and eye-hand coordination measures is shown in Figure 3.

In our test of strength, endurance and recovery, there was an increase in strength (both trials) and a decrease in endurance. This relationship is shown in Figure 4; the correlations between decreases in ALAD and each of these measures were significant.

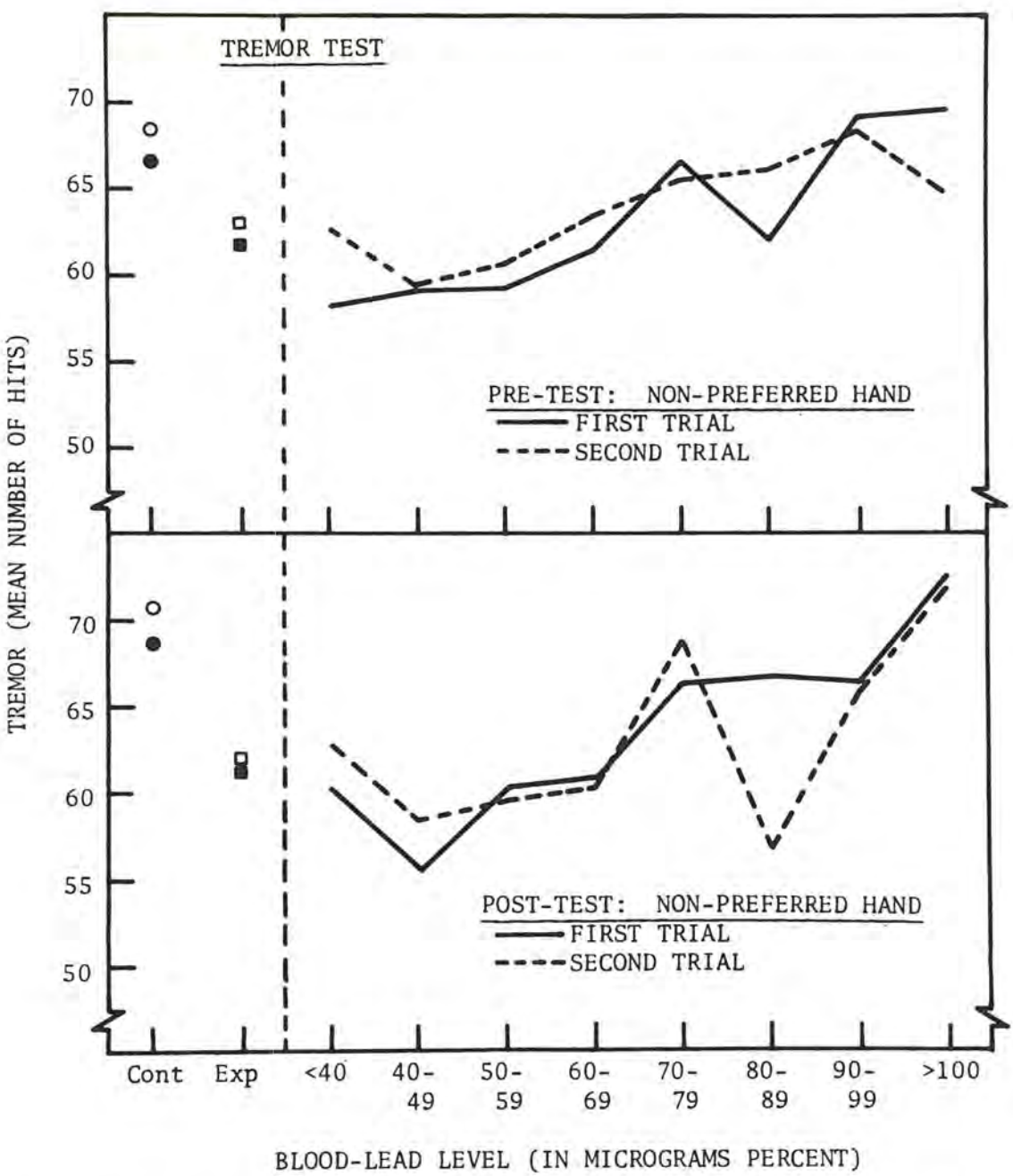

Figure 2 Mean tremor for the non-preferred hand of the experimental and control groups and as functions of PbB subgroups; the first and second pre-test trials are given in the top panel and the post-test trials are given in the bottom panel

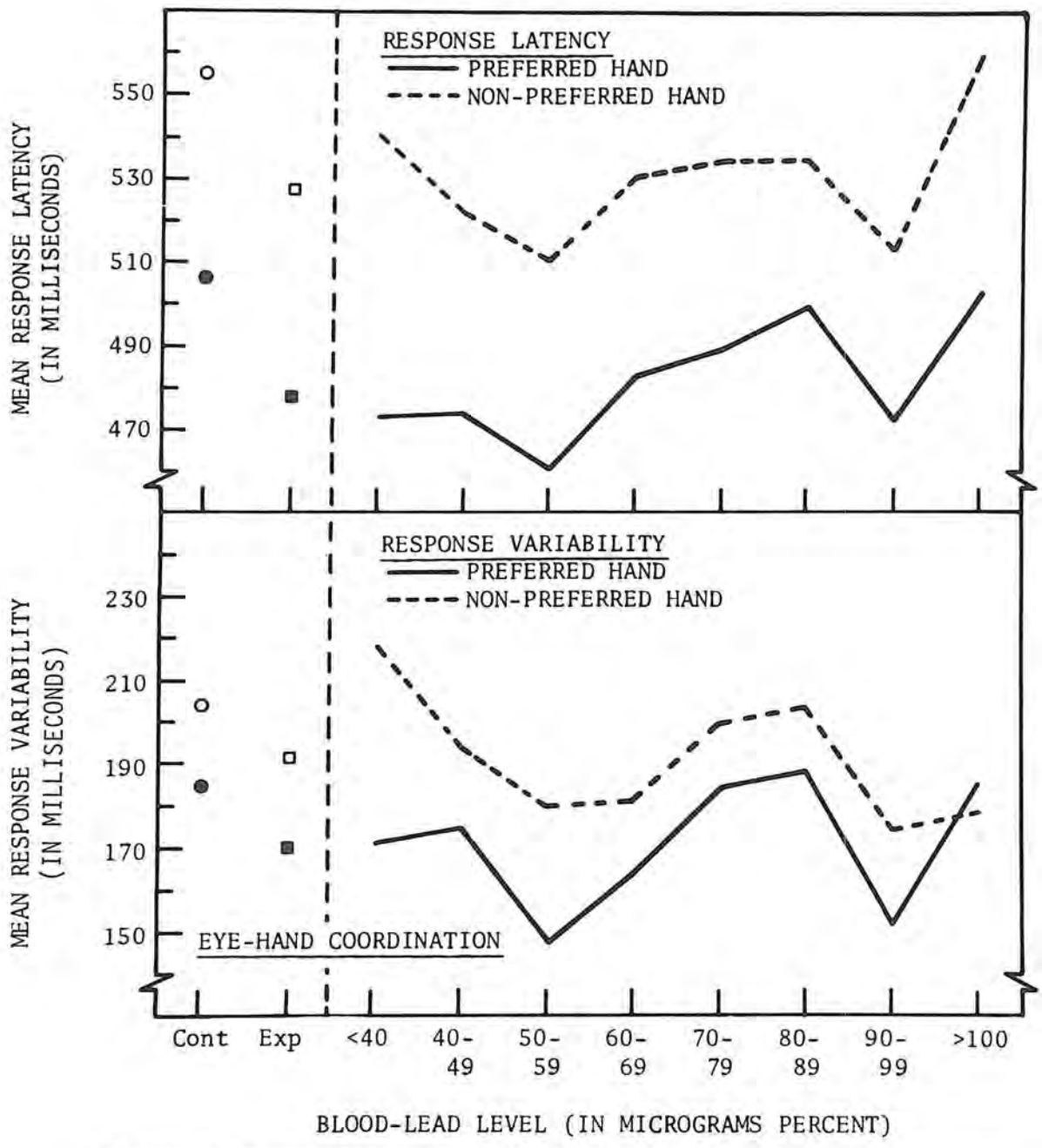

Figure 3 Mean response latency (upper panel) and mean response variability (lower panel) for the experimental and control groups and as functions of PbB subgroups

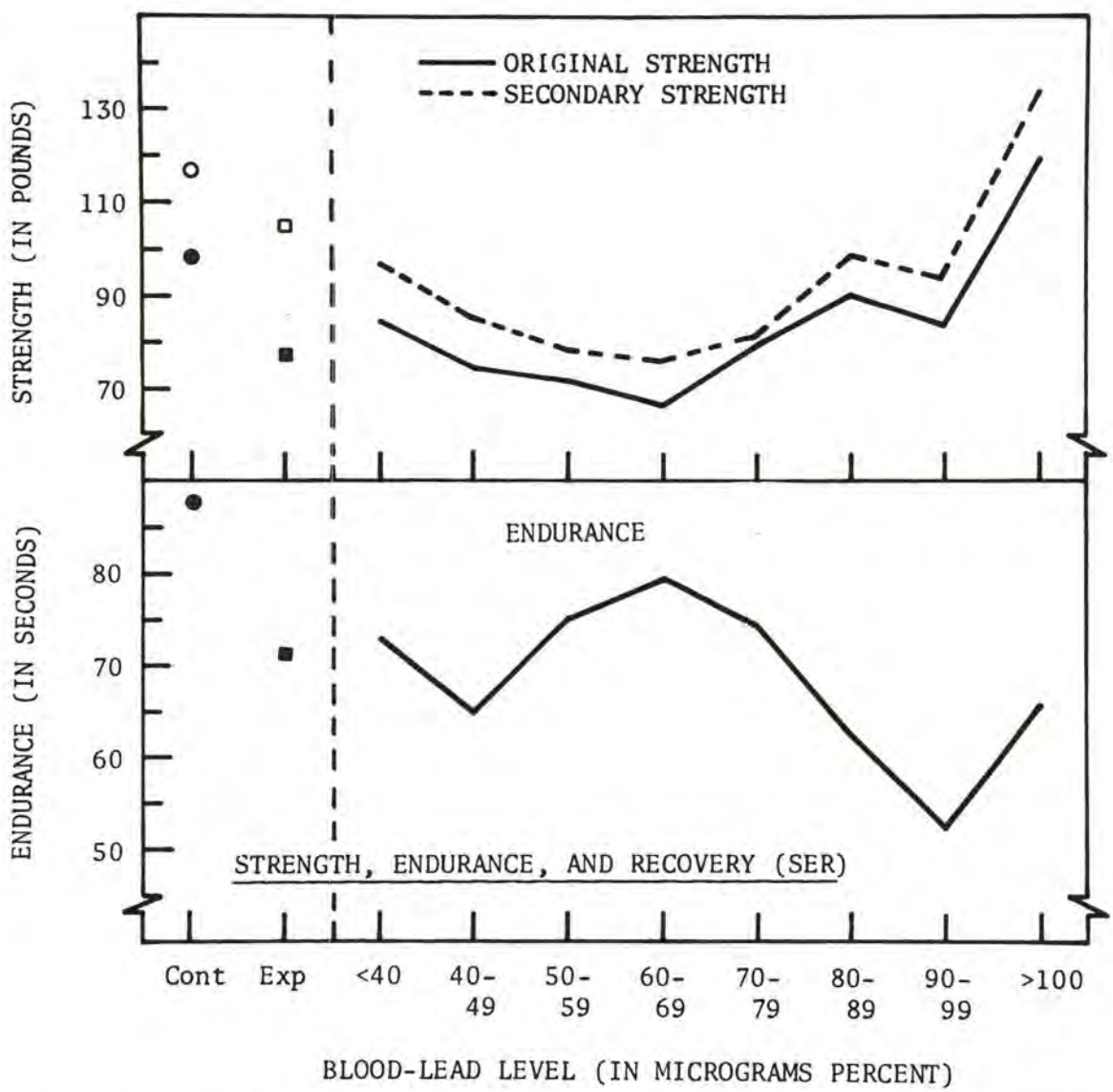

Figure 4 Strength (top panel) and endurance (bottom panel) for the experimental and control groups and as functions of PbB subgroups

Motor reflexes have been shown to be slowed in leaded workers.[30-31] Rubino, *et al*,[32] developed a method of measuring the patellar reflex which consisted of a stimulator (small hammer), electrodes, and an electromyograph. Normal latency of 25 control subjects was about 114 msec with values as high as 167 msec. These authors and others[33] recommend using EMG's as early detectors of lead intoxication. In recent studies by Seppalainen,[34-35] subclinical nerve damage was detected in lead workers with no other clinical neurological symptoms. She found that the conduction velocities in the ulnar and median nerve were significantly lower for the lead workers than they were for the control group. In one particular study[35] reductions in conduction velocity were observed in groups with blood-lead levels as low as 40 µg/100 ml of blood.

In summary, it is clear that lead intoxication, particularly at high levels, may result in various neuromuscular dysfunctions; the consequences of such dysfunctions will be to detrimentally affect the performance of tasks involving motor responses.

Psychological Functions

The final category, psychological functions, is one which has also received a great deal of research. Psychological responses to lead poisoning cover a wide range and are subject to large individual differences. Probably the most common psychological manifestation of lead poisoning cited in the literature is irritability and uncooperativeness of the patient.[19-36-37-38] Other behavioral characteristics which are cited include hostility, hyperactivity, moodiness, depression, delirium, and occasionally, mania or psychosis.[19-39] Unfortunately, the literature dealing with adult behavior resulting from lead intoxication tends to simply list the clinical characteristics with no description of the overt behavior (*e.g.* Freed[40]). Considering that many lead intoxicated patients suffer from headaches, insomnia, colic, constipation, and other medical symptoms, it is perhaps not too surprising that they exhibit abnormal emotions and personality traits.

The data which are most obviously lacking are those which would define the relation between the extent of these behaviors and the body burden of lead. While our data did not specifically answer this problem, scores obtained for the Multiple Affect Adjective Check List* of hostility, depression, and general dysphoria were significantly higher. We, therefore, felt confident in making the statement that the psychological impact of working in a leaded environment is one of increased hostility, depression, and dysphoria.

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**From Zuckerman, M., Lubin, B., Vogel, L. & Valerius, E, Measurement of experimentally induced affects, Journal of Consulting Psychology, 28,418-425, 1964.*

Recommendations

Because most industrial hygienists and governmental regulatory agencies employ blood lead as an index of the extent of exposure, any indicated changes in biomedical monitoring criteria must include this specific measure. Since the purpose of any exposure criterion is to provide maximum protection to the health and safety of the greatest proportion of the worker population, criteria should be based on actual changes in functional capacity as well as changes in medical measures. It is not sufficient that standards of exposure be based solely on medical criteria.

Therefore, *based on the behavioral data of this study, a biomedical standard of 70 µg/100 ml of blood lead is recommended.*

Moreover, since ALAD was found to be the strongest clinical measure of functional capacity, ALAD should be employed as a measure of the *effect* of exposure. Although blood lead and ALAD were significantly correlated ($r = -.29$), the data of this study indicates that ALAD is the dominant predictor of functional disorder. *Based, therefore on the behavioral data and the relationship between blood lead and ALAD, a biomedical standard of 21 units of ALAD activity is recommended.*

Any ALAD level less than 21 units of activity (and a blood lead in excess of 70 µg/100 ml) indicate not only that the exposure is excessive, but that the effect of that exposure is potentially hazardous to the worker's functional capacity.

I would also like to suggest that functional measures be utilized in routine health-monitoring programs. As soon as possible and practical, such programs should specifically include auditory and neuromuscular assessments. Appropriate auditory and visual tests are currently available to industrial hygienists; feasible neuromuscular tests must be developed and made available.

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MODERATOR-Dr. Jaroslav Vostal

Thank you, Dr. Repko.

CONFERENCE CHAIRMAN-Dr. Bertram Carnow

Thank you again. I would like to thank all of the participants.

We have a coffee break at this time. I would like to appeal to all of you to limit break time to fifteen minutes sharp so that there will be sufficient time to complete this session before lunch.

- -

MODERATOR-Dr. Jaroslav Vostal

We will reopen the session on the Toxicology of Lead. We have for a long time been interested in learning if it is true that there might be a specific symptomatology of low lead levels in children as a result of childhood poisoning. Dr. Ellen K. Silbergeld, a Fellow in Neurosciences in the Department of Environmental Medicine at Johns Hopkins University, will address the problem of the effects of lead intoxication on the central nervous system. Dr. Silbergeld.

NEUROCHEMICAL AND PHARMACOLOGICAL STUDIES OF CENTRAL NERVOUS SYSTEM LEAD TOXICOLOGY*

Dr. Ellen K. Silbergeld
Johns Hopkins University

A B S T R A C T

Clinical and experimental attention has focused on the effects of low level lead exposure on behavior and central nervous system function. Experimentally, hyperactivity occurs at doses below those associated with the onset of other signs of lead poisoning. Pharmacological and neurochemical studies suggest that chronic lead exposure produces a behavioral disorder characterized by altered response to aminergic and cholinergic agents, and, neurochemically, by increases in several parameters of noradrenergic function and decrease in cholinergic neurotransmission. The experimental data suggest that low level exposure to lead may result in a behavioral disorder similar to minimal brain dysfunction in its anomalous pharmacology.

Clinical attention has turned recently to low level, so-called asymptomatic or subclinical aspects of lead exposure.[1] Epidemiologically, as we have heard, this is the range of exposure in which significant numbers of urban children and workers in lead industries are now diagnosed on the basis of measurements of blood levels and body burdens of lead. Of concern in investigating low level exposure are: the first effects seen upon undue exposure to lead; the long term effects of chronic low level exposure; and the reversibility of these effects if such exist. Animal studies in this area are now investigating behavioral toxicology, specifically in terms of learning and performance deficits, and are correlating these with neurochemical and pharmacological abnormalities following exposure to lead. The animal studies to which I will refer have used rats, mice, sheep and rhesus monkeys, although the studies I shall mainly discuss use rodent models of lead poisoning.

The general protocol of exposure to lead in these animal studies, as mentioned earlier, is to expose suckling offspring indirectly through dosing the mother by means of adding lead to her food or water, or directly through injecting or force-feeding the offspring themselves. Varying times of exposure have been used as short as the first ten days of life or as long as life long exposure. High doses in animal studies can produce the full-blown symptomology of lead poisoning. In work by Michaelson[2], rats exposed to lead demonstrate severe growth retardation,

**Supported in part by NIEHS grants 00034, 00454, a Research Starter Grant from the Pharmaceutical Manufacturers Association, and a Fellowship from the Joseph P. Kennedy, Jr. Foundation.*

ataxia, peripheral paralysis and incontinence. Eventually these animals die in convulsions. As shown in Figure 1 (courtesy of Dr. Michaelson), brains of these animals, when compared to brains taken from control animals of the same age, show edematous swelling of the frontal lobes and the cerebellar hemorrhaging characteristic of lead encephalopathy.[3-4]

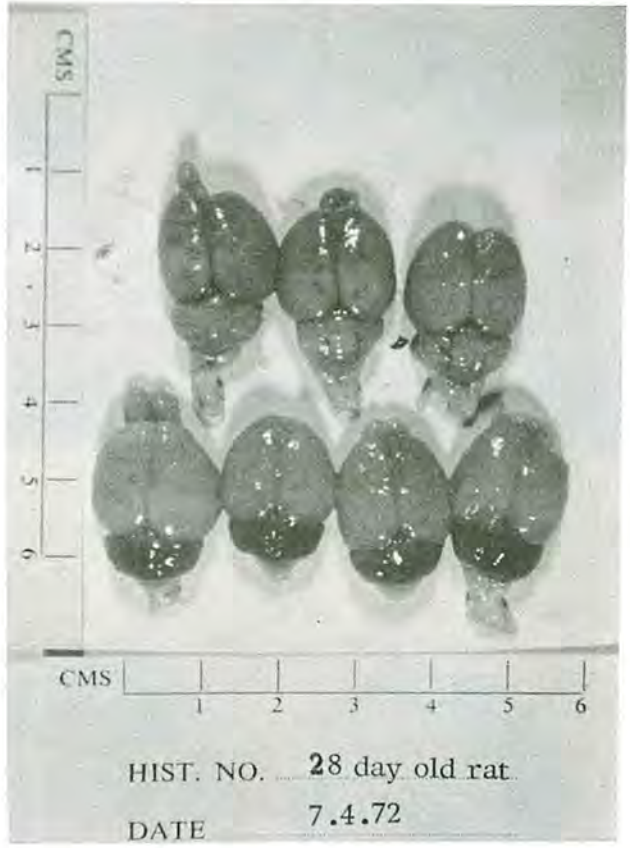


Figure 1 Brains from lead-treated, encephalopathic rats (four lower brains) compared with brains from age-matched controls (three upper brains). Cerebella from lead-treated animals are haemorrhagic; frontal areas edematous.

Slide courtesy of Dr. I. A. Michaelson.

Low levels of exposure under similar protocols do not produce these effects on gross appearance of the animal. A 40-day old mouse exposed to 10 mg/ml lead in its drinking water from birth has a slight problem in walking, but no significant growth retardation and no paralysis.[5] These animals live a normal course of life, see Figure 2.

Brains taken from these animals show no edematous swelling, no hemorrhagic appearance in the cerebellum, see Figure 3.

Figure 2 Effects of exposure to lead on appearance in mice: animal at upper right of picture was given water containing 10 mg/ml from birth; lower animal is age-matched (40 days old) control.

From Silbergeld and Goldberg, 1974.[5]

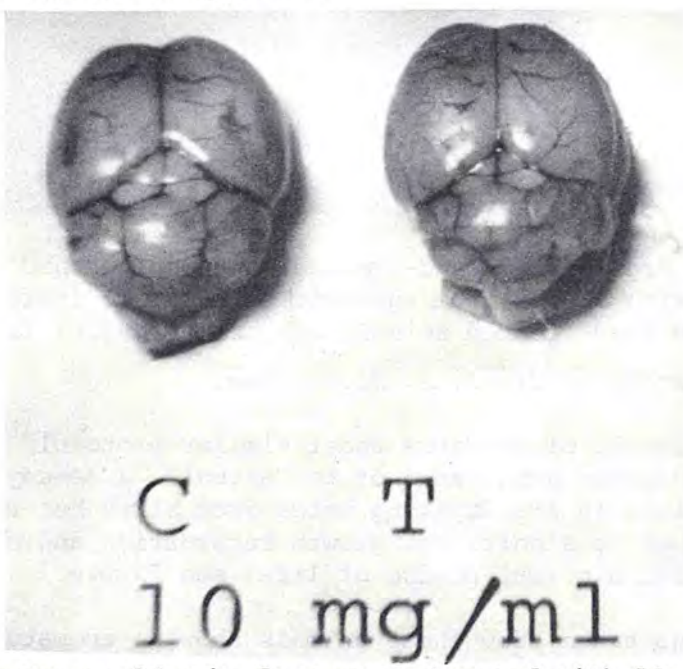


Figure 3 Appearance of brain from mouse treated with 10 mg/ml lead acetate in drinking water (right) as compared with brain from age-matched (40 days) control mouse (left).

Upon light and preliminary electron microscopic examination of selected cortical areas of these brains, there is no ultrastructural damage ascribable to lead. It is important to note that the behavioral and neurochemical toxicology to be described herein is not apparently associated with extensive structural damage to the brain.

These lead-exposed animals display several significant differences when compared to controls. In Table I, developmental landmarks as measured by several standard indicators of rodent development eye opening, full incidence of body hair, co-ordinated walking and weaning are delayed in their appearance in the lead-treated animals.[6] In the case of weaning, the delay is as much as eight days when compared to controls in our laboratory and to data for the strain (Swiss Webster outbred CD-1) as developed by the breeding laboratory. Most significantly, however, the behavior of these animals is significantly altered.

TABLE I

DEVELOPMENTAL LANDMARKS IN
LEAD-TREATED AND CONTROL MICE*

	Day of Occurence		
Landmark	Strain Data[a]	Controls	Lead (10 mg/ml)
eye opening	14	13	17
full incidence of hair	16-17	16	20
Coordinated walking	17-18	18	25
weaning	21	22	30

[a] *information on CD-1 mice supplied by Charles River Laboratories.*

**Data from Silbergeld and Goldberg, 1973*[6]

Figure 4 presents data on spontaneous motor activity in mice for three life long doses of lead, 2, 5, and 10 mg.ml in drinking water as compared to control. These three doses produce approximately 2 to 3 fold increases in spontaneous motor activity. This effect is not dose dependent, which suggests to us that one of the earliest symptoms associated with low level exposure may be increases in spontaneous motor activity. With continued or increased levels of exposure, hyperactivity may be compromised by the induction of other toxic effects such as ataxia and problems in neuromuscular

control.[7-8]

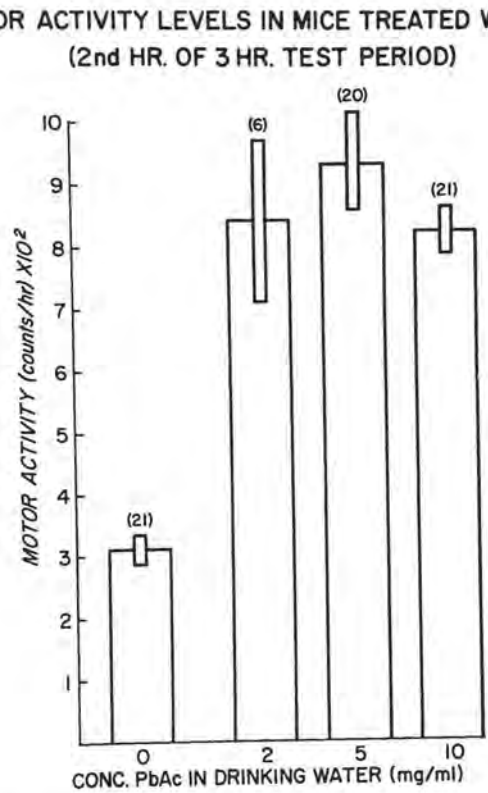


Figure 4 Motor activity levels in mice treated with 2, 5, and 10 mg/ml lead acetate in drinking water from birth, as compared to controls. *Data from Silbergeld and Goldberg, 1973.*[6]

We have been interested in examination of this behavioral alteration hyperactivity, in terms of pharmacological responses, Table II.[9] Our interest prompted me to ask Dr. Baloh the question about possible psychotropic medication of the men he has been examining. Most interesting to us has been the fact that the stimulant drugs, d and l-amphetamine, dimethylaminoethanol, and methylphendiate (Ritalin) produce paradoxical sedation of the hyperactivity of these animals, as indicated by two downward pointing arrows in the table. These drugs have the expected stimulatory effects upon control animals. Also, the sedative phenobarbital, exacerbates the hyperactivity of these animals at a dose with a slight sedative effect upon controls. Chlorpromazine, a tranquilizer in widespread use, sedates both groups of animals. However, in the lead-treated hyperactive animals, the effect of chlorpromazine is greatly attenuated both in terms of onset of sedation and duration of sedative action.[9] Some of the other drug effects listed in Table II may be of interest to the pharmacologist, and will be of interest in terms of neurochemical alterations we have observed in these animals.

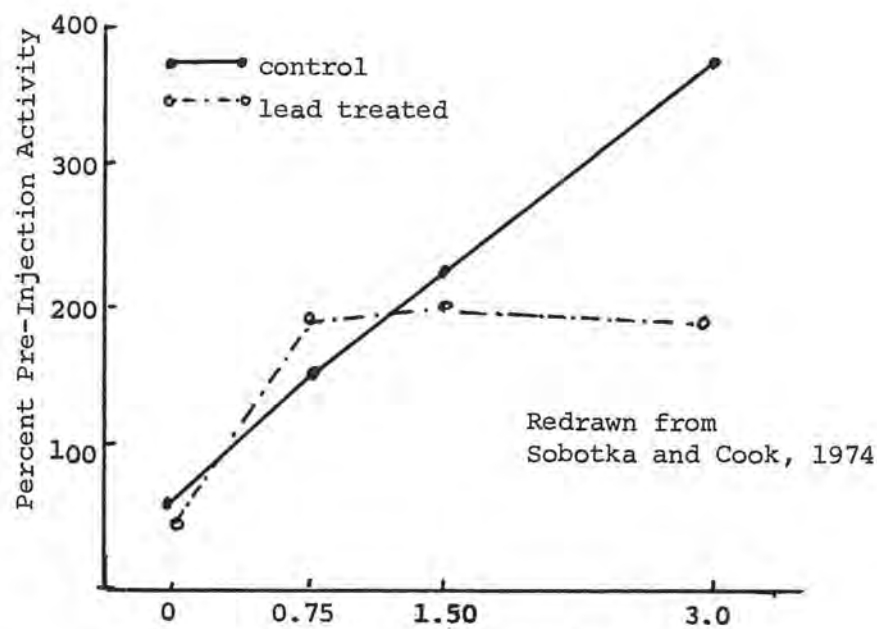
TABLE II

EFFECTS OF DRUGS ON LEAD-INDUCED HYPERACTIVITY[a]

Drug (Dose mg/kg)	Effects on Lead-Treated Hyperactive/Controls		Comments
α-methylparatyrosine (50)	↓↓	0	In treated, produces "normal" response to amphetamine; In controls abolishes amphetamine response
d-amphetamine (10)	↓↓	↑↑	In controls, some stereotypy
l-amphetamine (10)	↓↓	↑↑	
dimethylaminoethanol (200)	↓↓	↑	
chloral hydrate (100)	sedated	sedated	
fenfluramine (20)	↓↓	↑	
methylphenidate (25, 40)	↓↓	↑↑	
oxotremorine (0.08)	↓	0	
physostigmine (0.1-0.5)	↓↓	0	
apomorphine (10)	0	↓	In treated, induces stereotypic circling and increases reactivity
chlorpromazine (5)	sedated	sedated	In treated, onset of sedation delayed and duration shortened
atropine (0.01)	0	0	In treated, increases reactivity
benztropine (15)	↑	0	In treated, increases reactivity
l-dopa (50)	↑↑	0	In treated, increases reactivity
phenobarbital (20)	↑↑	0	
caffeine (50)	↓↓	↑	

[a] *Data from Silbergeld and Goldberg, 1975.*[9]

The other point we have drawn from these data is the interesting parallel between experimental lead-induced hyperactivity and the hyperkinetic syndrome common to behavioral disorders in children with drugs of choice in paradoxically calming hyperkinesis seen in children.[10] In addition, as shown in Figure from Sobtka and Cook[11] (1974), the importance of altered drug response may be to indicate the first effects of lead as a central nervous system toxicant. Lead-treated rats in this study were force-fed 80 mg/kg lead during critical developmental stages from days 0 through 20 of life. As adults, they were compared to controls for their behavioral response to increasing doses of amphetamine. These animals were not hyperactive, although they had some trouble in learning a cross-over response test. As can be seen in Figure 5, the controls showed normal dose-related increases in motor activity with amphetamine expressed as percent of pre-injection activity. Beyond the first dose, lead-treated animals show significant attenuation of amphetamine response. At the highest dose used, 3 mg/kg, these lead-treated animals reversed their learning deficit.[11]



Adapted from data of Sobotka and Cook, 1974.

Figure 5 Amphetamine dose-response study of lead-treated and control rats (lead-treated rats received lead acetate 81 mg/kg/day *per os* from day 3 to 21 after birth). Activity was measured in a photoautometer for 15 minute periods following intraperitoneal injection of saline or d-l-amphetamine and compared to the 15 min. period prior to injection. In the absence of

drug treatment, activity levels were not different between lead-treated and control animals.

The alterations in drug response strongly suggested to us significant changes in brain chemistry resulting from lead and associated with hyperactivity, Table III. We studied central nervous system acetylcholine metabolism because of long-standing reports in the literature of the effects of lead on neuromuscular function. Acetylcholine is the neurotransmitter chemically coupling nerve and muscle. In other studies, we and others have shown that at the neuromuscular junction the release of acetylcholine is decreased significantly upon *in vitro* exposure to lead equivalent to 0.2 mg/100 ml of blood.[7,8,12] Similar effects are evident on the release of acetylcholine in the central nervous system using cortical slices from the hyperactive animals chronically exposed to lead.[13]

We also looked at choline, the precursor of actylcholine, which is synthesized in neural tissue into the neurotransmitter. The incorporation of this precursor into nervous tissue may be an important regulatory step in nervous system function. In the animals chronically treated with lead, synaptosomal incorporation of choline is decreased 50 percent as compared to controls.[9] In work by Michaelson and by us, we have found significant enhancement of noradrenergic function in the brain. This is expressed in increased levels of norepinephrine[9,14] and increased turnover rate of norepinephrine[14] which is a more sensitive measure of function. Increases in the accumulation of tyrosine seen in tissue from lead-treated animals are consistent with elevations in levels and in turnover of norepinephrine, since tyrosine is the metabolite precursor for that transmitter.

Effects of lead on norepinephrine metabolism are important because this may provide a means of estimating the impact of lead on central nervous system function useful in clinical screening. Metabolites of norepinephrine appear in the urine and can be measured to estimate the status of central and peripheral nervous system noradrenergic function. The metabolite of serotonin, 5-hydroxyindoleacetic acid, is reported elevated in the urine of asymptomatic Yugoslav lead workers.[15] We have not seen changes in levels of serotonin or in its transport; however, we have not completed measurements of its metabolites and turnover studies have not been done.

In conclusion, the data support the hypothesis that lead can, at low levels of exposure, exert specific and significant effects upon animal behavior, pharmacology, and neurochemistry. These are manifested in altered behavior, specifically hyperactivity, and in decreases in learning. Lead-induced behavioral dysfunctions are associated with changes in two important CNS neurochemical pathways, acetylcholine and norepinephrine.

TABLE III

NEUROCHEMICAL STUDIES OF LEAD POISONING

COMPOUND	ASPECT STUDIED	RESULT	REFERENCE
Acetylcholine	levels	no change	(1)
	stinulated release:		
	CNS	decreased 40%	(2)
	ganglia	decreased 40%	(3)
	neuromuscular junction	decreased 30%	(4)
Choline	Transport	decreased 50%	(1)
	levels	no change	(2)
Norepinephrine	levels	increased 27%,13%	(1,5)
	turnover	increased	(6)
	transport	no change	(1)
Dopamine	levels	no change	(1,5)
	transport	decreased 20%	(1)
	turnover	no change	(6)
GABA	levels	no change	(7)
	transport	no change	(1)
Glycine	transport	no change	(1)
5-HT	levels	no change	(7)
	transport	no change	(1)
Tyrosine	transport	increased 15%	(1)
Phenylalanine	transport	no change	(1)

1. *Silbergeld and Goldberg, 1975, Levels and trasnport in whole forebrain tissue from hyperactive mice chronically exposed to 5 mg/ml lead acetate in drinking water.*

2. *Goldberg, Carroll and Silbergeld, 1975. Levels and release determined in brain tissue from hyperactive mice exposed as in 1.*

3. *Kostial and Vouk, 1957. Release determined in ganglia perfused with 2.4 μM Pb^{++}.*[16]

4. *Silbergeld, Fales and Goldberg, 1974b. Change in release estimated as percent decrease in in vitro neuromuscular contraction after 2-hour treatment with 5.0 μM Pb^{++}.*

5. *Goldbert and Michaelson, 1975. Turnover and levels determined in hyperactive rats fed diets containing 400 ppm lead.*

6. *Michaelson, Greenland and Roth, 1974. Turnover determined in vivo in hyperactive rats as in 5.*[17]

7. *Sauerhoff and Michaelson, 1973. Levels determined in brains of hyperactive rats fed diets containing 40 ppm lead.*

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MODERATOR-Dr. Jaroslav Vostal

Thank you Dr. Silbergeld for an informative presentation.

I would now like to introduce our last speaker in this session, Dr. Robert Goyer, Professor and Chairman of the Department of Pathology at the University of Western Ontario. Dr. Goyer will address the questions pertaining to the toxicology of lead and effects on the kidney and other organs. As you can see, we started at the center of our system and we are going down.

TOXICOLOGY OF LEAD ON KIDNEY AND OTHER ORGANS

Dr. Robert A. Goyer
University of Western Ontario

A B S T R A C T

Renal effects of lead in man are of two types. Children with acute lead poisoning have a proximal renal tubular defect characterized by amino-aciduria, glycosuria, and hyperphosphaturia. Adults with chronic lead poisoning have a toxic or interstitial nephropathy with nonspecific morphological changes. Alcohol and dust, apart from renal function, may influence susceptibility to lead intoxication. A case will be presented in which an asymptomatic, former lead worker developed a reversible neuropathy and biochemical features of lead poisoning during an episode of acute alcoholism and low dietary intake.

In this brief presentation, the pertinent renal effects of lead will be summarized and two topics introduced for discussion which, I believe, should receive more study. The first is a possible decrease in the ability of an individual with chronic lead nephropathy to excrete lead, and the second is the role of alcohol, nutrition, and other metabolic factors in alteration of susceptibility to lead toxicity.

First, the pathological effects of lead on the kidney will be reviewed before introducing these two topics.

Figure 1 summarized the morphologic and functional effects of lead on the kidney. There are at least two stages in the development of lead nephropathy. The first stage is an acute reversible effect usually seen only in children. It consists of morphological and functional changes in proximal renal tubular lining cells. These changes include alterations in mitochondrial structure and function, and the formation of intranuclear inclusion bodies or lead-protein complexes. These changes are accompanied by an increase in urinary excretion of amino acids, glucose, and by an increase in urinary excretion of amino acids, glucose, and phosphate. These changes are reversible with chelation therapy and it has recently been shown that the initial large excretion of lead within twelve hours of a dose of EDTA is associated with mobilization of inclusion bodies from nuclei of renal tubular lining cells.

Stage I	Swollen proximal tubular lining cells Mitochondrial changes Nuclear inclusion bodies Proximal tubular dysfunction
Stage II	Fewer inclusion bodies Interstitial fibrosis Tubular atrophy and dilatation
Stage III (rats only)	Renal tumors

Figure 1 Stages of Lead Nephropathy

Whether acute lead nephropathy, treated or untreated, influences the development of any form of chronic nephropathy without continuous lead exposure is uncertain. Follow-up studies of children in this country with documented acute lead poisoning show no evidence of higher incidence of renal disease as adults, so the evidence is that Stage I lead nephropathy is completely reversible.

Stage II nephropathy can be produced in experimental animals by feeding a high dosage of lead for more than a year. Similar changes are found in workmen with excessive lead exposure for more than two or three years. The interstitial fibrosis becomes progressively more severe with tubular atrophy and eventually reduced glomerular filtration and renal failure. This process may progress for many years without renal failure occurring so there are many little known influencing factors. Of course, the actual level of lead exposure and frequency are more important factors of chelation therapy.

With continued feeding of lead to rats, renal tumors occur, but only in rats, and have not been observed in other species of animals or as a result of chronic lead exposure in man.[1]

These illustrations show the renal effects being discussed[2,3].

An example of stage I or acute lead nephropathy is shown in Figure 2. It is a biopsy from a young man with only eight-months experience as a ship wrecker in Sweden. In his job he burned off heavy layers of lead paint from old naval vessels with an acetylene torch, an occupation that may result in heavy exposure to lead. The nucleus of the proximal renal tubular lining cell contains a lead-protein complex or inclusion body.

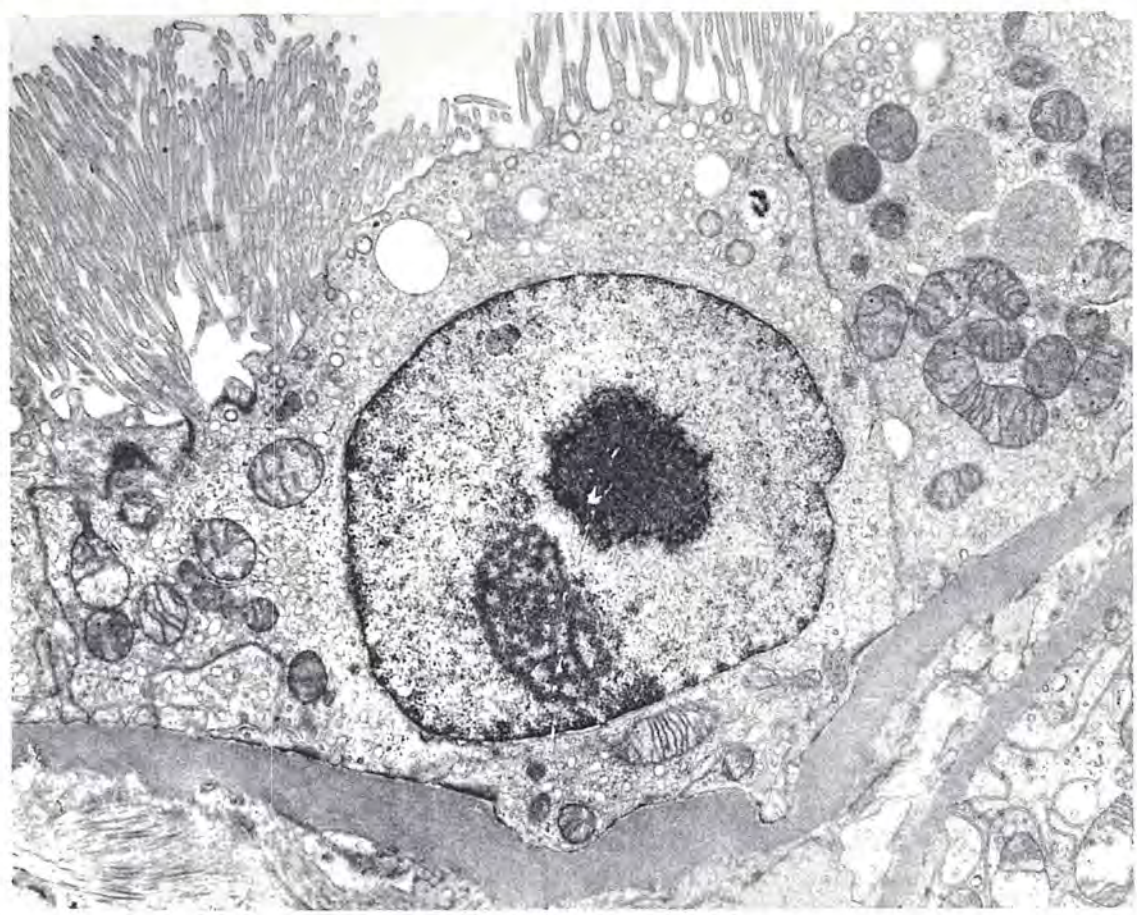

Figure 2 Renal biopsy of a 28 year old shipwrecker shows a dense intranuclear inclusion body characterized by a fibrillary outer margin and independent of the nucleolus. Mitochondria have abnormal arrangement of cristae.

From Cramer, Goyer, et al, Brit J Indust Med, 31:113-127, 1974

The abnormal mitochondria are better seen at higher magnification in Figure 3. These mitochondria show swelling, abnormal arrangement of christae and attempts at cleavage or budding. All of these changes are reversible with EDTA therapy.

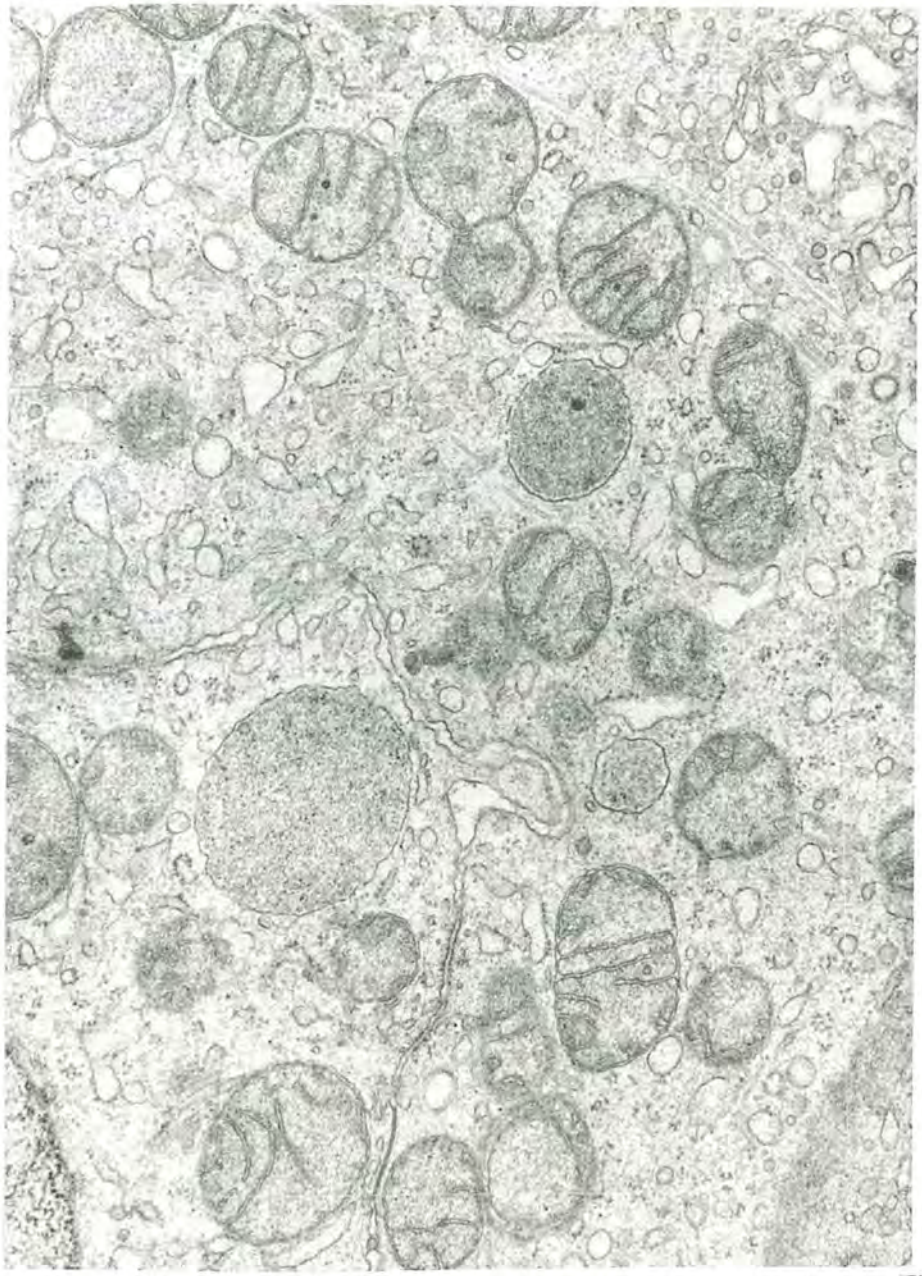

Figure 3 Higher magnification of cells seen in renal biopsy shown in Fig 2. Mitochondria show evidence of cleavage or budding.

From Cramer, Goyer, et al, Brit J Indust Med, 31:113-127, 1974

Figure 4 shows an inclusion body beginning to break up, 24 hours after an injection of EDTA to a lead poisoned rat.

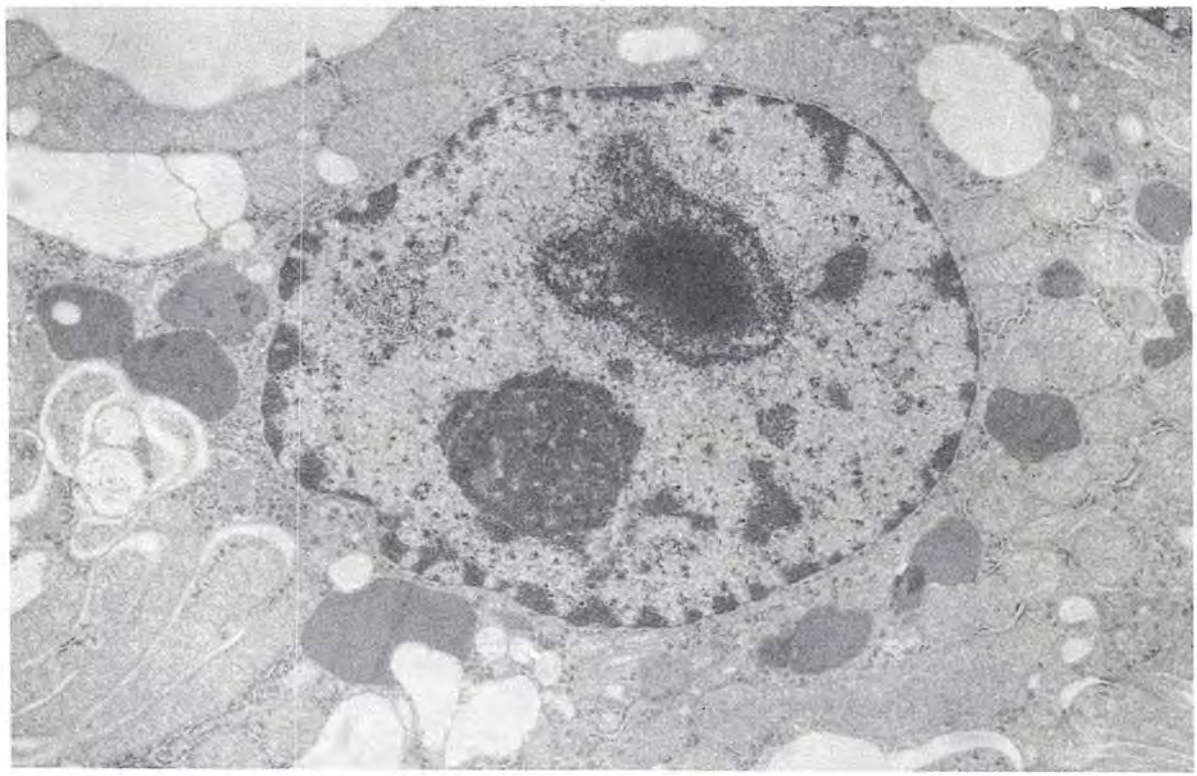

Figure 4 Lead induced inclusion body in the nucleus of a proximal renal tubular lining cell of a lead poisoned rat 24 hours after a single injection of EDTA. There is slight disruption of the periphery of the inclusion, and the fibrillary margin is loosened.

From Goyer and Wilson, Lab Invest, 1975

In Figure 5 there is formation of nucleo-cytoplasmic channel for passage of the inclusion body into the cytoplasm.

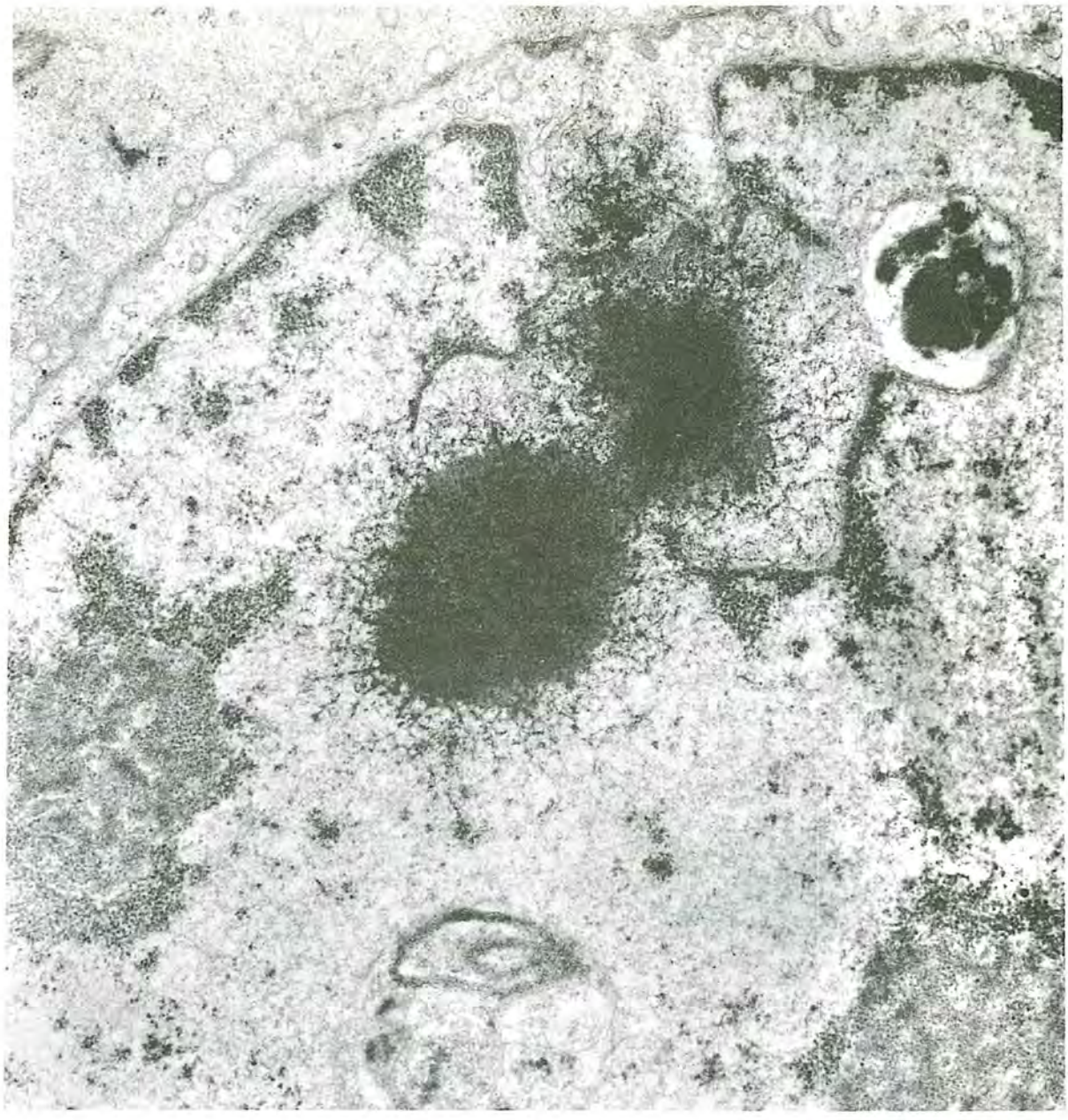

Figure 5 Migration of nuclear inclusion body through channel in nuclear membrane of renal tubular lining cell, 24 hours after a single injection of EDTA

From Goyer and Wilson, Lab Invest, 1975

Finally, Figure 6 shows a cytoplasmic vacuole containing a body which looks like a nuclear lead-protein complex.

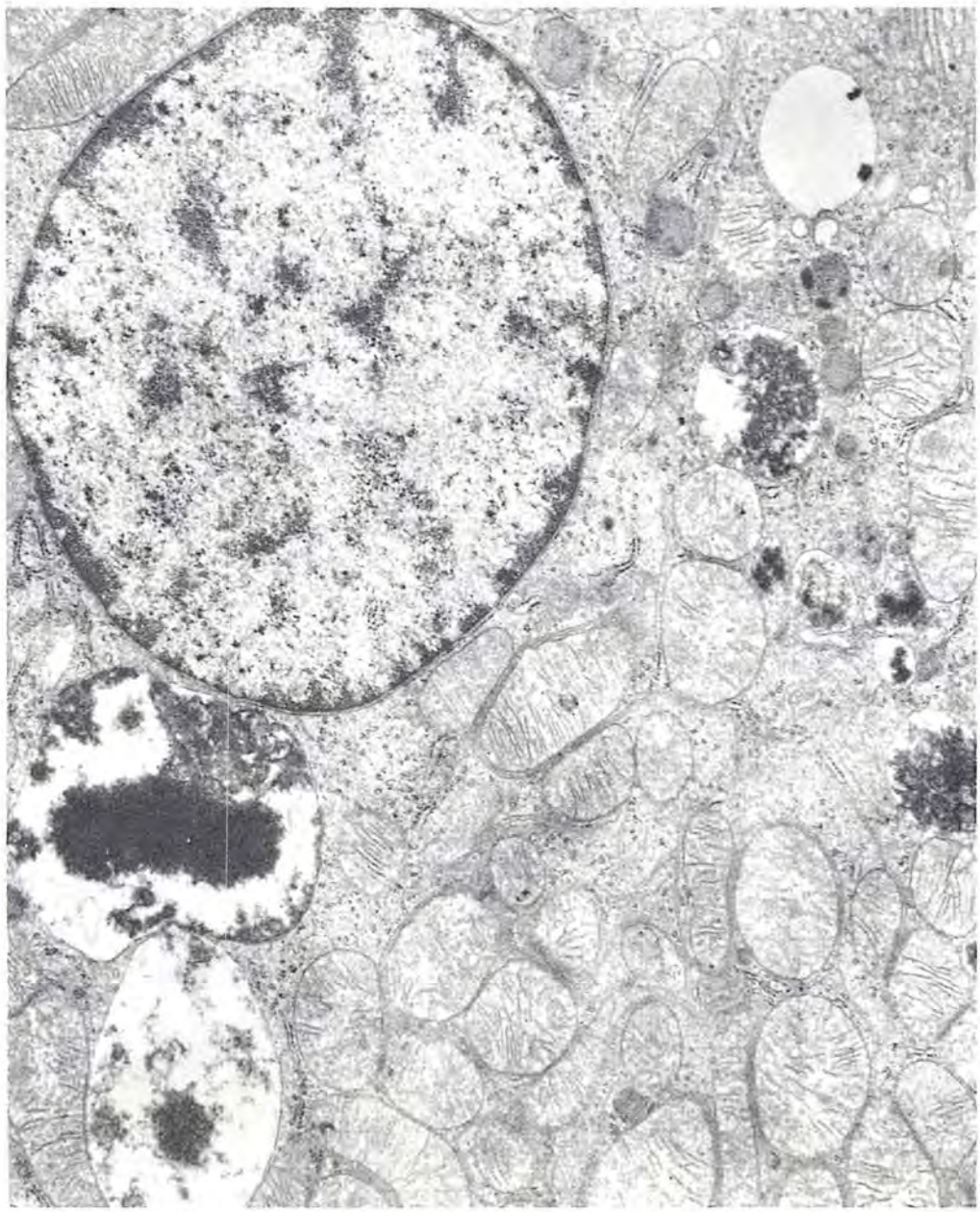

Figure 6 Vacuoles in cytoplasm of proximal renal tubular lining cell, 24 hours after three daily injections of EDTA. The nucleus does not contain an inclusion body. A cytoplasmic vacuole contains a dense body which is probably the remaining portions of a lead-inclusion body following disruption and migration from nucleus.

From Goyer and Wilson, Lab Invest, 1975

There are no inclusion bodies remaining in tubular lining cells after a 72-hour course of EDTA therapy. Also, the mitochondria appear normal and renal tubular function is normal, indicating that acute lead nephropathy is reversible by EDTA. Versenate is a form of EDTA and in view of some comments made this morning, I do not want to imply that it is a completely innocuous substance. Long term or repeated exposure to EDTA does have pathological effects on renal tubular lining cells.

A biopsy from an older workman with chronic lead nephropathy is shown in Figure 7. It shows interstitial fibrosis, tubular atrophy and dilatation, some hyperplasia of cells in functioning tubules and no inclusion bodies. These changes are non-specific.

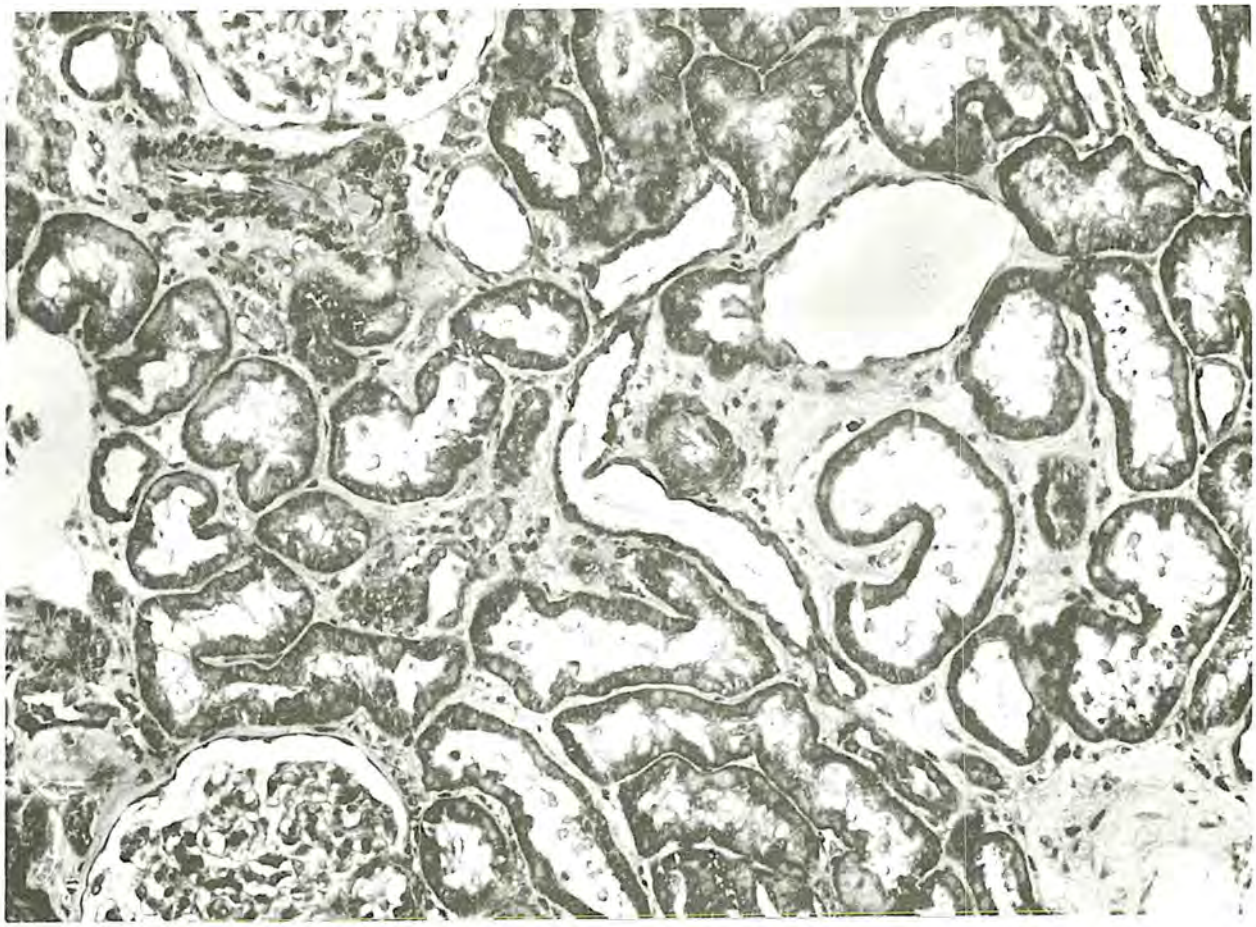

Figure 7 Renal biopsy from a ship-wrecker with many years of excessive exposure to lead. Photomicrograph is from cortex of kidney and shows a diffuse interstitial fibrosis with atrophy of some tubular lining cells.

From Cramer, Goyer, et al, Brit J Indust Med, 31:113-127, 1974

Table I is a summary of renal function in five ship workers with different lengths of exposure to lead.

TABLE I

SUMMARY OF RENAL FUNCTION IN FIVE SHIP WRECKERS WITH DIFFERENT LENGTHS OF EXPOSURE TO LEAD

Age	Exposure in years	Renal Clearance mls/min/1.73^2		Pb-B µg/100ml	Pb-U µg/24 hr	U-ALA mg/100 ml
		Insulin	PAH			
Normal values		125	600	<60	<150	<4
26	8/12	101	596	103	366	4.7
35	6/52	128	888	129	458	4.7
41	12	65	600	138	259	16.4
47	8	108	710	77	263	7.0
66	10	121	693	109	192	5.7

The top line contains normal values. The first two men have acute lead nephropathy, with inclusion bodies. The first man has an 8-month work history; the second man, 6 weeks. The most interesting point here is that the last three men with chronic lead nephropathy by renal biopsy have lower urinary lead excretion per 24 hours than the two with acute nephropathy. This introduces the first point for discussion.

It is an important consideration in terms of whether workmen with chronic lead nephropathy are, in fact, able to excrete lead as readily as individuals with only acute lead effects, and this observation needs further investigation in larger numbers of workmen, as well as information on lead as determined by bone biopsy or EDTA provocation.

The other topic to be introduced for discussion is the question of whether an asymptomatic workman, even one who is retired from work and no longer has excessive exposure to lead, can, under particular metabolic conditions, mobilize enough lead from storage depots in bone to produce symptoms of lead toxicity.

Studies in experimental animals with various levels of lead intake have shown that both iron deficiency[4] and low calcium intake[5] can result in higher absorption of lead as well as mobilization of lead from bone to soft tissues. It is known that symptoms of lead poisoning relate to blood lead levels and soft tissue levels regardless of the body burden in bone.

In a recent study a case of lead poisoning in an older man emphasizes this question. This patient was under the care of Dr. N.M. Jaatoul, Westminster Hospital, London, Ontario. A 60-year old retired male truck driver worked for a period of five years in Trail, British Columbia as a construction worker in the area of lead smelters while they were in operation. This was when he was between the ages of 20 and 25 years. He related no symptoms of lead poisoning at that time but other workers in the area became sick. Because he was not an employee of the smelter, he was never tested for lead poisoning. He later was in army combat in World War II and has worked as a truck driver since then. He had no other known exposure to lead. In the past two years he had repeated, severe episodes of acute alcoholism, and in July of this year was admitted to the Veterans' Administration Hospital (VA) with acute alcoholism, mild diabetes mellitus and polyneuropathy which included ataxia. Because testing did not show motor involvement typical of alcoholism or diabetes and red blood cell smears showed the basophilic stippling typical of lead poisoning, blood lead and ALA analyses were made and elevated blood lead levels were found. He was then treated with EDTA for 3 days and blood lead levels decreased and remained lower; however, he continued to drink and nutrition was generally poor after he was discharged from the hospital. There is no way to ascertain that he did not have recent exposure to lead. It is doubtful that his problem can be attributed to lead contaminated moonshine, since he insisted that he only drinks good clear Canadian whiskey.

On the basis of the known effects of metabolic factors, particularly low dietary calcium as demonstrated in experimental animals, I would like to raise the question of whether bone lead in individuals can be mobilized into diffusible and potentially toxic metabolic compartments such as blood and soft tissues, under the stress of poor nutrition and possible other calcium mobilizing illnesses such as fever, acidosis, or even long term catabolic illness, such as cancer.

A great deal more in-depth study of metabolic influences on blood lead levels in such people will be required before such a relationship can be established. I believe that blood and perhaps urinary lead determination of a few selected individuals could greatly help our understanding of the potential long-term effects of an increased body burden of lead and, at the same time, tell us what factors are important in preventing any potential adverse effects.

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MODERATOR-Dr. Jaroslav Vostal

Thank you Dr. Goyer for your presentation.

Now I would like to open for discussion and questions.

QUESTIONS, ANSWERS, COMMENTS

COMMENT-Dr. Charles Hine

I would like to comment on this problem of clinical lead intoxication at levels below 80 µg/100 ml. I have reviewed data representative of 5000 man-years, about 20,000 analyses, carried out by a laboratory of excellent and highest quality. I have never seen clinical symptoms in a man whose lead value was less than 80. It has never been reported in this group. At exposures leading to blood lead values about 80 and up to 120 µg/100 ml, we have seen probably an average of one man a year who had symptoms of lead intoxication. To explain reports in the literature of clinical damage or clinical symptoms occurring below this level (80 µg/100 ml), I refer back to your original remarks, doctor, that the variabilities in the efficiency of lead analysis is considerable among most laboratories.

COMMENT-Dr. Morris Joselow

That may be, but there are just too many reports in the literature to be ignored and explained by analytical error alone. In a very recent study commissioned by the International Lead Zinc Research Organization Inc., the average content of the thousands of lead workers examined ran around 60 µg/100 ml, yet in this group the incidence of kidney problems, nephritis, nephrosclerosis, was significantly different from control groups. There certainly are clinical manifestations. The work of Beritic, who observed lead colic with blood lead levels in the 40-89 µg/100 ml range, the reports of Gibson, Sappalainen, Waldron, Lilis, our own work in New Jersey, and others, were careful investigations. We just cannot dismiss all of these as being based on faulty data.

COMMENT-Dr. J. C. Calandra

Dr. Joselow is correct that bad data on blood lead values has been "enshrined in the literature." However, we should not enshrine the line of reasoning that leads to the suggestion that blood values of 8 µg/100 g in the adult and 4 µg/100 g in children are the maximal acceptable lead blood levels. These values are unattainable even if lead was abolished from all industrial uses.

COMMENT-Dr. Morris Joselow

I recognize with you, of course, that blood lead values of 8 µg/100 ml for adults and 4 µg/100 ml for children are unattainable in our present world. But attainability is not, or should not be, a factor that enters into a judgment on safety. Such judgments should involve considerations only of physiology, pharmacology, biochemistry, etc. In making decisions

on safety, we determine not what is, but what should be, based on sound and proper toxicological principles. Unfortunately, and altogether too often, regulatory officials in air and water pollution confront this problem every day. We are compelled to adapt to the real world and compromise on safety. Academicians may permit themselves the luxury of a hard, uncompromising line on safety and health. Others will have the more difficult problem of deciding how much to yield for the sake of practical expediency.

QUESTION-Dr. Kenneth Bridbord

One point I want to make is that Drs. Stivik and Zielhvis* have recently shown that women compared with men with similar blood levels showed evidence of greater biochemical effects. The question is, was there any account made for men's doing heavier work with a greater oxygen demand and increased ventilatory function compared to women?

ANSWER-Dr. Badi Boulos

Yes, the type of work was sometimes blamed for these differences. With regard to women workers who came from low socioeconomic families, they needed to work at home to care for their families and this would be an additional stressor in increased fatigue, so she would have increased susceptibility. However, as I mentioned before, blood lead levels in the University of Illinois Hospital showed such trends of higher levels of lead in women's blood than in men's blood. As you suggest, there may be other factors, such as biochemical transformation, hormonal differences or differences in rates of excretion, which enter into these differences.

QUESTION-Dr. Peter Bertozzi?

In regard to this difference of proteins and hormones in the blood of men and women, are there any factors that make the measurements of lead higher than the actual values of lead in women's blood?

ANSWER-Dr. Badi Boulos

I agree that proteins can bind with lead and make differences in measurement values. However, the data reported were for total blood lead levels. This point could have an effect if we determine only lead in plasma or serum, but since we were determining total blood lead, this binding capacity did not affect the measurements.

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**Stivik, E. J. and Zielhvis, R. L., Increased susceptibility of females to inorganic lead, Proc Int'l Symposium-Environ and Hlth, Paris, June, 1974*

QUESTION-Dr. Ellen Silbergeld

I wonder if any of the cases that you or other physicians have come across were tested in terms of psycho-medication for personality changes?

ANSWER-Dr. Robert Baloh

I did not go into that aspect at all. We are currently trying to do more sophisticated neuropsychological testing in these workers. When they are treated, they are treated symptomatically. We have not systematically studied the effect of treatment, but they appear to respond to medication like any other patient under similar circumstances. We are attempting to quantify possible neuropsychologic abnormalities seen in lead workers and I hope to be able to report on these studies at some future time.

COMMENT-Dr. Sidney Lerner

People that work with lead are not immune from developing every other disease known to mankind. As such, I think we ought to all be very careful before we identify the cases of illness that occur in people who are not exposed to lead as even being suggestive of the relationship to lead without further and more extensive data. I would furthermore suggest that the neurologists provide the same degree of quality control to the EMG studies and long term follow up as be required of analytical workers in their determinations of blood leads.

COMMENT-Dr. Robert Baloh

I would have to agree with both points that you made. I presented these cases as examples of the dilemma that can confront the neurologist when attempting to make a diagnosis of lead poisoning and yet, we had little laboratory evidence to support this diagnosis, at least at the time we saw them.

COMMENT-Dr. Sidney Lerner

I was simply making a plea about the quality control of the EMG.

COMMENT-Dr. Robert Baloh

There is no question that EMG studies require quality control. The EMG's on these patients were done by myself and a colleague at the UCLA EMG lab.

QUESTION-Dr. Dwight Culver

I am Dr. Culver from the University of California. In your study of

hearing loss among lead workers, Dr. Repko, did you attempt to correlate the exposure to lead with the exposure to noise?

ANSWER-Dr. John Repko

We did not make that specific corrolation, but in all cases, I think, of the 316 people we had only 2 incidents of workers who were exposed to noises greater than 85 dB in the sample of workers we tested. I might add also, that in the analysis we did run some analyses in which we held age as a co-variant, so we did controls for the effects of age.

QUESTION-Dr. Dwight Culver

I understand that you conducted those tests without the use of an audiometric booth.

ANSWER-Dr. John Repko

That is correct. One place in the plant was identified as a high noise exposure area. I think that is the part of the plant in which these 2 particular workers were employed. We have some environmental sampling data, noise data, for the time of testing, where we could get it and these data were not above 85. There were some instances where we could not get in to get the correct data.

QUESTION-Dr. Dwight Culver

Do I understand correctly that you conducted those tests without the use of a sound chambers?

ANSWER-Dr. John Repko

That is correct.

QUESTION-Dr. Dwight Culver

And the ambiant background sound levels ranged between 65 and 80 Db.

ANSWER-Dr. John Repko

We had ear muffs which attenuated the background to approximately 50 or less dB, ear muffs which the individuals were wearing. Also, the data, rather than absolute, are relative. In other words, both the control and the experimental group of subjects were, in fact, tested under the same conditions and we still got these differences.

COMMENT-Dr. Dwight Culver

Same difference in the same variability in background noise even in

different plants?

ANSWER-Dr. John Repko

Oh, yes. We still had the same range of noise values under all conditions. In fact, we have separated out some of those data which are not in the report. There were certain circumstances under which the noise backgrounds were at 70 and below and these data also are in line with the overall data of the study. This was a group of individuals in which the controls and experimental were drawn from different plants, but the testing was actually conducted in the same room. In other words, we were at one location for those two samples and we still got the same results. So since they were the same I did not treat them differently.

QUEATION-Ms. Shirley Norman

Dr. Repko, did you have test lab audiograms for these employees prior to exposure to lead?

ANSWER-Dr. John Repko

No, we did not.

QUESTION-Ms. Judy Bellin

You suggest or seem to indicate that there were serotonin as increased levels, yet an increase in serotonin metabolism has been reported. Do you know if lead acts as a MAO effector and has anyone looked at this? It was also reported that lead in the brain is sequestered in the mitochondria, yet MAO is a microsomal enzyme.

ANSWER-Dr. Ellen Silbergeld

Studies showing deposition of lead in mitochondria are at significantly higher doses than those at which we have been working. Visually, we have not found a distribution of lead in various organelles in the brain. There has been some work on lead in monomaine oxidase; again, I believe, at high *in vitro* concentrations of lead. I would like to point out that although steady-state levels of serotonin are reported unchanged in lead-treated animals,[9*] this does not mean that turnover, that is functioning of serotonergic pathways, is the same as in controls. Much more study in terms of turnover and synthesizing and degrading needs to be done. The neurochemical data are not conclusive at the present time.

QUESTION-Dr. David Parkinson

I wonder if in your ultrastructure examinations you looked at a number of dissected bronchi. The second question, did you find a correlation between ALA that was in the blood plasma and your systemical and neurologic

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* See Reference 9 on Page 83

disturbances.

ANSWER-Dr. Ellen Silbergeld

Examination of electron micrographs of the caudate region of the brain showed no obvious changes in myelination, synaptic structure or vesicular structure. We have as yet been unable to find any structural changes associated with lead-induced hyperactivity. However, histopathological studies of brain tissue are continuing. In response to your second question; we are now attempting to correlate patterns of urinary metabolites of norepinephrine with ALA measurements, blood and urine measurements in children and adults exposed to lead. On the basis of preliminary estimate data, there is a coincidence between increased excretion of lead, ALA, and elevations in urinary vanillyl mandelic acid.

QUESTION-Dr. Dwight Culver

Dr. Silbergeld, is it my understanding that you worked with young and teen animals or did you do some work with **adults?**

ANSWER-Dr. Ellen Silbergeld

Most of our work, as you mention, has concerned the development of the behavioral paradigm of lead-induced hyperactivity in terms of childhood lead exposure. However, we have also looked at continuing exposure throughout adulthood and *in vitro* exposure of brain tissue and peripheral nervous system tissue from adult animals to define the specific mechanisms of lead's neurotoxic action. The age-related differences in toxic sequelae of lead exposure have a great deal to do with the accessibility of the brain and nervous tissue to lead. But given that a sufficient amount of lead may reach the brain or may reach the peripheral nervous system, the toxic effects of lead would not necessarily differ on the basis of age.

COMMENT-Mr. Gerald Kennedy

I should be pointed out that the levels of exposure in the experiment described are high doses (5 mg/ml in the drinking water is equivalent to one gram/kilogram of body weight in the mouse). Granted that the blood lead levels are approximately 20 µg/100 g, the increased body burden or specific organ burden such, as the brain or central nervous system, may not be adequately reflected by this relatively low blood level.

QUESTION-Dr. Robert Eckhardt

To keep our perspective, it is necessary for us to define what we mean by low, medium, and high lead exposures. For instance, Dr. Silbergeld exposed animals to 2-10 mg/ml of lead in their drinking water. If this is related to human exposure, it has been estimated that the average daily

intake is about 300 µg, with a range of perhaps 100-1000 µg. If it is assumed that the average human consumes from 1000-1500 cc of water daily, Dr. Silbergeld's animals would have been exposed to an equivalent human daily intake of from 2,000,000 to 15,000,000 µg. Dr. Silbergeld continually referred to her work as "low level of exposure to lead." Is this truly a "low level" or should it better be classified as a "high level?" It is in this context that I think we must define our terms.

ANSWER-Dr. Silbergeld

Two comments submitted in writing challenge the description of our studies as "low level" lead poisoning. It is not possible to extrapolate our dose of 5 mg/ml in drinking water to a per gram body weight number because the toxicologically important time of exposure is during the suckling period when the offspring are *indirectly* exposed by suckling on leaded mothers. The most satisfactory method of determining the clinical analogue to our studies is to consider the symptoms resulting from this level of exposure. None of the classical signs described are seen,[7-8]* such as extreme body weight reduction, paraplegia, alopecia, cerebral edema, cerebellar hemorrhage, and gross pathology of the brain is observed.[11]* Additionally, other studies show that derangements in behavior and pharmacological response similar to those we have reported can be produced in rodents given controlled doses of lead which do not significantly elevate blood lead levels.[1-17]*

COMMENT-Dr. J. C. Calandra

At the present time there is no solid evidence that allows one to conclude that bone lead is preferentially mobilized in any specific disease state to produce signs and symptoms of lead intoxication. Dr. Goyer is correct when he said that a great deal needs to be learned about the effect of metabolic disturbances on the release of lead from bone.

COMMENT-Mr. Clark Cooper

I think that this afternoon our epidemiologic studies of lead workers will come up for discussion, but I want to comment on some of our findings that relate to what Dr. Goyer has said. Among rather unequivocal excesses in deaths we found a group of causes, including nephrosclerosis and chronic nephritis. The number was small, 41 deaths when about 19 had been expected in 103,000 persons-years of observation. We are now trying to track down histories and path reports to learn more about this group. Also, Dr. Goyer mentioned renal tumors. We did not find any excess renal tumors. In fact, only 3 such deaths occurred out of 1200 deaths. This was a group of individuals, many of whom had extraordinarily high lead exposure. There were hundreds of persons who had average blood lead concentrations of 80 µg/100 ml or more over a working lifetime. There were many who had lifetime averages over 100 µg/100 ml. There was one other

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References listed on pages 83 and 84.

result relevant to cardiovascular renal disease. We did not find an excess of deaths due to cerebrovascular accidents in the population.

MODERATOR-Dr. Jaroslav Vostal

Are there any more questions or comments? Since I have been told by Dr. Carnow that we can extend our morning session I would follow the order of the program and open for discussion of all the papers presented in this session.

QUESTION-Mr. Willard Christoffer

I guess Dr. Joselow is no longer present. Perhaps someone can answer my question. In a recent issue of the Journal of Occupational Medicine which covered the February lead conference in San Francisco, it was reported that a consensus was reached that atmospheric sampling was not a very good indicator for lead exposures and that blood was really the only way to go. In view of the remarks during this conference on the very poor results of blood exposures by current methods, do you have any viable alternatives?

ANSWER-Mr. William Pallies

In answer to that I would like to comment. I have done a lot of blood lead analyses through the years and we have had difficulty occasionally in doing them. We found that there are certain laboratories which usually agree with our results, and other laboratories that do not. The only way out of this that I can see is, you must conclude that if there is great variation in the results but certain groups always come up with results which are reasonably the same, these results must be somewhere around what the true figures should be. Then apply this result to the inplant situations. Usually we do find that the high blood leads did come from an area of high exposure and the low ones from an area of low exposure. This is the only reasonable solution that I can offer in answer to this question, at least until someone comes up with a completely viable blood lead evaluation technique which can accurately determine the amount of lead in the blood.

I would like to make a comment on Dr. Joselow's statement about the diagnosis of lead poisoning. Although I am not a physician, maybe I can still do this. I notice that we get diagnoses of lead poisoning in plants that are called battery plants where we do not actually use lead. Now in these cases it generally can be demonstrated that this is not a case of lead poisoning. I still question whether some of the lead problem in lead plant workers would not have come up anyway if the workers had been in one of the plants where lead is not used.

COMMENT-Dr. Samuel Epstein

I would like to comment, on general grounds, that the only really

effective and accurate way of determining the extent of worker exposure to lead is by environmental monitoring, as opposed to biological monitoring. Biological monitoring is useful for back up purposes, but to suggest that this is the most accurate way of assessing exposure is, I think, inconsistent with the facts. First of all, as some workers are routinely treated on a prophylactic basis with Versenate (in my view, a highly improper practice), there is little use in determining blood lead levels and claiming that these are a measure of environmental exposure. Secondly, blood lead levels only reflect relatively recent exposure to lead; a worker can have high body burdens of lead with relatively normal blood lead levels. Therefore, unless blood lead estimations are made at very frequent intervals, the likelihood is that blood lead levels will provide misleading information. For this reason, I would strongly recommend that in accordance with basic concepts of industrial hygiene, exposure be measured relative to ambient levels of the toxic agent rather than by measuring biological sequelae.

COMMENT-Dr. Paul Caplan

I would like to comment on that and speak again in defense of environmental monitoring. Up until the last few years, it has been relatively difficult, as Ken Nelson mentioned, to get good environmental data, particularly the amount of the time weighted average exposure to a particular individual. There are several reasons for this:

1. The equipment that is used is very cumbersome and it was difficult to keep it close to the breathing zone of the worker.

2. There is the factor of the unknown use of respirators. How effectively are they used; are they efficiently used; are they used in all cases or not used in some?

In most reporting of environmental data there is no comment made as to whether or not workers are required to use respirators or whether they are actually being used. So, quite often high atmospheric exposures are reported with low blood lead levels, simply because respirators are used. In other cases, the respirators are used poorly. However, in the last several years, as most of you know, equipment for determining breathing zone samples by the use of personal samplers attached to the worker's belt with a sample filter directly within 3 or 4 inches of the nose and kept there for a full 8-hour exposure everyday, is now a method for getting good environmental data. Along this line, as you may know, NIOSH is developing some statistical programs that will evaluate how statistically valid both the environmental data as well as the biological data are. So, I think that in the future we will have much better monitoring both environmental and medical.

COMMENT-DR. Sidney Lerner

The problem that I see as a physician in trying to maintain the health of people that work with lead and using blood lead is no different than what I face in doing any biological monitoring on anybody, whether it is a measurement of the blood glucose or the red blood count or the white blood count. In inter-laboratory studies of almost anything you have terrible results but this does not mean to say that we should throw away the laboratory as a basis for which to practice medicine. When one has the opportunity to follow lead workers, you also have the opportunity to repeat the studies on the same individual with different samples of blood. As such, if you get a spurious high or a spurious low, just like the doctor does in clinical practice and says, "Gee, let's repeat that study, it falls out of line." That is available to the doctor in practice as well, and on that basis the blood lead still serves to me as the best indicator of everything that is happening. That is the end indicator. Now at the same time I do not want to throw away the usefulness of the atmospheric monitoring of lead to additionally alert me to what the problems are. If, for instance, I have someone that is exposed to a low level of lead in the air, he may have a high level of lead in the blood and I have to ask myself as a doctor, "What's cooking; what is going on?" So either it can be that he is getting a level of exposure from a non-air source or there is something wrong with the air measurement. I would have a false-negative sense of confidence if I simply went on the lead in air level for that man. So I think we really have to use both tools, neither to the exclusion of the other, for the ultimate determinant of whether there is an effect. After all, we are trying to protect man, so let us study man.

COMMENT-Dr. Paul Caplan

In attempting to determine the biological effect of lead in air, we feel the difference hinges on whether the particle size is large or small. By large, I mean about a couple of microns and by small, I mean half a micron. For example, lead fumes from smelting can produce very small particles, whereas, some of the lead particles produced by a pigment process can be relatively large. The large particle of lead behaves in the body as though it were orally ingested, and the dose, regardless of whether it is measured in air or not, has an uptake of somewhat less than small particle lead. Those of you who are working in an effort to compare respired doses from different occupational circumstances must take this into account or the relationship between respiratory exposure and biologic effect will not be very valid.

QUESTION-Dr. Michael Utidjian

I want to ask any member of the panel, or anybody here who has done work in histochemistry and electron microscopy on lead toxicology, a question concerning something I read years ago. It was not reported in an original

research paper, but in some text, that lead was deposited in motor end plates in the form of lead phosphate. I have always been rather skeptical about that and I wonder if you would care to comment on it, Dr. Silbergeld?

ANSWER-Dr. Ellen Silbergeld

Yes, we had some correspondence with Dr. B. Csillik, who did that work which was at very high doses of lead *in vitro*. In our studies of both *in vivo* and *in vitro* motor neuron effects of lead on neuromuscular function, we have found that it is a presynaptic effect of lead on the release neurotransmitter which is calcium-sensitive.[10,11*] The binding of lead, probably to sulfhydryl groups, at the postsynaptic end-plate might result from the overwhelming presence of lead.

COMMENT-Dr. Hector Blejer

I have a comment about the biological *versus* the air monitoring which seems to be almost academic. In some particular plants that I know of, people are actually picked out when they show urine blood levels of more than 200 µg/liter in any two successive months. In some of these plants the individual workers are being given Versenate and/or penicillin amino-cupermine, which is another name for a penicilliamine. Then the company continues doing blood leads with increasing frequency. Now, in one well known corporation, this policy is, I believe, not dictated by the medical director but by the industrial hygiene corporate director. Putting all these things together, the analytical unreliability of blood leads and the selective or pre-selection of individuals who have been over-exposed (only when they show more than 200 µg of lead in the urine in two successive months) we are really talking about what, to me, is a fairly disastrous situation. We are looking for the ideal, but we are not working with the ideal condition.

MODERATOR-Dr. Jaroslav Vostal

I would like to point out that the questions and comments we have just now heard are not relative to the toxicology and biological monitoring of lead only. They are also very relevant to the preventive aspects and TLV values. They certainly will be discussed again in the afternoon sessions. I am sorry that we don not have more time for this fruitful discussion. I would like to thank all speakers and all discussants.

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* See References 10 and 11 on Page 83

CONFERENCE CHAIRMAN-Dr. Bertram Carnow

Thank you Dr. Vostal. We will start our lunch at 12:30, and since there is no luncheon speaker, we would like to resume our meeting promptly at 1:30.

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CONFERENCE CHAIRMAN-Dr. Bertram Carnow

The moderator of the Session on Epidemiology of Lead is Dr. Kenneth Bridbord, Medical Officer on the Special Studies Staff of the National Environmental Research Center of the Environmental Protection Agency. Dr. Bridbord.

SESSION III - EPIDEMIOLOGY OF LEAD

EPIDEMIOLOGY OF LEAD EXPOSURE AMONG OCCUPATIONAL GROUPS

Dr. Kenneth Bridbord, Moderator
Environmental Protection Agency

A B S T R A C T

The epidemiology studies presented in the 1972 NIOSH Criteria Document on Inorganic Lead are briefly reviewed. The most consistent long term effects of lead presented in these studies involve renal damage. A recent mortality study of workers exposed to lead in smelters and battery plants also provides evidence of kidney damage caused by lead. Other chronic effects of lead suggested include carcinogenic effects involving the digestive and respiratory systems and hypertensive diseases. Areas of future research needs include chronic effects due to lead, effects of lead upon fetal development, and interactions between lead and other chemicals.

I would like to very briefly review some of what we know from the literature with respect to the epidemiology of lead in occupational situations and then give each of the panelists a chance to present some important new information. In general, while our knowledge of the acute effects of lead is reasonably good, we cannot say that what is known about the chronic effects of lead is equally as good. Some of the reasons why relatively little is known about the chronic effects of lead relate to problems with respect to the basic strengths and weaknesses of epidemiologic studies. Briefly, among the strengths, epidemiologic studies deal with observations in man and natural exposures from which information on long-term, low-level effects can sometimes be obtained; among the weaknesses are problems quantifying exposure, the fact that there usually are many covariants present which are difficult to control, and the whole question of separating associations from causations.

I would like to very briefly consider chronic health studies, the epidemiology studies that were reviewed in the NIOSH Criteria Document. Lane[1] observed that lead storage battery workers had an excess mortality compared to the general population. This was primarily attributable to vascular lesions in the central nervous system. Dressen *et al*[2] observed, in 1941, that the incidence of arteriosclerotic hypertensive disease was not increased in workers exposed to high levels of lead as compared to a low-level lead exposure group. Dingwall-Fordyce and Lane,[3] in 1963 observed an excess of death attributable to cerebrovascular accidents in a high lead exposure group, compared to the general population.

No consistent association was found between malignant disease and

lead absorption. It is notable that there was no dose-response relationship in this case but in this particular study there was slight indication of an excess in cancer rate among workers with low lead exposure. Malcomb,[4] in 1971, observed no occupationally induced hypertension and no increased frequency of cerebrovascular disease deaths in lead exposed workers when compared to the general population.

Henderson and Inglis,[5] in 1957, observed chronic nephritis related to excess lead absorption, based upon lead levels in bone. Lane,[6] in 1949, observed death from renal failure in men exposed for long periods to high concentrations of lead.

In summary, there is at least some suggestive evidence of adverse health effects related to long term chronic lead exposures, based on the studies in the NIOSH Criteria Document. Certainly conclusive evidence is not available, except perhaps for the somewhat consistent findings of renal disease in workers exposed for long periods to lead.

I tried to review the recent literature; however, I may have missed important studies. Two studies relating to chronic lead health effects were reviewed. One study was carried out by Dr. Theodore Robinson, who is on our panel, and the other is the Tabershaw Cooper Study, by Cooper and Gaffey in 1974. Robinson[7], in 1974, observed that TEL and non-TEL workers do not experience a reduced life expectancy compared to the general population. In reviewing this particular paper, I was struck by what appeared to be a 50 percent excess of total cancer deaths among older TEL workers compared to non-TEL workers and suggest that this may deserve further follow-up, particularly with respect to the results of the Cooper and Gaffey study.[8] Cooper and Gaffey found the SMR for all malignant neoplasma was 133 for smelter workers and 111 for battery plant employees; but again, no association was found between cancer and duration of employment.

Most excess cancer involved the digestive and respiratory systems. It is important to note, and I believe it was referred to this morning, that SMR's in smelter and battery plant workers, respectively for other hypertensive disease were 389 and 223, and for chronic and unspecified nephritis 264 and 175. The SMR's for all causes in both worker groups were 107 and 99. I believe this may suggest a poorer health experience compared with other working populations. Again I stress, *compared to other working populations*.

Before closing, I would like to identify a few areas that may merit some further exploration. As mentioned before, certainly the need for additional studies of possible long term chronic effects due to lead would fall into this category. One is concerned about the possibility of life shortening effects of lead, particularly through kidney damage and carcinogenic effects of lead which also should be in this same category. I would add that, if lead were a carcinogen, it would have to be a very

weak one. However, there certainly is some evidence in toxicology that it may act, at least in certain circumstances, as a co-carcinogen. Certainly the significance of interference in porphyrin metabolism is very important, and the inhibition of the metabolism in other tissues besides the mature red blood cell should be investigated. A good example of such inhibition that may be important is lead related interference in porphyrin metabolism in the liver.

Effects of lead on children of workers is also important. I hope Dr. Landrigan will refer to this both with respect to children in communities near lead stationary sources and children of the workers. Susceptibility of the female workers is also an unresolved issue and one that I hope will elicit some further study among members of the audience.

Finally, the whole question of interactions is extremely important. We tend to forget that exposures to chemicals are combined. One lead interaction that may be important to study is lead and benzo(a)pyrene. Kobayashi[9] found an interaction between lead oxide and benzo(a)pyrene in Syrian hamsters, I believe, with respect to causing lung cancer. The whole question of interactions between lead, arsenic and cadmium may be extremely important, particularly with respect to smelter workers. I suggest the questions of lead interacting with organic solvents may be another area for study, particularly since some of the organic solvents also interfere with porphyrin metabolism pathways.

Lead and tritium is a final example. In EPA laboratories in North Carolina, we have observed that lead and tritium may interact in causing behavioral effects in animals. I would like now to give the panel members a chance to give their presentations. For future reference, after our session is completed, will anyone asking questions, please state their names before presenting questions. It will be very much appreciated.

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2. Dressen, W.C., Edwards, T.I., Reinhart, W.H., Page, R.T., Webster, S.H., Armstrong, D.W., Sayers, R.R., The control of the lead hazard in the storage battery industry, PH Bull. 262. Federal Securing Agcy. U.S. PHS, Govt. Prntg Off, 1941

3. Dingwall-Fordyce, I., Lane, R.E., A follow-up study of lead workers, Br J Ind Med 20:313-15, 1963

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5. Henderson, D.A., Inglis, J.A., The lead content of bone in chronic Bright's disease, Australasian Ann Med 6:145--4, 1957

6. Lane, R. E., The care of the lead worker, Br J Ind Med 6:125-63, 1949

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8. Cooper, W.C., and Gaffey, W.R., Mortality of workers in lead smelters and lead battery plants, J Occ Med 17:100-7, Feb, 1975

9. Kobayashi, N., and Okamoto, T., Effects of lead oxide in the induction of lung tumors in Syrian hamsters, J Nat Can Inst 52:1605-8, May, 1974

MODERATOR-Dr. Kenneth Bridbord

The first speaker in this session will be Dr. Theodore Robinson, Plant Medical Director for the Ethyl Corporation. Dr. Robinson will discuss Health, How Can It Be Measured? Dr. Robinson

HEALTH, HOW CAN IT BE MEASURED?

Dr. Theodore R. Robinson
Ethyl Corporation

A B S T R A C T

A reasonably comprehensive evaluation of the health experience of a given group of industrial workers over a long period of time would be achieved by study of mortality, morbidity, and other medical data to form judgments on these data. Comparison yard stick information from the general population or preferably from a different group of industrial workers of similar age, sex, race, socioeconomic and geographic characteristics is required. Correlation of this information with exposure to agents encountered in the workplace require identification and quantitation of the agents in the work environment, exposure and results of biological monitoring data. Studies done on tetraethyl lead (TEL) workers over periods of time ranging to 20 years or longer are given to illustrate this approach. The results of these studies indicate that these workers have not suffered detectable impairment of their health from their occupation.

Studies using the workers at a TEL plant will illustrate how health can be measured. Most of you probably have little cause to be particularly interested in TEL. However, access to information on this population of workers was available for study and the type of studies that will be outlined can be done by almost any practicing physician. The motivation to perform such studies was quite simple; there was the desire to be able to relate to workers that everything that was known in the work situation, that may have an effect on their work and health, had been checked out.

Two main kinds of studies are reported here. One is a mortality study with a twenty-year, essentially 100 percent complete follow-up.[1] Most of the workers involved had long-term exposure to TEL and a lesser degree of exposure to inorganic lead. A few had exposure for a shorter period of time. The earliest comprehensive listing of employees at this facility was 1947, when the union seniority list came into being. The initial population established by these lists was followed-up to the time the study began (end of 1967).

The other study being reported has not, as yet, been submitted for publication. It deals with health findings in people who have had twenty or more years of continuous service in working with TEL. It is important that any health studies on occupational groups include some sort of quantitative estimate of the exposure of the people concerned. There is

about three cubic feet of data on lead-in-air analyses for this plant, which have been worked on, off and on, for about ten years by a number of people, competent in analysis of this type of data, and we have been unable to correlate environmental measurements with urine leads or with any other clinical data. This information will not be reviewed today, however, since it is not available.

Figure 1 shows the eight to ten year blood lead mean, calculated each year for each worker, with the annual mean then averaged to a ten-year mean for each individual.

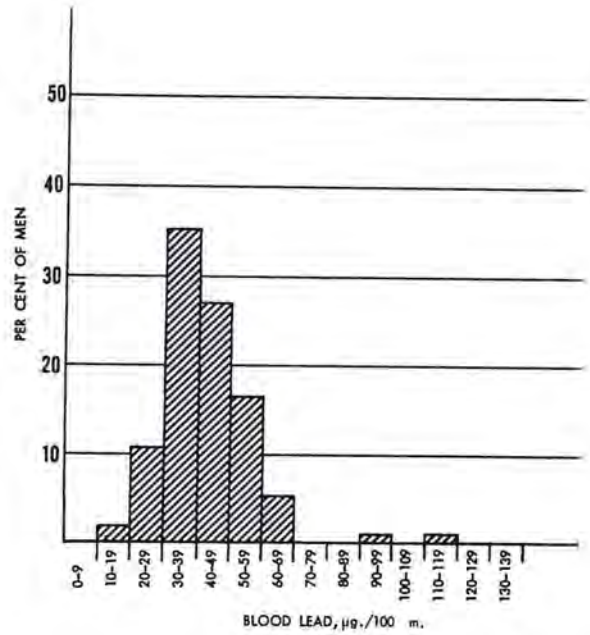

Figure 1 8-10 Year means for Blood Lead for 101 of 153 TEL Workers

This figure shows the distribution of those means. It should be pointed out that blood is a relatively insensitive indicator of absorption of TEL. Blood leads usually were done only on those people who had high urinary leads and on the few workers who may have had reasonably significant exposure to inorganic forms of lead, so, this information is biased on the high side, but the overall mean for this group of workers is 48µg/100 ml of blood. This is not a "normal" mean value. It indicates some degree of excess lead in the blood in this group of people.

Figure 2 shows the eight to ten-year mean of lead in urine of a goup of of TEL workers. This figure certainly does not represent a "Normal" for an unexposed population. The overall mean over this period of time for these workers is 89 µg of lead per liter of urine. These two measurements provide the best available estimate of the magnitude of exposure to lead for these workers.

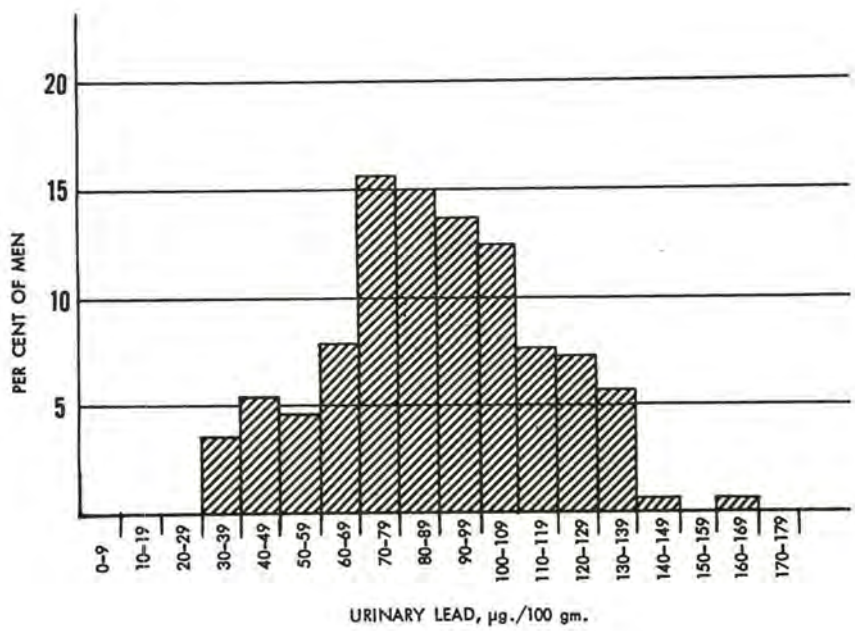

Figure 2 8-10 Year Means for Urinary Lead for TEL Workers

Mortality is, basically, a very simple thing to measure. It is a distinct event that is recorded in some manner. As mentioned, this mortality study covered a period of time from 1947 to 1967, and involved approximately 600 TEL workers with essentially 100 percent follow-up. Table I shows mortality results for the TEL workers with a comparison to the experience that would be expected from published information on the general population.

TABLE I
COMPARISON OF EXPECTED AND OBSERVED DEATHS FOR TEL WORKERS OVER
A 20-YEAR TIME PERIOD (12/31/47 - 12/31/67)

		Causes of Death																			
		Int.Par/asitic		Neo/plasms		Cardio/vascular		Influ. Pneumo. Broncho.		Certain Degen.		Motor Veh.		Other Violence		Other & Unknown		All* Causes	
Age	Man Yrs.	Exp	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp	Obs
20/24	222	-	-	-	-	-	-	-	-	-	-	0.2	-	0.1	-	-	-	0.4	-
25/29	991	-	-	0.2	-	0.2	-	-	-	0.1	-	0.4	-	0.5	2	0.1	-	1.7	2
30/34	1666.5	0.1	-	0.4	-	0.6	-	0.1	-	0.2	-	0.6	2	0.9	1	0.3	-	3.3	.3
35/39	2386	0.1	-	0.8	-	1.9	1	0.1	-	0.5	-	0.7	-	1.5	1	0.7	-	7.0	2
40/44	2456.5	0.2	-	1.4	1	4.5	5	0.3	-	0.9	-	0.8	1	1.8	2	1.0	-	11.7	9
45/49	1851.5	0.2	-	2.1	2	5.6	-	0.3	-	1.0	-	0.6	3	1.5	2	1.1	2	14.3	9
50/54	1183.5	0.2	-	2.3	2	7.5	6	0.3	-	0.9	1	0.4	1	1.1	1	1.0	-	14.3	11
55/59	480.5	0.1	-	1.6	1	5.0	5	0.2	1	0.5	-	0.2	-	0.5	2	0.6	-	9.0	9
60/64	183	0.1	-	0.9	2	3.0	2	0.1	-	0.3	-	0.1	-	0.2	-	0.3	-	5.1	4
65/69	37	-	-	0.3	-	0.9	2	-	-	0.1	-	-	-	0.1	-	0.1	-	1.5	2
70/74	9	-	-	0.1	-	0.1	-	-	-	-	-	-	-	-	-	-	-	0.5	-
75/79	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.1	-
Tot.	11467.5	1.0	-	10.1	8	29.3	21	1.4	1	4.5	1	4.0	7	8.2	11	5.2	2	68.9	51

**Only those causes of death for which a death actually occurred in the study groups are shown--therefore the "Expected" deaths in the "All Causes" category are slightly greater than the sum of the individual categories listed.*

Let me comment that there has been a trend in literature in recent years to be telegraphic, to omit everything possible and only present the so-called pertinent information. For my purposes as a practicing physician with limited time and somewhat limited resources, it is very disconcerting in attempting comparisons of the information I have collected with other published information to find that important items of information are missing from the published material. For example, "man-years at risk" information often is omitted from publication, which makes such comparison impossible unless additional information can be obtained from the authors. I would like to suggest some reversal in this trend. Such information should be included and is necessary if comparisons of studies are going to be made.

The comparison of "yard-stick" in this case is the experience reported for the general population. The overall ratio of observed to expected deaths of the TEL workers in this tabulation is 74 percent. That is TEL deaths were 26 percent less than predicted on the basis of a general population. Most industrial populations show a better mortality experience than the general population shows. In order to provide an additional comparison, I also studied a group of workers, who because of pecularities of the design and operation of this plant, have had no opportunity for TEL exposure to any other form of lead. This group was not a matched control group, but the numbers, ages and lengths of service were quite similar to the TEL population. The mortality findings shown in Table II, were also quite similar. The ratio of the observed to the expected deaths in this group overall were 69 percent. Thus, for this group, there was a 31 percent advantage somewhat greater than for the TEL group. The statisticians tell me that, in this study, 69 percent and 74 percent cannot be said to be different.

Another means for evaluating health lies in the information gained from things like periodic health examinations and records of absence due to personal illness. The following information is on all of the workers who have worked continuously as operators in the TEL area for twenty or more years, 1947-1967. This information is compared to similar information obtained on a "control" group of workers matched for age and length of service to the TEL workers.

The first sets of data concern information on absences from work over a six year period of time due to personal, non-occupational illness. Unfortunately plant medical records concerning such absences were not retained for the full period of time for which they had been collected. This six year collection represents all the medical records that were available at the time of the study.

TABLE II

COMPARISON OF EXPECTED AND OBSERVED DEATHS FOR NON-TEL WORKERS OVER A 20-YEAR TIME PERIOD (12/31/47 - 12/31/67)

		Causes of Death																			
		Int.Par/asitic		Neo/plasms		Cardio/vascular		Influ. Pneumo. Broncho·		Certain Degen.		Motor Veh.		Other Violence		Other & Unknown		All * Causes (*) Table I	
Age	Man Yrs.	Exp	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp	Obs
20/24	127	-	-	-	-	-	-	-	-	-	-	0.1	-	0.1	-	-	-	0.2	-
25/29	757.5	-	-	0.1	-	0.1	-	-	-	0.1	-	0.3	1	0.4	-	0.1	-	1.3	1
30/34	1509.5	0.1	-	0.3	-	0.5	-	0.1	-	0.2	-	0.5	-	0.8	1	0.3	-	3.0	1
35/39	2350.5	0.1	1	0.8	1	1.9	1	0.1	-	0.5	-	0.7	-	1.5	-	0.7	-	6.9	3
40/44	2722.5	0.2	-	1.6	2	5.0	1	0.3	-	1.0	-	0.8	-	2.0	3	1.1	1	12.9	7
45/49	2283.5	0.3	-	3.1	2	9.8	7	0.5	-	1.5	-	0.8	-	2.2	5	1.6	1	21.0	15
50/54	1625.5	0.3	-	3.2	1	10.3	11	0.4	-	1.3	1	0.5	1	1.5	-	1.3	1	19.7	15
55/59	812	0.2	-	2.7	2	8.4	10	0.3	-	0.9	-	0.3	-	0.9	1	1.0	3	15.2	16
60/64	334.5	0.1	-	1.7	2	5.4	2	0.2	1	0.5	-	0.2	-	0.4	-	0.6	-	9.4	5
65/69	138	0.1	-	1.0	1	3.4	2	0.1	-	0.3	-	0.1	-	0.2	-	0.4	-	5.6	3
70/74	36	-	-	0.4	-	1.4	1	0.1	-	0.1	-	-	-	0.1	-	0.1	-	2.2	1
/79	12	-	-	0.2	-	0.7	-	-	-	-	-	-	-	-	-	0.1	-	1.1	-
80/84	0.5	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-		0.1	1
Total	12709	1.4	1	15.1	11	46.9	36	2.1	1	6.4	1	4.3	2	10.1	10	7.3	6	98.6	68

Figure 3 shows the average annual frequency of absences by certain disease categories. Most obvious in this graph is the apparent excess of absences for TEL workers in the categories of respiratory, gastro-intestinal, and ENT, which includes headache and sinus trouble and many people in Louisiana report having sinus trouble. The statistician reported that the apparent differences between the two groups of workers for these categories is not statistically significant. For the moment, I accept this judgment, but I am trying to devise a more accurate means for evaluation of this.

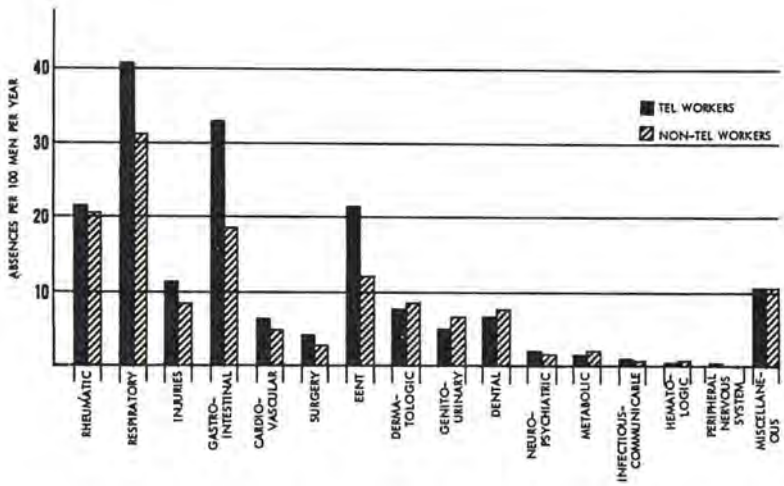

Figure 3 Frequency of absences due to categories of non-occupational illness and injury for TEL and non-TEL Workers, 1962-1967.

Figure 4 shows the average duration of illness in the various disease categories for the two groups. The average duration is quite similar for TEL and non-TEL workers.

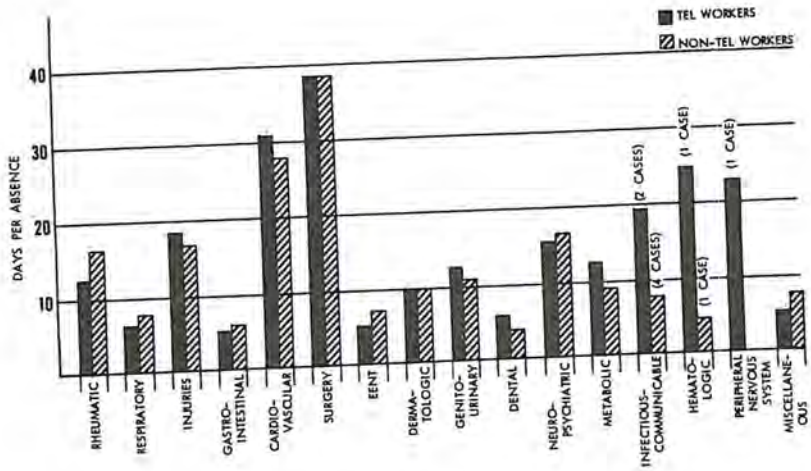

Figure 4 Severity (average duration) of Absences in categories of non-occupational illness and injury for TEL and non-TEL Workers

Table III presents miscellaneous health information. A listing of all recorded diagnoses was obtained by reviewing all entries on each individual chart for any record of a diagnosis. The diagnoses came from periodic exams, from reports obtained from people who were "off sick," and from information provided by workers who "just dropped by" to provide some information concerning their health. The TEL and non-TEL workers appear to be very similar in terms of cumulative diagnoses over the twenty year period.

TABLE III

CUMULATIVE DIAGNOSES-ALL SOURCES
(139 MEN IN EACH GROUP)

Diagnosis	TEL		Non-TEL	
	No. Men	%	No. Men	%
Hypertension	18	12.9	27	19.4
Myocardial infarction	3	2.2	5	3.6
Angina pectoris (without MI)	2	1.4	3	2.2
Arrhytmia (only)	2	1.4	1	0.7
Abnormal EKG (only)	1	0.7	7	5.0
Cerebrovascular disease	1	0.7	-	-
Other peripheral artery disease	1	0.7	2	1.4
Phlebitis, thrombophlebitis	5	3.6	4	2.9
Anemia	1	0.7	-	-
Polycythemia	-	-	1	0.7
Other blood disease	-	-	-	-
Pyelonephritis	3	2.2	2	1.4
Renal stones	7	5.0	12	8.6
Other renal disease	-	-	3	2.2
Liver disease	2	1.4	4	2.9
Gallbladder disease	4	2.9	3	2.2
Gastric or duodenal ulcer	16	11.5	18	12.9
Colon disorder	-	-	-	-
Chronic lung disease	5	3.6	2	1.4
Peripheral neuritis	1	0.7	-	-
Neuropsychiatric	3	2.2	3	2.2
Thyroid disease	-	-	2	1.4
Diabetes mellitus	3	2.2	7	5.0
Gout	4	2.9	3	2.2
Rheumatoid arthritis	-	-	1	0.7
Lumbago	22	15.8	26	18.7
Cancer of skin	7	5.0	4	2.9
Other cancer	-	-	-	-
Glaucoma	1	0.7	3	2.2
Cataracts	-	-	-	-
Obesity, 20-29%	42	30.2	29	20.9
Obesity > 30%	40	28.8	39	28.1
Total Diagnoses	194	-	211	-
Diagnoses per person	1.4	-	1.5	-
No diagnosis	22	15.8	29	20.9
Obesity only diagnosis	37	26.6	22	15.8

Next is information provided by periodic exams. Fig 5 provides a comparison of the initial (preplacement) weights of TEL workers with their weights on the last periodic exam. You can see that most of the men have gained weight during their twenty or more years on the job. Fig 6 is information for non-TEL workers which shows the same pattern as for the TEL workers.

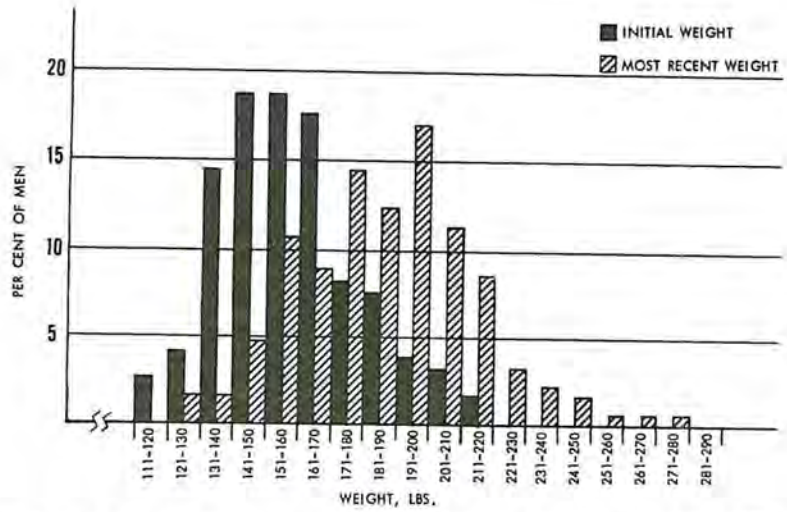

Figure 5 Initial and most recent weights of 124 of 153 TEL workers

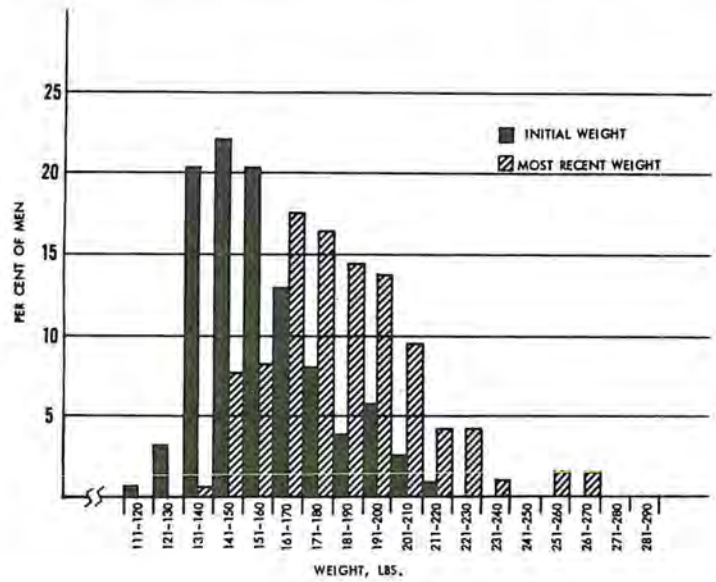

Figure 6 Initial and most recent weights of 124 of 153 non-TEL workers

Figure 7 shows the change in weight for each individual over this period of time.

On the average, both groups have gained 28 pounds during their employment. The distribution of the gains or losses experienced by each individual in the two groups was essentially the same.

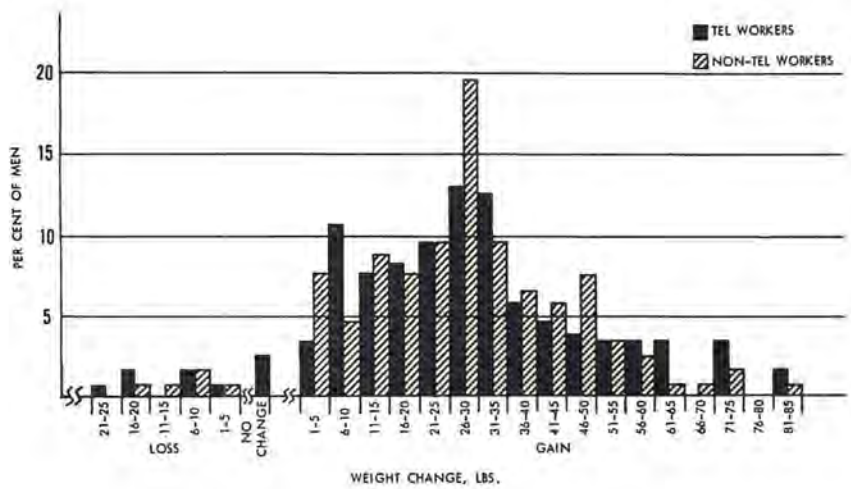

Figure 7 Change between initial and most recent weight for each individual TEL and non-TEL Worker

The same kind of comparison is shown for systolic blood pressures in Figure 8 and Figure 9. Systolic pressures were a little lower on the last periodic exam than on the preplacement examination. The two work groups show the same pattern.

Diastolic blood pressures, shown in Figure 10 for TEL workers and in Figure 11 for non-TEL workers, have gone up slightly, about 5 or 6 mm of mercury on the average for both groups, over the years.

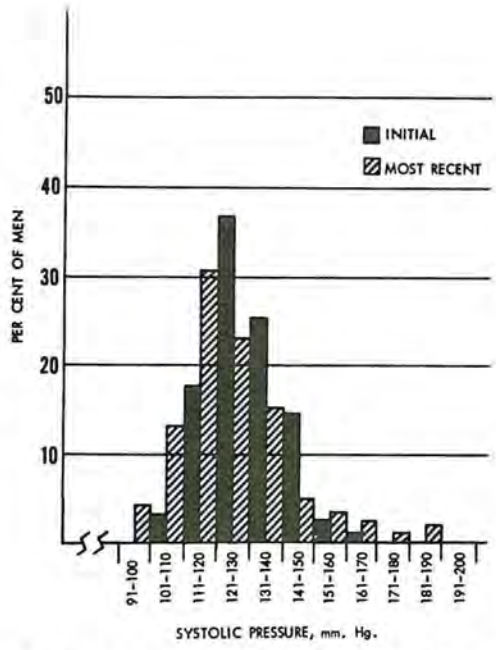

Figure 8 Initial and most recent systolic blood pressures for TEL Workers

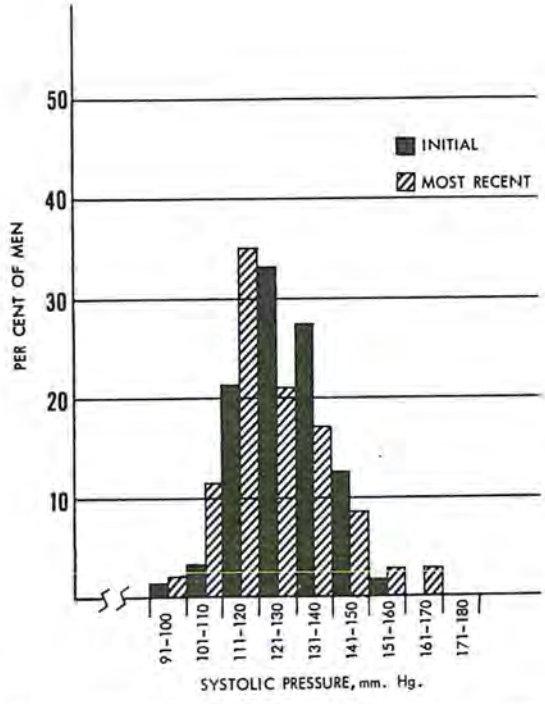

Figure 9 Initial and most recent systolic blood pressures for non-TEL Workers

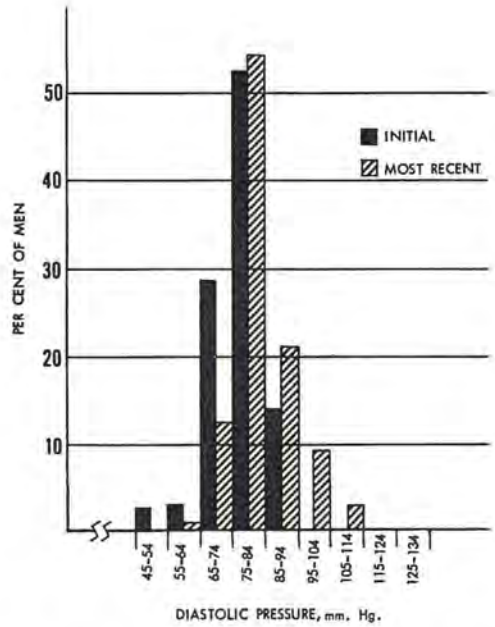

Figure 10 Initial and most recent diastolic blood pressures for TEL Workers

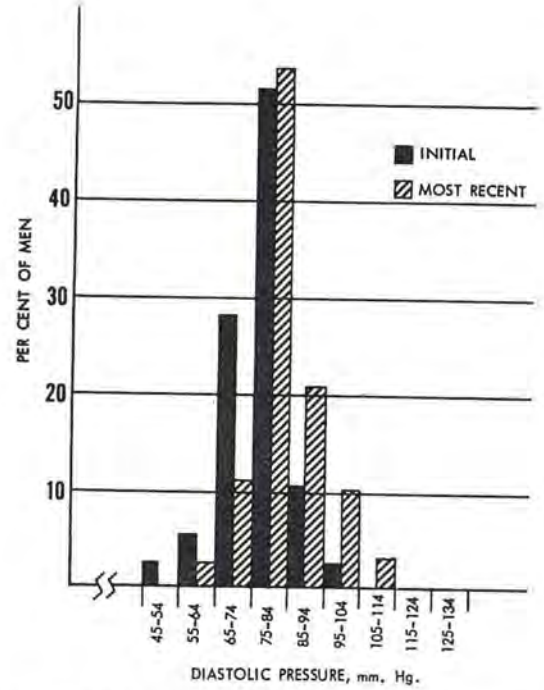

Figure 11 Initial and most recent diastolic blood pressures for non-TEL Workers

Figure 12 compares diastolic pressure changes for individuals in the two groups since their preplacement examinations. Both groups show almost identical changes. Hemoglobin on the last periodic examinations are shown for both groups in Figure 13. The mean hemoglobin value for the TEL and non-TEL workers is exactly the same, 15.6 grams per 100 grams blood. The differences in distribution of values that can be seen is said to be statistically significant at the .05 level.

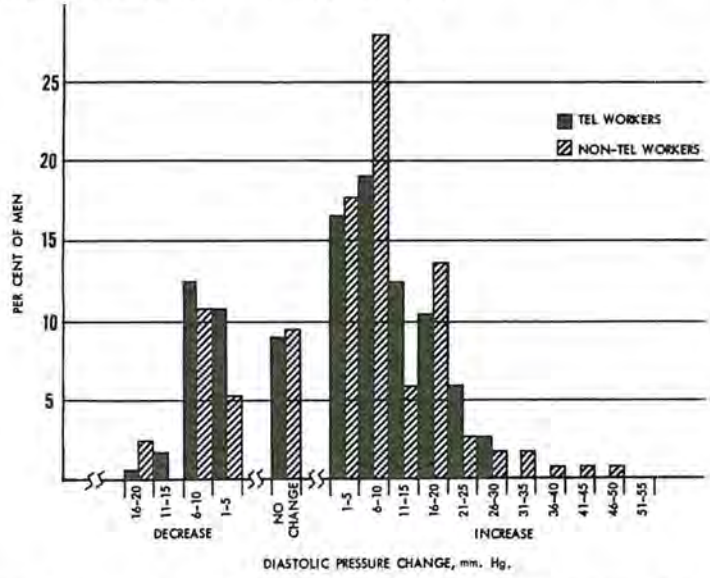

Figure 12 Change between initial and most recent diastolic pressure for each individual TEL and non-TEL worker

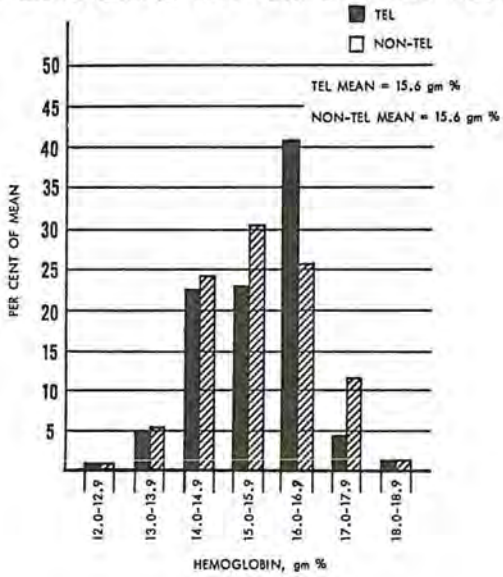

Figure 13 Hemoglobin on most recent periodic examinations for TEL and non-TEL Workers (153 men in each group)

No comparison with preplacement values is possible because the laboratory method used during the time of the initial examination of these workers subsequently was proven to be inadequate for the purpose of quantitation of hemoglobin. The inadequacy was such that almost every person hired recorded hemoglobin levels of 13 g/100 g of blood or less, as shown by the test used. This pecularity was recognized about 1955 and a different method for determining hemoglobin has been in use since that time.

The final portion of these studies deals with a group of workers of various ages and lengths of service. This group has no particular correspondence with the groups previously described except that they did work in the TEL area. The survey was limited in time and scope and results have been reported in the literature.[2] Figure 14 shows the relationship found between ALA in urine and lead in urine in these workers.

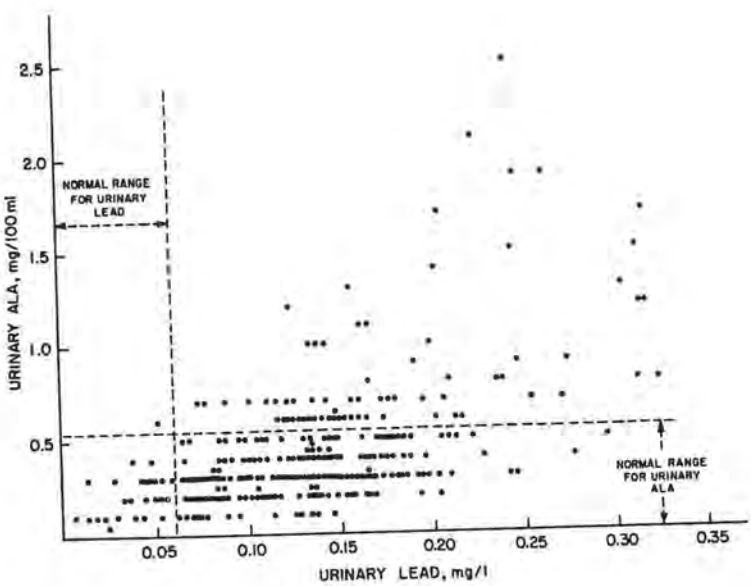

Figure 14 Relationship between ALA in Urine and Lead in Urine of Workers

The degree of correlation is said to be .5 and a wide scatter is evident. There is a rather vague, general correlation between ALA and lead in

urine. In Figure 15 information is given for some of the individuals in the group who were somewhat higher in excretion of lead in urine. A much better correlation between urinary ALA and urinary lead seems apparent in this group and there is no explanation, the seeming difference between the group data and the data on individuals. My overall comments as far as ALA in urine is concerned, is that I really do not know what this information means. All the other information reported here strongly indicates that workers such as these have been in good health over the years. At this moment, the tentative conclusion is that the degree of urinary elevation of ALA shown in this study probably is compatible with good health.

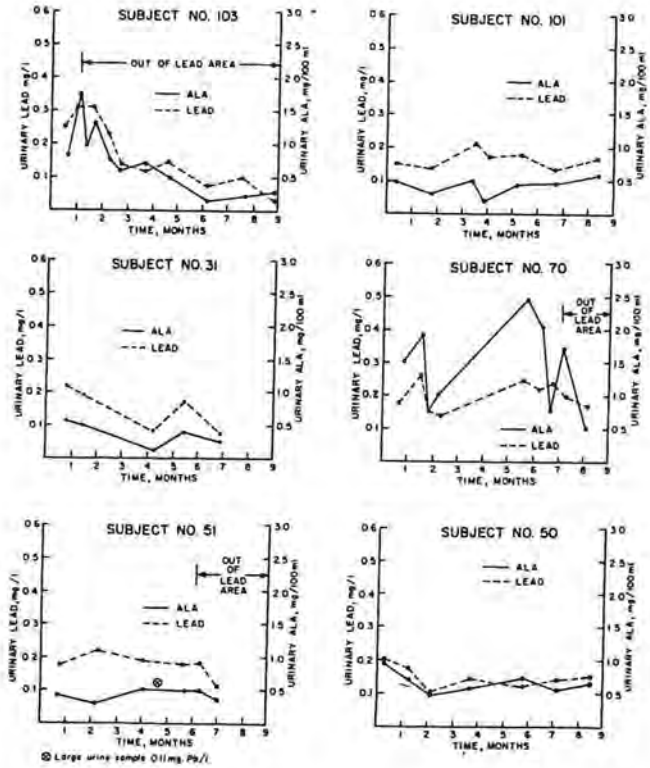

Figure 15 Comparisons of ALA and Urine Lead in individuals in the group having higher levels of excretion of lead in urine

There are many possible measurements that are not included here. It has been considered to attempt to work with records of symptoms as recorded at the time of periodic exams over the years, but I have little confidence in these examination records. I know from experience that in periodic examination at this facility, the interviewer largely determines the kinds of symptoms that will be elicited and recorded. For this reason, I have had no interest attempting to tabulate and analyze this information.

I do not know how to measure "quality of life". I also do not know how to do nerve conduction tests (it is doubtful if workers would accept them). Certainly work of this nature is of great interest, but I think that avant-garde tests of somewhat unclear clinical significance (nerve conduction, flicker fusion, etc.) are things that the plant physicians ordinarily are not able to do.

So, for whatever value they may possess, the studies reported here represent an attempt by a practicing physician in industry to measure the health of workers for their benefit. I would affirm what practicing physicians in the audience have already recognized: "Anybody can do it!"

Thank you for your kind attention.

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MODERATOR-Dr. Kenneth Bridbord

Thank you for your presentation, Dr. Robinson.

Our next speaker will be Dr. Dwight Culver, Associate Clinical Professor of Community and Environmental Medicine at the University of California, Irvine, College of Medicine. Dr. Culver's presentation will be the Epidemiological Considerations of Occupational Lead Exposure. Dr. Culver.

EPIDEMIOLOGICAL CONSIDERATIONS OF OCCUPATIONAL LEAD EXPOSURE

Dr. B. Dwight Culver
University of California, Irvine

A B S T R A C T

Diagnosis of occupational lead poisoning in the adult depends largely upon the presence of overt signs and symptoms and a variety of laboratory tests, some of which have not been clearly related to clinical findings. Cases are presented to illustrate differences in clinical response among lead exposed workers. Some of these cases cast doubt upon the margin of safety provided by the widely recognized blood lead level of 80 µg/100 ml. Generally accepted criteria for the diagnosis of adult lead poisoning are needed as a basis for epidemiological studies that can define the magnitude of today's occupational lead problem.

In the epidemiology of occupational lead exposure, we seek to understand the cause and prevention of lead's detrimental effects on workers. We need to know where in industry these effects occur and with what frequency, what characteristics of the work environment contribute to the disease, and what characteristics of the exposed worker contribute to an adverse response to lead exposure.

Despite the fact that lead poisoning was studied by the ancients and its symptoms and cause described by Hippocrates or the accumulation of a voluminous literature on the subject, our presence here at this conference gives testimony that our knowledge remains imperfect. Further testimony is found in the fact that we cannot come to agreement on the standards for worker protection and is further found in the observation that occupational lead poisoning is still a major problem today.

In some ways, such ignorance today seems more profound that it did during the early decades of this century. Alice Hamilton[1] reported information on the frequency of lead poisoning in various industries. Based upon calculations of her data given in Table I, it appears that frequency per million man hours worked ranged from 45 for printers to 220 for rubber manufacturers. This latter figure is equivalent to one case of lead poisoning for every two workers exposed. Today our information on the incidence of occupational lead poisoning is probably less precise than that given us for the period 1911-1916 by Dr. Hamilton.

In recent years, it has been customary to look to the statistics collected by the California Department of Health for information on the occurrence of occupational disease. The data collection system for occupational disease in California is often pointed to as being unique in

TABLE I

FREQUENCY OF LEAD POISONING
(Period 1911-1916)

Trade	Frequency/10^6 Man Hours
Battery Manufacturing	90
Casting	8.6
Pasting	97.0
Oxide mixing	200.0
Enameling	182
Lead Smelting	118
Pottery Manufacturing	67
Printing	45
Rubber Manufacturing	200

that doctors' reports are required by the State of California and payment by Workmen's Compensation insurance carriers depends upon receipt of the doctors' report. This system, however, appears to have broken down, at least so far as lead poisoning is concerned.

Many cases of lead poisoning are referred directly to a specialist knowledgeable in the diagnosis and treatment of lead poisoning by plant health care personnel rather than to industrial physicians who are accustomed to treating and reporting the usual injuries and ills of industrial patients. Instead of filling out the standard Doctor's First Report of Injury form, which serves as the basis for statistical analysis by the State Health Department, the specialist writes a narrative report to the insurance carrier; thus, California reported only 79 cases in 1970, 82 in 1971, 101 in 1972, and 81 in 1973. Although these totals may be low, if errors in reporting are uniform throughout industry, the percentage distribution of cases among lead using industries may be fairly accurate.

An analysis of the California data shows that 61 percent of cases resulted from battery manufacturing, 7 percent from construction and building wrecking, 5 percent from primary metal industries, 4 percent from machinery manufacturing, 3 percent from the fabrication of metal parts, 3 percent from the wholesale trade, including scrap metal, and 3 percent from workers in state and local governments. During the 4-year period, less than 1 percent of the cases reported were from the ceramic industry and less than 1 percent of the cases were from mining.

Without data about the number of workers at risk, we have no information on incidence to compare with Dr. Hamilton's. Reliable epidemiological information also depends upon uniformity of diagnosis.

Criteria for the diagnosis of lead poisoning were rather clearly set forth in the early 1920's; today's criteria are vague. Newmann *et al*[2] at that time set forth signs and symptoms in two groups, see Table II.

TABLE II

SIGNS AND SYMPTOMS FOR LEAD POISONING

SYSTEM	SIGNS AND SYMPTOMS	
	Group A	Group B
General Appearance	Marked Pallor and Profound Anemia	Pallor, Anemia, Emaciation, and Drawn Expression
Digestive System	Colic Obstinate Constipation	Loss of Appetite or Repugnance to Food Breakfast Anorexia Vomiting on Eating Solid Food Sweetish or Metallic Taste Gastric Disturbances Constipation Pain in Abdomen Parotitis
Muscular System	Muscular Incoordination	Loss of Strength Malaise and Tiring Easily
Nervous System	Peripheral Motor Paralysis of Certain Extensor Muscles Wrist & Ankle Drop Atrophy of Most Used Set of Muscles	Headache, Insomnia Mental Lethargy, Tremor Dizziness, Convulsions Mental Affections, Arteritis Encephalopathic Conditions
Vascular System	Blood-Basophilic Degeneration with Diminished Hemoglobin	Arteriosclerosis Hypertension
Special Organs and Findings	Gums: Lead Line Stools and Urine-Lead Miscarriages-Repeated Liebermann's Test-Positive	Eyes-Impairment of Vision Muscular incoordination Joints-Various Pains Blood-Basophilic Degeneration with Diminished Hemoglobin

Adapted from Newmann et al, 1921

The Group A signs are considered major manifestations, and in Group B, more generalized, less specific signs and symptoms.

In the author's opinion, the diagnosis of lead poisoning requires signs from at least two systems of Group A and several symptoms from Group B, in addition to a clear history of exposure; or alternatively, when only one

Group A sign is present, signs and symptoms from at least two separate divisions of Group B must be present. When manifestations from only Group B exist, they must be from three separate divisions in order to make a tentative diagnosis of lead poisoning. Aub[3] stated in 1926 that the development of distinct toxic symptoms after exposure is necessary for definite diagnosis.

The confidence with which physicians were able to make diagnoses of lead poisoning during the first decade of this century was in part facilitated by higher exposures than exist widely today and perhaps in part by the absence of readily available laboratory measures of lead absorption and enzyme inhibition. The fact that such laboratory tests do exist today has in many cases led physicians to confuse increased lead absorption with lead poisoning. An attempt to clarify the confusion between increased absorption and poisoning was made by an international group of 18 physicians with broad experience in the lead industries.[4] Their statement emphasizes the use of clinical findings together with biochemical evidence of increased absorption and, if possible, evidence of unusual exposure. Also, emphasized is the fact that the clinical findings in lead poisoning are symptoms and signs of other conditions and, thus, such other causes must be excluded.

As laboratory tests become more widely available to industry, there is, appropriately, greater attention being focused upon biochemical response and less demand upon the presence of a constellation of signs and symptoms. As a result, diagnoses of lead poisoning are being made at an earlier point in the natural history of the disease. The trend today is to make a positive diagnosis, even if only a few minor symptoms compatible with lead poisoning are present, so long as indicators of increased absorption and indicators of biological response are present. This trend may have an impact on the choice of standards for the protection of lead workers.

As an illustration of this point, the case of V.L., with three years of employment in the lead acid battery industry is reviewed. His blood lead values have always been well below the 80 µg/100 ml level, considered by many to be the lower limit of excessive absorption. As can be seen in Figure 1, hemoglobin levels, except for two episodes, have been above 14 gms. Early in 1973, we added urinary ALA to our surveillance program. Concern for elevated ALA values led us to require respirator protection, even though time weighted exposure to airborne lead was well below 0.2 µg/cu m. In October of 1973 the patient reported to the plant nurse that he was having mild constipation and feeling increasing fatigue. There were no other findings on system review or physical examination, urinary coproporphyrins were 1355 µg/liter and urinary ALA was 5.2 mg/100ml. This case was diagnosed as being one of early lead poisoning. Because respirator protection had been unsuccessful, he was transferred to work which did not involve exposure to lead with a resultant gradual drop in blood lead levels and a marked decrease in his excretion of ALA and a

disappearance of symptoms. Returned to his regular work on the paste line in February, 1974, has not resulted in an increase in blood lead but his excretion of ALA tells us that he may be headed for trouble again.

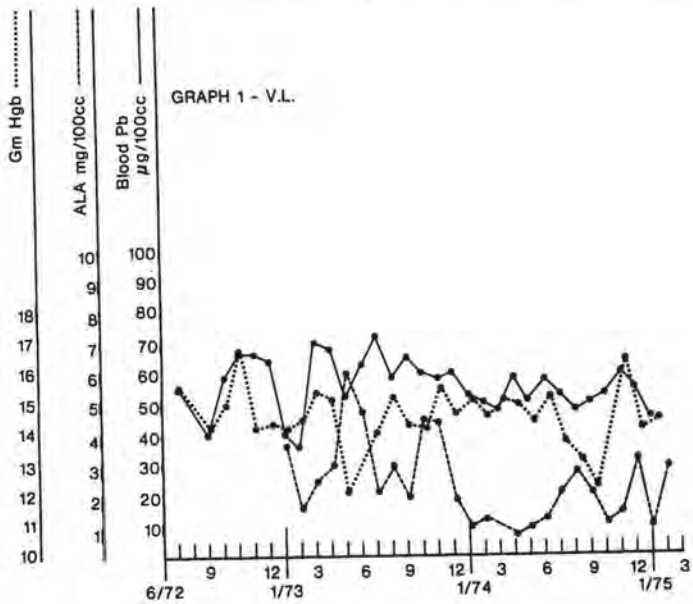

Figure 1 Graph of Laboratory Results for Worker V.L.

A somewhat different response in a worker exposed to lead is seen in the case of P.M. See Figure 2.

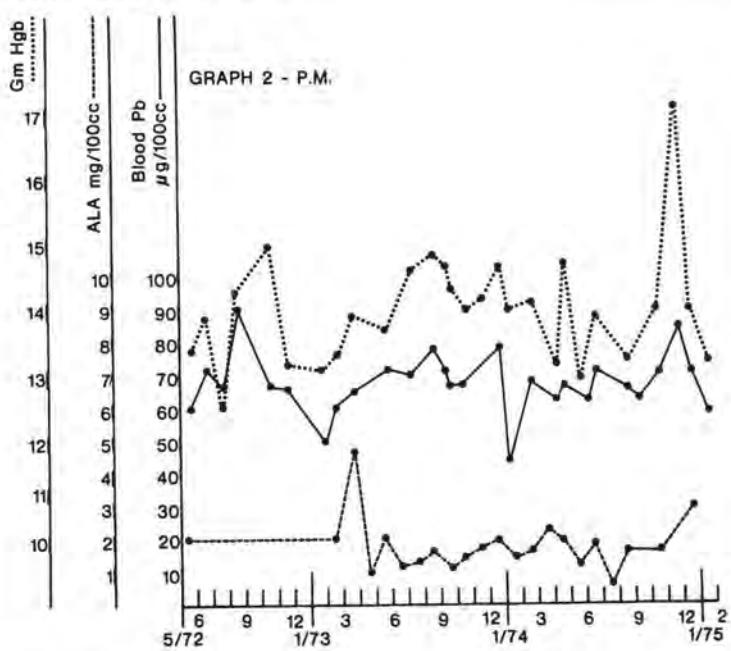

Figure 2 Graph of Laboratory Results for Worker P.M.

His blood lead levels hovered around the 70 g/100 ml level with some peaking above 80 g. In contrast to the consistently higher blood lead seen in the preceding case, excretion of ALA in this worker has generally been much lower. At no time during our period of observation have we been able to elicit symptoms or signs compatible with lead poisoning.

The case of F. L. provides support to the impression that monitoring of blood lead provides little insight into the biological activity of lead. Fig 3 shows pre-exposure base-line blood lead levels of 17 g/100 ml. With the onset of employment involving lead exposure, blood lead rose over a 5-month period to 53 g/ml. This is not a precipitious rise for lead workers and from this point, there is a gradual decrease in blood lead levels to 40 g/100 ml. The reason for this decrease was rigid enforcement of respiratory protection and personal hygiene prompted by evidence that this case responded markedly to absorbed lead. This response can be seen in part in the plot of hemoglobin which shows a precipitous drop from pre-exposure baseline levels of 15 gms to 10.3 gms in the initial 5-months of exposure. The gradual climb to near baseline levels may in part be the result of better control of exposure and in part, possibly, by reduced biological response.

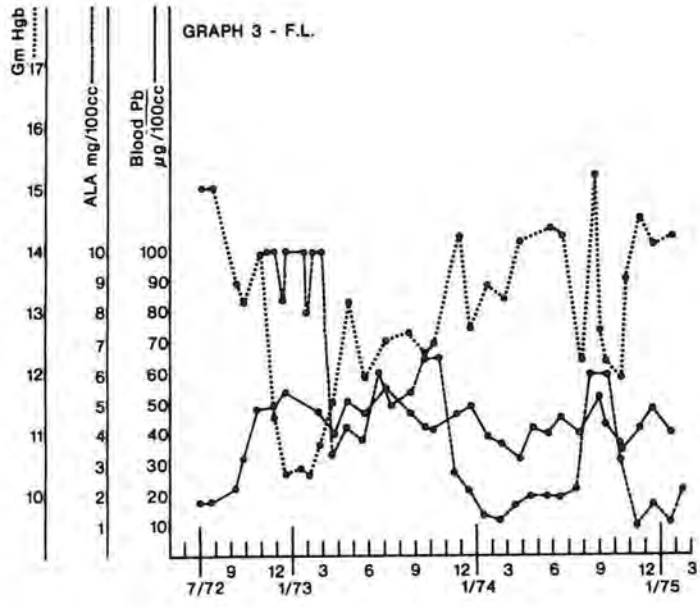

Figure 3 Graph of Laboratory Results for Worker F.L.

A further indication of marked biological response in the face of only moderate blood lead levels can be seen in the urinary delta amino-levulinic acid levels. On this graph initial values are shown with a maximum of 10 mg/100 ml. In reality these initial values may have been considerably in excess of this number but the analytical method used without an extra dilution step is unreliable above 10 mg. When looking at the ALA values for this case, it should be kept in mind that acceptable levels for lead workers have a maximum of 2 mg/100ml and values above this are considered excessive.[4] With few exceptions, the values shown here are well in excess of 2 mg, probably indicating high reactivity to lead absorption. Other causes of anemia and high ALA excretion were sought in this case and excluded. At no time have we been able to elicit clinical signs or symptoms of lead poisoning in this worker.

An evaluation by Malcolm[5] of epidemiological data of workers in the storage battery industry poses the question: are the standards of human safety now employed in the lead industries capable of eliminating the effects of absorption of small amounts of lead on the general health, the susceptibility to other disease, andthe length of lives of exposed workmen? He states that in this study of workers who, since 1930, have generally not been exposed to air lead concentrations in excess of 0.15 mg/cu m, he is unable to answer the question with assurance.

Today, as we observe enzyme responses to lead at levels consistent with exposure below 0.15 mg/cu m, we need to undertake prospective epidemiological studies using methods available to us to probe for lead related damage in order to answer Malcolm's questions. As indicated in this morning's session, it is unlikely that the enzymes of heme synthesis are the only enzymes in man which are affected by lead exposure.

We are, thus, justified in making diagnoses of lead poisoning on the basis of mild, vague symptoms when accompanied by laboratory evidence of biological response to lead. Further, it is in the best interest of both management and labor that early manifestations be recognized. The feelings of fatigue, vague physical discomfort, anxiety and fear of the unknown can lead to accidents and greatly reduce productivity. These are sufficient reasons, even if chronic pathologic changes do not occur at low levels of lead exposure.

Thus, I recommend the establishment of criteria for the diagnosis of lead poisoning at the earliest point in the natural history of lead poisoning. Widely accepted criteria will allow the epidemiologist to define for us the magnitude of today's lead problem.

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MODERATOR-Dr. Kenneth Bridbord

I would like to thank Dr. Culver for his presentation of some very interesting data.

Our next speaker in this session is Dr. Bruce Fowler, Senior Staff Fellow in the Environmental Toxicology Branch of the National Institute of Environmental Health Sciences. Dr. Fowler will present the results of his research in Lead Levels on Dover Sole Collected from Southern California Isolated Waters. Dr. Fowler.

LEAD LEVELS IN DOVER SOLE COLLECTED FROM SOUTHERN CALIFORNIA COASTAL WATERS

Dr. Bruce A. Fowler
National Institute of Environmental Health Sciences

A B S T R A C T

The many tons of trace metals, including lead, released annually into the California coastal basins have resulted in high concentrations in sediments of these basins. Frozen muscle sample from *Microstomus pacificus* collected in this area were examined for lead levels using both atomic absorption spectroscopy (AAS) and proton-induced X-ray emission analysis (PIXEA). Considerable inter-animal variation was observed with levels higher than that commonly measured in canned foods being recorded. Findings suggest the need for epidemiological evaluation of human populations consumption of fish comparing the absorption of lead from ingested fish with that of lead from other sources.

This presentation is concerned with what is beginning to be considered a significant potential route of human exposure to a number of trace elements, including lead, namely, the accumulation of or the body burden levels of trace metals in marine organisms, living in coastal waters adjacent to highly urbanized areas of the continent.

The urbanization and industrialization of coastal regions may lead to dissemination of large quantities of trace metals into the adjacent marine environment. Many potentially toxic metals, including lead, have been reported in high concentrations in recently deposited bottom sediments in Baltimore Harbor and the Southern California and New York Heights. Studies concerning levels of toxic metals in marine organisms inhabiting these areas are limited. This report concerns the levels of lead in muscle of the Dover sole, *Microstomus pacificus*, collected from the Southern California Bight, as measured by proton induced x-ray emission analysis, hereafter referred to as PIXEA and atomic absorption spectroscopy.

In order to place these data into a proper context, some background information concerning the sources and known levels of lead in the Southern California Bight is presented. Figure 1 is a map of the Southern California Bight. The two areas from which the Dover sole were collected are off the Whites Point Outfall near Los Angeles (marked b) and approximately off Santa Barbara (marked a). Table I gives the estimated levels of lead in metric ton per year emitted into the Southern California Bight from various sources. You can see that there are significant

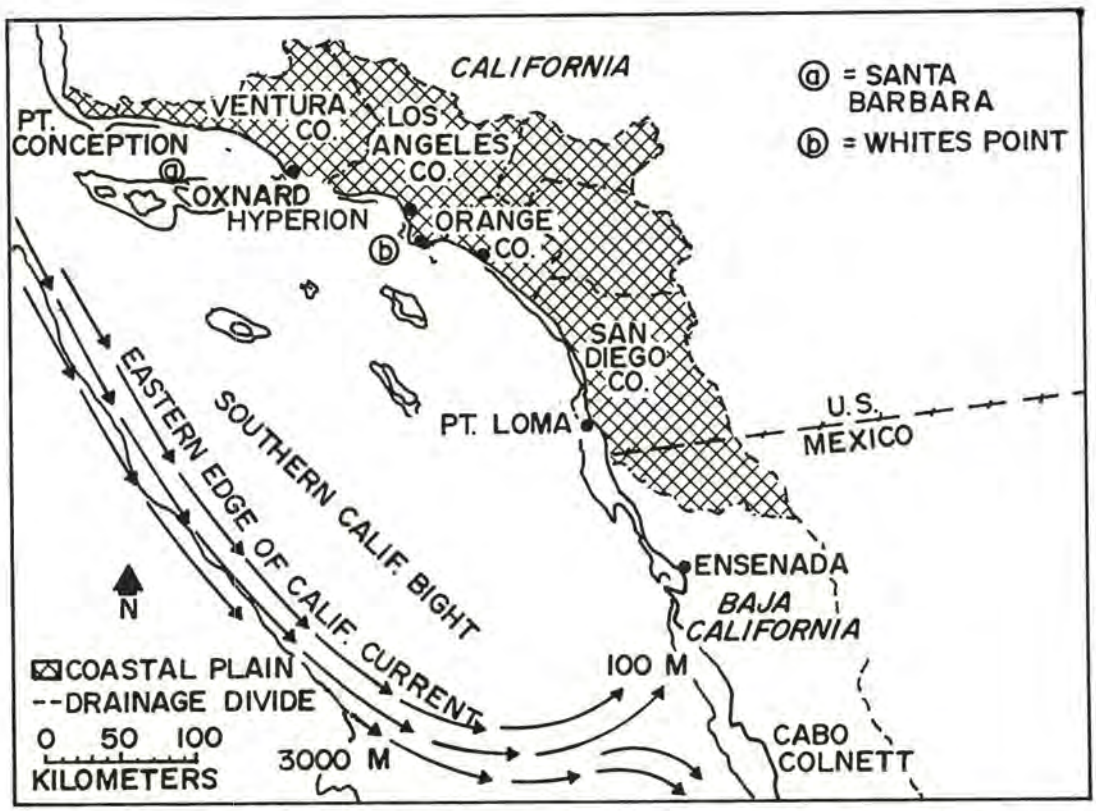

Figure 1 costal plain of southern California and the adjacent marine waters in the southern California Bight.

amount of lead going into this area. The main source, which probably is not obvious, is advective transport. This refers to the movement of metals into the bight with the California Current, a rather complicated process in which metals are moving in with the current, metals are moving out with the current, and metals are swirling in the current. Research, presented in his doctoral thesis by Dr. James Galloway at the University of California in San Diego in 1972, shows that some of the levels of lead in the bottom sediments at the Whites Point Outfall reach several hundred ppm. In recent years, this particular phenomenon has undergone rather extensive study by others and there are a good number of reports concerning the levels in the bottom sediment as well as the water column.

TABLE I

ESTIMATED EMISSION RATE OF LEAD (METRIC TONS/YEAR) FROM VARIOUS SOURCES INTO THE SOUTHERN CALIFORNIA BIGHT*

SOURCE	LEAD (Metric Tons/Year)
Municipal Waste Water	210
Surface Runoff	90
Direct Rainfall	1000
Dry Fallout	2400
Vessel Coating	10
Ocean Dumping Maxima	28
Advective Transport	6000
Total	9738

* *Adapted from D. R. Roung, C. S. Young, and G. E. Hlavka, "Sources of Trace Metals from Highly Urbanized Southern California to the Adjacent Marine Ecosystem" in Cycling and Control of Metals. EPA, Cincinnati, 1973*

The area around the Whites Point Outfall will be referred to hereafter on slides of Dover sole as the contaminated area, and the area of Santa Barbara as the control area. A rather characteristic PIXEA x-ray spectra from the muscle of one of the Dover sole collected near the Whites Point Outfall is shown in Figure 2. The lead value is at the bottom. In this particular sample there was about 1.4 ppm by the method being used. There were 11 Dover sole collected by trawling off the Whites Point Outfall and 12 Dover sole of matched comparable size collected off Santa Barbara. These were collected by Dr. Rimmon Fay of the Pacific Bio-Marine Supply Company. If the samples with below detectable levels of lead are counted as 0 the mean comes out to be about .5 ppm. There are also other elements here, but this is one of the things that should be considered a bit further.

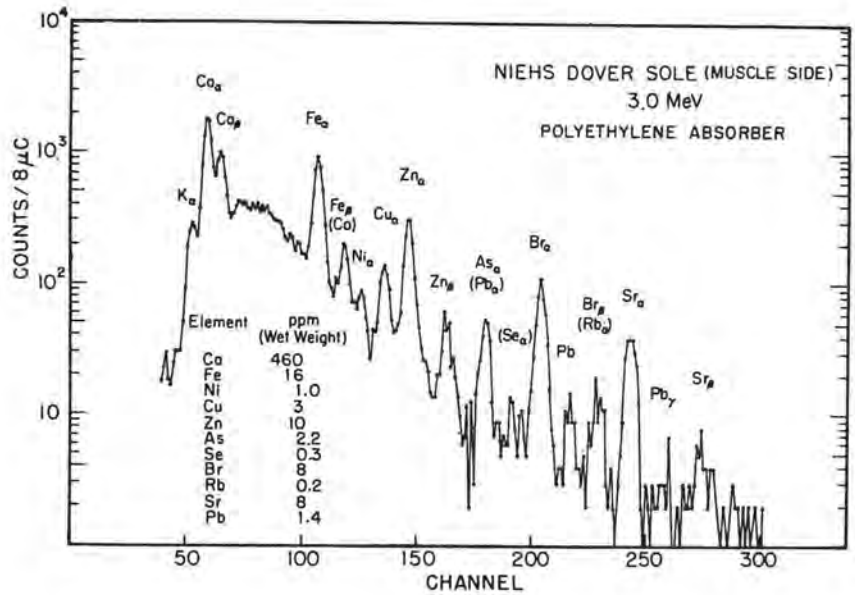

Figure 2 PIXEA X-ray Spectra from the muscle of a Dover sole Collected near the Whites Point Outfall

Most of the elements to which man is exposed do not occur singly, or at least man is not exposed to a single lone element by itself. People are constantly being exposed to a number of potentially toxic elements. PIXEA analysis of Dover sole from the control region showed an .8 ppm level of lead, when assuming that the fish with below detectable levels of lead are counted as 0. If the total of 9 of the 23 animals from both areas having detectable levels of lead are analyzed separately, the mean for the combined group is 2.8. The atomic absorption values of those fish were computed to be 2.3 overall, if the animals without detectable levels of lead are analyzed separately.

Conclusions and thoughts I would like to leave with you are that lead values in Dover sole, as analyzed by two very different methods, seem to indicate that lead is present within some marine animals at levels higher than that commonly found in canned foodstuffs. It is currently not possible to conclude that these levels are the result of the accumulation of elements such as lead in the bottom sediments in which these animals are living. I would also, like to suggest that it might be worth considering populations of humans who consume large amounts of fish and shellfish in performing epidemiological evaluations of human

populations. Another related point is the need for more experimental evidence concerning the absorption, distribution, etc. of elements, such as lead, when these elements are consumed in fish tissues, as compared with placing animals in water containing toxic elements.

Finally, I would like to suggest the need for examination of marine fisheries in areas of high metal contamination to see if the massive influx of these potentially toxic elements is, indeed, deliterious to the organisms and their attendant fisheries.

MODERATOR-Dr. Kenneth Bridbord

Thank you Dr. Fowler for your interesting discussion.

The last speaker this morning and for this session is Dr. Philip J. Landrigan, Chief of Environmental Hazards Activities in the Cancer and Birth Defects Division of the Bureau of Epidemiology at the Center for Disease Control, who will discuss the Exposure of Children to Lead from Industry, Epidemiology and Health Consequences. Dr. Landrigan.

THE EXPOSURE OF CHILDREN TO LEAD FROM INDUSTRY EPIDEMIOLOGY AND HEALTH CONSEQUENCES

Dr. Philip J. Landrigan
U. S. Center for Disease Control

A B S T R A C T

Particulate lead of industrial origin may reach children through various routes to cause increased lead absorption and occasional lead poisoning, including direct absorption as the result of inhalation or ingestion of lead particles, the transplacental fetal accumulation in offspring of women exposed to lead in industry, and trans-generational or vertical from exposure of parental germ cells to lead before conception. The first two epidemiological mechanisms have been well documented, the third is more speculative. Recent work indicates that there may also be subclinical correlations to the hematologic and neurologic effects in children as well as anemia, encephalopathy, and chronic renal disease.

Introduction

Particulate lead has recently been rediscovered as a potential cause of lead exposure and lead poisoning in children. Much attention lately has been directed to particulate lead from automotive exhausts, which accounts for over 98 percent of atmospheric lead emissions in the United States.[1] This brief review will consider the exposure of children to particulate lead from industrial sources.

It has been recognized, at least since the investigations at Broken Hill, Australia in the late 19th. Century,[2] that children who live in the vicinity of lead smelters and other lead works may be exposed to high concentrations of particulate lead. Especially intense exposures may occur when climate and geography minimize opportunities for particulate dispersal. It is, therefore, possible to investigate in detail the routes by which children are exposed to particulate lead in such localities. Several of these epidemiologic mechanisms as well as the hematologic, neurologic, and possible renal consequences of such exposure will be discussed.

Exposure to Emitted Lead

An estimated 2,300 tons of particulate lead are discharged into the atmosphere each year by industrial sources in the United States.[1] Depending primarily upon particle size, this lead may either be inhaled or ingested by children living in the vicinity of such sources. Respiratory lead abosrption is inversely proportional to particle size and at least 30 percent of particles below 2 µg in diameter are retained and subsequently absorbed in the lungs. Between 10 and 30 percent of the 2 to 5 µg particles and almost none of those above 5 µg are retained;

however, larger particles may be swallowed and contribute to gastrointestinal absorption.[6]

Our group has recently had the opportunity to collaborate with the City-County Health Department in El Paso, Texas, in an investigation of childhood lead absorption around a lead smelter.[3] This smelter has emitted over 1,100 tons of lead into the atmosphere in the preceding 3 years.[4,5] Concentrations of lead in the soil adjacent to the smelter were high, decreased with distance, and reached background values at approximately 6.5 miles, Figure 1. Similar patterns were noted for lead levels in air and dust. Increased lead absorption in children, as defined by a blood lead level $\geq$ 40 µg/100 ml,* was found in 69 percent of the 1-4 year olds living within 1 mile of the smelter and in 27 percent of those living between 1 and 4.1 miles. Children living within a 1-mile radius were exposed to high levels of lead in the air.

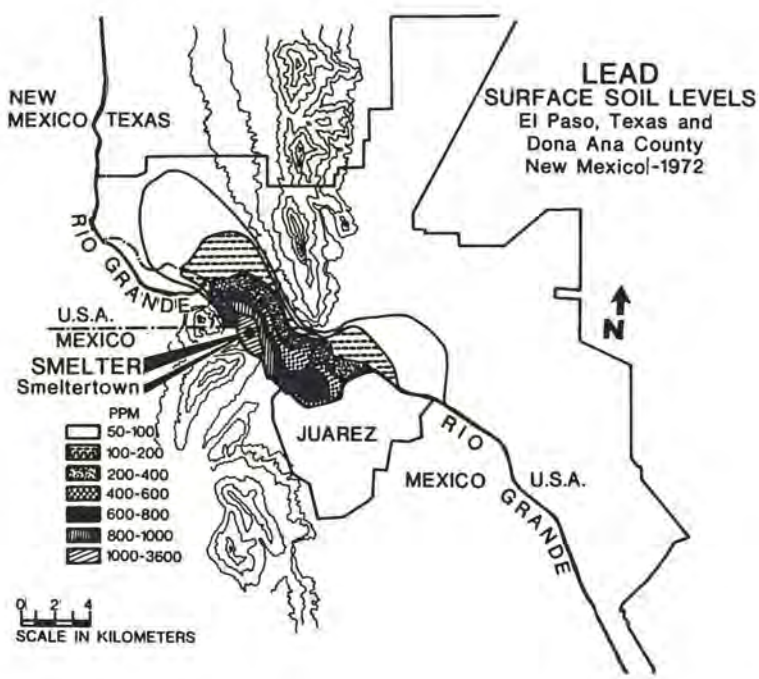

Figure 1 Map of El Paso, Texas and Dona Ana County New Mexico, showing lead surface soil levels

**A whole blood lead level of 40 µg or more per 100 ml is considered by the Surgeon General to represent increased lead absorption, while a confirmed level $\geq$ 80 µg per 100 ml represents lead poisoning.*[6]

In addition, a highly significant relationship was found in these children between lead levels in blood and levels of lead in household dust; a similar, though less striking relationship was noted between blood lead and soil lead levels, shown in Fig 2. These data were taken to indicate that chronic exposure to particulate lead deposited in air, dust, and soil by the smelter had been the major cause of increased lead absorption in the children living near the El Paso smelter.

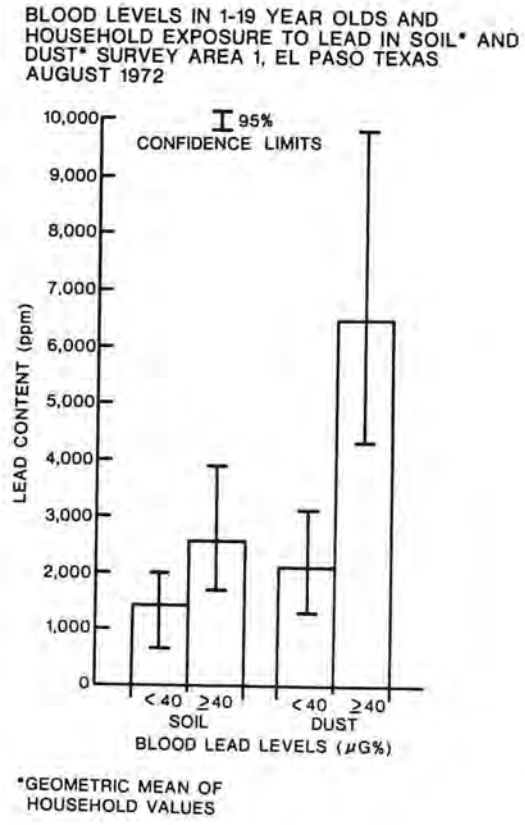

Figure 2 Blood Levels in 1-19 Year Olds and Household Exposure to Lead in Soil* and Dust* Survey Area 1, El Paso, Texas, August, 1972

Similar situations in which increased lead absorption and lead poisoning in children have been traced to industrial lead emissions as reported in Australia,[2] previously noted, in Toronto,[7] in Idaho,[8] in Montana,[9] in Italy,[10] in Britain,[11] and in Chile.[12]

Exposure of Lead Workers

Exposure of lead workers constitutes a second mechanism by which children may be exposed to industrial particulate lead. Recent surveys in Britain of blood lead levels in children living near lead smelters have shown that workers' children were more likely than their peers to have blood lead levels $\geq$ 40 µg/100 ml.[11] It was hypothesized that the workers had carried lead particles home to their children on their persons and clothing. The same phenomenon was observed 60 years ago in the wives of lead workers who, being unliberated, hand-washed their husbands' clothes and developed wrist-drop.[2] These situations are reminiscent of those noted elsewhere among the children of asbestos, beryllium, and trichlorophenol workers in whom mesothelioma,[13] berylliosis,[14] and chloracne[15] resulted, apparently from exposure to the parents' clothing. Such episodes can clearly be prevented by the enforcement of such work practices as changing and showering at the factory at the end of each work-day.

Exposure *in utero*

A third possible mechanism of exposure to industrial lead is exposure *in utero*. In the earlier literature, it was reported that antenatal lead exposure produced increased numbers of miscarriages and stillbirths in female lead workers, and that their live-born children were highly susceptible to neonatal convulsions.[2] High concentrations of lead have been demonstrated in the placenta, liver, and brain of infants born to lead workers.[16] It seems likely that such events would occur with less frequency in the United States today, given the general improvement that has occurred in industrial hygiene. Nevertheless, it does not seem reasonable, even today, to simply dismiss those older reports. Longitudinal studies of the outcome of pregnancy in female lead workers are needed to assess whether *in utero* exposure to lead remains a problem.

Exposure Before Conception

A fourth, still more speculative mechanism by which children may be exposed to industrial lead, is through exposure of their parents' germ cells before conception. While it would be impossible in female workers to distinguish this mechanism from exposure *in utero*, earlier studies of the offspring of males employed in the lead industry[2] showed fetal loss rates (miscarriages plus stillbirths in wives) as high as 50 to 80 percent. The relevance of those data is unclear; however, cohort studies in the families of lead workers would seem a reasonable means of assessing the current risk of this mode of exposure.

Health Consequences of Childhood Lead Exposure

Anemia, encephalopathy, and interstitial nephritis have for many years been recognized as the end-results of increased lead absorption in childhood. The major focus of interest today, however, is on the possibility that there may be subclinical antecedents to each of these easily recognized, but often irreversible, end-results.

Hematologic Consequences

The hematologic effects of lead absorption, both clinical and subclinical, have probably been the most thoroughly studied. It has been demonstrated that lead causes enzymatic inhibition of heme biosynthesis at several points in the metabolic pathway, with resulting increase in the blood levels of free erythrocyte protoporphyrin (FEP), increased urinary excretion of coproporphyrin and uroporphyrin, and decreased levels in red blood cells of the enzyme, delta aminolevulinic acid dehydratase.[1] This work has contributed to the emerging concept that there may really be no threshold for the metabolic and physiologic effects of lead on children, but rather that each atom of lead which is absorbed has the capacity to inhibit some enzymatic interaction.[17] Such a conclusion is suggested by extrapolation from data relating blood lead levels in children near smelters to levels of FEP, Figure 3.

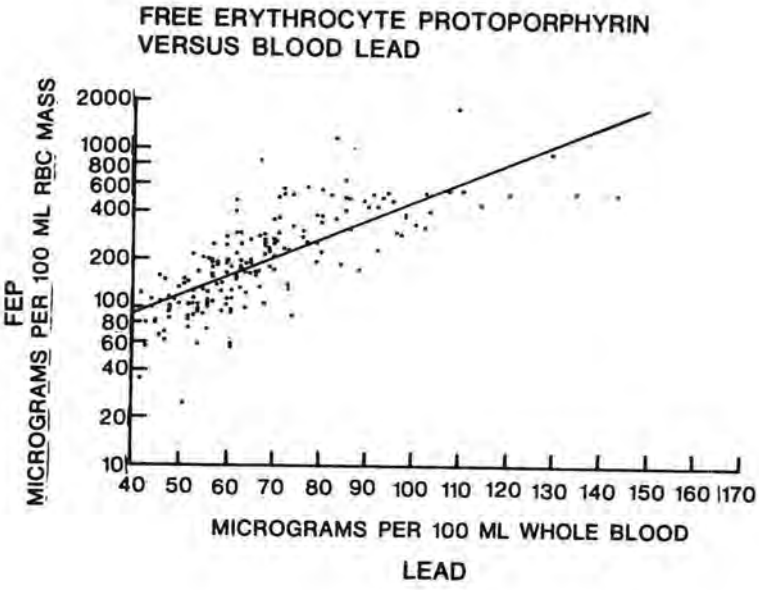

Figure 3 Free Erythrocyte Protoporphyrin *versus* Blood Lead in Children Living Near Smelters

Neurologic Consequences

Perhaps the most controversial topic today in the entire dialogue on lead in childhood is whether asymptomatic increased absorption of lead can cause subclinical alteration of neurologic or psychologic function. The central methodologic problem here, I suspect, is a lack of simple parameters which can be measured simply. While decreased enzyme levels

tell the whole story of increased lead absorption in the red blood cell, straight forward neurologic measurements, such as the well-documented abnormalities of peripheral nerve conduction observed in children with increased body lead burden,[18] do more than hint at the possible effects of lead on higher neural function. At the same time, attempts to measure higher function directly in children with increased lead exposure are subject to all the difficulties of physiologic adaptation and observer bias inherent in such testing. Yet, despite these difficulties, a trend may be emerging.

A wide variety of neurologic and psychologic abnormalities have been reported in recent studies of children exposed to lead. They have included slowing of motor nerve conduction velocity,[18] peripheral muscular weakness,[19] decreased fine-motor function scores on the Stanford-Binet intelligence test,[20] decreased scores on the McCarthy scale of intelligence in children,[21] and behavioral hyperactivity.[22] Also in our own blind studies of neuropsychologic function in El Paso,[23] we evaluated 46 asymptomatic children, ages 3-15 years, with blood lead concentrations of 40-68 µg/100 ml (mean 48 µg/100 ml) and 78 ethnically and socio-economically similar controls with levels <40 µg/100 ml (mean, 27 µg/100 ml). All children lived within 6.6 kilometers of the smelter and, in many cases residence there had been lifelong. Mean age in the lead group was 8.3 years and in the controls 9.3. Testing with Wechsler intelligence scales for school children and preschoolers (WISC and WPPSI) showed age-adjusted performance I.Q. to be significantly decreased in the group with higher lead levels (mean scores, WISC plus WPPSI, 95 vs 103, $p<0.01$). Children in all ages in the lead group also had significant slowing in a finger-wrist tapping test. Full-scale I.Q., verbal I.Q., behavior, and hyperactivity ratings did not differ.

In few of these instances have individual test results been frankly pathologic. Indeed, study design usually excluded children with such findings. Nevertheless, the gradient of abnormalities from exposed to unexposed children has been consistent and often statistically significant. Taken as a group, the results suggest that increased absorption of lead during childhood does cause a neurologic lesion, but that the lesion is diffuse and subtle. The histologic substrate may be a diffuse degeneration of neuroglia and other supporting cells, as has been suggested in several animal models.[24]

Of course, there have also been studies which have failed to demonstrate any neurologic or psychologic abnormalities in children with increased lead absorption. Two general sorts of criticisms may, however, be directed toward those studies: either the tests used, such as the Denver Developmental Evaluation, were relatively insensitive,[25] or the study and control groups were so constructed that there was little difference between them in degree of exposure to lead. For example, in the studies of Lansdown[26] in England and of McNeil and Ptasnik[27] in

El Paso of neuropsychologic function in children living near lead smelters, a high proportion of the children in the exposed groups had blood lead levels below 40 µg/100 ml and thus appear to have differed rather little from control subjects.

Renal Consequences

The effects of lead absorption upon the kidneys have been more difficult to study in children than the hematologic and neurologic effects. End-stage renal disease has been recognized in Australia among young adults who, as children, consumed high doses of lead in paint.[28] Also, acute, generally self-limited renal injury in the form of the Fanconi Syndrome, has been seen in a large proportion of children hospitalized in this country with acute lead encephalopathy. It is, however, not known whether chronic exposure to lower doses of lead in particulate form has any adverse effect upon the kidneys. Studies of this problem should perhaps be undertaken among groups of children who have lived near lead smelters or other lead works and have been chronically exposed to particulate lead.

Conclusions

To summarize, I have discussed several epidemiologic mechanisms by which children may be exposed to particulate lead of industrial origin, and I have described some of the possible ill consequences to health that might result from such exposure. Clearly, the best documented epidemiologic mechanism for the transfer of particulate lead from workplace to child is through exposure to airborne emissions or through exposure to lead workers. Of the health effects, the hematologic are supported by the firmest evidence. The rest should be taken with the cautions offered.

While any extrapolation is dangerous, it seems reasonable to extrapolate from the studies of lead absorption among children living near smelters to children living in cities and near highways who are exposed to particulate lead from automobiles. While children near roadways are generally exposed to lower levels of lead in air and dust than children living around smelters, there is no *a priori* reason to suspect that these children avoid inhaling and ingesting the particulate lead in their environment or that they escape the metabolic consequences of such absorption. The concept of a socially acceptable level of absorption must certainly be considered in a situation of low-level of exposure. That concept must, however, be weighed against the thought that the most deleterious effects of lead on children may be precisely those subtle but far-reaching and possibly irreversible aspects which have been most difficult to demonstrate.

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MODERATOR-Dr. Kenneth Bridbord

Thank you Dr. Landrigan. We should open immediately for questions.

QUESTIONS, ANSWERS, COMMENTS

COMMENT-Dr. Hector Blejer

I have an observation about the work presented by the last speaker. In regard to children living in the neighborhood of lead smelters, the work done in this study may, I think, be repeating some of the industrial hygiene mistakes that are still being made and have often been made in the past such
all of those I know about, are copper, zinc and/or lead smelters. Consequently, other substances such as cadmium, zinc, arsenic, and others also come out. These have some other deleterious effects. In some cases, such as with cadmium, they can also be nephro-toxic. Therefore, the measurement of the concentration of one single toxic entity, as if it were the only one affecting the worker, as well as the children in the surrounding community, is a bit simplistic. I would consider such studies, at least in my opinion, as being fairly incomplete. To ascribe environmentally all or any of the effects found in these cases specifically to lead alone is a mistake which we are also making occupationally through bad industrial hygiene. I would hate to see it repeated environmentally. The other observation I have concerns something which Dr. Culver mentioned. In California some of the electric lead storage battery and other lead plants which have in-house or other preventive medical services, cases of lead poisoning which occur within the walls of these plants are never reported. However, among the 8-million workforce in California, there are about 40 electric lead storage battery plants with a total of approximately 3,000 production workers. Therefore, a crude rate of lead-produced disease among these California lead workers can be calculated even with the incomplete reporting of lead poisoning cases in that State.

COMMENT-Dr. Jerome Cole

I would like to address my comment to a criticism by Dr. Landrigan of a study that was conducted by Dr. McNeil in El Paso. He repeated a criticism he has made previously that the control group vs the exposed group overlap and therefore, the comparisons may not be valid. In fact, this was not the case. While there were children in the overall exposed group with blood leads below 40 µg/100 ml of blood, they were included in one comparison group because they lived in the high lead exposure area. This reluctance to throw these data out of the exposed group was because of the possibility that children may have had a high blood lead level at one time in their live. This was the only comparison made. Indeed, there were comparisons made in children having over 40 µg, under 40 µg, and from 40 µg to 49 µg, with their matching controls. There were several

parameters of exposure, length of residence, elevated FEP results, etc. I think Dr. Landrigan's characterization of this study is unfair.

COMMENT-Dr. Philip J. Landrigan

It's somewhat difficult to interpret the data from Dr. McNeil's study from the manner in which they have been presented to date and I think the major criticism must still stand; 37 percent of the children in the so-called lead group who had blood leads below 40 µg at the time they were studied may also have had exposure to lead in the past. However, I don't see how any researcher can reasonably determine this, short of serial measurements.

QUESTION-Mr. George Becker

I would like to address my question to Dr. Culver. I am very much interested in the chart that you presented which showed some differences in the blood lead level *versus* the hemoglobin and the ALA test results. Do you know whether or not this employee or any of the employees you checked had been taking oral Versenate or other chelating medication, and, if this was the case, would this have affected the differences you projected? I would like to have an opinion from you as to what effect you believe prolonged use of an oral Versenate would have in this particular area. Also, I would like to ask Dr. Culver or anyone else on the panel if there are results available of epidemiological studies that have been conducted in connection with prolonged Versenate usage?

ANSWER-Dr. Dwight Culver

In the case that I presented Versenate was not used, and I'm happy to say that no industry with which I am associated uses Versenate as a prophylactic material. Let me make one other point with regard to oral Versenate. It probably is not very well absorbed and not very effective. If an oral medication is to be used, it might be preferable to use penicillamine. There is also a question of whether or not oral medication of that sort promotes an uptake of lead from the gut. That's still very much a concern about this.

QUESTION-Mr. George Becker

Will Versenate pull out other metals besides lead?

ANSWER-Dr. Dwight Culver

Yes, it will. I can't give you the relative binding strikes but it will indeed pull out end metals.

COMMENT-Dr. Bertram W. Carnow

I'd like to comment on Dr. Landrigan's paper. It's something like, "Will the real El Paso study please stand up." There have been three studies in El Paso. It might be of interest to the audience to know how these children were found. I was asked by the City of El Paso to consult for them regarding sulphur oxides coming from the smelter. On examining the emission data, I found that an extraordinary amount of lead (more than 800 tons over 2 years) had been emitted into the air. I suggested to the city officials that while they might have a SO^2 problem, they almost certainly did have a lead problem.

At that point, I was told that there were no known cases of clinical lead poisoning in El Paso. I suggested to the health commissioner that blood be drawn from children living near to and remote from the smelter. This was done and the blood was analyzed in Chicago, at Cook County Hospital by Dr. Eleanor Berman who found large numbers of children with very high blood lead levels. Some of the children with the highest levels were examined, after which they and many others were hospitalized.

The other two studies were carried out after the children had long since been treated and were out of the hospital, Dr. Landrigan's a year later and Dr. McNeil's even later than that. We found gross pathology in these children, including basophilic stippling, anemia, hyper-excitability, and fatigue. During a follow-up study, in the first 10 children we found a significant number with abnormal EEG's and learning deficits similar to those found by Dr. Landrigan. This was an unfunded clinical study which followed the findings I noted.

Since I was not consulted, or even informed, regarding the development of either of the subsequent studies, I had no input into them. It may well be that hospitalization, chelation, and removal of the subjects from the contaiminated area before the other studies took place explains the absence of acute symptoms or clinical findings. I would suggest that the criticism leveled at Dr. Landrigan regarding the McNeil study is not a valid one. It is inconceivable to me that 3 studies having been done should show such diverse results. It might be good to have an impartial committee examine all three studies to determine why the McNeil study finds normal children while the other two uncover many abnormal clinical, laboratory and pathological findings.

COMMENT-Dr. Jerome Cole

I just wanted to say that in response to Dr. Carnow's suggestion, I would certainly agree that a committee should be formed to look into these three studies and I would be happy to ask Dr. McNeil for his complete cooperation with such a committee. I think this is needed since there has been so much controversy concerning these studies.

COMMENT-Dr. Samuel Epstein

I would like to make a brief comment, if I may, as President of the Society for Occupational and Environmental Health. At yesterday's Council meeting, the question was raised as to whether the Society would, under certain circumstances, be prepared to act as an "ombudsman" in situations where there are conflicting data or conflicting interpretations of data. On behalf of the Council, I would like to express an interest in accepting Dr. Cole's suggestion concerning the El Paso studies that we set up a committee with balanced representation from all interested parties to examine such facts and report back to the Society in due course.

COMMENT-Dr. J. C. Calandra

Dr. Carnow's suggestion, which has been supported by Drs. Epstein and Cole, should be implemented as quickly as possible. It is important that the three studies mentioned be reviewed. The questions about the "sub-clinical" central and peripheral nervous system effects of lead at low levels of exposure in children need to be answered without bias or recriminations.

I would like to suggest that other equally pivotal studies should be discussed pro and con as to validity, applicability, etc. The facts should be brought out into the open; then we can proceed with completion of the job of protecting the workers and the public.

COMMENT-Dr. Samuel Epstein

Ladies and gentlemen, on behalf of the Society for Occupational and Environmental Health, I should now like to formally announce our intent to create an *ad hoc* committee for the evaluation of the El Paso data. The chairman of this committee will be Dr. Warren Muir, of the Council on Environmental Quality. I would like to briefly indicate some of the guidelines governing the future function and the role of this committee. First of all, the committee will be appointed by the Society and its membership and will reflect balanced representation of the widest possible range of diverse viewpoints and disciplinary interests. Secondly, all those who were directly or indirectly involved in the El Paso study will be ineligible for membership, but can act as consultant to the committee. Finally, all data submitted to the committee will be treated in a freely open fashion and will be freely available to outside members of the Society on request. I would like to request nominations for membership of this committee, from any of those present here today, which should be submitted to Dr. Warren Muir. We would appreciate it if such nominations could be submitted within the next ten days or so. Thank you.

CONFERENCE CHAIRMAN-Dr. Bertram Carnow

The topic for discussion by this panel this afternoon will be the Threshold Limit Values for Inorganic Lead. The discussion leader for the panel will be Mr. Timothy F. Cleary, Chairman of the Occupational Safety and Health Review Commission. Mr. Cleary.

SESSION IV- PANEL DISCUSSION ON TLV's FOR LEAD

Timothy F. Cleary, Discussion Leader
Chairman, Occupational Safety and Health Review Commission

The interpretation of what constitutes a proper TLV with regard to a given toxic agent is generally a lively subject for discussion, as witnessed by the recent proposed and adopted standard on vinyl chloride and the subsequent litigation concerning the standard. I am confident that the discussions this afternoon will be just as stimulating.

The panelists will detail this subject for you, but before calling upon them I would like to refer briefly to some experiences of the Occupational Safety and Health Review Commission. The Commission is an independent agency created under the Occupational Safety and Health Act of 1970 to adjudicate disputes arising from enforcement actions between employers, employees, and the Secretary of Labor.

In the short period of time that I have been associated with the Society for Occupational and Environmental Health, sponsor of this conference, I have been deeply impressed by the dedication of the officers and membership in their pursuit of societal goals. I am fully confident that all present will play some part in helping to achieve the purpose for which the Occupational Safety and Health Act was enacted; that is, to assure, so far as possible, that every working man or woman in this country has a safe and healthful work environment.

Each year there are some hundreds of thousands of new cases of occupational illnesses in the United States. In order to reduce this tragically high figure, the Secretary of Labor has promulgated standards which set exposure limits for hundreds of toxic agents, and outlined the necessary preventive and corrective measures required for workplace areas in the presence of toxic agents and other health hazards, such as noise. In fiscal year 1974, for example, the Labor Department issued citations for some 11,000 health violations; however, this figure represents only about 4 percent of the total number of violations cited. While this number may appear to be relatively low, one thing is certain; the number of complaints, inspections, citations, and contested cases involving health hazards will dramatically increase in the near future. The Commission has only started to scratch the surface in this area.

There have been relatively few cases before the Commission dealing with inorganic lead; nevertheless, the cases which have already been decided have laid the ground work for future adjudication of health hazard cases.

In July, 1971, a citation was issued to an Omaha lead smelting plant in which there were airborne concentrations of lead significantly exceeding

the standards for safe levels. Because the standard dealing with airborne lead did not become effective until August, 1971, the company was cited under the general duty clause, which requires that each employer shall furnish his employees a place of employment which is free from recognized hazards that are causing, or likely to cause, death or serious physical harm. It was the Secretary of Labor's position that any exposure in excess of .2 mg/cu m of airborne lead constituted a recognized hazard in the industry. I might add that the NIOSH Criteria Document advocates a .15 mg/cu m standard.

Seven representative workers were equipped with air sampling devices to collect data at this Nebraska smelting plant. The results ranged from a low of .10 mg/cu m to a high of 2.85 mg/cu m. In all, five of the seven employees worked in areas having readings in excess of .2 mg/cu m of air.

After the hearing, the Review Commission found the company in violation and the judge noted that the employer failed to require the use of respirators or to utilize adequate engineering controls. In addition to an assessed penalty, the company was ordered to provide the necessary engineering controls within 6 months of the issuance of a final order of the Commission. In review, a majority of the Commission members affirmed the disposition of the case.

The order of the Review Commission was upheld by the United States Circuit Court of Appeals for the Eighth Circuit. Of particular importance was the Court's approval of air sampling as a method of detecting violations. While stating that biological monitoring, including urine and blood sampling, is also accurate, the court stressed that air sampling is the most efficient and practical way for the Secretary of Labor and employers to determine airborne lead levels for the purposes of enforcement actions under the Occupational Safety and Health Act. In this regard I would point out that the Commission has long approved this sampling technique for other health hazards, particularly in noise cases.

Some of you might ask why a decision involving exposure to lead under the general duty clause is important when the Secretary of Labor has a standard dealing with lead and improvements in that standard are being planned. It is important because most, if not all, of the significant health standards adopted by the Secretary of Labor following rule making proceedings, have been legally contested. Some were stayed and not in effect during the litigation and others have been declared invalid. In the event of a Stay, with a court decision holding that a new lead standard is invalid, the general duty clause would come into play. In applying this clause, what is recognized as a hazard in a particular industry is most important.

All of you and those on the panel with me will have much to say about what is recognized as hazardous. This is an important responsibility

and I look forward to hearing the comments as this conference progresses.

Before closing I would like to mention one of the problems presented in all of our cases. Section 17-K of the Act states in part that "a serious violation shall be deemed to exist in a place of employment if there is a substantial probability that death or serious physical harm may result from a condition which exists..." The problem,in cases involving exposure to health hazards, such as lead, arsenic, etc., is to determine at what point in time and at what level of exposure within the purview of the standard that a violation becomes serious enough to cause physical harm or death.

We at the Commission are well prepared for the expected influx of health cases. The hazards of exposure to excess levels of lead, arsenic, mercury, beryllium, silica, asbestos, and other substances, are well documented and tragic. It is time to eliminate these hazards.

With this I would like to begin the panel discussions. I also would ask the audience to withhold questions until all of the panelists have had an opportunity to make their presentations.

I would like to turn the microphone over to Dr. Hector Blejer, who is the Deputy Director of the Division of Field Studies and Clinical Investigations at NIOSH, for his comments on Inorganic Lead; Biological Indices of Absorption-Biological Threshold Limit Values. Dr. Blejer.

INORGANIC LEAD: BIOLOGICAL INDICES OF ABSORPTION-- BIOLOGICAL THRESHOLD LIMIT VALUES

Dr. Hector P. Blejer
National Institute for Occupational Safety and Health

A B S T R A C T

Lead concentrations of 80 µg/100 ml in blood and 200 µg/1000 ml in urine traditionally have served as biological TLV's in determining "safe" levels of occupational exposure. Studies using more than one biological index have shown that metabolic and enzymatic changes and organ dysfunction and/or damage can occur from chronic lead exposures resulting in blood lead levels lower than 80 µg/100 ml. Other occupational, clinical data show that overt lead poisoning can occur among lead-exposed workers with blood lead concentrations $\leq$80 µg/100 ml. Preventive medical programs should include biological indices, in addition to blood and urinary lead determinations, and also incorporate the recognition that untoward effects, including lead poisoning can occur at lead levels below 200 µg/1000 ml of urine and 80 µg/100 ml of blood.

Introduction

The scope herein is restricted to the preventive occupational medical aspects of "Biological Threshold Limit Values for Inorganic Lead" or, as is preferable to call them, "Biological Indices of Inorganic Lead Absorption."

The definitive *primary* occupational control of lead absorption is that of maintaining the work air concentration of lead at a mimimum, that is, as low as possible below the hygienic work standard--be that a TLV, maximum allowable concentration (MAC), or time-weighted average (TWA). Thus, the preventive medical use of biological indices becomes secondary when adequate controls of lead exposures in the work atmosphere and environment are achieved. However, the situation regarding the effectiveness of such industrial hygiene engineering and other controls in the lead industries of this and other countries is generally not that good, for in many of those workplaces the TLV's, MAC's or TWA's for airborne lead are exceeded, often grossly. Until adequate controls are instituted, what can be done medically to protect the worker from such respiratory overexposures? Moreover, industrial hygiene measurements of airborne lead generally cannot quantify precisely the respiratory exposure of an individual worker, or other contributory occupational exposures such as the swallowing of airborne lead and the lead ingestion which results from poor work hygiene practices.[1] In such cases the medical use of biological indices becomes essential to protect exposed workers against undue occupational lead absorption and resultant toxic effects.

To discuss the proper preventive role of biological indices, it is necessary to review what biochemical changes or toxic effects they determine. It is also necessary to review briefly the validity of the, until recently, almost sacrosanct blood lead threshold of 80 µg/100 ml, the concentration below which supposedly nothing untoward to health happens.

Occupational use and function of biological indices

As used in an occupational medical program for lead-exposed workers, the functions of biological indices include:

1. To ensure proper medical placement of all workers;

2. To monitor where inadequate industrial hygiene engineering or other controls have allowed the occurrence of lead overexposure, over absorption and resultant toxic effects, and thus;

3. To help achieve implementation or improvement of industrial hygiene controls which will adequately prevent further over-exposure;

4. To prevent immediate (acute) or remote (chronic) toxic effects of lead overexposure;

5. To assess the degree of recovery of lead-affected workers and allow safe return to a healthful work environment.

Types of biological indices

Table I presents various biological indices. The first and third groups include tests which determine various biological effects of absorbed lead.[1,2] The second group lists indices which measure the concentration of absorbed lead in tissues and urine.

Biosynthesis of heme

A brief review of the biosynthesis of heme shows the basis for the specificity in determining the effects of absorbed lead of certain indices listed in the first group of Tables I and II.

TABLE I

INORGANIC LEAD: BIOLOGICAL INDICES OF EXPOSURE, BY TYPE

I. INTERFERENCE WITH HEME SYNTHESIS

Urinary Index

- *delta*-AMINOLEVULINIC ACID (ALA)
- COPROPORPHYRIN
- UROPORPHYRIN
- PORPHOBILINOGEN

Hematopoietic Index

- BLOOD ALA
- ERYTHROCYTE ALA-DEHYDRATASE ACTIVITY
- ETYTHROCYTE NON-HEME IRON
- ERYTHROCYTE PROTOPORPHYRIN
- ERYTHROCYTE ZINC PROTOPORPHYRIN
- BONE MARROW SIDEROBLASTS
- RETICULOCYTES (Immature Erythrocytes)
- PUNCTATE BASOPHILIA ("Stipple" Cells)
- ERYTHROCYTE LIFE SPAN (Increased Fragility)
- HEMOGLOBIN-HEMATOCRIT

II. LEAD ABSORPTION/DEPOSITION/EXCRETION

Index

- BLOOD LEAD
- URINARY LEAD
- HAIR LEAD
- NAIL LEAD
- BONE LEAD

III. OTHER TYPES OF INDICES

- BONE DENSITY (Radiographic)
- ELECTROMYOGRAPHY
- SERUM PROTEINS
- RENAL TUBULAR FUNCTION
- ENDOCRINE FUNCTION
- NEUROBEHAVIORAL FUNCTION

TABLE II

INORGANIC LEAD: BIOLOGICAL INDICES OF OCCUPATIONAL EXPOSURE BY TYPE AND SUGGESTED USEFULNESS

I. INTERFERENCE WITH HEME SYNTHESIS

Increased Concentration

- ERYTHROCYTE PROTOPORPHYRIN[a]
- ERYTHROCYTE ZINC PROTOPORPHYRIN[a]
- URINARY δ-AMINOLEVULINIC ACID (ALA)[b]
- URINARY COPROPORPHYRIN[c]

Decreased

- ERYTHROCYTE ALA-DEHYDRATASE ACTIVITY[a]
- HEMOGLOBIN[d]

Increased Count

- STIPPLE CELLS (Punctate Basophilia)[e]

II. LEAD ABSORPTION

Increased Concentration

- BLOOD LEAD[f]
- URINARY LEAD[f]

III. OTHER TYPES OF INDICES

- ELECTROMYOGRAPHY[g]
  - Motor Nerve Conduction Slowness--Extensor Muscle Weakness
- RENAL TUBULAR FUNCTION[g]
  - *Proximal Tubular Dysfunction*

[a] Specific for biochemical effect of absorption

[b] Semispecific for biochemical effect of absorption

[c] Semispecific, as above; valuable for screening

[d] Nonspecific; corroborates overabsorption

[e] Nonspecific; too variable and not useful

[f] Specific for degree of lead absorption

[g] Nonspecific; useful in early detection and diagnosis

NOTE: *See text for more precise information on footnote comments*

Fig 1 depicts a simplified schematic of the metabolism of heme.[3] Essentially, any amount of absorbed lead inhibits the activity of the enzyme δ-aminolevulinic acid dehydratase (ALAD) which is necessary to synthesize porphobilogen from two molecules of δ-aminolevulinic acid (ALA) (Stage 1, Fig 1).

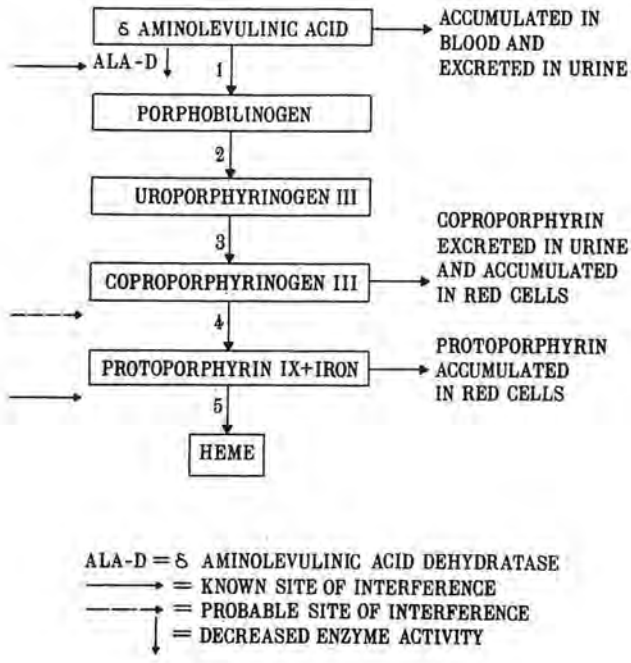

Figure 1 Biosynthesis of heme
From J.J. Chisholm, Lead Poisoning, Scientific American, 1971

As there appears to be a reserve of this enzyme, the ALAD activity needs to be sufficiently inhibited by enough absorbed lead (at blood lead levels $\geq$ 30 μg/100 g) for ALA to build up in the red blood cells (ALA-B) and be excreted in greater than normal amounts in the urine (ALA-U).[3-4] Thus, three tests of the biological response to the absorbed lead are obtained: ALA-D, ALA-B, and ALA-U.

The absorbed lead also interferes specifically with the conversion of protoporphyrin and non-heme iron into heme, so that free erythrocyte protoporphyrin (FEP), non-heme iron and also zinc protoporphyrin (ZP) accumulate in the red blood cells where each can be measured separately. Absorbed lead also acts in a poorly understood way elsewhere in the biochemical chain of heme synthesis (Stage 4) so that coproporphyrin (CP) accumulates in red blood cells and is excreted in the urine (CP-U) where it can be measured.[4]

The effects of absorbed lead on the biosynthesis or metabolism of heme are thus productive of all the changes listed under the first category in Tables I and II, including anemia, immature types of red blood cells, and bone marrow red blood cell precursors.

Occupational usefulness of selected biological indices

Indices of practical use for occupational medical monitoring are included in Table II. Urinary coproporphyrin (CP-U), blood lead (Pb-B) and urinary lead (Pb-U) determinations are the indices used most commonly by many industries to monitor lead-exposed workers. CP-U is subject to a high variance but, when done semiquantitatively, results are obtainable quickly and provide for rapid in-plant screening.[1] The value of Pb-B and Pb-U is somewhat limited, however, in that *per se* they measure only the amount of absorbed lead and do not determine its biochemical effects. Moreover, Pb-B and Pb-U results have a common disadvantage: they are subject to a frequent error of $\pm$ 10-15 percent, regardless of the analytical method used.[1] In addition, urine specimens from lead-exposed workers are often contaminated with extraneous lead.

The stipple cell count is a nonspecific test, which shows a very large variance within individuals, between individuals and between clinical laboratory observers. This test today has no occupational value by itself, even as an additional index.[5,6] Although not specific, hemoglobin or hematocrit determinations are particularly important as baseline and periodic measurements, especially when levels and effects of lead overabsorption are indicated by other indices and/or symptomatology.[5,6]

Currently, ALA-U is occupationally the most commonly used of the newer biochemical indices discussed under "Biosynthesis of Heme." At Pb-B levels greater than 40 µg/100 g or 100 ml, a good coorelation exists between ALA-U and Pb-B. As reported by Kehoe, this relationship gives the ALA-U index "an extremely useful place in the armamentarium of occupational health in the lead-using industries."[1] Moreover, its method of analysis is reliable and quick, and the results cannot be altered by contamination of the urine specimen with lead.

Other biochemical indices which indicate an interference of absorbed lead with enzymatic or other steps in the formation of heme are CP-U, already discussed, as well as ALA-D, FEP, and ZP. Presently, these last

three appear to be the most specific, reliable and sensitive indicators of related biochemical effects, especially those produced by levels of lead absorption considerably below widely accepted biological threshold limits. However, the sensitivity of ALA-D has been ascribed as too great to be of practical occupational value in differentiating between mild and severe exposure to and absorption of lead; and greatly limited in biological monitoring of workmen in the lead industries.[1]

Nonspecific and new indices of other effects of absorbed lead include measurements of certain electromyographic, behavioral and kidney function changes.[2] As discussed under "Blood Lead Threshold," these indices are uncovering subclinical and other evidence of dysfunction or damage among lead workers with Pb-B at levels below those generally considered occupationally acceptable.

Categories of biological indices

Various occupational and other categories of inorganic lead absorption have been developed in the last decade. Table III presents the tests and values listed in the "1968 British Statement" four categories: Normal, Acceptable, Excessive, and Dangerous,[5] with the cutoff between Acceptable and Excessive for Pb-B listed at 80 µg 100 ml.

TABLE III
INORGANIC LEAD:
1968 "BRITISH STATEMENT" BIOLOGICAL INDICES*

INDEX		LIMIT VALUES			
		NORMAL	ACCEPTABLE	EXCESSIVE	DANGEROUS
BLOOD LEAD	(µg/100 ml)	< 40	40 - 80	80 - 120	> 120
URINARY LEAD	(µg/100 ml)	< 8	8 - 15	15 - 25	> 25
URINARY CP	(µg/100 ml)	< 15	15 - 50	50 - 150	> 150
URINARY ALA	(µg/100 ml)	< 0.6	0.6 - 2	2 - 4	> 4

Adapted from R.E. Lane, et al, Brit Med J, 1968

In Sweden, a different approach had been taken since 1967.[7] As shown in Table IV, three occupational categories of increased lead absorption are included under Limit Values: Acceptable, Acceptable for work but with Precaution, and Unacceptable. Values for Pb-U and CP-U are not included, and the Unacceptable limit for Pb-B is any concentration greater than 70 µg 100 ml.

TABLE IV

INORGANIC LEAD:
1967 SWEDISH OCCUPATIONAL INDICES*

	LIMIT VALUES		
INDEX	ACCEPTABLE	ACCEPTABLE FOR WORK BUT WITH PRECAUTION	UNACCEPTABLE
BLOOD LEAD	< 50 µg/100 ml	50–70 µg/100 ml	>70 µg/100 ml
URINARY LEAD	< 1.5 mg/100 ml	1.5–2.5 mg/100 ml	> 2.5 mg/100 ml

**Adapted from Selander, S. and Cramer, K., Brit J Industr Med, 1970*

By contrast, Table V presents the single category of indices recommended by the 1968 Conference on Inorganic Lead[1-7] which met in Amsterdam a few days after the "British Statement" was published.[7] The single category is that of an Upper Permissible Value for occupational exposure, with a Pb-B of 70 µg/100 ml.

TABLE V

INORGANIC LEAD:
1968 AMSTERDAM OCCUPATIONAL INDICES*

INDEX	UPPER PERMISSIBLE LIMIT VALUE
BLOOD LEAD	70 µg/100 ml
URINARY LEAD	13 µg/100 ml
URINARY CP	30 µg/100 ml
URINARY ALA	1.0 mg/100 ml

**Adapted from Selander, S. and Cramer, K., Brit J Industr Med, 1970*

In 1971 the American Medical Association (AMA) developed the statement "Diagnosis of Inorganic Lead Poisoning."[6] As shown in Table VI, the categories of Normal, Acceptable, Excessive, and Dangerous recur. The AMA statement is virtually identical to the British and, except for Normal values, all the values listed under the last three categories are

lower. The AMA's cutoff between the Acceptable and Excessive values for Pb-B is 60 µg/100 ml.

TABLE VI

INORGANIC LEAD:
1971 AMA BIOLOGICAL INDICES*

INDEX	NORMAL	ACCEPTABLE	EXCESSIVE	DANGEROUS
BLOOD LEAD µg/100 ml	< 40	40 - 60	60 - 100	100
URINARY LEAD µg/100 ml	< 8	8 - 12	12 - 20	20
URINARY CP µg/100 ml	< 15	15 - 30	30 - 100	100
URINARY ALA mg/100 ml	< 0.6	0.6 -1.5	1.5 - 3.5	3.5

**Adapted from Diagnosis of Inorganic Lead Poisoning, AMA, Chicago, 1971*

TABLE VII

INORGANIC LEAD:
OCCUPATIONAL BIOLOGICAL INDICES#

INDEX	"NORMAL" VALUE	UPPER ACCEPTABLE LIMIT VALUE	DANGEROUS LEVEL
BLOOD LEAD µg/100 ml	< 30	60	> 100
URINARY LEAD µg/100 ml	< 8	12	> 20
URINARY CP µg/100 ml	< 15	30	> 100
URINARY ALA mg/100 ml	< 0.5	1.5	> 3.5

#Adapted from Diagnosis of Inorganic Lead Poisoning, AMA, Chicago, 1971 and Selander, S. and Cramer, K., Brit J Industr Med, 1970

Discussion

Different preventive occupational approaches--and at times arbitrary value judgements--are built in the various categories or risk included in Tables III through VII. Also, irrespective of which limit values are considered adequate to prevent toxic effects among lead-exposed workers, a growing body of occupational medical data is effectively challenging the scientific preciseness of all the upper acceptable values given, particularly the existence of a threshold for blood lead.

Categories of risk

Both the British and AMA Statements explicitly state that their four categories of lead absorption are arbitrary divisions.[5,6] This is most evident in the case of Excessive and Dangerous, for if a degree of lead absorption is considered excessive, then it must also be deemed dangerous. However, both statements address indirectly the concept of occupationally unacceptable lead absorption, for they define their Excessive categories partly as levels of absorption which, even in the absence of symptoms and signs, are *unacceptable* because of the possibility of toxic effects and long-term sequelae.[5,6]

In contradistinction, the Swedish categories of Acceptable, Acceptable for Work but with Precaution, and Unacceptable, address the occupational issue directly, and so does the single Amsterdam category of Upper Permissible Limit. Moreover, both of these approaches readily transmit descriptive information of pragmatic use in the biological monitoring of lead-exposed workers. Also, notable is that the Amsterdam values were not meant to indicate limits between safe and unsafe. They were recommended as guidelines, with the proviso that no undue reliance be placed on a single index.[7]

The approach shown in Table VII is essentially a hybrid which incorporates related guidelines developed in California in 1972,[8,9] the Amsterdam single-category guidelines and the AMA upper acceptable values It is an attempt by the author to overcome certain occupational shortcomings of and bridge major differences between the other four approaches.

As discussed below, however, newer data are questioning the preventive effectiveness of the limit values given in all the preceding categories of acceptable or permissible risk.

Blood lead threshold

Lately, the previously widely accepted concept of a blood lead threshold which prevented harmful effects and below which overt, clinical symptoms and signs did not occur is being challenged. As reviewed succintly and recently by Waldron,[10] there is mounting evidence which effectively questions the validity of this concept and the accuracy of presently accepted biological threshold levels--be they Pb-B of 80 µg/100 g associated most closely with Kehoe,[11] or lower limits of 70 and 60 µg 100 g.[6,7] Occupationally, these data are of two kinds. Among lead-exposed workers with Pb-B of *less* than 80 µg 100 ml subclinical effects such as neuropathy[12] neurobehavioral dysfunction[13] and nephropathy[14,15] have been demonstrated in the *absence* of any conventional clinical sign of lead intoxication. The second is the well-documented occurrence of overt, acute clinical symptoms such as lead colic in lead-exposed workers with Pb-B of less than 80 µg/100 g.[14,16] Additionally, a recent review of the California State official data

compiled from the "Doctor's First Reports of Work Innury" revealed that for the period 1968 to 1974, there were 52 cases of lead-exposed workers with Pb-B of less than 80 µg/100 ml. In 45 of these lead workers the reporting physician described acute symptomatology due to lead, diagnosed lead poisoning, prescribed specific treatment, such as chelating agents, and/or recommended removal from lead exposure.[17]

Further, as noted by Waldron, the 80 µg/100 g threshold limit for Pb-B was derived exclusively from the experience with *male* workers in lead industries.[10] As such, this occupational blood lead threshold may be inapplicable to female lead workers, especially those who can become pregnant. Waldron concluded that Pb-B in adults generally should not be permitted to rise above 50 µg/100 g, and he cautioned that even this lower limit may be higher than is consistent with health.[10]

Occupationally, the new data discussed above[12-17] strengthen Waldron's further caveat that "threshold values should not be regarded as fixed and unchangeable but must always be subject to revision in the light of new knowledge."[10]

Conclusions and summary

Although primary prevention can be achieved only by engineering controls, the medical use of biological, monitoring indices is still needed to protect workers occupationally exposed to inorganic lead. Essentially, these indices are of two types, those which measure the degree of absorbed lead and those which determine biochemical or other effects of that absorption. All have specific occupational shortcomings and, consequently, the use of one index from each of the two types is indicated (*e.g.*, Pb-B and ALA-U) in addition to special monitoring of hemoglobin.

Recent occupational data strongly indicate that the previously widely accepted blood lead "threshold" of 80 µg/100 g is too high to prevent untoward health effects among male lead workers. Moreover, other recent data appear to indicate either that a threshold level for blood lead does not exist, or that it should be set much lower, in the range of 50 to 60 µg/100 g for female and male adults, with corresponding values for other biological indices, including ALA-D and FEP. In any of these cases, a TLV or TWA of 150 µg/cu m for airborne lead does not provide an occupational exposure level at which no worker will suffer impaired health or impaired functional capacity.

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DISCUSSION LEADER-Mr. Timothy Cleary

Thank you very much Dr. Blejer. I would ask the audience to withhold questions until all of the panelists have had an opportunity to make their presentations.

The next speaker is Dr. Jerome Cole, Director of Environmental Health for the Lead Industries Association who will discuss Occupational Health Standard for Lead. Dr. Cole.

OCCUPATIONAL HEALTH STANDARD FOR LEAD

Dr. Jerome F. Cole
Lead Industries Association, Inc.

A B S T R A C T

While TLV's have been successfully used by occupational health practitioners as guidelines, for some substances, most notably lead, the worker serves as a better environmental sampler than mechanical air sampling devices. The use of the lead content of the blood as an index of the "effective total exposure" for workers has been shown to provide a useful index of lead exposure. There are many inadequacies in air sample measurements, currently preferred by NIOSH and OSHA to determine compliance with the Occupational Safety and Health Act. Air samples do not represent the amount of absorbed lead because they do not reflect differences in particle size and solubilities or measure ingestion exposure. The Biological Limit Value (BLV) of 80 µg/100 g of blood is in the best interest of all concerned, especially exposed workers.

The subject of this discussion is the Threshold Limit Value (TLV) for lead exposure in industry. Normally, a TLV is thought of as a time-weighted-average airborne concentration, which should not be exceeded in the work place. Over the years, industrial hygienists and occupational physicians have utilized these values as guidelines (as they were originally intended to be used) rather than as strict standards.

For certain substances, notably lead, the TLV took a back seat to what has been generally regarded by widely respected, professional, occupational health practitioners as a superior means of quantifying lead exposure to the worker-namely biological monitoring. Simply stated biological monitoring employs the worker, as the environmental sampler, rather than depending on mechanical sampling devices.

Such an approach, if feasible, eliminates the many vagaries of air-sampling and measures the true "effective total exposure" of the worker to a substance in question.

It is recognized that biological monitoring for all substances encountered in the workplace is not practical, but, at least from a theoretical point of view, biological monitoring should be considered superior to simple air monitoring. With lead, there is a long history of experience and study. It can be safely stated that lead has been the subject of more toxicological, epidemiological, and environmental study than any other substance. Certainly, there is need for further study and

and corroboration of controversial research findings; but the wealth of existing information provides a comparatively good understanding of the pharmacodynamics and toxicologic thresholds of lead.

There are a large number of biological indices which may have some values in assessing lead absorption, such as lead in blood, lead in urine, urinary coproporphyrin, urinary delta-aminolevulinic acid, hemoglobin, hematocrit, lead in hair, lead in bone, etc. It is emphasized that the purpose of biological monitoring of lead workers is to prevent lead poisoning and not to diagnose lead poisoning.

It is generally agreed that lead in blood is the most accurate and useful measure of lead absorption. Blood lead is a measure of the overall concentration of lead in soft tissue. It is a measure of the absorption of lead and not the effect of lead, and should be regarded as a number to define risk.

Dr. Kehoe has reported the range of values for lead in blood and in urine, Table I, which are indicative of normal levels of absorption, abnormal but safe, and potentially dangerous. It appears to be well-documented by experience that in adults a level of lead in blood of 0.08 mg/100 g will protect the most sensitive individual.

TABLE I

RANGES OF LEAD IN BLOOD AND LEAD IN URINE
REPORTED BY KEHOE

Lead in Blood

Normal (or usual) - - 0.01 through 0.04 mg/100 g

Abnormal but safe - - 0.05 through 0.07 mg/100 g

Potentially dangerous minimum - - 0.91 mg/100 g

Lead in Urine

Normal - - 0.02 to 0.10 mg/liter

Abnormal but safe - - 0.10 through 0.15 mg/liter

Dangerous - - 0.20^{+} mg/liter

The NIOSH Criteria Document also states that absorption of lead in amounts resulting in blood lead concentrations of 0.08 mg/100 g or less will not lead to adverse effects on health. Although levels below 0.08 mg/100 g are indicative of acceptable occupational absorption, it is important to point out that it cannot be concluded that lead poisoning will occur if the level exceeds 0.08 mg/100 g. However, increases in blood levels above 0.08 mg/100g increase the risk of symptomatic illness.

Lead in urine is also a useful index of lead absorption. However, it is generally accepted that urine lead levels are more variable than blood lead measurements and are a somewhat less useful index of lead absorption.

TABLE II

RANGES OF LEAD ABSORPTION

TEST	NORMAL	ACCEPTABLE	EXCESSIVE	DANGEROUS
Blood Lead	< 40 µg/100 ml	40-80 µg/100 ml	80-120 µg/ 100 ml	> 120 µg 100 ml
Urine Lead	< 80 µg/liter	80-150 µg/liter	150-250	>250 µg/liter
Urinary Coproporphyrin	<150 µg/liter	150-500 µg/liter	500-1500 g/liter	>1500 µg/ liter
Urinary ALA	<6 mg/liter	6-20 mg/liter	20-40 mg/ liter	> 40 mg/liter

Table II presents ranges of lead absorption agreed upon by a group of international experts and reported in the British Medical Journal in 1968. In addition to blood and urinary lead, values for urinary coproporphyrin (COPRO) and delta-aminolevulinic acid which are considered as useful biochemical indices, are also given. These tests best reflect the biological response to lead.

Some have suggested that, instead of relying on biological monitoring to determine the exposure of workers to lead, air sampling is preferred. NIOSH and the Occupational Safety and Health Administration (OSHA) prefer air sampling to biological monitoring to determine compliance with the Occupational Safety and Health Act. Currently, the only standard for lead exposure in industry is that exposure must not exceed 200 µg/cu m of lead. NIOSH has proposed we believe, on faulty grounds, that this airborne lead standard be reduced from 200 µg/cu m to 150 µg/cu m. Both these levels are supposed to represent a time-weighted average exposure of the workmen.

There are many inadequacies in attempting to evaluate an exposure by air samples.

1. One of the major weaknesses in air sampling for lead is that air samples do not represent the amount of lead absorbed into the body because of differences in particle sizes and solubilities. Air samples currently used by OSHA measure "total mass." Since mass is directly related to the radius of the particle cubed, an increase in particle size from 1 micron to 10 microns represents a thousand-fold increase in mass. Therefore, particles which are too large to be inhaled and contribute nothing to absorption may contribute most of the mass.

Figure 1, taken from Morrow, represents a graphic summary of particulate deposition in the respiratory tract as a function of particle size. The deposition, retention, and absorption of particles in the respiratory tract is very complex and difficult to evaluate because of differences in particle size, shape and density all of which affect the aerodynamic size and because of differences in solubilities. However, measurement of blood lead or other biological indicators of lead absorption eliminate the uncertainty due to particle size, shape, density and solubility.

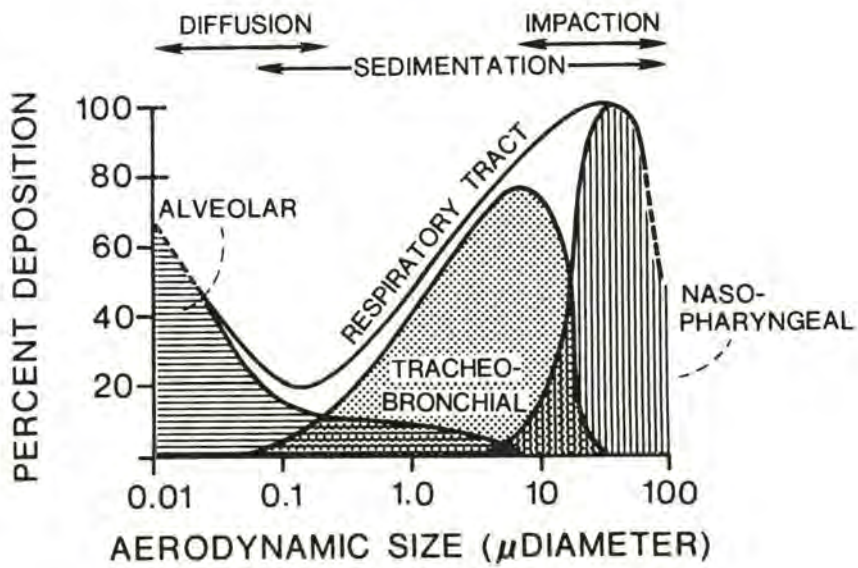

Figure 1 Particulate disposition in the respiratory tract as a function of particle size

2. Air samples represent only a small fraction or aliquot of the total volume of air inhaled by an individual. The NIOSH Document recommends a sampling rate of 2 liters per minute (range of 1-4) with a minimum volume of 100 liters. Therefore, the sampling time could be as brief as 25 minutes or an average of 50 minutes.

There are wide fluctuations the workplace throughout the day, week, and year in airborne concentrations of lead. Samples of short duration will most likely not be representative of an individual's exposure.

Dr. Stanley Roach of the United Kingdom has indicated that fluctuations in airborne concentrations of a pollutant, on a time scale of less than 1/10th of the biological half-life of the pollutant, are unimportant for practical purposes. Short sampling periods measure fluctuations in airborne concentrations which may be on the high or low side of the actual exposure, but these high and low fluctuations are unimportant for compounds, such as lead, which have a long biological half-life.

There is no biological significance in determining rapid fluctuations. Roach estimated the biological half-life for lead to be six months, and recommended a sampling time of ten work shifts. Blood and urine serve as dampening devices in that they attenuate unimportant short-term fluctuations in exposure.

3. An additional reason for biological measurements being more reliable indicators of lead absorption than air measurements is that a standard for lead in the air does not take into consideration the potential exposure from ingestion. While it is recognized that inhaled lead represents the major source of lead absorption in occupational exposure, variation in personal hygiene habits of employees may lead to variations in lead absorption resulting from poor work habits, which cannot be detected by air sampling. Biological indicators of lead absorption measure lead from all sources.

4. Short-term sampling with low flow rates, as is the case with personal-type air samples, is subject to rather large errors, especially due to contamination of and positioning of the sampling heads.

5. Another important obstacle to obtaining accurate estimates of exposure from air sampling is related to the physics of the entry of particulates into sampling heads. This entry may be affected by their sedimentation, their inertia, the geometry and orientation of the sampling head, and the strength and direction of air currents. The complete theory of particulate entry is very complicated and most sampling practice is not well-defined with regard to this aspect. Again, the use of biological measurements overcomes these uncertainties.

In summary, we recommend a biological standard based on blood lead determinations as the best means of monitoring the exposure of the worker and determining compliance with Occupational Safety and Health Act. In contrast to those opponents of this concept who state that biological monitoring is the last line of defense, I would contend that biological monitoring only moves you closer to what we are really trying to protect and assess, and therefore, has to be more accurate. Biochemical indices provide a much more accurate assessment of possible hazard to lead exposure than do air concentrations.

From a compliance standpoint, it would appear that much less effort

is required to obtain a biological sample (which is much more meaningful in assessing exposure) than is required in obtaining air samples (which, at best, provide a rough estimate of exposure). It would appear that the effort incurred in obtaining reliable air samples could be utilized more efficiently in monitoring the worker by biological means. I would suggest that this discussion should really be a discussion of BLV's (Biological Limit Values) rather than TLV's.

Our view is that the BLV and OSHA compliance standard should be a blood lead concentration of 80 µg/100 g of blood. Further, we recommend certain action levels, means of reduction of exposure, and frequency of sampling. The details of all of these recommendations can be found in our "Position Paper, Industrial Inorganic Lead Poisoning-A Program For Prevention," summarized in a paper authored by Dr. D.R. Lynam appearing in the February, 1975, issue of the Journal of Occupational Medicine.

I recognize that there is likely to be a lively discussion concerning what the BLV should be and which biological tests are the most meaningful. We have our views on this and I am sure others do too. However, it appears that before entering into a detailed discussion, there should be an agreement in principle, among the various interest groups represented that it is in the best interest of all concerned, most importantly the worker, that a BLV rather than a TLV be adopted as the primary lead standard by OSHA.

DISCUSSION LEADER-Mr. Timothy Cleary

Thank you Dr. Cole for a very forceful argument in favor of biological monitoring.

The next panelist will be Dr. Bertram Carnow. I am sure that most of us are aware he is Professor and Director of Occupational and Environmental Medicine at the University of Illinois School of Public Health. He will express some concerns and thoughts on Threshold Limit Values. Dr. Carnow.

DISCUSSION OF TLV'S FOR LEAD

Dr. Bertram W. Carnow
University of Illinois School of Public Health

Thank you. As Dr. Blejer pointed out, virtually everything has been said. I should like to present some of my concerns regarding TLV'S. These relate directly to the advisability of relying on biological monitoring as a measure of health impact of environmental stressors. This concept has come under considerable discussion with some suggestions that it be used as a substitute for environmental monitoring.

The TLV, by definition, is a level of environmental contamination at which workers can carry out job activities for eight hours a day, forty hours a week, presumably over an entire working lifetime, without any adverse health effects. In studies we have carried out over the past ten years, examining the health effects of ambient air pollutants on communities, negative health effects were found at levels considerably lower than are found in occupational settings. For example, in community studies SO_2, which has a TLV of 5.0 ppm, has been shown to cause a sharp increase in acute exacerbation of bronchitis in those with chronic disease and increased cardiac and respiratory deaths at levels between 0.2 and 0.3 ppm.[1-2] These levels are 15 to 25 times lower than those stated to be safe for occupationally exposed workers. This raises the whole question of whether or not the threshold concept is a valid one. I think not.

It must be recognized that humans are in a constant struggle with their environment, which is essentially hostile and the outcome of this host-environment contest, in which all humans and other biological organisms participate, depends on the adaptive capacity of the host as well as the toxicity and level of the environmental stressor. Our studies suggest that there is a high degree of variability in individual response to varying levels of air pollutants. Further, some segments of the population appear to be at much higher risk than others. In fact, it would appear that there is a highly variable dose-response relationship in a heterogeneous population so that at every level of a contaminant, depending on the adaptive capacity of the individual observed, there may be an increase in symptoms, prolongation of illness, and, in some cases, premature death.

The critical question, therefore, is not, what is the magic, albeit mythical, number symbolizing *safe*, but rather how many workers are adversely affected at each level of the pollutant. Other critical questions which must also be asked are: how serious are the effects, how reversible are they, what organs are affected, and how can we best measure the effects: I contend that in order to answer these questions many more studies need to be carried out looking at populations who may

be at higher than normal risk, so that a level may be defined that will really protect all, or at least most people. Many factors which will be briefly discussed, have either not been considered at all or were only superficially considered in examining safe levels. This may, in part, be responsible for a TLV for lead of 200 µg/cu m of air and of 500 µg for arsenic, neither of which, as this conference has shown,is safe.

Multiple Insults of Single Target Organs

Many TLV's are set as though the agent under study was the only one present in the environment. This, of course, is usually not true. There are a number of trace metals, such as cadmium, lead, and mercury, as well as arsenic, which may affect the central nervous system. The effects of these impacting on a single target organ system, the central nervous system, has not been adequately considered, even though some of them frequently appear together in processes like smelting. The problem of multiple insults on a single target organ is certainly real, and must be examined more carefully in relation to arsenic, which is one of many toxic materials etiologically related to lung cancer.

Single Agents Causing Multiple Disease

Another problem relates to the possibility that a single agent may cause multiple diseases and we may be looking at the wrong one in assessing a safe level. Studies reported here by Repko suggest that there are significant negative health effects of lead at levels of 70 to 80 µg/100 ml of blood, a level previously considered by some to be safe. His findings of significant personality changes, sensory loss (hearing), and neuromuscular and psychomotor abnormalities, are quite troubling. These were not the organs or functions that were looked at in determining whether or not lead toxicity was present in a worker. Instead, gross measures, such as anemia, abdominal colic, or wrist drop, were the endpoints, along with a level of 80 µg/100 ml of blood.

Dr. Repko's studies and the studies of others give me very little confidence in the reliability of blood lead levels, even if accurately measured, as a determinant of whether a level is safe. Seppalainen's study of 26 workers, most of whom had less than five years of exposure,[3] revealed that a high percentage had pathophysiologic findings, even though the levels of blood lead, found during very frequent testing over a five-year period, were between 35 and 60 µg/100 ml. Neurologic dysfunction was also found to be present, including decreased maximum motor conduction velocity, sensory conduction velocity, and slow motor fiber conduction velocity.

Dr. Goyer's report on renal pathology suggests more attention should be paid to kidney disease. It also gives one little comfort that workers are remaining healthy, or being protected when the blood lead levels are 80 µg/100 ml.

Multiple Sources of Single Pollutants

The problem of multiple sources of a single agent like lead is also given little consideration in the establishment of a TLV. Cigarette smokers accumulate considerably more lead than other individuals. Lead may also be taken into the body from airborne particles, resulting from automobile exhausts, the leaching from cheap pottery, the consumption of vegetables grown in urban areas, and from other environmental sources. If workers live near the plants in which they work, they may also be exposed to additional elevated air, soil, and dust levels of substances like lead or arsenic. This is particularly true in communities surrounding smelters.

Synergistic Effects

An additional important parameter, which has received little consideration in determining safe levels in the workplace, relates to the synergistic effects of these materials with other stressors. It has been shown in animals that dietary deficiency in chromium,[4] iron,[5] and calcium[6] increase lead absorption and, therefore, toxicity. Gastrointestinal infections, like salmonella,[7] were shown to cause an increase in the release of lead from bone into the blood. Increased alcohol intake and possibly other factors relating to habits or diets may enhance the negative effects of lead on the body.[8]

Greater consideration must also be given to the age of onset of exposure as well as the length of exposure, not merely to blood or air lead levels found. Since there is a strong suggestion from data presented that it is possible to develop asymptomatic lesions, without symptoms, over a long period of time, and some of these effects almost certainly are irreversible. Many smelter and other lead workers, because they are at a low socioeconomic and educational level, cannot easily move from job to job, so they may have such long-term exposures.

It is no wonder, that the present TLV is inadequate to protect the health of workers. Even if achieved and adhered to, it will result in blood lead levels in many workers of close to or exceeding 80 µg/100 ml. Since safe implies a "no effect" level plus a safety factor, this would appear to be greatly in excess of such a level. Many other TLV's are in this same category.

I am also concerned about the paucity of epidemiologic data. Dr. Cole suggested that lead is possibly the best documented metal, epidemiologically. We, however, had considerable difficulty during the planning of this meeting, in finding more than a very few, methodologically sound epidemiological studies.

For all of these reasons, therefore, I would suggest that we cannot even remotely consider major dependence on biological monitoring. What is required is many more epidemiologic studies with the generation of considerably more and better data, including better definition of

measurement of body burden, and more sensitive tests to detect early pathology. In addition to examining multiple organs for early pathophysiologic changes and reviewing blood lead *versus* ALA, FEP, and ALAD, to determine the best measurements for assessing body burden, the quality of the instruments used for monitoring air levels of lead needs more attention. There is some evidence that possibly 25 percent or more of airborne lead may be passing through the filters of testing devices, and, since most of the lead present in the air is in submicron particles, this may cause gross under estimation of the air lead burden.

Appropriate consideration of all of the above factors will, I believe, make possible the setting of a level for air lead contamination and body lead at which all, or at least most, workers will be able to work out their entire working lives without adverse health effects. TLV's generally would appear to be based on studies carried out on survival populations, that is those who had not become ill, died, and were not driven out of the industry because of illness. I do not believe that these are appropriate cohorts for study.

In conclusion I would suggest that:

1. TLV's generally, and particularly for materials which are known to cause chronic disease or cancer, be qualitatively evaluated.

2. Biological monitoring alone is not an appropriate way to assure safety and health for workers. Both environment and hosts must be monitored to assure low levels of contaminants for the continued health of workers. This is particularly true for materials which may cause chronic disease, cancer, or genetic or reproductive abnormalities.

3. We develop tests of greater sensitivity which correlate well with early pathophysiologic changes. In the case of lead, ALAD would appear to be such a measurement and is apparently far superior to blood lead levels.

4. We continue to carry out studies to ascertain all those who are at high risk because there are males or females in the reproductive age range and because of other chronic diseases, genetic deficits, or nutritional or other factors so we can quantitatively define the level of risk by matching good environmental measurements with sensitive biological endpoints.

5. We then promulgate standards which will protect all workers and not seek to exclude those who might be at higher risk, such as pregnant women, and others.

6. We carefully examine the question of whether current levels of technology will adequately protect workers by assuring low levels of environmental contamination in industry and, where these are not available, to make this a research priority.

It is only in this way that the workers will, indeed, be able to carry out work activities eight hours a day, forty hours a week, for a working lifetime without seriously affecting their health.

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DISCUSSION LEADER-Mr. Timothy Cleary

Thank you Dr. Carnow for your interesting presentation.

I will now turn the microphone over to Mr. John Zalusky, who will be the last speaker on this panel. Mr. Zalusky is the Research Director of the Allied Industrial Workers, American Federation of Labor (AFL)-Committee for Industrial Organization (CIO). Mr. Zalusky will comment on the Design of the Lead Standard - Focus of More Attention on Worker Needs.

THE DESIGN OF THE LEAD STANDARD - FOCUS OF MORE ATTENTION ON WORKER NEEDS

Mr. John Zalusky
Allied Industrial Workers, AFL-CIO

A B S T R A C T

The labor movement represents a large number of workers in industries associated with lead hazards, including auto battery workers, workers in brass foundries, cable makers, workers in the electronic industry, welders and cutters, scrap metal workers and others. The major concern of representatives is the problems of health hazards in the lead industry and the need for a swift solution to these problems in order to protect the workers' health.

My reaction to TLV's is that they are job related and not worker related, meaning that they are based upon time weighted averages that assume an 8-hour work day. You do not need to check very far into the Bureau of Labor Statistic's data to find that the average worker does not work 8-hours a day; he works more like 41 or 42 hours a week (at least he did before this depression). In many industries using lead, the replacement auto battery industry, particularly, there is a work period during the year of high overtime usually in the fall. The workers put in a great deal of overtime during this high demand period. Yet, when air lead samples are taken, the assumption is made that exposure will be for an 8-hour work day. The fact is it very often is a 10 or 12 hour day for many workers.

Another assumption that indicates that OSHA standards are not worker related, is that the standards are based on males. Reviewing the literature on lead exposure indicates that, yet today, we have a number of females working in the battery industry.

One employer, whose employees are union members, has two separate divisions. One deals with electronics and the other makes replacement auto batteries. The employer, because of the rules of the equal employment opportunities commission, encouraged the transfer of women from the electronics division to the better paying jobs in the battery division. The result is that we have an increased number of females exposed to lead hazards. Yet, the OSHA lead standard is based on the male exposure and the proposed NIOSH standard does the same. These standards must consider the effect of lead on the female workers, not just males to realistically meet the needs of workers. We learned today that women can have very serious health problems stemming from lead exposure and that such exposure can effect their offspring. This needs to be reflected in

the new standard to allow females the opportunity to hold these jobs without peril to their health.

The lead standard must be worker based, not job based, and to do this other sources of lead exposure must be recognized. There should be a substantial margin of safety for the worker exposed to lead, to allow for off the job exposure and diseases that attack the same part of the body in the same way as lead. This happens if a worker gets a large dosage of lead and also has some other ailment that affects the kidneys. The lead may not be the first cause, but could contribute to a workers illness. What about people in lead work who have a second job and lives in urban areas, both of which can contribute to body burden of lead? Does the proposed lead standard offer these workers a margin of safety necessary for total lead exposure? This is doubtful. The standard is related to the job, not the workers as a total person with possible additional ailment living in a total environment that includes non-occupationally related lead exposures.

The standards rely too heavily on biological monitoring rather than environmental control. A standard that truly considered workers' health would give much more weight to controlling exposure so that biological monitoring can be reduced. A worker should not be used as a test instrument for the work environment, rather the emphasis must be on testing the environment to benefit the worker. Another problem with biological monitoring is that workers simply do not like to be stuck with needles, to draw blood samples, so they avoid it. Additionally, all workers know that if they have high blood lead levels they will be removed from the job. It may be a high paying job or a relatively pleasant job and they could be moved to a job that does not pay as well and is not as desirable, so they avoid taking biological tests. In organized plants workers wages are protected, it is doubtful if non-union workers are this fortunate. A worker will stay home to avoid or postpone a biological test in order to keep his position. The safety standard must recognize the true industrial facts of life and protect the workers economic interest as well as protecting health.

The environmental monitoring proposed by NIOSH and used by OSHA does a poor job of sampling worker exposure. Let us assume that in a battery plant with approximately 200 workers that a sample will be taken of approximately 30 workers once every three months, based on the NIOSH proposed standard. These samples run about 50 minutes each. The sample would be about 100 hours of exposure during a year. That same 200 workers will work at least 400,000 hours during that period, probably more. Thus, the proposed sample will be one hour in every 4000 hours of worker exposure. I do not believe this is adequate. There must be better environmental sampling or a continuous monitoring device used in these shops to protect workers.

One must also consider the type of samples being taken and when and where they are being taken. In other words, how random are the samples? They probably will be taken during the day shift when supervision and controls are at their very best. What happens during the night shift when supervision sometimes is more lax?

The proposed standard for lead and present enforcement relies too heavily on personal protective equipment. This has the effect of transferring the burden of protection to the worker and away from environmental controls. Personal protective devices present a lot of problems for workers. A brief bizarre example concerns a factory producing auto batteries in an old building. The EPA told the employer to close the windows because they were emitting lead oxide into the environment. At about the same time, the employer had moved the lead casting operations next to the pasting machines. The result was that the heat producing casting operation was near the pasting operation which produces most of the airborne lead in such an operation. With the windows closed, it was too hot, so the employer installed fans. The result was lead dust blown all over the plant. OSHA inspected the plant and required that the fans be shut off and that the employees wear respirators. During July, August, and September of 1973, workers in this area had to wear respirators; the plant windows were closed; and the operations produced additional heat. Working conditions were so bad that perspiration collected under the respirators until it was above the workers' chins. The workers had to take the repirator off to wipe the perspiration from their faces. Obviously, this resulted in the ingestion of more lead from their soiled hands. There is no easy answer to this set of conditions, but an abatement period from OSHA did nothing to help the workers involved. Two and a half years of wearing a respirator in a hot environment is not a worker oriented means of dealing with such a problem.

The primary reason for opposing biological monitoring is it is after the fact of excessive lead exposure. The worker's body has already acquired a large dose of lead by the time test results are tabulated. The standards propose the use of the worker as a testing device.

From what has been presented today, it is very possible that some of these men and women may already be sick by the time it shows up as excessive blood lead. I wonder just how many of those who are proposing the use of the biological monitoring would opt to work in this kind of situation. We, in the Allied Industrial Workers Union suggest that NIOSH rewrite its proposed lead standard and reduce the work place lead exposure to much less than the .150 mg/cu m they are now proposing.

NIOSH should look at the standard for lead of other industrialized countries. The Soviet Union has a standard of .010 mg/cu m. Perhaps the USSR does not enforce the standard, but I suggest to you that OSHA in

giving three year abatement periods, is also pretty casual in their enforcement. TLV's from some of the other countries should also be noted. Japan has a TLV of .050 mg/cu m.

NIOSH is recommending that OSHA adopt a TLV of .150 mg/cu m -- the same used in the U.S. prior to 1958. Yet, the American worker comes to the job today from an environment with much higher exposure than the levels in 1958; also higher than workers in other industrialized countries. It seems that we should base the lead standard on worker needs and improve on the example being set by other industrial countries in the world.

QUESTIONS, ANSWERS, COMMENTS

DISCUSSION LEADER-Mr. Timothy Cleary

Thank you very much Mr. Zalusky. I note we are running some 25 minutes behind schedule but this is not entirely the TLV panel's fault and I would like to take time for the panel to entertain some questions from the audience.

QUESTION-Dr. Lawrence Plumlee

I have a question for Dr. Cole. Today we have heard about multiple sources of lead outside the work place. Dr. Landrigan talked about the relationship between blood lead and lead in air, soil, and dust. Dr. Fowler talked about lead in fish and shellfish. We know that lead comes from other sources, such as wild game and Dr. Goyer made reference to lead in moonshine whiskey. People are present who are in the water supply field and they are concerned about lead in water pipes. We have heard about lead glazed pottery which can produce elevations in blood lead, etc. Is it possible that there might be some temptation for an industry which found elevated blood leads in its workers and which wasn't doing any air monitoring in the factory to attribute the elevations in blood to some of these other sources?

ANSWER-Dr. Jerome Cole

Certainly this could occur. However, if the guidelines we have proposed are followed, you would obtain a blood lead initially when a person starts work, so therefore you know whether or not an employee engages or has engaged in some kind of activity in which there was exposure to environmental lead sources. There may be some danger in this, Dr. Plumlee, but I think it far better to have this information available. I think most people in the lead industry would be willing to accept the responsibility to see to it that workers do not develop a blood lead over 80. This could be accomplished by periodic monitoring. It would be far worse, I think, to discard biological monitoring and not know about prior exposure when a worker will be exposed to more lead.

QUESTION-to Dr. Carnow

You and others have speculated on the possibility that there is no threshold for the dose-response relationship with lead. If this should turn out to be true, what rationale could you turn to for establishing a threshold for exposure?

ANSWER-Dr. Bertram W. Carnow

Well let me suggest that the rationale that we have is not rational, and I think that to make an assumption that above a level everything is cheerful and rosy, and below some level everything is devastation and death is to permit very little leverage for making any kind of cost-benefit assessment. I am suggesting, and we have been carrying out this exercise in relation to health costs of energy, that we find all significant populations at high risk. We must then attempt to quantitate the level of risk and examine the level of contamination produced by a product; that is, determine the number of people at risk at any level of contamination and evaluate societal needs for the product. Then, if the level of technology does not permit total control, some people at high risk will not be able to be involved in production of the product. Clinicians, in dealing with common air pollutants or low temperatures in big northern cities, advise patients they should go to Arizona or some warmer climate if they cannot tolerate this type of pollution. So we have made such cost-benefit evaluations for patients, and I think this is what we are going to have to continue doing. This does not mean screening out workers, allowing dusty air, and removing workers when their blood lead levels become dangerously high. It means maximum use of technology and the creation of a work environment that will be harmless to all workers.

We have no quantitative assessment of risk when we take an arbitrary number which really has little meaning. We have been making the assumption that the TLV (the magic number) protects most or all of the workers. I would submit that what was heard here today suggests that it does not. So I think you quantitate risk and determine at what point the risk becomes acceptable societally, and we must also consider the socioeconomic risk.

COMMENT-Dr. Robert Eckardt

I would just like to support Dr. Cole's concept of biological monitoring by giving a brief example of where it was extremely useful. We were doing monthly urinary leads on workers in some inorganic lead operations in a refinery and, all of a sudden, we noticed that there was a general updrift in urinary lead excretion. We wrote to the refinery medical department. What we found out was that the men were working a 12-hour day 7 days a week simply because there was a large building program going on within the refinery. Had we not been doing biological monitoring this never would have been detected. Once the force went back to an 8-hour day, 5 days a week, their urinary leads came right back down to where they had been beforehand. So, I think that biological monitoring has far better opportunity of protecting the worker, which is what we want to do more than anything else.

MODERATOR-Mr. John Zalusky

Is there a response from the panel or may I proceed?

COMMENT-Dr. Jerome Cole

I would just like to respond to Dr. Eckhardt's comment. I certainly am in agreement with him and I think that Mr. Zalusky also indicated his agreement, so perhaps we have some kind of consensus. It is noteworthy that every time air leads are mentioned here, or particular TLV's, they are related back to a blood lead concentration. This gives evidence of what really is important. We recommend that air sampling be done and that air monitoring also be done, comprehensively throughout the plant. The idea here is not to determine whether or not you are over a particular level but rather to determine the effectiveness of your engineering controls.

COMMENT-Dr. Hector Blejer

One of the problems in this whole field is that there is a lack of data which correlate air concentrations and exposures to the effects of lead, be it blood lead or otherwise. The only fairly good correlations that exist came from England and they were done by Williams, King, and Walford.* I believe they showed that, at an air concentration of 150 µg/cu m of lead, there was little margin of safety, *vis-à-vis* the blood lead level of 80 µg/100 ml. In fact, the 150 µg, air lead level correlated with a blood lead level of 60 µg/100 ml. Separately, Waldron, and I am quoting here from his November, 1974, article from the Archives of Environmental Health, based the following conclusions on the world-wide mean of 17 µg of blood lead, as calculated by Goldwater,# "On this basis, adult blood lead concentrations should not be permitted to rise above 50 µg. For children the value of 30 µg found as the 97.5 percentile by Delves, *et al*, should be accepted as the upper limit. Even these values may be higher than are consistent with health and it is important that threshold values should not be regarded as fixed and unchangeable but must always be subject to revision in the light of new knowledge." We really have not done that in the last 20 years.

QUESTION AND COMMENT-Dr. Charles Hine

I have a question for Dr. Blejer. Hector, you quoted that new standards were arrived at in California. I am on the committee which acts as an advisory for TLV's in California and I do not recall a specific official recommendation. As further comment, Dr. Culver recited

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Brit J Ind Med, 26:202, 1969
#Arch Environ Health, 15:60, 1974

some data reviewing incidents of reported lead intoxication in California. I think it is time to look at perspectives in the field. Now granted that these data are subject to question; they may be under reported or they may be over reported. However, that first "work report of injury" stated that the physician saw a man who he thought had symptoms that were compatible with lead intoxication. I have looked at some of these as an independent medical examiner (in which I have the advantage over Hector in seeing these people and sometimes in reviewing their reports) and I find that some of these reports are incorrect. I am sure there are other intoxications that occur from lead in California that are not reported, but let me put this in perspective. We have a labor force of 10 million people; we have 1 million reports, first reports of injury and, or, disease. More than half of the diseases reported are forms of dermatitis. So when we get down to this we are talking about a report of 75 people with possible intoxication in a work force of 10 million in a one year period. This is pretty typical of what I have reviewed over the last 5 years. The other point relative to this is disability. Now our goal is zero disability. This is the goal of physicians in occupational and preventive medicine. Our goal is zero, but 75, in a great number of workers who are exposed to lead, is a pretty small number of persons to be involved. Let me report further, that I know of no deaths which have occurred.

ANSWER-Dr. Hector Blejer

One, in 1971, a 28-year old black male who worked at a battery plant in Oakland, California.

QUESTION-Dr. Charles Hine

I know of no deaths that can be attributed to this, nor are there permanent disabilities (such as occur for example, with the back injuries at the rate of many thousands per year in California). So putting this in perspective, I think it is realistic to look at these figures of 75 cases in a total work force that we have just covered. Now if you know of permanent disabilities, or if you know of a death, it is certainly an exception; however, in reference to chemical substances such as pesticides, with which we are also involved, this may not be the case.

ANSWER-Dr. Hector Blejer

I know of quite a few, but not from the Workmen's Compensation arena in which we work at times. Moreover, if you are going to negate the vital statistics of a state or a nation, then you might as well discount 30, 40, or 50 percent of all causes of death reported on death certificates. If you want to revise them by yourself, or if anyone can, then please do so. We must rely on the fact that the average physician in the community is reporting correctly. If you are an expert and disagree with a physician, please educate him so he can diagnose as well as you do. We must

rely on reports as having been filed by competent professionals. That is all we can do. The 52 reports I mentioned earlier in my presentation would not have necessarilly all appeared in the past in those California statistics of which you are aware. Up to 1968 or so, Dr. Rutheford T. Johnstone --consultant to the then Bureau of Occupational Health where I used to work--had prevailed not to have included in the official California statistics any Doctor's First Report of Work Injury which mentioned only an elevated lead level in blood or urine. This was done even in reports mentioning symptomatology of and/or treatment specific for lead poisoning. So, for almost two decades no such reports were included in the California statistics unless the specific words "lead poisoning" had been used by the physician. By the same token, if some of the California occupational disease reports are false positives, then the large number of non-recorded occupational diseases are by definition false negatives. As mentioned, there were individual reports of blood leads of, let us say, 130 µg--or equivalently high urinary lead or ALA levels--which described symptomatology of frank lead poisoning. If the reporting physician did not call it lead poisoning and called it increased lead absorption instead, then the report would not have been classified officially at all then. So it works both ways, but usually against the worker.

COMMENT-Dr. Charles Hine

Dr. Blejer, I disagree with you. It always works in the protection of the worker in compensation court actions, and this is the way it should be. I do not disagree with this. The shadows of doubt have been given to the worker.

COMMENT-Dr. Hector Blejer

In California, this is the major occupational health surveillance technique which does not exist elsewhere in this nation.

COMMENT-Dr. Charles Hine

The major reports on these things are not serious intoxications. They are not anemias; they are malaises, headaches or fatigue. These are the presenting symptoms on those "First Report of Injury" cases and this is significant, I think, in the lack of serious disabling lead disease in the country.

COMMENT-Mr. David Cameron

As an industrial hygienist, I feel I should support accepted and proper industrial hygiene practices. The present debate about environmental *vs* biological monitoring is incredulous. Engineering controls, environmental sampling, medical monitoring and good personal hygiene all must be employed in order to control occupational exposure in a lead environment.

COMMENT-Dr. Jerome Cole

Just a very quick response, I am in 100 percent agreement with that also as an industrial hygienist. I would like to see OSHA take the same position and if they are going to use air standards as their compliance standards they should also use blood leads, or some biological index.

QUESTION-Mr. George Becker

One question for Dr. Cole. I would be very much interested in learning what his organization's position would be concerning "on the job" use of oral Versenate in order to control workers' blood lead levels to the level recommended by Dr. Kehoe. I would like to add that on the job usage of oral Versenate is not in isolated incidents in the United States. There is at least one major lead producer that used it routinely throughout all their plants. We are fearful that if biological testing is adopted, such usage would be more widespread as a method of controlling level limit recommendations.

COMMENT-Dr. S. Calandra

I wish to express my view as a physician who is responsible for the health care of workers in two lead plants. The administration of Versenate routinely in place of good engineering and industrial hygiene controls in unconscionable. It is a physician's responsibility to fight such practices at every opportunity.

ANSWER-Dr. Jerome Cole

Mr. Becker, I can respond to that quite briefly. I will read you a paragraph from the Lead Industries Association position paper in which we say "the prophylactic use of oral EDTA, sometimes called preventive medicine, is strongly discouraged on the grounds that prolonged use of EDTA may have adverse consequences and such use masks the need and discourages proper inplant corrective measures." So I am in agreement with your position.

COMMENT-Dr. Sidney Lerner

Reference has been made to the Williams study as a basis for reducing the present Threshold Limit Value of 200 to 150. I would suggest that everyone read the study carefully and please note a couple of facts. The study was for a total duration of two weeks. The number of patients studied was 39. The variability of lead in air as measured by personal monitors was 400 percent. The total number of blood leads taken from 39 workers was 195; 50 of these 195 blood leads were discarded by the author with a statement that they were contaminated. I have a couple of points to make: the large variabilities acknowledged by the author and the discarding of 50 samples without explanation, and I think there is

no valid basis on which to lower the present value based on this study.

COMMENT-Dr. Hector Blejer

If I may respond, the person standing right behind you had to defend that specific charge regarding the Lead and Zinc Industries Association's recent objection to the current TLV for lead of 150 µg/cu m set by the TLV Committee of the American Conference of Governmental Industrial Hygienists. Mr. Caplan, would you like to comment although you are not on the panel?

COMMENT-Mr. Paul Caplan

There is not very much of a safety factor, it is true, but I want to mention in answer to your comment that OSHA should have biological monitoring standards in addition to TLVs. As you probably know, OSHA and NIOSH together are working on a supplemental standards completion program for the 400 materials on the TLV list that OSHA now has. These supplemental standards will consider information from medical programs, biologic standards, and environmental standards. In addition, there are action levels, mostly when the environmental level reaches 50 percent of the environmental standard, when biological testing will be required for many of the materials being included in the new OSHA standards.

DISCUSSION LEADER-Mr. Timothy Cleary

On behalf of the panel, I would like to thank all of you for your attention.

I would like to now turn the microphone over to Dr. Robert Baloh, Assistant Professor in Residence, Department of Neurology, University of California, Los Angeles, who was presented to you earlier when he participated in the Toxicology of Lead Session. He will be the Discussion Leader for the Panel Discussion of the Problems of Application and Future Needs. Dr. Baloh.

SESSION V - PANEL DISCUSSION OF THE PROBLEMS OF APPLICATION AND FUTURE RESEARCH NEEDS

Dr. Robert W. Baloh, Discussion Leader
University of California, Los Angeles

A B S T R A C T

The final topic for the lead conference is a panel discussion on the problems of application and future research needs. Most investigators would agree that there is a great deal of research needed in this area. Dr. Carnow did an excellent job of summarizing some of the areas that need further research and outlining possible approaches to this research. We will pursue these matters further in our discussion.

A multidisciplinary group of investigators at the University of California recently met to discuss the topic of Problems of Application and Future Research Needs, and it was agreed that there are six areas where further research is needed, as shown in Table I.

TABLE I

1. Evaluate sensitivity and practicality of presently available screening techniques for identification of increased lead absorption.

2. Identify earliest signs of tissue damage and behavioral impairment and correlate these with the measurements of increased lead absorption.

3. Investigate blood lead distribution with particular emphasis on plasma/RBC ratio and protein binding and correlate any observed shifts in RBC or protein binding of lead with clinical symptoms and signs.

4. Evaluate the safety of CaEDTA therapy and mobilization test with particular emphasis on possible nervous system and renal damage from mobilized lead and cadmium.

5. Evaluate the effectiveness of CaEDTA in treatment of so-called sub-clinical lead poisoning (i.e. nerve conduction abnormalities, perceptual motor impairment, subjective CNS symptoms.)

6. Evaluate significance of concomitant increased absorption of other heavy metals.

I emphasize multidisciplinary research because I believe that this is the only way to study the effects of a toxin, such as lead. Lead has multiple target organs, and, in any given individual, each organ may have varying susceptibility depending on genetic and environmental factors. Therefore, only multidisciplinary studies can assess the impact of increased lead absorption on the entire individual.

In commenting on the list in Table I, over the past few years, numerous new techniques have been developed for the assessment of increased lead absorption.[1] However, the interrelation of these tests has not been adequately evaluated. It will be necessary to make measurements on a large number of lead workers, using all of these various techniques, and then compare how these results correlate with evidence of tissue damage.

Techniques are available for assessing protein binding of various elements including lead.[2] The constance of binding can be determined and the protein that binds lead in the plasma can be characterized. Preliminary reports suggest that varying susceptibility to increased lead absorption may be related to variation in the binding of lead protein.[3-4]

Intravenous infusion of CaEDTA is generally considered the most effective treatment for acute lead poisoning. There have been reports, however, suggesting that through the release of tightly bound cadmium, CaEDTA may be harmful to the kidneys and nervous system.[5] The effectiveness of CaEDTA and other chelating agents in treating the so-called sub-clinical effects of increased lead absorption is unknown (i.e. nerve conduction slowing, visual-motor impairment, etc.)[6]

Finally, the significance of concomitant increased absorption of other heavy metals, has only recently received attention. Children and adults with increased lead absorption have been found to have increased absorption of other heavy metals as well.[5-7] Particularly worrisome is cadmium absorption since cadmium is significantly more toxic than lead at equal dose levels.

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DISCUSSION LEADER-Dr. Robert Baloh

I would like to present for the first discussion on this panel, Dr. Katherine R. Mahaffey from the U.S. Food and Drug Administration, who is representing Dr. Stephen Krop who is unable to be here today. Dr. Mahaffey.

DISCUSSION OF RESEARCH NEEDS IN LEAD EXPOSURE

Dr. Katherine R. Mahaffey
U.S. Food and Drug Administration

Areas of biomedical research on lead exposure in adults that require additional investigation are:

1. Evaluation of neurological effects produced by industrial lead exposure.

2. Determination of long term effects of chronic lead exposure on the development of renal disease.

3. Investigation of lead metabolism.

Research needs in the first two areas have been described by Dr. Baloh and Dr. Goyer. In the area of metabolism it is important to develop information that combines knowledge of lead exposure obtained through use of personal monitors for air lead concentrations with monitoring of biological effects of lead through measurement of such parameters as urinary delta-aminolevulinic acid. Without knowledge of both of these areas, meaningful conclusions on safety of a particular level of exposure to metals cannot be established.

Although we have certain types and a certain amount of information on how humans metabolize lead, much of this data has been derived from studies involving very few subjects. For example, gastrointestinal absorption of lead is frequently considered to be approximately 5-10 percent of intake; however, when the data from individuals are carefully reviewed, it is evident that the percentage absorption is substantially more variable than the suggested 5-10 percent. Additional studies defining the range of human variability as it affects susceptibility to the effects of lead are needed.

Factors that influence human susceptibility to lead toxicity include both endogenous metabolic factors and environmental factors, such as nutrient intake. Research studies with experimental animals have shown that dietary deficiencies of iron or calcium will increase susceptibility to lead intoxication. Additional dietary factors, such as zinc and copper, also influence susceptibility to lead toxicity, and it is likely that there are other dietary factors. It is also likely that a number of other environmental factors, such as concurrent exposure to other toxicants, will influence tolerable levels of exposure to the metals, lead or arsenic. Other than determination of gastrointestinal and pulmonary absorption of lead, very little is known about the mechanisms of human metabolism of lead. There are studies that have attempted to develop models for lead metabolism in humans; however, these are only in the earliest stages of development and employ data

on very few subjects. Factors that influence lead metabolism are poorly defined (i.e., factors that determine the portion of lead that is deposited in bone and what influences release of lead from bone).

In order to adequately define tolerable levels of exposure of humans to lead and arsenic and to select reasonable methods of monitoring human exposure, it is necessary to know how the metals are metabolized. In order to provide adequate safety factors for metal exposure, it is important to know the amount of variability that exists in human response and factors that determine this variability.

DISCUSSION LEADER-Dr. Robert Baloh

Thank you for your comments Dr. Mahaffey.

The next speaker on the panel will be Dr. Robert Goyer who was also a speaker on the Toxicology of Lead Panel earlier today. Dr. Goyer.

APPLICATIONS AND FUTURE RESEARCH NEEDS IN HEALTH EFFECTS OF LEAD

Dr. Robert Goyer, Professor
University of Western Ontario

These brief comments reflect, more or less, my own special interest. In all the study that I have done with the effects of lead on the kidneys, experimentally and in lead workers, I still do not know very well the mechanism by which lead is excreted. There has been a great deal of study about the excretion of sodium, potassium, water, chloride, exchange of hydrogen, and maintenance of acid-base balance by the kidney, but when it comes down to the mechanisms in normal people (people who do not have excessive exposure to adverse or potentially toxic substances) there has been very little effort given to definition of the mechanisms for excretion of most environmental pollutants. There have been some studies that we have depended on, almost entirely for what we know and we use these studies to interpret our experimental lead data. However, they're really quite sparce and they could be greatly expanded upon through use of the same techniques that are used to study the processes mentioned.

Given the knowledge that we now have concerning changes in the kidney in lead exposure (i.e. the lead protein complexing), we should know a little about the role of this process on the excretion of lead and whether or not it is protective to the whole organism, to the complete person, and what it costs the body. Finally, from the pictures that I presented of the morphology of the kidney, the structure of the kidney is quite different in persons with long term exposure to lead. Lead does appear in the urine and the mechanism by which it does this certainly must be greatly different in the newly exposed worker from individuals in the general population.

Finally, one other long-time question of mine is has a great deal of thought been given to the possible use of body stores.

There are two approaches to the debate about the use of blood and urine as biologic monitors; one to measure body burden directly and the other is to get bone biopsies. I'm not advocating this as routine monitoring of workmen, but periodic bone marrow aspiration can be performed.

In the process of performing a bone marrow test, one uses a trephine to go through the bone; and, with the microanalytic procedures that are available to measure lead now, this little bit of bone can be correlated with blood leads, period of exposure, and urinary excretion of lead. This is not the kind of test one would want to do regularly, but I'm sure that many bone marrow aspirations are performed around the country on various people, however the lead content in bone is not measured.

Finally, as a university scientist, I can only plead for support, not just economic support, but also opportunity to interact with individuals and organizations that do have material that could perhaps be looked at by more than one group of scientists.

DISCUSSION LEADER-Dr. Robert Baloh

Thank you Dr. Goyer.

Dr. Theodore Robinson, Plant Medical Director of the Manufacturing Department at Exxon Corporation was also introduced to you earlier. He will be the next speaker on this panel this afternoon. Dr. Robinson.

CONTINUING MEDICAL SURVEILLANCE OF LEAD WORKERS

Dr. Theodore R. Robinson
Ethyl Corporation

I would like to speak sitting down because if I stand up I may make a lengthy speech and I promised the "iron claw" that I would not do this. I do have three comments and perhaps one suggestion, however.

First, the use of the term biological monitoring during today's discussions has been irritating to me. At the Ethyl Corporation plant there has been a program of continuing medical surveillance for some 37 years which has provided essentially 100 percent effective protection of workers' health. Rats were not used; rabbits were not used; and dogs were not used. Workers were looked at and were surveyed by physicians. The program is under the complete control of the physician in charge and he has the responsibility for the program. I object very strenuously to the term biological monitoring and suggest that this reference places emphasis in the wrong place. Emphasis should be on programs of continuing medical surveillance.

The second aggravation I have found with today's presentations has been the apparent gathering of different forces with "daggers pointed at each other" concerning environmental and medical programs. It follows logically that if you set a TLV at an environmental level of anything other than zero, the purpose for setting this level is to limit absorption. It can be called exposure, but all interested persons are actually concerned with limiting absorption to some level that is considered to be safe. Medical monitoring and surveillance programs have this same purpose, limiting absorption to a level that is compatible with good health. Obviously, there can be misapplication. If action is delayed until illness occurs, this is not medical monitoring in a program of preventive medicine.

The third aggravation today has been the continuous references to apparent malpractice on the part of some physicians in industrial medicine in dealing with lead related health problems. It is not suggested that this does or does not occur; but no evidence was presented to establish this point. If such incidents, as were mentioned today, actually occurred, then, not only was the doctor at fault, but the worker, his union representatives, and the employer were also negligent. If there is a case of overt lead poisoning, then the courts should consider the damage arising as a result of negligence. Usually, in legal terms, this means a physician is not conforming to the standards of the community or his specialty. In this case, one does not need any new regulations for OSHA to effectively pursue this. If such practice procedures were recognized and allowed to persist for many years, then,

surely all the people concerned are seriously at fault and the physician is the key person in such cases.

My final comment is that any physician, who has experience and knowledge in industrial medicine, does not need any new tools to operate an effective occupational health and preventive medical program to assure that workers do not become ill from lead exposure. The tools have been available for a long time. If people are still getting sick from lead exposure, someone, somewhere, lacks the will to apply the corrective measures available to them.

My somewhat naive suggestion is that accurate mortality evaluation studies of occupational exposure diseases could easily be conducted if vital statistic information was attainable through some legally, ethically, morally, etc. acceptable process. I have dug around and been all over the country trying to obtain death certificate information for mortality studies. Perhaps some sort of national registry could be formed which could draw vital statistics information from the states. It surely would require some expenditure of money and may be expensive. However, such information could be handled with great facility by computers. All that is required is to feed the computer the information, and someone, somewhere, should consider making this type of information available from some central source, on request from legitimate, authorized investigators.

QUESTIONS, ANSWERS, COMMENTS

MODERATOR-Dr. Robert Baloh

I would like to thank the panel members for their remarkably brief discussions. Because of that we probably can answer a few questions.

COMMENT-Dr. Bertram W. Carnow

There has been some talk about death certificate data. In 15 years in clinical medicine, I have not seen among my colleagues a large number who have done blood lead with strokes, with peripheral neuropathy, with any other central nervous system lesion or with renal disease. I think that these would make sense. The average clinician has a very low level consciousness regarding lead and other trace metals as etiologic factors in disease. I think that when clinicians begin to think more about this, then what you suggest would be very important. However, at this point, we are dealing with the tip of the iceberg and I think we would get very little relevant data and develop a false sense of security if we depend on death certificate data at this point in time.

COMMENT-Dr. Robert Baloh

I would like to make a comment on the point Dr. Carnow made. The literature in this area is remarkable for the lack of prospective studies. There is a great deal of information to be gotten from dealing with individual cases of suspected lead poisoning. We have come to the point where it is necessary to spend the additional money necessary for a well designed prospective study.

COMMENT-Dr. John R. Goldsmith

First I am delighted to hear an endorsement of what I think is a needed tool for epidemiologists which is called a National Death Index. A National Death Index means only a list of people and identification of the causes for their deaths and where they died so that the death certificate information can be obtained. This is near to being accessible; it does not involve any problems of confidentiality; it will help everybody and I think it is one of the things which even if some of us disagree about other things, we would find useful. There are other types of data, however, that are not so widely sought and which I think ought to be examined more systematically with respect to the ultimate effects of lead exposure and other occupational problems. This has to do with the Social Security Disability information. The Social Security

Diability system certifies by medical examination, using relatively uniform criteria, the people who before the age of 65 are no longer able to work. These data could and should be used to evaluate the extent to which the present dependence on the workmen's compensation system is providing a suitable motivation. Indeed the excess disablement that occurs, tabulated by occupation and types of illnesses, will provide some evidence about the extent to which we are being ineffective in preventing early disability. I think that from the point of view of the principle that Dr. Carnow has spoken about, cost-benefit, until we begin to examine these data much more systematically we will not know how poor a job of prevention we have been doing in some types of occupational disease. This is a very straight forward thing to do. The data are collected and they are of considerable value. The last time any systematic tabulations were made was in 1962.

COMMENT-Dr. Douglas Frost

I am a consultant in nutrition and biochemistry in Schenectady, N. Y. I want to raise the question, as was mentioned briefly earlier, about the role of nutrition. I think the young lady who mentioned nutrition talked about the probable accentuation of toxicity from other elements. I would also like to raise the question of inadequacy of certain other elements. Many of you know that selenium is far and away the best antagonist to the toxicity of silver, mercury and cadmium. Very tiny amounts are quite effective against those toxicities and it is presumed that all of them affect availability of selenium in the body, particularly since selenium has been well determined in recent years to be included as an essential nutrient.

In the case of lead, we know very little about it. One thing that is known, lead shot toxicity in water fowl does not occur in areas where the availability of selenium is high, as in the Rocky Mountain areas of Canada. It is very common, though, in Ontario and Northeastern United States. It has been observed in water fowl grazing in fields where selenium levels of corn are known to be very low. These are the birds that suffer from lead shot toxicity. Water fowl, like ducks, having good ordinary diets do not suffer lead shot toxicity, but those on selenium deficient diets do. Little is known concerning possible adverse effects of lead on selenium metabolism, and this needs to be studied further.

ANSWER-Dr. K. R. Mahaffey

I think you are really bringing up some of the same things I was saying. With the nutritional elements it is somewhat more difficult. There is a need to define quantitatively where the requirements are met and where toxicity begins. As I mentioned earlier, we are also getting the habit of thinking of interrelations between two elements, because a number of variables are involved. I think the time of the very large multiple factorial experiments is coming. They are going to be exceedingly difficult

to do. This particular conference is addressing research needs in occupational health. However, to evaluate factors influencing susceptibility, we need very controlled conditions. In many cases it may not be possible to obtain adequately controlled conditions using human subjects or the experiments may not be appropriate for human subjects. In circumstances of this type laboratory animals can prove very valuable.

QUESTION-Mr. Lee Norman

I work for a firm of industrial consultants who handle a great majority of lead producers and lead workers throughout the United States. I would like to follow that line of thought for just a moment and see if there is anyone here today who has had extensive use of a new food supplemental nutrient for industrial lead workers under the trade name of Lead X. This apparently is something new on the market but seems to be picking up a lot of sales velocity. It has been recommended to industries to use as a food supplement for lead workers who are exposed to inorganic lead.

ANSWER-Dr. K. R. Mahaffey

I have heard a very limited amount about this and it is all strictly anecdotal. We would be quite interested in where this is sold, how it is sold, how it is labeled and a number of other things. If anyone does have information on it, we would appreciate knowing it.

COMMENT-Mr. Lee Norman

It is presently being distributed by Miller Pharmaceuticals Co., I believe out of Chicago. I believe a Dr. William Miller is handling it.

DISCUSSION LEADER-Dr. Robert Baloh

If there are no more questions, I'll turn the meeting over to Dr. Carnow who will close the meeting.

CLOSING REMARKS - LEAD CONFERENCE

Dr. Bertram Carnow, Conference Chairman

Unlike Dr. Robinson, I am not irritated; in fact, I am delighted. I think that a lot of ideas were aired and a lot of data were presented. I was particularly intrigued by the neurophysiological data and think that much standardization of these is in order. I believe that there are methods for simplifying and making less traumatic tests that may provide us with some knowledge regarding earlier pathology. I think that surface EMG, for example, is a testing method which has only begun to be explored. Everything has been covered today and I more or less summarized the proceedings in the previous panel discussion.

I would like to thank you for participating, the speakers, participants, and to suggest to you that the attitude adjustment hour, which starts in a very few minutes, is one which will smooth out all differences.

ARSENIC CONFERENCE

February 25, 1975

OPENING REMARKS

Dr. Bertram Carnow
Conference Chairman

Good morning and welcome to the second day of our Conference on Health Effects of Occupational Lead and Arsenic Exposure. This is the arsenic day, and we hope that it will be a fruitful day of discussion.

Since everyone will be trying to catch a plane, we are going to maintain a very strict schedule and would like those people who address from the floor to identify themselves and to maintain the one-minute limit that we have set.

As you know, the Society for Occupational and Environmental Health is the sponsor of this meeting, and those of you who are interested in joining the Society may request to do so. The rules and application blanks are in the foyer for those of you who are interested.

Now, we will get on with the program. Mr. Richard A Lemen, who is an epidemiologist in the Division of Field Studies and Clinical Investigations at NIOSH, will moderate this morning's first session. Mr. Lemen.

SESSION - VI SOURCES OF ARSENIC, MONITORING THE WORKPLACE AND PROBLEMS INVOLVED

Mr. Richard Lemen, Moderator
National Institute for Occupational Safety and Health

In hopes of keeping within our time schedule, I think that I will go right to the first speaker who is Mr. Kenneth Nelson, Vice President of Environmental Affairs for the American Smelting and Refining Company. He presented during the conference on lead yesterday. Mr. Nelson.

ARSENIC TRIOXIDE PRODUCTION

Mr. Kenneth Nelson
American Smelting and Refining Company

A B S T R A C T

Arsenic trioxide is a by-product, principally of copper smelting. The arsenic is present in small percentages in copper ores and concentrates. It is volatilized, oxidized, and recovered as a dust in the several stages of smelting. The crude product is refined and marketed to be used in glassmaking or as the raw material for arsenical compounds, important in agriculture and industry.

The term arsenic actually refers to arsenic trioxide (As_2O_3), which is the arsenic of commerce and the raw material from which other arsenical compounds and arsenic metal are made. Arsenic is really not a metal; it is a metalloid. It might be useful to tell you a little bit about how arsenic is produced. Actually, it is largely a by-product of copper smelting operations. Small arsenic concentrations are widespread in the earth's crust and tend to be associated with non-ferrous metal ores, copper, lead and zinc, in the form of arsenopyrites or more complex minerals. So, it is inevitable in mining and in concentrating copper, lead, and zinc ores that the arsenic goes along with the arsenopyrites and other minerals to the smelter where it appears in the various pyrometallurgical smelting processes.

When it appears, it actually volatilizes, because of the high temperatures required in roasting reverberatory furnace treatment, and conversion in the copper industry, and sintering, and blast furnace treatment in the lead industry. At these high temperatures, the arsenic is volatilized, oxidized, and appears as in waste gases from these processes a particulate. Particulates, are collected by bag filtration or by electrostatic precipitators. The arsenic content of the collected material may range from a few percent to as high as 50 percent. These collected flue dusts are then re-roasted and the arsenic is fractionally sublimed from the crude mixture. The vapor passes into flues and is then sent to long labyrinthian brick chambers where the gas is gradually cooled. As it cools, the arsenic trioxide vapor condenses out on the surface of the chambers and is later removed. These condensing chambers are called kitchens. Strange, but that is the name that has been attached to them for many, many years. So now we have the arsenic trioxide that is packed and shipped off to many and varied users. A view of a packing machine having a complete dust control mechanism is shown in Figure 1. The containers are the usual kind in which arsenic trioxide is shipped.

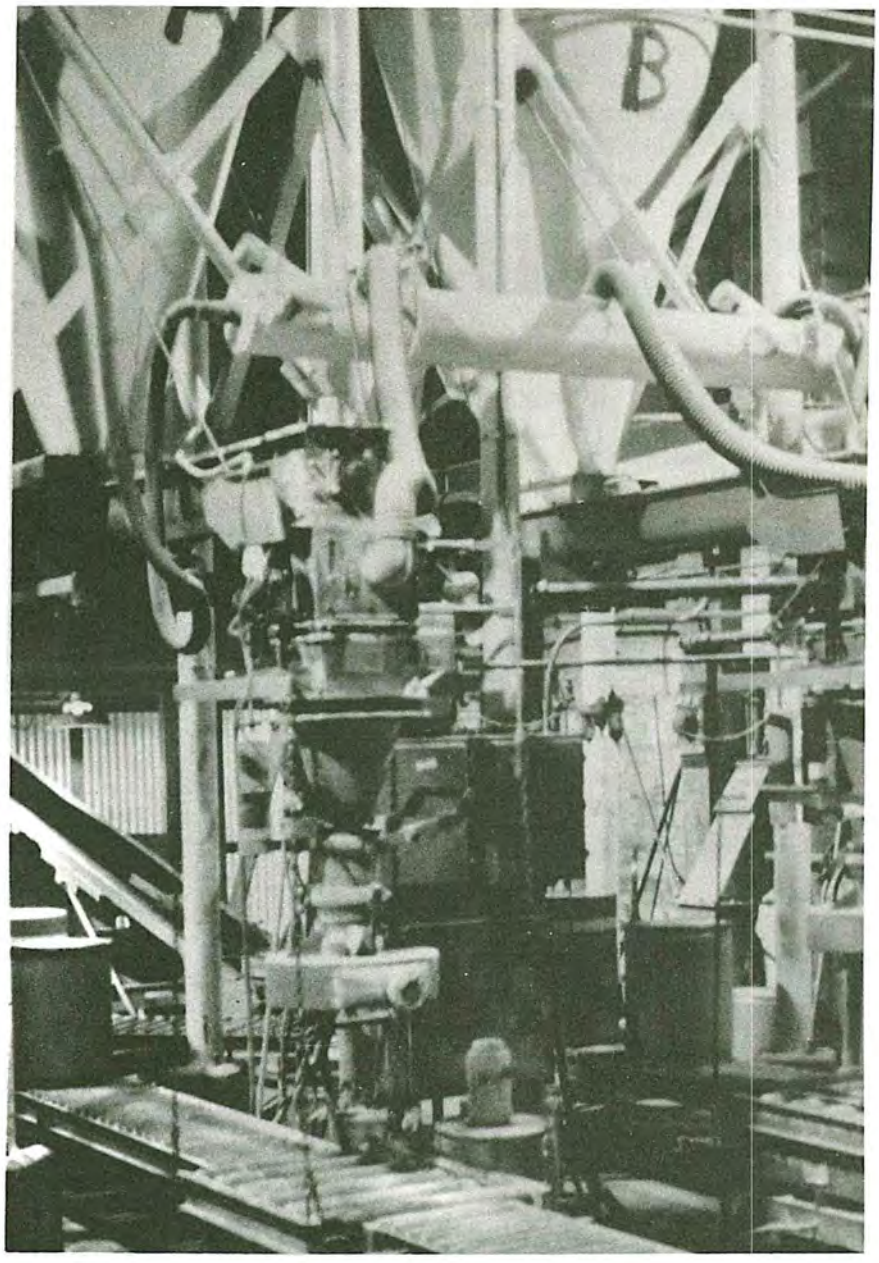

Figure 1 View of equipment used in packaging refined As_2O_3

During smelting of arsenic ores and concentrates, there are opportunities for dust and fume dispersal and in some instances there have been very significant exposure to airborne arsenic. It is routine in our plants for workers in the arsenical areas to wear respiratory protective equipment, protective clothing, etc.

The men shown in Figure 2 are actually barring down and cleaning out one of the arsenic kitchens. The accumulated material on the side is encrustations of crude arsenic. The usual protective clothing is shown, however, the respirators these men are wearing are not the usual type worn. Because arsenic trioxide is highly irritating to the skin, it was found to be impossible to wear rubber face pieces next to the skin an any arsenical dust exposure areas, so these men are -earing Dr. Wood respirators, an ancient kind, made by the American Optical Company, which utilizes surgical wadding as a filter medium. Their efficiency is good and our men are able to work in arsenical exposures without suffering dermatitis.

Figure 2 Workmen removing AS_2O_3 from Arsenic Kitchens

The more arsenic is studied, the more uses are found for it. Historically, arsenical compounds were used medicinally and they are still being used in veterinary practice. Arsenic compounds and arsenicals such as lead, calcium arsenate, and copper acetoarsenite are used as pesticides and have very important applications in agricultures. Some Arsenical compounds are also used as defoilants in the cotton fields, where, without this defoilant action, mechanical cotton pickers could not be used. Sodium arsenite also is a weed killer and soil sterilant.

Arsenic is an ingredient in wood preservative formulations which have very important uses in housing, in grape vineyards for stakes, and in lobster traps for protecting wood against various biologic organisms. Small quantities of arsenic trioxide are used in glass making where the application of arsenic clears the greenish color that normally is imparted to glass by metal contaminants in the materials used. This makes possible the clear white glass for windows in automobiles, homes, etc. Organic arsenical compounds are routinely fed to turkeys and, in some cases, to chickens to prevent a certain kind of blackhead disease. These are a few of the many and varied uses of arsenic and, for some of these uses, there is no satisfactory substitute.

In the miscellaneous uses for arsenic there are probably some exposures for the workers involved, but the extent and nature of these exposures have not been studied as much as they could have been. There are relatively few data published about exposures in connection with handling arsenic trioxide in the manufacture of various arsenical compounds. However, at the present time, there is a great deal of activity in the sampling of these operations because of the proposed new OSHA standard for arsenic (2 µg/cu m being the action level, 4 µg for the TLV, and 10 µg as a peak exposure limit). This represents almost zero exposures to particulate arsenic.

There have been a few reports recently in the literature which suggest that arsenic trioxide has enough vapor pressure to create significant concentrations of arsenic in the air immediately above the processing compound. We have tried, but we have not yet been able to verify this point or make certain that there is sufficient arsenic in the air to exceed the proposed TLV. We have used all the routine sampling instruments for sampling particulate arsenic in our operations; the same instruments we use for lead and other particulate dust and fumes. Nothing remarkable was developed in the samples. We are now making extensive use of the personal sampler and are getting a much better idea of actual individual exposures during the course of a work day; but the method of sampling is subject to the same criticisms that were mentioned yesterday, particle size considerations and others. After all, very few particles of a very small size could easily weigh 2 to 4 µg. The illustration in Figure 3 is an attempt to give you some idea of the quantities. The head of the common pin has been blown up to the size of the large red circle and the next circle represents 1 µg.

Actually, you cannot see 1 µg nor can you see 10 µg. Perhaps you might be able to see a speck of arsenic that equals 50 µg. The point of all this is that just a very few particles, respirable or not, collected by a sampling device would exceed the TLV. It may be possible

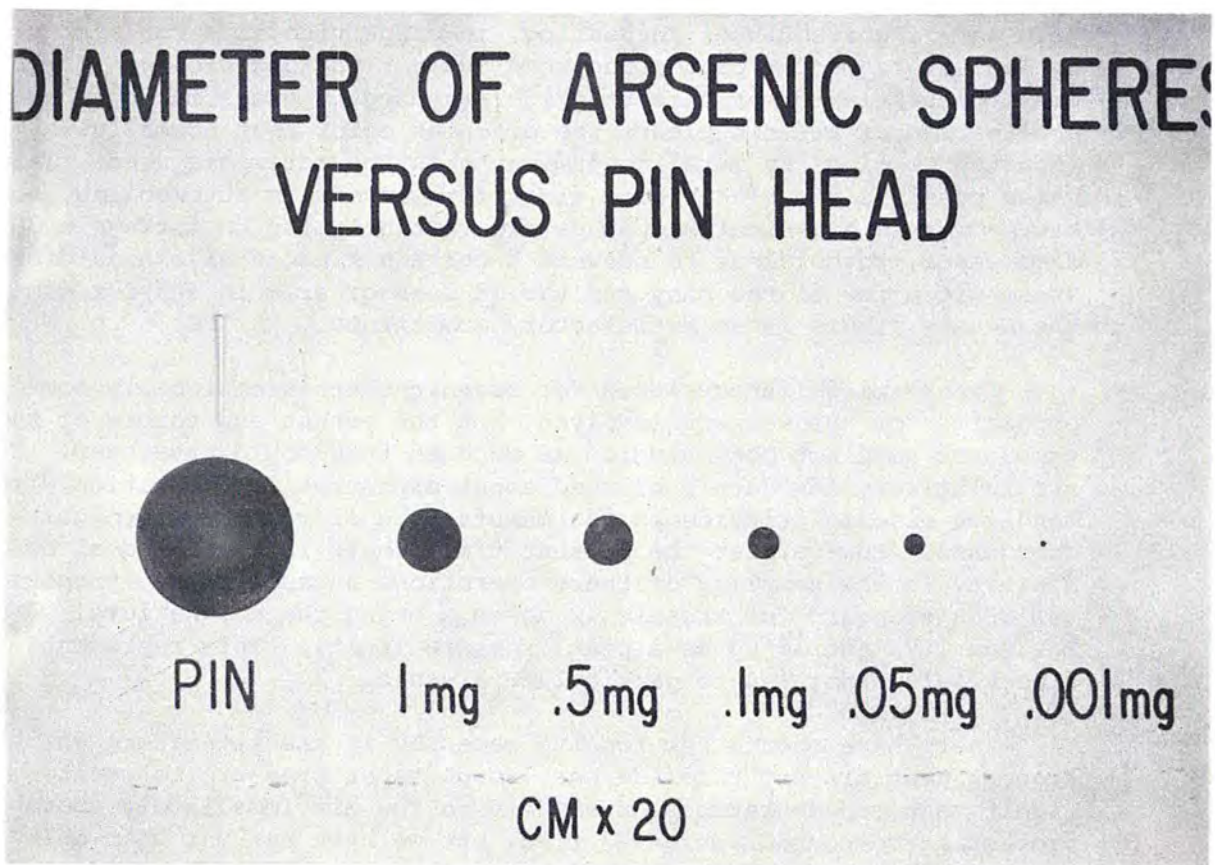

Figure 3 Size Comparison of Head of Common Pin with Arsenic Particles

that the TLV could be maintained in a clean room operation such as one in atomic energy establishments; but this level of cleanliness can never be achieved in a pyrometallurgical smelter.

Some results of the sampling done very recently in an attempt to correlate urinary arsenic levels with ariborne arsenic are outlined in Figure 4.

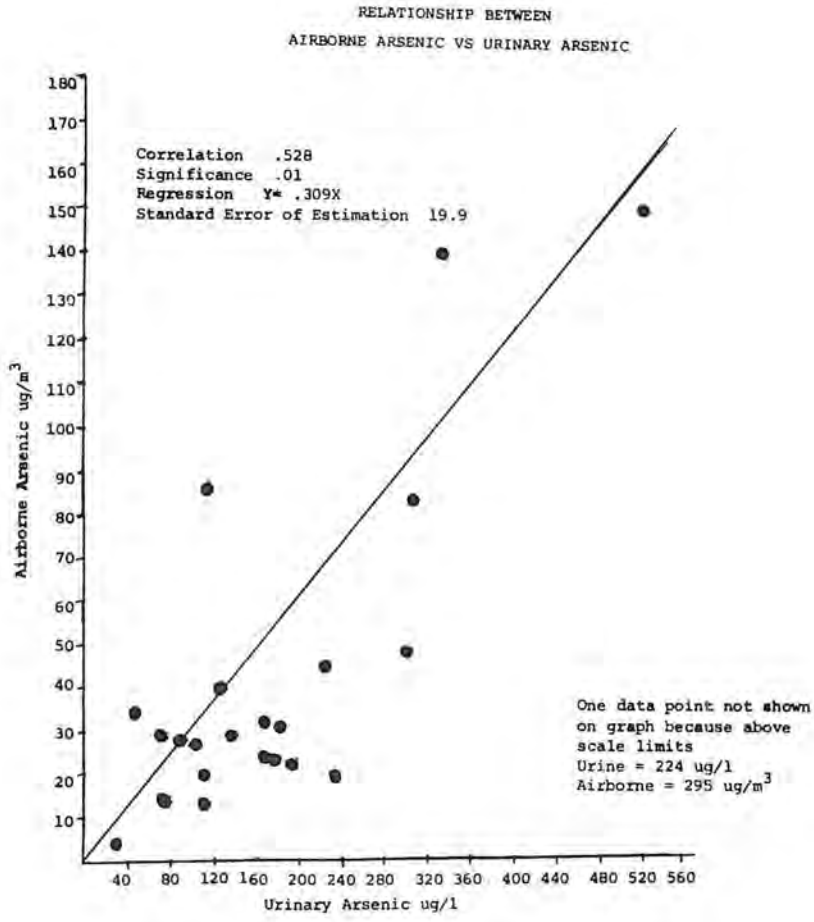

Figure 4 Correlation of Urinary and Airborne Arsenic Concentrations

On the ordinate the µg/cu m is shown and on the abcissa the urinary arsenic values corrected for specific gravity of 1.018. There were correlations; however, these men were not wearing respirators and we do not know whether there would have been any correlation if they had been wearing them.

MODERATOR-Mr. Richard Lemen

I believe *in lieu* of the time that we will keep our questions until after our second panelist has completed his presentation. Mr. William Wagner, Senior Industrial Hygiene Engineer with the Western Area Occupational Health Laboratory of the National Institute for Occupational Safety and Health, located in Salt Lake City, will be our second panelist. Mr. Wagner.

SOURCES OF ARSENIC, MONITORING THE WORKPLACE AND PROBLEMS INVOLVED

Mr. William L. Wagner
National Institute for Occupational Safety and Health

An overview of arsenic exposure in the United States copper smelting industry is presented, including measurements of airborne concentrations, respirability, and urinary excretion levels. Areas of high exposure are identified, and exposure of copper smelter workers is compared to exposure of users and manufacturers of pesticides. Problems encountered in collecting arsenic data and evaluting human exposure are also discussed.

The topic of the usual sources of arsenic exposure has been adequately covered by Mr. Nelson. However, you should be aware of recent NIOSH recommendations to the Department of Labor which make the copy of the inorganic arsenic criteria document given to you obsolete. It is being substantially revised. The airborne concentration currently recommended by NIOSH is "no detectable amount" using a certain method. The method given would detect 2 µg/cu m in a 15-minute sample. Also, in view of the current OSHA proposal for a standard of 4 µg/cu m as an 8-hour time weighted average, there will be a lot of other industries and operations where industrial hygienists are going to have to look for arsenic exposures. For instance, there is arsenic which is released into the environment when coal is burned. Another example is a material of special interest in this energy conscious time, oil shale. Some Colorado Plateau oil shales contain about .005 percent arsenic. This is much more arsenic than is found in many copper ores and even in some copper concentrates. The shale oil itself may be contaminated with as much as 50 ppm arsenic, and in the manufacture of synthetic crude oil, this arsenic must be removed. Obviously, a tremendous amount of arsenic will have to be handled in that industrial process.

I have been advised that waste material handled in the building of roads contains as much as 0.1 percent arsenic, a relatively considerable amount. To give you an idea of typical airborne environmental concentrations of arsenic, EPA data, collected in the mid 1950's, and data, collected by some states in the early 1960's, indicate that in smaller towns in the United States where there is an insignificant arsenic source, typical airborne levels are equal to or less than about 0.02 µg/cu m. In larger cities, arsenic levels are usually equal to or less than around 0.1 µg/cu m, with occasional excursions of higher levels. In smelter

towns values will occasionally exceed 2 µg/cu m.

Figure 1 shows a comparison of some typical environmental airborne background concentrations of arsenic. The bars on the left represent the air levels of arsenic found in some towns in Montana. This data was collected during 1961 and 1962 and you can see that the levels are all below 0.1 µg/cu m with the exception of Anaconda, where a rather large smelter is located. The levels on the right side are for the cities of Portland, Cincinnati, Chicago, New York, and Los Angeles.

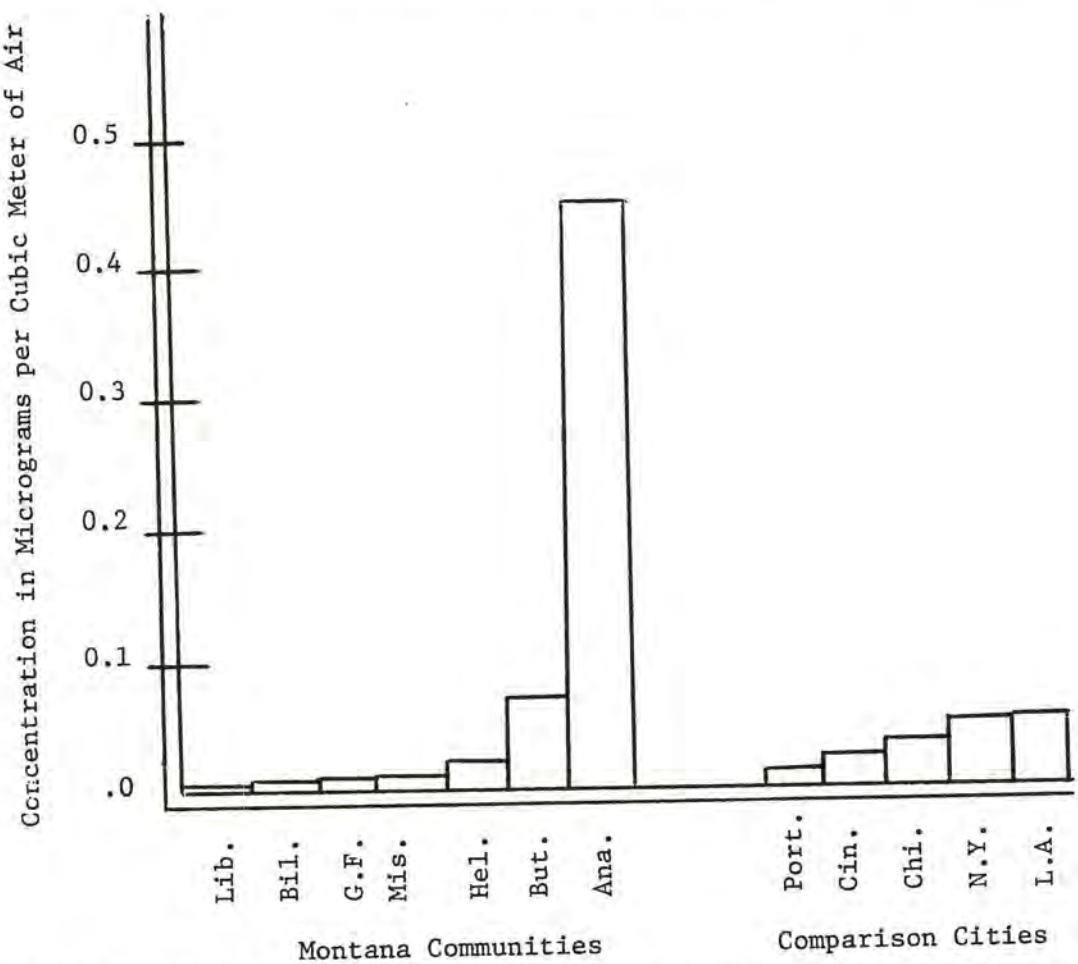

Figure 1 Average Arsenic in Air Content for Seven Montana Communities, June 1961 - July 1962

One of the major industries where there is exposure to inorganic arsenic is the smelting of copper. Data from some of the copper smelter survey reports from NIOSH's Salt Lake City facility give you an idea of

the range of airborne levels of arsenic in that industry. Based on the Salt Lake City data, it appears that copper smelters fall into three groups with differing ranges of airborne arsenic concentrations based on the percent of arsenic in their concentrate. There are 15 copper smelters in the United States and we have some information on 14 of them. None of these smelters would fall into the lowest category having concentrates that contain about 0.001 to 0.01 percent arsenic. The airborne levels found usually were from equal to or less than 0.001 mg/cu m up to about 0.01 mg/cu m. These figures compare with the current OSHA proposal for an inorganic arsenic standard.

An intermediate group would include 3 smelters with the concentrate usually containing from about a 0.1 to 0.4 percent arsenic and airborne levels averaging about 0.05 mg/cu m. Keep in mind that these are ballpark values, because there are excursions and exceptions in every smelter.

The high group includes 2 smelters where the arsenic content in the feed is from about 1 to 7 percent. We have found airborne values in these smelters from essentially undetectable up to above 10 mg/cu m.

Table I shows data taken from a smelter where the concentrate was 0.003 percent and is a good example of some of the airborne values found in one of the cleaner smelters. Notice that almost all values are equal or less than 1 µg/cu m.

Table I, AIRBORNE ARSENIC - SMELTER PROCESSING CONCENTRATE WITH 0.003 PERCENT As

Location	Arsenic mg/cu m
#3 Side #2 Reverb., Chargers Floor, Converter End	<.001
#3 Side #2 Reverb., Chargers Floor, Converter End	.001
#6 Side #3 Reverb., Chargers Floor, Skimming End	<.001
#6 Side #3 Reverb., Chargers Floor, Skimming End	<.001
#6 Side #3 Reverb., Chargers Floor, Skimming End	<.001
#6 Side #3 Reverb., Chargers Floor, Skimming End	.001

Data in Table II is from a smelter where the concentrate content is about 0.01 percent arsenic. On the day these measurements were made the feed was 0.0008 percent. All the values are quite low, except the

boiler repairman's personal sample, which was 0.5683 mg/cu m, was a value exceeding the current TLV.

Table II, AIRBORNE ARSENIC - SMELTER PROCESSING CONCENTRATE WITH 0.01 PERCENT As

TYPE	LOCATION	As mg/cu m
Personal	Tappers' Helper, South Side, Reverb. #1	<0.0002
Personal	Boiler Repair	0.5683
Personal	Spoutman	0.0043
Personal	Crane	<0.0002
Personal	Laborer, Anode Casting Area	<0.0003
Personal	Reverb. #2, North Side, Center, Charge Floor	<0.0002
Personal	Crane #1, South	<0.0002
Personal	Crane #2, Middle	<0.0010
Personal	Concentrate Feed Deck Between Crane #1 & #2	0.0077
Personal	Reverb. #1, South Side, Charge Floor	<0.0001
Personal	Reverb. #2, South Side, Center, Charge Floor	0.0298
Personal	Reverb. #1, North Side, Center, Charge Floor	0.0004

Two ways for exposure with arsenic in a copper smelter to occur are: (1) exposure to fume and dust (the fugitive emissions) from the heating and concentrate handling processes, and (2) exposure to flue dust by workers who routinely handle this material and by those who come into incidental contact with the dust while performing maintenance tasks. A boiler repairman was in an area where there was a lot of flue dust and consequently the filter he was wearing accumulated a lot of arsenic.

Data in Table III shows a smelter processing a concentrate containing about 0.2 to 0.4 percent arsenic. Notice that the airborne levels are higher than those in the preceeding Table II. Higher figures have been reported from this smelter.

Table III AIRBORNE ARSENIC - SMELTER PROCESSING CONCENTRATE WITH 0.2 - 0.4 PERCENT As

LOCATION	As mg/cu m
Converter Skimmer on #3	0.03
Converter Skimmer on #3	<0.01
Converter Skimmer on #3	<0.01
Center of Charge Floor, West Side	0.15
Center of Charge Floor, East Side	0.02
North East Side of Charge Floor	0.01
Center of Charge Floor, West Side	0.05
Slag Skimming Area, No. Side of #4 Reverb.	0.02
Matte Tapping Area, #4 Reverb., 15' Away	0.01

Data in Table IV is from a smelter where a concentrate containing about 1 percent is processed. Only data from the converter side is shown. Information from the reverb side showing levels as high as 8.2 mg/cu m are available.

TABLE IV, AIRBORNE ARSENIC - SMELTER PROCESSING CONCENTRATE WITH 1 PERCENT As

LOCATION	As mg/cu m
Crane Cab - No. 2	0.02
Puncher Aisle (Behind No. 2 Converter)	0.05
Skimmer Shack No. 5	0.06
Skimmer Shack No. 3	0.13
Skimmer Shack No. 1	0.10

Table V presents a composite of a number of samples taken in some 14 copper smelters in the United States and gives a pretty good idea of the exposures of the working population as a whole. It also identifies the higher risk workers. Notice that the reverbatory charge floor workers work in the highest airborne concentrations. We see this pattern repeated in smelter after smelter, so we are confident that these workers have the higher risk. There are, however, certain other maintenance workers and flue dust handlers who can also get some high exposures. These values represent 8-hour time weighted average exposures if one does not consider the use of respirators. Also, this arsenic is about 75 percent respirable.

TABLE V, AIRBORNE ARSENIC - INDUSTRY-WIDE AVERAGES

LOCATION	As mg/cu m
Reverberatory Furnace Charging Deck	0.04
Reverberatory Furnace Operators Deck	0.02
Converter Aisle	0.01
Anode Casting	<0.01

Our definition of respirable material is that which passes through miniature cyclone. This fact has been verified by other investigators who have found that the airborne arsenic in copper smelters is from 68 to 80 percent respirable.

Table VI contains an average of 156 samples taken again from 14 copper smelters in the United States. The average, 23, is quite low; the highest value reported, 170, is also reasonably low. We do have some

other data, where in the smelters with higher airborne levels, the values are up to around 225 ug/liter in the urine. Again, nothing really excessive.

Table VI ARSENIC CONCENTRATION IN URINE

Element	Concentration in ug/liter Average	Highest Value	No. Samples
As	23	170	156

In sampling the environment for arsenic and in attempting to determine human exposure, we experience all the problems with airborne sampling for lead discussed yesterday. There is an additional problem too. Usually when surveying a smelter or any other type of industry, the investigator is looking for many things besides arsenic. With a given filter, one can get information on lead, zinc, cadmium, nickel, molybdenum, copper, and many other metals. If one wants data on arsenic, then all this other information is lost because of the requirements of the analytical procedure. So, in the past, the tendency has been to look for the other materials because the levels for arsenic were always low in relation to the TLV.

MODERATOR-Mr. Richard Lemen

According to my watch, I think we have time for about two questions for the panelists.

Since there are no questions, we will go to the next part of this morning's program, the Session on Toxicology of Arsenic - Non-Carcinogenic Effects, which is being moderated by Dr. Michael Utidjian, Director of Occupational Medicine and Toxicology at Tabershaw-Cooper Association. Dr. Utidjian.

SESSION VII - TOXICOLOGY OF ARSENIC

Dr. Michael Utidjian, Moderator
Tabershaw-Cooper Associates, Incorporated

A B S T R A C T

Arsenic, long notorious as a criminal poison, presents several uniquely interesting features in the field of occupational toxicology. Arsenic exposure most often produces cutaneous manifestations in man and can produce cardiotoxic and electrocardiogram changes that could be confused with ischemic heart disease. The carcinogenicity of arsenic is probably its most critical toxic property.

While reviewing the literature during preparation of the NIOSH Criteria Document* it struck me that arsenic is really a most intriguing and versatile poison. Historically it is one of the most celebrated criminal poisons, and from Medieval times into this century, by a curious philosophic process, highly poisonous substances have been considered to have some medicinal values when taken in small doses. Much of the human toxicology of arsenic stems from experiences in medication with inorganic arsenical preparations.

Arsenic is quite versatile. It has toxic manifestations through the central and peripheral nervous systems of man and other animals and is cardiotoxic. In fact, it can produce electrocardiographic changes which closely simulate those of ischemic heart disease. This is a property it shares with antimony, its close elemental analogue. Arsenic is also toxic to the kidneys. Yet arsenic , with its lengthy suspicion record, has just recently emerged in its true light as a subtle but definite carcinogen.

In the field of occupational toxicology, greater numbers of workers are significantly exposed to arsenic in the form of the trioxide. Some of these workers are not engaged in the metallurgy of arsenic for its own sake or in the preparation or use of the trioxide. Non-ferrous metal smelter workers in general are exposed because so much of the material they work with, copper ore in particular, is arseniferous, and the trioxide is volatile at ore roasting and smelting temperatures.

In the United States for some years all the primary arsenic trioxide production and refining has been conducted in one plant. Small numbers of

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**Dr. Utidjian was involved with the preparation of preliminary drafts of the NIOSH Criteria Document for Arsenic.*

workers are potentially exposed in the use of arsenic, usually initially as the trioxide, in pharmaceutical manufacture, the production of pesticides and herbicides, and manufacture of pigments, special glasses and special alloys. Exposures to arsine, the gaseous trihydride, are almost invariably inadvertent and episodic, when arsenic-containing metals or drosses come into contact with nascent hydrogen from water or dilute acid. The salient effect of arsine is acute intravascular hemolysis.

Arsenic trioxide is now increasingly accepted as an occupational carcinogen to the lung, to the skin, and, with less certain evidence, to the liver. The evidence for its carcinogenic potential is again unusual in being entirely human, epidemiological and anecdotal (the latter for iatrogenic cancer), unsupported by any animal experimental evidence. No animal model for arsenical cancer has so far been established, despite many attempts to find one. This lack of animal evidence has probably delayed acceptance of the human cancer risk from arsenic for many years. At the same time arsenic has been incriminated by some authors for many other occupational cancers now attributed to other agents, for example, Pott's scrotal cancer in chimney sweeps, cancer of the paranasal sinuses in nickel carbonyl process workers, lung cancer in uranium miners, etc. There is some slender evidence that arsenic, probably in the pentavalent rather than the trivalent form, is an essential trace element in some animal species, if not in man. The very different metabolic handling and toxicity of pentavalent *versus* trivalent arsenic in mammals is another point of considerable interest, and a complicating factor when attempts at biological monitoring for arsenic exposures through urinary arsenic levels have been made.

Perhaps most interesting of all cutaneous manifestations of arsenic toxicity is the apparent deposit of arsenic in the skin and in all keratinous appendages. Most readers of detective novels and "who-dunnits" know about hair and fingernail analyses for arsenic in the forensic process of identifying criminal arsenic poisoning.

Systemically absorbed arsenic is laid down in the skin and other keratinous appendages of the human body, and in a sense is slowly excreted by this route, as these appendages are shed or slough away. On this route out of the body, however, it produces lesions, disorders of pigmentation and hyperkeratoses, and ultimately skin cancer. At the same time prolonged exposure of the skin directly to arsenic trioxide dust or arsenites seems to produce skin lesions clinically indistinguishable from the cutaneous manifestations of systemic arsenicalism. In addition, arsenic is acutely cardiotoxic and produces changes in the electrocardiogram which could readily be confused with the effects of myocardial ischemia. Perpheral neuritis with sensory changes and motor paresis are also features of chronic arsenicalism.

Before introducing our first speaker, I just want to relate a bit of

anecdotal information. Dr. Walter Davis, a carcinogen chemist with the International Agency for Research on Cancer in Lyon, France, recently visited government agencies in Rockville. Within a few weeks prior to his visit, a colleague had shown him a patient with hemangiosarcoma of the liver in the presence of severe arsenical dermatitis in which there had been no known exposure to vinyl chloride. So with that thought I am going to introduce Dr. Andrew Reeves, Professor of Occupational and Environmental Health at Wayne State University.

Before turning the microphone over to Dr. Reeve who will make the first presentation on the Toxicology of Arsenic - Non-Carcinogenic Effects panel, I must convey the personal apologies of Dr. Stephen Krop of the Food and Drug Administration. He called me about two weeks ago to explain he had just returned to work after having been ill, and is busy trying to catch up with his work. He also was unable to recruit a delegate for the FDA presentation, so we will have only two speakers rather than the three that were planned.

Now we will hear from Dr. Reeves.

THE TOXICOLOGY OF ARSENIC - NONCARCINOGENIC EFFECTS

Dr. Andrew L. Reeves
Wayne State University

A B S T R A C T

The historic popularity of arsenic (As_2O_3) as a poison owes more to its tastelessness than to its extraordinary toxicity. Arsenic, as a conventional poison, has a worse public image than what is warranted by fact. On the ACGIH Threshold Limits list, about a dozen other elements have lower values than arsenic. The element is ubiquitous in biological material; in seafood, the levels may reach 80 ppm. In humans, arsenic is stored in keratinous tissue with normal levels of 0.5-5.5 ppm. Occupational arsenic poisonings of non-neoplastic nature are relatively rare and have followed a decreasing trend during this century. The new exposure standard recommended by NIOSH is 0.5 mg/cu m (1/10 of the present TLV).

The Greek word, *arsenikon*, means potent, referring to the toxicity of the element; however, to characterize arsenic from the toxicological point of view in one sentence, it is the element in the periodic table with the worst "Public Relations" department. The word has been almost synonymous with poison throughout history, and it has inspired literary and theatrical works some of which are memorable.*

Actually, however, if you believe that arsenic is the most poisonous substance known to man, you are far from right, at least on the quantitative values lower than arsenic. Of course, you are aware that the TLV list might not be used as "God's own word" regarding the toxicity of any substance, and some people think that it contains far too liberal or far too conservative assessments. On the other hand, whatever is true of arsenic can be equally true for other elements listed on the TLV list. So it might be of interest to know that the following other elements have TLV values lower than arsenic: beryllium, cadmium, cobalt, copper, indium, mercury, selenium, silver, tantalum, tellurium, thallium, and vanadium, and in no case does the name connotate as strongly the concept of toxicity as that of arsenic.

A listing of threshold limit and other values with respect to inorganic arsenic compounds is contained in Table I. According to Patty,[1]

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*Dr. Reeves showed a few scenes from the Broadway production of J. Kesselring's "Arsenic and Old Lace".

a concentration of 1000 mg/cu m of arsenic is needed in order to reach the LC_{50}. Of course, much less than that, between 50 and 250 mg/cu m could be regarded as dangerous in a one hour exposure. At least in 1963 the values between 25 and 125 mg/cu m were regarded as tolerable by man for a short exposure. Furthermore, no symptoms were seen at concentrations below 10-40 mg/cu m, see Table I. Arsenic itself, that is, arsenic trioxide, is tasteless, but the gas (AsH_3) is not. It has a distinct odor of garlic and that indeed, can be perceived on the breath of the persons poisoned with arsenic in view of metabolic transformations. The odor threshold of arsine is about 2 mg/cu m, and for this specific compound that might perhaps serve as an indicator of a truly dangerous concentration. On the other hand, TLV values of MAC values in different countries are at the present time between 0.3 and 0.5 mg/cu m. As you know, one subject for discussion is the new standard recommended by NIOSH[2] which is 1/10 of what the TLV values used to be.

TABLE I
THRESHOLD VALUES FOR INORGANIC ARSENIC COMPOUNDS

Value	As mg/cu m
Recommended NIOSH standard (1973)	0.05
MAC(USSR) also adopted in Hungary, E. Germany	0.3
TLV(ACGIH) also adopted in Britain, W. Germany	0.5 (0.2 for AsH_3)
Odor threshold	about 2 (AsH_3 only)
Slight symptoms after exposure of several hours	10-40
Maximum concentration for 1 hour without serious consequences	25-125
Dangerous on 1 hour exposure	50-250
LC_{50} on 1 hour in humans	1000

Adapted from F. A. Patty, Interscience Publications, New York, 1963

Arsenic is, certainly, the most popular and deliberate form of poisoning,or at least it has been, although not the most poisonous substance. No less than 1/3 of all the cases of criminal poisoning in the 19th century of France were attributed to arsenic. Some of the other materials which

were also used for this purpose are shown in Table II.

TABLE II
FAVORITE POISONS IN 19TH CENTURY FRANCE

	Percent of Cases
Arsenic	33.1
Phosphorus	30.1
Copper	18.3
Mineral Acids	5.4
Cantharides	3.5
Strychnine	1.4
Opiates	1.2
Mercurials	0.9
Antimonials	0.6
Cyanides	5.0
Others	5.0
	100.0

Table III indicates that arsenic is biologically natural. There are measurable normal levels in almost everything and seafood has been known as a very rich source of arsenic from way back.

TABLE III
ARSENIC LEVELS IN FOOD

Food	As, ppm
Dry Milk	0.5
Oysters*	5
Shrimps#	25
Lobsters	40
Crabs	50
Clams	80

You can see that clams, certain clams at least, reach 80 ppm, which is a fairly high concentration of arsenic. Lobsters and shrimps have substantial quantities of arsenic. Even dry milk from completely normal and not knowingly exposed cows have as much as .5 ppm of arsenic. Now with that kind of dietary intake, you can imagine that our own arsenic concentration in

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**As caught in the Thames. Portuguese oysters were found to have 7-8 X this concentration.*
#One value of 175 ppm was found in a large shrimp.

tissue is more than zero. Indeed, Table IV gives the completely normal burdens; these are values which are taken as averages from the general population without any known occupational, medicinal or other exposure. As was already pointed out, keratinous appendages of our bodies, hair, and nails are the highest in arsenic and even though this is perhaps a method of eliminating the element, we do carry them on our bodies for awhile, with fairly measurable arsenic concentrations.

TABLE IV

NORMAL LEVELS OF ARSENIC

Material	ppm
Urine	0.01 - 0.33
Blood	0.10 - 0.50
Hair	0.50 - 2.00
Nails	0.50 - 5.50

There is an "arsenic cycle" in nature shown in Figure 1,[3] and you can see that this quantity of arsenic does have its way of getting around. The arsenic compounds in soil, land, etc., as we have them do not appear in plants, microbes, and marine crustaceans. Also, they are cycled into the higher animals. There organic arsenicals are some kind of conjugate which has not been adequately studied.

Arsenic has a high affinity to sulfhydryl groups and there is reason to believe that certain thiol compounds (e.g., cystein or glutathione) probably are accumulators of inorganic arsenic. Once they are excreted and subject to decomposition, they might become volatile arsines and thereby the cycle is completed.

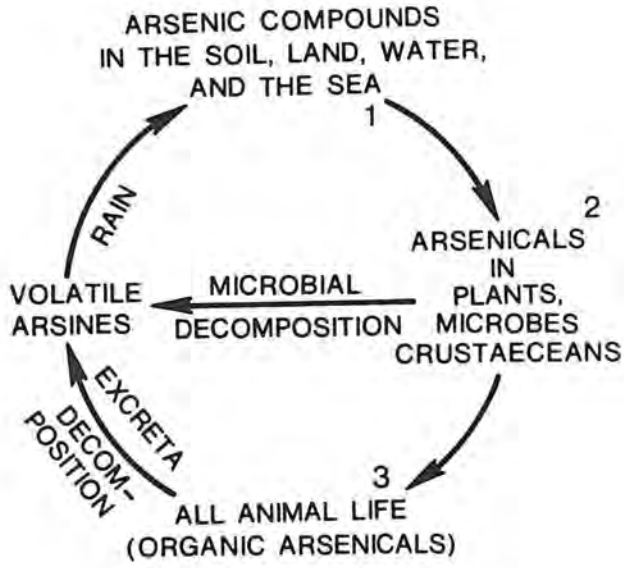

Figure 1 *1.* The cycle in nature involves organic arsenicals, few identified.
2. Marine algae may contain up to 9 ppm As, land plants generally less than 0.5 ppm As.
3. Edible tissues of food animals contain an average, below 0.5 ppm As, fish 0.5-3 ppm, crustaceans 3-100 ppm.

Adapted from Frost, D. V., Fed. Proc.

Table V gives you the clinical details of arsenic poisoning both in humans and in animals. Among animals, it is farm animals in which this is most often observed. But experimental rodents, etc. are subject to the same type of symptoms. The symptoms might be subdivided into five groups showing that even though arsenic is not very poisonous on a quantitative basis, it does do quite a few things if the concentration gets high enough. Gastrointestinal, dermatologic, musculoskeletal, circulatory, and neurologic are the groups into which the effects of arsenic can be classified. Thus, each human symptom and sign has its counterpart in veterinary practice.

TABLE V
SYMPTOMS AND SIGNS OF ARSENIC POISONING

Symptom Group	Human	Veterinary
Gastro-intestinal	metallic taste in mouth garlic odor of breath dryness of mouth and throat burning pain in stomach profuse diarrhea blood "rice water" stool	 intestinal inflammation distress due to abdominal pain profuse diarrhea bloody mucous stool
Dermatologic	skin eruption skin ulceration perforation of nasal septum	depilation dry ("leathery" or "papery") skin ulceration of nasal sinuses
Musculoskeletal	muscular cramps	muscular twitching
Circulatory	rapid, feeble pulse cold, clammy extremities increased capillary permeability sighing respiration cyanosis	weak pulse
Neurologic	frontal headache vertigo depression stupor convulsions	 tremors

The next question is, why would arsenic be that poisonous to that many different systems? The proper answer to that is the enzymatic inhibitory property of arsenic which is generally true for all those enzymes which depend for their activity on the SH group. The enzymes which are listed in Table VI are known to be such enzymes and these are the first which become inhibited. Of course, as the concentration goes up the

number of enzymes which are significantly inhibited probably also goes up. So, that is the fundamental molecular reason for the toxicity of arsenic.

TABLE VI
ENZYMES INHIBITED BY ARSENIC

Glutamic-oxaloacetic transaminase	Choline oxidase
Pyruvate oxidase	Glucose oxidase
Monamine oxidase	Urease

Figure 2, from a biochemistry textbook,[4] shows the metabolic integration, the final common pathway of all nutrient bio-transformations in man which includes anaerolic glycolysis as well as the tricarboxylic and cycle. It has been known, well known from old times, that one reaction in the tricarboxylic acid cycle is specifically sensitive to arsenite. The conversion of malate to fumarate, or *vice versa*, is blocked by arsenite more efficiently than by any other known inhibitor.

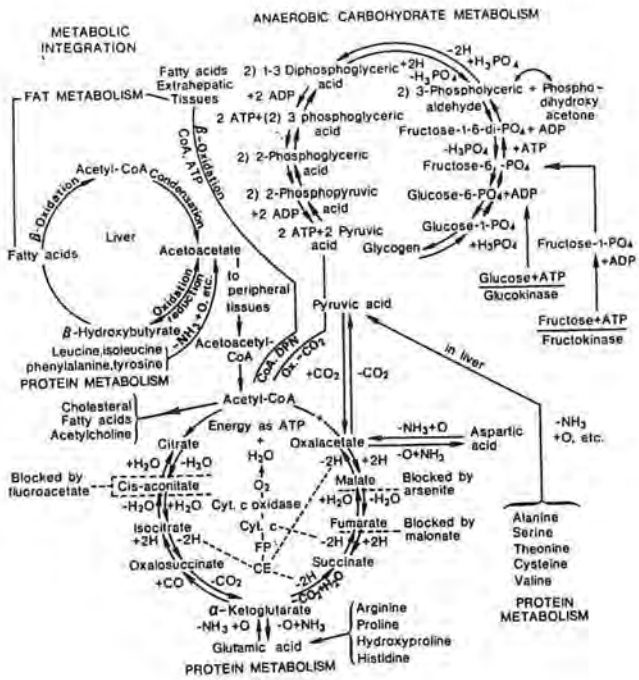

Figure 2 Anaerobic Carbohydrate Metabolism

Adapted from: *Textbook in Biochemistry*, *Macmillan, New York, 1955.*

That is, of course, because it depends upon an enzyme which is particularly sensitive to arsenite deactivation. Since this is a very general and very essential reaction occurring in every cell, it gives a good idea why arsenic should adversely affect that many organ systems.

One of the interesting discoveries regarding arsenic toxicity is its teratogenic effect.[5] This, so far, has not been observed, or known to occur in humans, but has been observed in experimental animals. In the golden hamster, arsenic specifically affects the development of the kidney and the development of the encephalon. In Figure 3 the effect of arsenic is being compared to the effect of some other metals, lead, indium and cadmium, each affecting the development of the golden hamster at different embryologic sites. The mechanism of why arsenic should concentrate in these particular tissues or why it should preferentially damage the development of these tissues, is not understood.

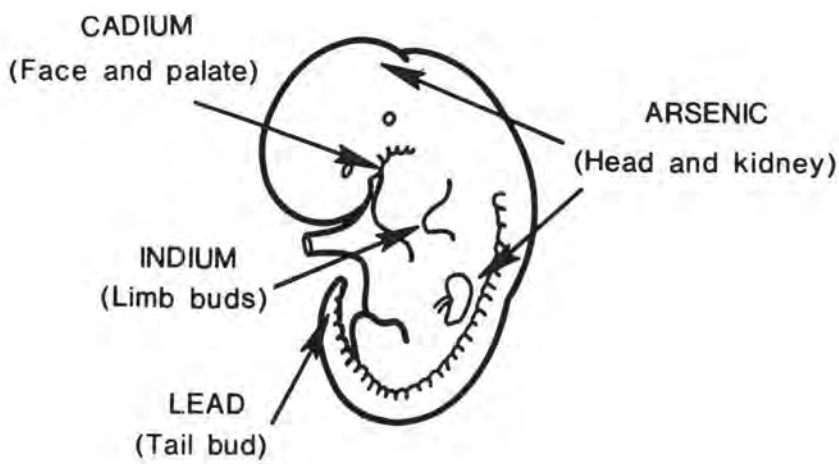

Figure 3 Summary of teratogenic effects of 4 different elements on embryonic development in the golden hamster. Each of these teratogens was administered under identical conditions. Development is affected in different ways by these different teratogens.

Adapted from Ferm, V. H., Adv. Teratol.

The classification of cases in Table VII is by Buchanan[6] of different incidences of arsenic poisonings in trades, as it occurred in England during different decades or groups of decades in this century. In England the manufacture of sheep dip has been the most frequent cause of occupational arsenic poisoning. The figures in parenthesis are deaths, and the figures before the parenthesis are cases, both lethal and non-lethal.

TABLE VII
ARSENICAL POISONING BY PROCESS OR COMPOUND

Process or occupation	1900-1918	1919-1939	1940-1959
Manufacture of arsenical colour	53(1)	4(1)	1
Manufacture of sheep dip	4	14(5)	8(2)
Refining arsenious oxide, etc.	10	4	4(1)
Manufacture of various arsenites	--	4(2)	--
Manufacture of various arsenates	--	4	2
Arsenious chloride	18(1)	1(1)	--
Tannery depilatory	1	2	--
Taxidermy	3	--	--
Manufacture of wallpaper	1	--	--
Manufacture of anti-fouling paint	2	--	--
Lead shot manufacture	1	1	--
Miscellaneous or information lacking	12	11	7
	105(2)	45(9)	22(3)

Adapted from Buchanan, W. D., Toxicity of arsenic compounds.

You can see from Table VII that the frequency of arsenic poisoning in other countries has also gone down. In the decades preceding our own time there were substantially fewer cases of arsenic poisoning than before. This is, of course, relating to non-neoplastic arsenic poisoning and with respect to that particular set of effects, one is justified in saying that occupational hazards have been controlled. The discovery of the neoplastic effects has introduced us to a whole new ballgame, but that will be discussed in the next segment.

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MODERATOR-Dr. Michael Utidjian

Thank you, Dr. Reeves for an informative presentation.

Now it is my pleasure to introduce Dr. Bruce Fowler, a Senior Staff Fellow at the Environmental Toxicology Branch of the National Institute of Environmental Health Sciences, the second speaker on the panel. Dr. Fowler also participated in the Epidemiology of Lead Panel yesterday afternoon.

ENVIRONMENTAL ARSENIC TOXICOLOGY

Dr. Bruce Fowler
National Institute of Environmental Health Sciences

A B S T R A C T

It is important in discussing the toxicity of environmental arsenic that we distinguish between the different chemical forms of arsenic; arsenite, As^{+3}; arsenate, As^{+5}; and arsine gas, AsH_3; since organo arsenicals vary in their degree of toxicity. Arsenite is considered more toxic than arsenate, although arsenate is the more common environmental form. Arsine gas is a potent hemolytic agent of occupational concern in some industries.

This presentation is largely confined to a discussion of the mechanisms of inorganic arsenic toxicity to cellular respiratory systems. The first form to consider is arsenate. The toxic effects of arsenate on cellular respiration have been extensively used to study the uncoupling of oxidative phosphorylation in isolated mitochondria, and the formation of the unstable arsenate esters which substitute for phosphate esters during formation of ATP.

In a recent study done in collaboration with Martha Brown, Dr. Bonnie Rhyne, and Dr. Robert Goyer, we have reported[1] the *in vivo* ultrastructural and biochemical effects of arsenate on the rat kidney proximal tubule. In this particular study, male rats which were allowed access to drinking water containing arsenate at concentrations of 45, 85 and 125 ppm for a period of 6 weeks were used. Ultrastructural changes in the kidneys of these animals were correlated with oxygen electrode studies of renal mitochondria from the same rats. An electron micrograph of a proximal tubule cell from one of the rats exposed to the 85 ppm dose level of arsenate is shown in Figure 1. Notice the swollen mitochondria (see arrows) and the electron dense membranous lysosomal bodies which were increased in number in the proximal tubule cells of animals in the 85 ppm and 125 ppm dose groups.

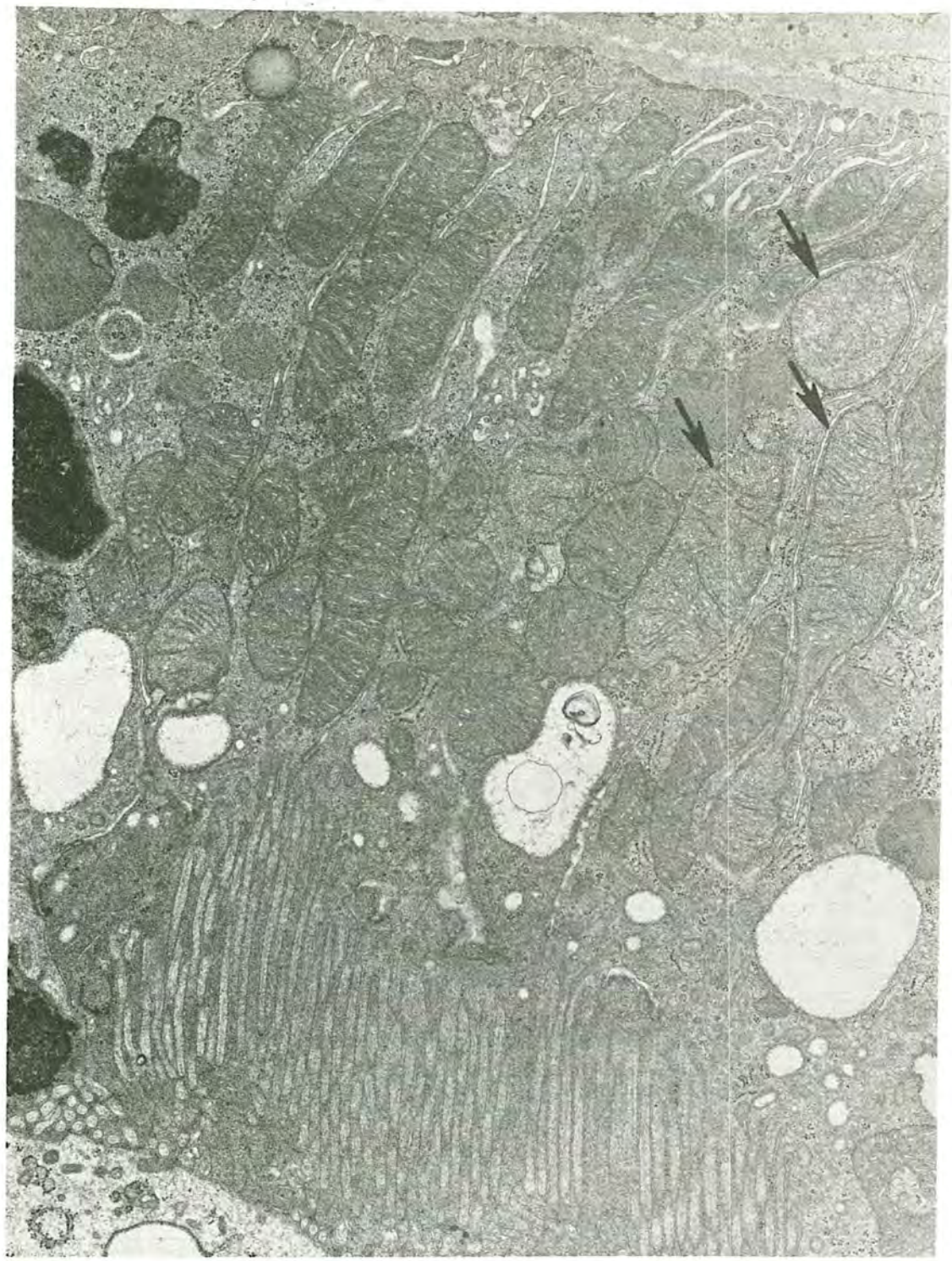

Figure 1 Electron micrograph of a proximal tubule cell from rat exposed to 85 ppm dose level of arsenate.

The oxygen electrode data from these same animals are presented in Table I. One main effect of arsenate was observed as on the State 3 respiration where there was a decrease. The studies in Table I show that control animals are matched with the treated animals. The top number is the mean for the control group, the next number is the mean for the treated group, and the values below are the mean differences. The other major effect was on the respiratory control ratios which are also decreased.

TABLE I
RESPIRATORY PARAMETERS* MEASURED ON SUSPENSION
OF MITOCHONDRIA FROM CONTROL AND ARSENIC FED RATS

Arsenic μg/ml H_2O	40	85	125
n	10	5	8
Control *versus* Expected	C As (D±S.E.)	C As (D±S.E.)	C As (D±S.E.)
State 4 μg O/g prot./min.	29.6 29.6 (0.05± 1.34)	27.7 26.4 (1.30± 1.25)	30.4 29.1 (1.31± 1.50)
State 3 μg O/g prot./min.	80.4 75.4 (4.7 ± 2.33)#	76.3 67.3 (9.0 ± 3.98)#	81.5 72.5 (8.75± 2.81)#
ADP: O	2.48 2.42 (0.06± 0.05)	2.59 2.48 (0.10± 0.18)	2.58 2.33 (0.24± 0.11)#
Respiratory Control Ratio	2.73 2.78 (0.04± 0.14)	2.99 2.55 (0.44± 0.16)#	3.00 2.63 (0.37± 0.13)#

**Respiratory parameters from a mitochondrial preparation from the kidney of a control and arsenic fed rat were measured simultaneously. Upper numbers are means of actual measurements; lower numbers are mean and S.E.M of paired differences between control and arsenic fed rats. #Differs from control, $p<0.05$*

Looking at the total arsenic levels in the kidney, Table II, and in the washed mitochondria from these animals, there is a fairly extensive accumulation of arsenic in both the kidneys and the mitochondria. The leveling here between 85 and 125 ppm dose group is probably due to decreased water intake in the 125 ppm group.

TABLE II

MEAN TOTAL ARSENIC LEVELS OF KIDNEYS AND WASHED MITOCHONDRIA (Mw)*

Arsenic g/ml H_2O	0	40	85	125
n	18	9	4	9
Kidney (µg/g±S.E.M.)	7.4 (±2.1)	39.8# (±6.5)	84.4# (±18.2)	84.8# (±10.0)
Mw (µg/g prot.±S.E.M.)	14 (±4.6)	52 # (±16.1)	105 # (±9.8)	64 # (±13.9)

**Concentrations expressed as ppm of wet weight*
#p <0.

The next form of arsenic to be examined is arsenite (As^{+3}), which is considered generally more toxic to cellular respiration than arsenate, although its mechanism of action is thought to be somewhat different. Dr. Reeves alluded to this rather substantially. In a preliminary study, higher renal levels of total arsenic in animals given arsenite in the drinking water were observed, as opposed to arsenate.

The data in Table III were from animals exposed to either 3 or 30 ppm of arsenate or arsenite in their drinking water for 14 weeks. Both male and female rats were used. The total arsenic levels in the kidney were significantly higher in rats given arsenite than in the animals exposed to arsenate. Another aspect, concerning toxicologists, is that male rats seem to accumulate higher renal levels of arsenic than females.

TABLE III

ARSENIC IN KIDNEYS OF RATS GIVEN DRINKING WATER CONTAINING ARSENATE (As^{+5}) or ARSENATE (As^{+3}) FOR 14 WEEKS

CONTROL	Arsenate**		Arsenite**	
	3.0	30.0	3.0	30.0
M 1.098± .845	6.571±2.36	14.065± .825	11.319±4.75	91.038±32.40
F 2.865±1.05	4.199±1.95	5.744± .725	9.015±2.30	30.118± 8.60

*** Administered Dose Levels, Mean ± S.E.M. Renal Levels in ppm of total*

One of the proposed general reactions for the interaction of arsenite with sulfhydryl groups of proteins is shown in Figure 2. Any group can be double bond O and P, protein. Notice that the arsenite can form bonds with the sulfhydryl groups and thereby inactivate them. In the case of the pyruvate oxidase system, its mechanism of action is thought to be through interaction with one particular molecule, namely lipoidic acid, which has 2 sulfhydryl groups on one chain, rather than where we have 2 separate proteins, as shown in Figure 2.

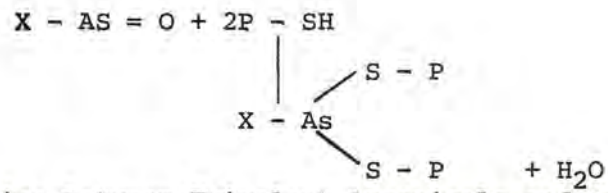

Figure 2 Proposed Reaction Between Trivalent Arsenicals and Proteins

A clear understanding of the mechanisms of arsenate or arsenite toxicity is complicated by their *in vitro* metabolism. Arsenate has been reported to be reduced to arsenite *in vivo* by renal proximal tubule cells of laboratory animals. Methylarsenic acid and dimethylarsine have also been reported in the urines of humans. It seems reasonable that a thorough understanding of arsenical toxicity is predicated on a complete understanding of their metabolism.

A third form or inorganic arsenic is arsine gas. Arsine gas is another form of potentially toxic arsenic, generated when arsenic is reduced by *nascent* hydrogen. This gas is a potent hemolytic agent which can cause massive hemolysis in ambient concentrations of about 5 ppm. The mechanism of hemolysis is unknown, but there is speculation that it is related to an oxidized metabolyte such as arsenious acid. Hemolysis, without rigorous clinical intervention, is usually followed by death from renal failure. The renal toxicity of arsine has been attributed to anoxia or hemoglobin blockage of renal tubules. Studies by Hughes and Levy,[2] however, have also demonstrated arsine inhibition of respiration in both liver and kidney slices *in vivo*.

In conclusion, the toxicity of inorganic arsenic is highly dependent upon its chemical form and oxidation state. The inhibition of cellular respiratory systems is a common feature of all of these arsenicals. A precise understanding of the mechanisms by which these agents produce toxicity is, however, obfuscated in a chronic or subacute context by their metabolic "interconversations."

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1. Goyer, R.A., Brown, M.M., Ryne, B.C., and Fowler, B.A., Dose response of renal mitochondria to oral ingestion of arsenate (Na_2 As · $7H_2O$) in the rat, Amer J Pathol 74:57a, March, 1974

2. Hughes, W., and Levy, G.A., The toxicity of arsine solutions for tissue slices, Biochem J 41:8011, 1974

QUESTIONS, ANSWERS, COMMENTS

MODERATOR-Dr. Michael Utidjian

We have rather more time for questions than has been the case in some of the sessions... since, as I explained, one panelist could not be here this morning. While you are thinking about questions, I would like to ask one. In a review of the biology of arsenic by Schroeder and Balassa, they made a general, somewhat aphoristic statement that they felt pentavalent arsenic was, in general, an essential trace element and rather less toxic in some forms of life, as Dr. Fowler mentioned. It also is speedily excreted by the body and not substantially stored. On the other hand, trivalent arsenic is much more toxic, is presumably not an essential trace element in this form, and, in humans at least, is retained longer in the body. Could you agree with those statements in general?

ANSWER-Dr. Andrew Reeves

I am sure there is no question that the trivalent form is more toxic than the pentavalent form. The problem is that there is ready interconversion in most tissues. It is a common biotransformation, the reduction of the pentavalent form. So, strictly speaking, Dr. Utidjian's reference is correct, but that does not mean that pentavalent arsenic can be administered without harm.

QUESTION-Mr. Neil Krivanek

I would like to ask Dr. Fowler about the rats that drank water containing arsenic at concentrations up to 85 ppm. On your electron photomicrographs there is swelling of the mitochondria and electron dense material in the form of particulate. Was there a reversal of the mitochondrial swelling and clearing of the electron dense particles?

ANSWER-Dr. Bruce Fowler

The mitochondrial swelling, at least with arsenate, is thought to be reversible. Now I suppose it is as good a time as any to point out that one of the major sinks which cells have for handling materials such as degenerative mitochondria or toxic metals is the lysosomal system. We

have found that lysosomes tend to accumulate many of the other metals. Now there are two things inherent in this. We can get the mitochondrial swelling to subside but the electron dense lysosomal bodies, because the lysosomal system has a very slow turnover, will tend to remain for quite a while. This is also one of the problems with analytical chemistry which we are now being made aware of through x-ray microanalysis. One needs to be concerned not only with the total levels that are found in organs, but also the location of these metals within the cells. I suppose most of us think of lysosomal binding of metals as rather an inactivation process, although it does seem to have a rather marked effect on the function of the lysosomes themselves.

QUESTION-Mr. Neil Krivanek

The other question is, did you analyze that electron dense particulate by microprobe technique to verify that it contained arsenic?

ANSWER-Dr. Bruce Fowler

We have not x-rayed this particular group yet, but we have done this for mercury, iron, copper and a number of the other elements. The samples for this group are cut, and as soon as we can get some scope time, we will do this.

QUESTION-Mr. Anthony Camarano

Dr. Fowler, I understand that arsenic trioxide, sodium arsenite, and sodium arsenate have been studied extensively and their water solubilities are well known. I also understand that particle size and solubility do affect toxicity. I wonder if you can comment on the toxicity of insoluble compounds such as copper arsenate, sodium arsenate and their irritability as compared to arsenic trioxide.

ANSWER-Dr. Bruce Fowler

Well, having never worked with any of those particular compounds, I do not want to comment. As you know, there are many arsenicals and we have simply tried to pick the more common environmental forms which are our major concern. Dr. Reeves, have you got any information on that?

ANSWER-Dr. Andrew Reeves

Not any more than what you have said.

COMMENT-Dr. Michael Utidjian

In the famous or notorious sheep dip factory some of the exposures

were to sodium arsenate and that particular compound seemed to be at least as irritating as the arsenic trioxide itself. I think it is a mistake to think of arsenic trioxide as an irritant because it is a very weak acid. I think the irritant is the arsenic atom itself in that particular form, and I think it is equally active as a skin irritant in any of the simple inorganic arsenates or arsenites.

COMMENT-Mr. Anthony Camarano

Dr. Reeves has said, as the literature reveals, that arsine gas has a garlic-like odor. Indeed it does. I have made it and cautiously smelled it, but this is in relatively high concentrations. For the record, I would like it to be shown so everyone will know, that arsine can be present in fatal concentrations without noticeable odor.

COMMENT-Dr. Michael Utidjian

I would also like to make one little point that was not covered by either of the speakers. It is rather a peculiarity that there is one inorganic arsenic compound of commerce or industry, arsenic trichloride, which has dangerous properties. It is a fuming liquid which is extremely corrosive to the skin. In British annals there are reports of some 5 or 6 cases of fatal poisoning by arsenic trichloride where the exposure was almost entirely by skin alone. There was one incident where a man splashed this liquid on the skin of his legs and some of it was trapped on the clothing. It was washed off quite rapidly, according to the contemporary accounts, the clothing was removed; however, he died within twelve hours in the hospital. The skin was severely burned even by that time and moreover, high concentrations of arsenic were found in the liver, kidneys, and certain other organs. There is always the question, as it is a very volatile liquid, that there could have been some absorption via the inhalation route, but I think there is no doubt about it arsenic trichloride liquid has to be handled with extreme caution as a form of arsenic that can be readily absorbed through the skin.

QUESTION-To Dr. Fowler

Dr. Fowler, in your experiment in which you showed a possible change from arsenate to arsenite and build up of arsenite in rats, why did you pick rats instead of higher animals? Rats are known to accumulate arsenic in their systems, as Dr. Peeples has shown. As a matter of fact, could you comment on why there should be a difference between higher animals and rats, since Dr. Peeples' experiments with cows showed that there is no conversion of arsenate to arsenite in cows?

ANSWER-Dr. Bruce Fowler

There are two points I would like to make in answer to your questions. First, we did not do the studies on the conversion of arsenate to arsenite.

These have been reported by Ginsburg* in dogs and Lanz, *et al*#, in rats. Now the other thing, and I alluded to it yesterday, is that we are concerned in our laboratory not just with a single element such as arsenate, cadmium, mercury, or lead, but with all of them. The reality of the human situation is that we are being exposed to varying concentrations of a number of elements such as mercury and cadmium, and we are building what amounts to an animal model where each of these elements has been individually evaluated for its relative toxicity to a specific organ, the kidney. We think ultimately, there will have to be studies to look at co-stressors. It is somewhat artificial to say that the toxicity of arsenic occurs at some level in the kidney. One must take it in the context of the other toxicants that are present when the arsenic is measured. Our reason for using the rat is that we have been working with this particular model system for other elements. Arsenic is one component of that model system.

QUESTION-To Dr. Bruce Fowler

Both of you gentlemen seem to have considered arsenate as an SH. Apparently it is oxidized by the SH groups. Is there any possibility that it can be acting as a competitive inhibitor with phosphate in the mitochondrial cycle? Second, if it does act on SH groups, has anybody looked for inhibition of fatty acids synthesis, histologically or pathologically? Is there any evidence of this since it is very dependent on the SH group?

ANSWER-Dr. Bruce Fowler

The mechanism of action of arsenate, when in the +5 valence state, is thought to be through competitive inhibition with phosphate groups. During formation of various phosphate esters, such as glucose-1-phosphate, arsenate substitutes for phosphate and this product is unstable and breaks down. So in a sense, it is acting as a competitive inhibitor.

QUESTION-Dr. Bertram W. Carnow

In addition to utilizing different animal species, has any consideration been given to using animal models which might simulate the human experience (for example, the large numbers of people with idiopathic hypertension)? Have any hypertensive animal models been used to study lead effects, since the kidney seems to be a target organ? Specifically, how might such a kidney handle arsenic or what pathology might be induced in adequate kidneys as compared to normal organs in normotensive individuals?

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**Ginsburg, J. M., Renal mechanisms for excretion and transformation of arsenic in the dog, An J Physiol, 208:832-840, 1965*
#Lanz, H. Jr., Wallace, P. C., and Hamilton, J. G., The metabolism of arsenic in laboratory animals with As^{74} as a tracer, Univ of Calif Publ, Pharmacol, 2:263-282, 1950

ANSWER-Dr. Bruce Fowler

I am sure there are people working on that. I do not think I want to speculate too much really. You are aware that hypertension in rats with cadmium is subject to controversy, but, I do not know of anyone that has tried to do this with arsenic.

COMMENT-Dr. Bertram W. Carnow

I am talking about a Goldblatt kidney, for example, to examine the impact arsenic may have on an animal with an impaired kidney.

ANSWER-Dr. Bruce Fowler

It is a good idea.

QUESTION-To Dr. Michael Utidjian

I would like to ask a question relative to the occupational arsenic exposures of the kidney and the possible effects on the kidney. Does anyone have any experience or have you reviewed present data in our modern use of arsenic relative to damage on the kidney, liver, or other body organs in occupational exposures? I am prefacing this by saying we have a fair amount of data and a large number of people showing that there is no dysfunction, so far as the kidney is concerned, and there is no dysfunction as far as the liver is concerned. There certainly is a target organ that must be considered as subject to injury through exposure to occupational concentrations of arsenic. That is the skin and mucous membranes. Also, we have data covering many years of therapeutical arsenic useage and these data indicate that there is no liver or kidney dysfunction associated with such usage in the presence of the disease for which it was prescribed. I would like to have comments from anyone else who has had experience with exposures from agricultural and other sources. I think you reviewed the literature, Dr. Utidjian; if you could comment on this further, it would be of help.

ANSWER-Dr. Utidjian

Yes, I think I can in one area. I cannot offer any comment on kidney involvement in human occupational exposures. There is some controversial work from Germany on the wine dressers of the Mosel Valley, the hop district, etc. where, for so many years lead arsenate and other arsenical fungicide sprays have been used. The work of Butzengeiger* and later, Roth,# did claim a high incidence of cirrhosis of the liver and

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Butzengeiger, K.H., On peripheral circulatory disorders during arsenic intoxication, Klin Wochenschr, 19:523-27, 1940
#Roth, F., Virchows Arch (Pathol Anat) 331-119-37, 1958

of even sarcomas of the liver and hepatoma. Now this work has been challenged several times, and I think quite cogently in this country, since it is confused with the high rate of alcoholism in the same workers. I might share a little typographical joke with you here. In one of our early drafts of the criteria document it was pointed out to modify the statement concerning this high incidence of cirrhosis and certain cases of hepatoma that were reported in our draft. We had intended to say that the consumption of raw wine by the workers was considered one of the perquisites of the occupation. Our typist was unfamiliar with this term and transcribed it as prerequisite. So I got a cheap laugh at NIOSH. But that is the only occupational story I can offer you and that has been challenged.

COMMENT-Dr. Irving Selikoff

There is some additional information. Dr. Hans Popper of Mt. Sinai School of Medicine has received the slides of a liver tumor in a vineyard sprayer in Germany, diagnosed twenty years ago as angiosarcoma. There was the typical liver picture now being seen in vinyl workers. There is now known and reported in the literature, angiosarcoma of the liver that followed long term intake of Fowler's solution.

QUESTION-Dr. Sidney Lerner

Along the lines of what we are discussing now, do we know if arsenic accumulated in the liver and is the amount of arsenic accumulation or the toxicity of arsenic any different by sex?

ANSWER-Dr. Bruce Fowler

I suppose the answer is yes. I showed you that the kidney levels were higher in the males than in the females. Roughly the inverse of this is seen in the liver. In other words, females seem to be storing more of the arsenic in the liver than males. I can only speculate on the toxicity and cannot give you a firm answer. The animals in this particular study were not given sufficient levels of either form to make them sick in the profound sense. We observed some decreased weight gain; the females did seem to be more sensitive than the males with respect to that parameter, but in terms of distinguishing intracellular toxicity, I would be hard pressed to say that firmly.

QUESTION-Dr. Douglas Frost

I would like to make two or three comments to try to place the matter of the consideration of arsenicals in better perspective. Dr. Reeves showed slides from "Arsenic and Old Lace", but he did not explain the toxicity involved. As the author of that play clearly states, it was due

to strychnine and cyanide. They just used arsenic in the title. It was a part of the arsenic mystique.

Arsenic was used by the professional poisoners years ago. It was the best known toxin, by far, but it is a rather brutal type of poison and it was not the poison useful in painlessly killing elderly gentlemen quickly. It could not possibly do that. I think it is important to keep in mind that we tend to blame arsenic for all sorts of things.

Dr. Fowler, isn't it likely that the use of so much arsenate over-stimulates phosphorylations? A great many experiments were done with the organic arsenicals, and they seemed to over-stimulate phosphorylation. As you know, arsenic is always present in cells and acts as a catalyst for all phosphorylation. You used high levels of arsenic; very high levels. Isn't it possible that you encountered toxicity due to over-stimulation of phosphorylation?

ANSWER-Dr. Bruce Fowler

This is a point that is worth noting. Low concentrations of arsenate in the presence of phosphate are capable of stimulating the system somewhat. In higher concentrations, though, it is quite inhibitory. However, your point is valid in the sense that at extremely low concentrations it does seem to stimulate the respiration.

ANSWER-Dr. Andrew Reeves

One should add that, to the best of our knowledge, arsenic is not an essential trace element for any species and there is no demonstrated need even for the lowest level. However, I am reminded of a rumor I heard as an undergraduate to the effect that trace arsenic ingestion caused fattening of cattle and perhaps also of man.

QUESTION-Dr. Hector Blejer

I have more of a comment than a question which I do not know if anyone here can answer. It runs through my mind that in some Eastern European countries, arsenic is added to wines and/or the arsenic content of the wine may be high due to the soil content. Would anyone know whether this is a fact? Or, could it be checked out?

ANSWER-Dr. Michael Utidjian

I would imagine that the arsenical fungicides have been used for so long that they may well have built up a soil burden and I am sure that soluble arsenates would be taken up by plants. I had not heard of the actual deliberate doctoring of wine with arsenic.

QUESTION-Mr. Warren Ferguson

In the debates about mercury four and five years ago, there was a lot of discussion about competitive detoxicification among arsenic, mercury, and selenium. I wonder if the panel or any member of the audience might be able to comment on that.

ANSWER-Dr. Andrew Reeves

I think that the relation of selenium to arsenic is a very interesting question. A big paper was written on that by Dr. Frost in the Federation Proceedings six or seven years ago[3] in which he blamed essentially all the traditional toxicity attributed to arsenic to selenium. I think that was perhaps going beyond what he was intending to prove. There is no question that arsenic in sufficient doses is toxic. He mentions one of the notorious and historic cases of presumed arsenic poisoning which occurred in 1900, the turn of the century in Britain, cases of beer poisoning which were traditionally attributed to arsenic which somehow got into the beers made in Britain, and he shows by very interesting reasoning that this particular case might have been due more to selenium poisoning than to arsenic poisoning and from there he proceeds to suggest that most cases of presumed arsenic poisoning were due to selenium which I personally cannot quite agree with. But there is no question that there is a biochemical competitiveness, so to speak, or complementariness perhaps, between arsenic and selenium. It is being claimed that arsenic toxicity might better manifest itself in the presence of a selenium overdose and *vice versa*. These are questions, I believe, which ought to be explored in future investigations.

COMMENT-Dr. Michael Utidjian

So what you are saying, Dr. Reeves, is that there might be synergism between arsenic and selenium rather than antagonism. In the case of mercury, it has been considered an antagonist. My comment was that unlike the case with mercury, where it has been suggested that selenium may, in fact, antagonize alkyl mercury toxicity in food fish for example, that with arsenic, Dr. Reeves has suggested a synergism or additional effect.

COMMENT-Dr. Andrew Reeves

I am not sure that I should suggest that. I do not think that we know enough about it. I think that a synergism, as well as some kind of antagonism, is possible and which applies should be determined in future experimentation. There seems to be some kind of a biochemical interrelationship between these two elements; I do not think the nature of it is known.

COMMENT-Dr. Douglas Frost

May I comment? There is, of course, a very clear cut interrelationship

between arsenic and selenium. Arsenic is, on a weight basis, by far the best antagonist to selenium toxicity. Alvin Moton* showed that when he was at South Dakota State University years ago, and it has been shown by many others. It is just like turning a faucet. When arsenic is given, you turn off the exhalation of selenium as methylselenide. It is excreted through the urine or feces. It goes out through the bile. The precise mechanism should be shown by double labelling of arsenic and selenium. It can be done, I am sure. We did that sort of experiment at Abbott Laboratories with labelled arsenic; also, labelling the carbon ring of arsanilic acid. We could show thereby, that arsanilic acid had metabolic integrity. It was not broken down in the body at all.

One very interesting experiment that I think is worth mentioning here was done by Stokinger and David Groth# with others in Cincinnati. They fed high levels of mercury chloride along with high levels of sodium selenite and the two counteracted one another. Either of those compounds alone might have killed the animals, but when fed together, the rats got along perfectly well. They found black particles in the rat's livers and in other tissues. Those particles had not only high levels of mercury and selenium, but they also had some arsenic. I have tried to obtain relevant data from them about the part the arsenic may have played in detoxification of the mercury; however, this is still an open question.

COMMENT-To Dr. Andrew Reeves

These are all interesting possibilities. A similar situation that comes to my mind is antagonism between molybdenum and copper in farm animals. High dietary molybdenum levels (>5 ppm) lead to copper deficiency; low dietary molybdenum levels (<0.1 ppm) lead to rapid copper accumulation and potentially lethal copper poisoning, especially in sheep. On the other hand, added copper in the diet could prevent molybdenum poisoning in poultry.[7]** Now whether an analogous situation exists between selenium and arsenic should be better investigated. I do not think that an antagonism of this kind has ever been shown to the satisfaction of everybody.

QUESTION-Dr. John R. Goldsmith

Dr. Reeves, since we have been talking about lead you made the point earlier that when lead is taken by mouth in humans, a very small proportion, from 5 to 10 percent, usually said 8 percent, is absorbed metabolically from the gastrointestinal tract. I wonder if you could tell us what the range of figures is for arsenic. My understanding is that it is substantially higher and, if that is so, then the relationship between particle size, toxicity, and the possibility of inadvertent oral contamination of food becomes more important for arsenic. Do you happen to know what the figure is for the proportion metabolically taken up?

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**Moton, A. L. Science, 88:81, 1938*
#Unpublished data
**See Reference 7 on Page 246

ANSWER-Dr. Andrew Reeves

I do not have the figures at hand. I did not run across them while I was reviewing the material for this particular discussion. Since the levels we are dealing with here are low, I would probably assume that the retention of the organism is high. Because the two go hand in hand and under extreme loads the retention of the organism generally goes down for anything which is administered in traces, the degree of retention is higher. I cannot give you any figures.

MODERATOR-Dr. Michael Utidjian

Ladies and gentlemen, I have just been informed that coffee is served, so I think we will declare this session closed.

CONFERENCE CHAIRMAN-Dr. Bertram Carnow

Since we are a bit late starting after the break, I will introduce Dr. William Lloyd, Director of the Office of Occupational Health Surveillance and Biometrics of the National Institute for Occupational Safety and Health, who will be Moderator of the Panel on Carcinogenicity of Arsenic. Dr. Lloyd.

SESSION VIII - CARCINOGENICITY OF ARSENIC

Dr. William Lloyd, Moderator
National Institute of Safety and Health

In looking at arsenic as a carcinogen, we have a most interesting situation. Many of our arguments in the past concerning carcinogens have centered around the potential for human cancer, where we have only evidence from the lower animals of tumor induction. As previously pointed out, arsenic has long been suspected as a carcinogen; and, while there may be some disagreement concerning the levels which might induce the malignant neoplasms, the evidence that workers exposed to arsenic are at very high risk of developing cancer is considerable.

In contrast, we have been quite unsuccessful in demonstrating carcinogenic effects in the lower animals and this is primarily what our two speakers are going to consider.

We have two very distinguished speakers, one of whom, I learned this morning is associated with the theater arts. I was quite surprised to see Dr. Reeves put that slide up from "Arsenic and Old Lace," and even more surprised to find a member of the audience had, apparently, made a detailed study of the script. I, myself, had the distinction of playing one of the twelve dead men in a little theater production of "Arsenic and Old Lace" and I always thought it was the arsenic that got me. So we learn something new everyday.

Trying to anticipate Dr. Reeves, I thought about the titles of various plays and what he might come up with next, and I don't think I did very well. After considering a great many I finally decided that maybe the most appropriate title would be "Anything Goes." So here is Dr. Andrew Reeves, Professor of Occupational and Environmental Health at Wayne State University.

THE TOXICOLOGY OF ARSENIC: CARCINOGENIC EFFECTS

Dr. Andrew L. Reeves
Wayne State University

A B S T R A C T

Suspicion that exposure to arsenic may increase the incidence of cancer date from 1820, then referred to as carcinoma of the scrotum in copper smelters. Much of the efforts since then have produced questionable results in experimental studies using animals. Epidemiologic evidence has continued to implicate arsenic in human carcinogenesis. New evidence revealed clear dose-response relationship of the cancers to arsenic, making it unlikely that exposure to another agent may be the etiologic factor. Failure to reproduce arsenic cancers experimentally is puzzling. Perhaps species' specific differences play a role; the real carcinogen involved in these cases is not arsenic *per se* but a closely adhering contaminant. Definitive studies are needed to clarify this question.

The history of cancer observations are given in Table I. It all began in the 1820's and was attributed to a man named Dr. Paris who had observed cancer of the throat in copper smelters. Interestingly, in 1879, another group of investigators had noted cancer of the lung among uranium miners in Joachimsthal. This was some 16 or 20 years before the discovery of radioactivity and its biological effects were known. This was put into proper perspective, and it is believed that this was one of the findings which served to discredit arsenic as a carcinogen in the minds of most people.

Some of the other evidence which incriminated arsenic as a carcinogen was also flimsy. Cases of veterinary observations with deer and sheep in the 1930's also are listed in Table I.[1-2] Human evidence was not accumulated until after World War II. Both in England, where the main exposed population was sheep dip workers, and in Germany, where the main exposed population was vineyard workers, cases of arsenic carcinogenesis were suspected, and in some cases "proven". (It is uncertain to what degree we can use this word.) Lee and Fraumeni[3] conducted a classic study (to which references often are made these days) showing the excess of lung cancers in arsenic smelter workers. This is believed to be the first study which showed a clear-cut dose and effect relation between arsenic exposure and incidence of this cancer.

Another study of equal importance was published just a few months ago by a group from the Dow Chemical Company.[4] This study showed excess lung cancer, also dose related, among calcium and lead arsenate workers.

In this case, dose "relatedness" seems to be the real feature used to incriminate arsenic as the etiologic agent.

TABLE I

ARSENIC CANCERS

1820 Paris	Cancer of the larynx in copper smelters
1879 Harting & Hesse	Cancer of the lung in Joachimsthal
1937 Prell	Skin cancer in deer living downwind from As smelter
1939 Nieberle	Adenocarcinoma of the nasal sinuses in sheep
1948 Hill & Faning	Excess skin & lung cancer among sheep dip workers
1957 Roth	Lung, skin, liver, esophagus & bile duct cancers among Moselle
1969 Lee & Fraumeni	Excess lung cancers, dose-related, in As smelters
1974 Ott, Holder & Gordon	Excess lung cancers among Ca & Pb arsenate workers

Adapted from Prell, H., Arch Gewerbepathol Gewerbehyg and Nieberle, H., Z Krebsforsch

Obviously, as already pointed out, the proof of the pudding is the production of arsenic cancer under experimental conditions, which Table II summarizes. There have really been a frustrating set of data, as we all know. It all goes back to the 1920's again and you can see what kind of experiment was done in those days. In an experiment where about 2/3 of the animals die of arsenic poisoning of a nonneoplastic nature, few conclusions can be made as to what happens to the survivors. Indeed only one of a hundred survivors had two papillomas.[5] Indeed, that is weak carcinogenic evidence. The same experiment repeated a second time produced no malignant results.

In another study in 1942,[6] arsenic metal was implanted in the femur bone. We all know the significance of this and we know what trauma does to carcinogenesis. In this particular case no adequate controls were used. So, this also cannot be accepted as evidence. In Heuper's studies from 1942 on,[7] and in essence, according to the admission of the

author, there has been no positive demonstration that arsenic was carcinogenic under experimental conditions.

TABLE II

EXPERIMENTAL ARSENIC CANCERS

Leitsch 1922:	As_2O_3 in EtOH--paint on mouse skin
	67% died of As poisoning
	one of 100 survivors bore 2 papillomas
Leitsch 1923:	Repeat - negative results
Schinz 1942:	As metal implanted in femur bone of 4 rabbits
	1 developed sarcoma, no controls
Heuper 1942:	10 congenitally hairless rats fed $As(OH)_3$
	1 papilloma, no controls
Heuper 1954:	negative results on painting, feeding, injection

Table III shows some of the later data of Heuper and Payne.[8] This is a good example of the kind of "positive" evidence that one has to work with in order to claim that arsenic is carcinogenic in experimental animals. One can see that the controls had an incidence not significantly different from what the arsenic-dosed animals had.

TABLE III

DEATH DISTRIBUTION AND TUMOR YIELD IN RATS AND MICE
GIVEN ARSENIOUS OXIDE AND ETHYL ALCOHOL IN THEIR DRINKING WATER

TREATMENT	SPECIES	Months							Sites and Number of Cancers				
		0-6	7-0	10-12	13-15	16-18	19-21	22-24	PLEURA	LIVER	LYMPH NODE	UTERUS	SKIN
Arsenic + Alcohol Set I	Rats	1	3	3	5	10	12	16	3	2	4	2	2
	Mice	25	25	-	-	-	-	-	-	-	-	-	-
Arsenic ± Water Set II	Rats	4	2	2	2	5	2	32	2	1	2	-	-
	Mice	8	2	12	16	6	3	3	-	-	-	-	-
Alcohol Set III	Rats	6	1	4	4	7	13	15	3	2	1	-	-
	Mice	13	33	4	-	-	-	-	-	-	-		-
Water Set IV	Rats	0	0	2	1	9	10	28	1	5	2	-	1
	Mice	7	10	11	11	9	2	-	-	-	-	-	-

**Adapted from Hueper, W. C. and Payne, W. W., Arch Environ Hlth*

The new data, shown in Figure 1, are taken from the recent paper by Ott, Holder, and Gordon.[4] This, of course, is impressive because you would expect this kind of exposure if arsenic was the etiologic agent. However, it should be emphasized that this evidence is from an epidemiologic study; and no epidemiologic study could possibly identify with certainty an etiologic agent, because in a practical situation people are always exposed to a mixture of things. Also, it is always possible that there is a closely adhering contaminant, such as selenium or something else.

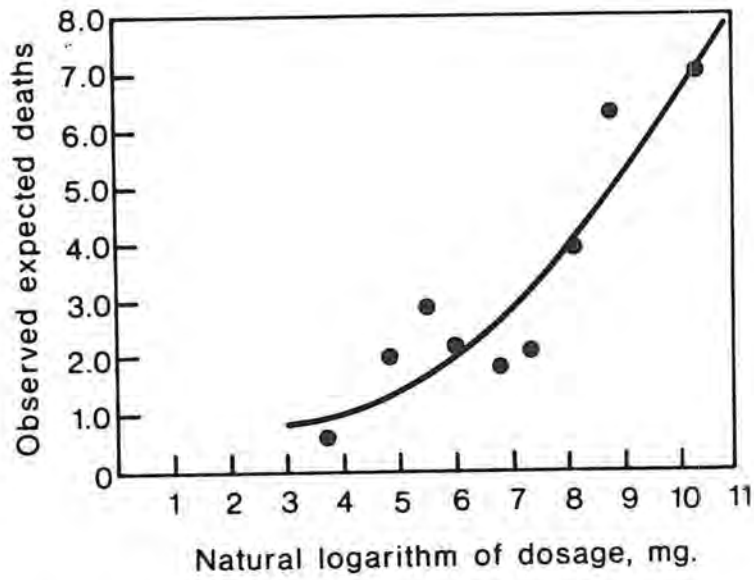

Figure 1 Ratio of observed to expected respiratory cancer deaths by dosage

Adapted from Ott, Holder, & Gordon, 1974

Epidemiologic evidence alone can only show a higher incidence of a certain disease in a certain population, but to attribute it to any one thing is extremely difficult. This is why experimental carcinogenesis work is so important in pinning down the etiologic agent. This, however, has not been done with arsenic. Some people believe that it is a "species specific thing" and that maybe the lower animals metabolize arsenic differently from humans. It is uncertain that this is accurate if it can be so, because there is no other evidence regarding this.

β-naphthylamine is regarded as unsuccessful as an experimental bladder carcinogen in all lower animals, but there are primates which

can perhaps be used and maybe such an experiment should be done. More arsenic carcinogenesis work needs to be done, which means research, more federal funding, and more report writing. Some ingenious novelists of the last decade or so had already anticipated this.*

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**The speaker concluded his presentation by projecting the title page of E. G. Loves' novel, "Arsenic and Red Tape."*

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MODERATOR-Dr. William Lloyd

Thank you Dr. Reeves.

Our next speaker is Dr. Herman Kraybill, Scientific Coordinator for Environmental Cancer in the Division of Cancer Cause and Prevention at the National Cancer Institute. Dr. Kraybill is at a disadvantage I spoke with him before we started here to see what kind of theatrical background he had and he said that, unfortunately the only performance he had ever given was in a barbershop quartet in which both of us sang.

CARCINOGENICITY OF ARSENIC
EXPERIMENTAL STUDIES

Dr. Herman Kraybill
National Cancer Institute

A B S T R A C T

Experimental work on arsenic and arsenic compounds covers a wide range of doses, with concentrations as low as .0004 ppm of the compound in solution to as high a level as 646 ppm in diet given to rodents. Skin absorption studies (skin painting) with mice also reflect a dose range from a low level of 0.4 percent to a high level of 1.8 percent. All of the studies were essentially negative insofar as neoplastic lesions were concerned. There were a few studies in mice which indicated some tumors, adenocarcinomas of the skin, lung, and lymph nodes, but these studies are difficult to interpret on the basis of inadequacy in the design.

Introduction

Arsenic and compounds of arsenic are widely distributed in the environment. To the general population, exposures have been reported from such sources as drugs, certain foods (especially shellfish) and from certain water supplies.[1,2] Shellfish have been shown to contain high amounts of arsenic when harvested from waters containing 0.14 to 1.0 ppm of this chemical.[3] Fish are known to concentrate arsenic, with black bass having levels as high as 40 ppm in southern United States waters.[4] The daily intake from water is about 20 µg.[2] The diet may lead to ingestion of 900 µg of arsenic per day,[2] with most of the pentavalent arsenate being excreted; however, trivalent arsenite may accumulate.

Recent concerns about arsenic exposure and its association with human cancer have been focused on the occupational cancers. It should be emphasized that the term "arsenic" has been used indiscriminately; the type of compound and valence state should also be specified. For example pentavalent arsenate is most common in the environment, but trivalent arsenic or arsenite is the most toxic. There have been no reports on causation of cancer from dietary exposure to arsenic in man, but studies in Argentina and Taiwan, where there is the multiple potential of cancers from ingestion of arsenic in potable water, revealed cancers of the skin, lung, liver, and other organs in man.[5,6] A cocarcinogenic effect was also suggested. The arsenic level in some waters was as high as 0.6 ppm. For areas where arsenicals were in high concentration, the skin cancer rate was 21.4/1000 of the population, while in areas of lower concentrations, the rate was 2.6/1000.

In drugs, such as sodium arsenate or Fowler's solution, arsenical compounds were once used widely. Bowen's disease, a precancerous lesion of the skin, was associated with a history of ingestion of or contact with arsenical compounds. Fowler's solution, lead arsenate, arsenious acid, and other injectables, and oral compounds of arsenic were associated with systemic or internal cancers.[7,8] Many of the pharmaceuticals containing arsenic are no longer in common use except for veterinary medicine applications for treatment of coccidiosis and heartworms in dogs. In man, it is used in amebiasis and sleeping sickness.[3] Arsenicals are used as a growth promoter in feeds for farm animals, where the arsenic compound is carried through leaving a residue in the meat of approximately 0.5 ppm; the significance of such an exposure is not known. It is of interest that despite the earlier use of neoarsphenamine in treatment of venereal disease, there has been no reference to suggest the carcinogenic potential of this drug.

Detailed reference will not be made to epidemiologic studies on workers exposed to arsenic and arsenic compounds. However, in the occupational exposures, one would indicate the respiratory cancer deaths in copper smelter workers suggesting a higher than expected lung cancer risk for these workers.[9] In a study of orchardists, Nelson and coworkers[10] did not show an increased cancer risk from arsenic sprays; however, later studies in the State of Washington suggest that this population may be at high risk of lung cancer. Lee and Fraumeni have reported on other occupational cancers, such as those seen in sheep dip operators in England and the vineyard workers in Germany.[11] The more recent reports of respiratory cancers and lymphosarcomas in workers at the Allied Chemical Company and the Dow Chemical Company reopened the issue of workplace exposure to arsenic and the cancer risk.[12] Because of these recent concerns, NIOSH recommended a new occupational exposure standard, reducing it from 0.5 to 0.05 mg/cu m of air for arsenic and its compounds, except arsine and lead arsenate.[13]

Experimental Observations

As early as 1820, arsenic was implicated as a carcinogenic agent when a Cornish physician alleged that poisoning in cattle from arsenic exposure induced cancer in the rump. He followed up this observation by recording that cancer of the scrotum seemed to be associated with copper smelting operations.[4] Thereafter followed a series of observations on occupational cancers from arsenic exposure.[7,5,14] There have been approximately 20 experimental studies on carcinogenicity of arsenic and arsenic compounds reported in the literature, which have been reviewed in a monograph published by the International Agency for Research on Cancer.[15]

It is of ancillary interest that arsenic and some arsenic compounds have been shown to produce cytological reactions, more specifically, chromosome aberrations in human lymphocytes in cases of chronic arsenic poisoning.[16] Inorganic arsenic apparently has an effect on DNA synthesis

of human lymphocytes *in vitro*.[17] One investigation indicated that arsenic might be carcinogenic and carcinostatic.[18] In this study, mice were placed on drinking water containing 0.01 percent of arsenic oxide and then skin tumors were induced by administration of methylcholanthrene. A low susceptible strain of mouse developed more cancers with this treatment, but the susceptible strain of C3H mice had less skin cancers than the control or untreated animals.

Association of arsenic exposure to the development of liver, lung, and skin cancer[19] might be related to the rapid absorption of soluble inorganic arsenicals from mucous membrane with some deposition in kidney, liver, intestinal wall, skin, spleen, brain muscle, and lung tissue. Induction of neoplastic lesions in the lung tissue might be associated with the inhaled arsenic particles in occupational stress along with other promoters. Additionally, arsenicals inhibit the intracellular SH enzymes needed for cellular oxidation which could mediate cellular proliferation due to abberant metabolic pathways.

In the various experimental studies described from 1940 to 1972 in the IARC review,[15] several species, sexes, and strains of animals were used. The mouse strains used were C57 Black, Swiss Rockland all purpose, and Balb. The rat strains used were Osborne-Mendel and Long Evans. If one consolidates the total number of rodents in the test groups, using various arsenic compounds, there were about 500 mice and 200 rats. In other studies there were 48 dogs and 6 rabbits.

The molecular form of arsenic and types of compounds used were arsenic in lanolin suspension, sodium arsenite and arsenate, arsenic trioxide, and tetra arsenic hexaoxide in potassium carbonate solution (Fowler's solution), lead arsenate and calcium arsenate. In the skin painting experiments with mice, the promoters used were croton oil, urethane and dimethylbenzanthracene.

In evaluating the carcinogenic response to a chemical, the dose given is of great importance. Equally significant is the route of administration, the adequacy of number of animals in test and control groups to permit statistical evaluation of experimental data, and the time frame of the study which provides an indication as to time to tumor formation and in turn, assessment of the carcinogenic potency of the insult to the animals. In summary, the aforementioned studies cover a wide range of doses with concentrations as low as .0004 ppm of the compound in solution to a level as high as 646 ppm of the arsenic compound in the diet given to mice. Comparable oral doses were given to rats. In most of the oral administration of the compound, the chemical was either given in the drinking water or in the diet. For skin absorption studies (skin painting) with mice, the concentration of solutions applied ranged from a low level of 0.4 percent to a high of 1.8 percent.

Beyond the challenge of the oral route or by skin absorption, some mice were given the arsenic compounds intramuscularly, subcutaneously, and intraveneously. Some rats and rabbits were given arsenic in a lanolin suspension by intramedullary injection into the femur. The duration of the studies ranged from 2 to 24 months.

While the great number of animal experiments failed to demonstrate carcinogenicity, those that may have are equivocal in that there were weaknesses in the design of the experiments and the data were so limited that interpretation is almost impossible. A couple of studies seemed to suggest some adenocarcinomas of the lung, lymph nodes, and skin, squamous cell carcinoma, skin papillomas and a few leukemias, but the design of these studies, unfortunately, was so deficient that a significant interpretation is not possible. While the general contention is that studies with animals to date are negative, there is one report where an arsenical did produce tumors. In a review paper by Kraybill and Shimkin[20] and the original work by Halver,[21] some hepatomas were induced in trout from feeding carbasone at a level of 480 mg/100 g of diet. The hepatoma incidence in trout from insult by this arsenical was highly significant in that an exposed group had 5 hepatomas in 50 exposed animals, contrasted with a zero incidence in the controls.

An interesting feature of the skin painting experiment with mice, using various arsenic compounds, was the failure of this chemical to act as a promoter in the presence of croton oil, DMBA and urethane. Some papillomas appeared, but they regressed. Where arsenic trioxide in drinking water was given to mice, methylcholanthrene applied to the skin also failed to evoke carcinogenesis.

In one experiment, where sodium arsenite was given to rats (Long Evans strain) in drinking water, some precancerous lesions of the liver were noted, but no angiosarcomas, as had been reported in the literature for humans exposed to arsenic compounds.

Evaluation and Further Studies

The epidemiological studies now establish rather convincingly that arsenic exposure in man yields an excess risk of cancer of the lung and lymphatic tissue. Arsenic remains as the one environmental and occupational carcinogen for man that does not have a counterpart in an animal model. The positive response in the trout and suggestive indicators in some deficient studies emphasize the need for further exploratory work to finally achieve this confirmation in an animal system.

The first argument that is advanced is that no satisfactory animal model has been found. In the literature, there are suggestions that the rat does not metabolize arsenic like man, and arsenic concentrates in the red blood cells of the rat to a greater extent than in those of man or other species. Since the main route of exposure for cancer induction in man is probably inhalation and absorption, further studies by inhalation might be considered in various species, including the rat, mouse, hamster, and guinea pig. The molecular form of the arsenic may play a role in carcinogenesis. Therefore, some deliberation on the types of arsenic compounds should be made in future studies.[22]

Dietary factors influence the impact of an arsenic stress and could be associated with the degree of toxicity and proclivity for neoplasia induction. As mentioned earlier, arsenic interacts with SH compounds and sulfhydryl enzymes and has an impact on iodine requirement. Arsenic also plays a role in hemoglobin production and the formation of selenium compounds, the latter element involved in the function of the hemapoietic system.

For mechanistic studies, one might then consider the following in future research.

1. Long term inhalation studies using intratracheal implants also, in various species, ascertaining effect of particle size and the role of synergists such as other metals (Hg, Pb, Te, Tl), and the gas SO_2, which all may be impurities in the smelting of ore.

2. Assessment of the role of selenium, even to the point of overloading with selenium to enhance the toxic and potential carcinogenic response. Arsenic directs selenium from lung to biliary secretion.

3. Since iodine or iodinated compounds may antagonize the effect of arsenic on the thyroid, a deficiency of an iodine such as potassium iodide might enhance arsenical cancers.

4. Methylation of arsenic might supress the carcinogenic activity. Therefore, modifying conditions should be explored, such as use of choline and methionine deficient diets. The role of various thiols might be studied. Arsenate differs from arsenite in that it does not affect many enzyme systems. Arsenate can act as a phosphate substitute *in vitro*. Arsenic can substitute for nitrogen in choline and lecithin.[23]

Most of the animal studies have been essentially negative with reference to carcinogenicity of arsenic and arsenic compounds. There is a minor exception in that carbarsone produced liver cancer in trout. The studies reported were deficient in several respects due to inadequacies in design (too few animals or too short a duration of exposure or too low a level of exposure). Earlier studies on man showed a clear causal relationship between skin cancer and heavy exposure to inorganic arsenic in drugs, in drinking water, or by exposure in the workplace. The risk of lung cancer of smelter workers and other groups, such as sheep dip and vineyard workers has been established. The recent reports from two industries, where arsenic pesticides were manufactured, showing increased deaths from lung and lymphatic cancer, provide unequivocal evidence as to the occupational risks from arsenic exposure.

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QUESTIONS, ANSWERS, COMMENTS

MODERATOR-Dr. William Lloyd

I would like to thank both of our speakers for covering a lot of territory in a very short time and raising some very interesting questions. Regarding the question of why we should do animal studies if we already know arsenic to be a human carcinogen, I think we all recognize the need to study the biological mechanisms. So it is obvious why we want to do the animal studies. Are there questions from the floor?

QUESTION-Dr. Michael Utidjian

I wonder if anybody has tried repeating experimentally the animal observations on deer and sheep, because those seem to be the two studies on historical record where cancers were observed in large animals with more sophisticated metabolisms.

ANSWER-Dr. Andrew Reeves

No, nobody has tried. That is a good idea, but if I were to suggest an animal model now, I would probably go to a primate.

QUESTION-Mr. William Wagner

In the smelting industry we have always assumed that the arsenic was in the trivalent form because of the ease with which it fumes off in the processes. I have seen some data just recently that suggests that maybe 90 percent of airborne arsenic is in a pentavalent form. What do you think might be the difference in the carcinogenicity of the two forms of arsenic?

ANSWER-Dr. Andrew Reeves

That is an interesting question, and I am not sure that anyone knows the answer. Since the toxicity of the trivalent form is so much greater than that of the pentavalent form, I think that most of us would instinctively incriminate the trivalent form in carcinogenesis also, but there is no evidence to prove that this is the case. But since the two forms are interconvertible *in vivo* which has been shown in several species, I do not think that this question has more than academic significance anyhow.

COMMENT-Dr. Irving Selikoff

I suggest that as Dr. Reeves goes to the primate model on the basis of Dr. Hine's observations, he might first teach his primates to smoke cigarettes.

QUESTION-Ms. Jane Shaw

Do I understand correctly that all previous epidemiological or mortality studies were inconclusive as to the carcinogenicity of arsenic before the Dow study? If not, could you clarify this?

ANSWER-Dr. William Lloyd

I think I will answer rather than ask one of our speakers. I would say that is not true. Many epidemiological studies did have points of dispute. Are there comments from the floor of anybody who disagrees that it is the concensus among people in the field of epidemiology that arsenic is carcinogenic for man? Some of the evidence was in dispute because there were other confounding factors. Maybe someone in the audience has some different interpretations. There will be more discussions on this when we get to the epidemiology after lunch.

QUESTION-Dr. Douglas Frost

I would like to ask why it is that animal experiments showing the value of arsenicals against cancer never seem to be mentioned. I reviewed the literature in connection with our efforts at Abbott Laboratories some years ago to re-establish arsanilic acid, which had been on the market at that time for eight years as a non-carcinogenic feed additive.

We fed arsanilic acid at graded levels and at the highest levels we found we had the fewest tumors and the longest life span in the tested animals. Subsequently, others reported that even arsenites, potassium or sodium arsenite, inhibited cocarcinogenesis in mice. Boutwell's work at Wisconsin was not significant, but it showed some effect along that line. Milner's work was significant. Kanisawa and Schroeder conducted life term feeding with arsenite and reported decreased lung tumors. The results of a study at Rockefeller University showed that an arsenical caused regression of cancers in animals. Frances Knock, here in Chicago, and Dr. Samuel Rosner, have used hexophenarsenic in the adjutant therapy of cancer. Dr. Knock tells me that the supply of Mapharsen is almost completely depleted. In fact, she has the last of the Mapharsen for studies being conducted in Florida now.

People are so afraid of "arsenic" that arsenicals are not being used in medicine anymore. Mapharsen, which was the best agent against syphillis and gonorrhea, is no longer made in the United States. I am simply asking why are these things not cited? Arsenicals do have value against cancer.

ANSWER-DR. Herman Kraybill

Dr. Frost, I believe I did make a reference to those few studies where arsenic had a carcinostatic effect. The other question I would like to ask you is, in your studies or other studies, to what degree were there

contaminants? If we do another study I hope we make sure that we are dealing with single molecular species. These studies, in the past, and I do not know about the arsenical you are dealing with, could be influenced by interactants or impurities. This is quite germane and we want to make sure that we are dealing with 99.9 percent pure chemical in the mechanistic studies or this could cloud the issue. This is why we want to incorporate this feature of contaminants into the study design in order to show the effects of the interactants and the contaminants.

COMMENT-Dr. Samuel Epstein

I would like to comment on Dr. Frost's question. I think the carcinogenicity data on arsenic relates only to inorganic arsenic. The extensive data on the carcinostatic effects of various arsenical compounds are yet further evidence of the carcinogenicity of arsenic. I refer you to the observation by Sir Alexander Haddow in the early 30's that most carcinogens are also carcinostats. Haddow undertook a detailed survey on a wide range of defined chemical carcinogens and demonstrated that the majority also had a powerful inhibitory effect on the development of tumors. Therefore, I think that the data on the carcinostatic effects of arsenicals, particularly inorganic arsenicals, are yet further presumptive evidence in support of its carcinogenicity.

COMMENT-Dr. William Lloyd

I do not know if I agree with the last point but I think the point was well taken.

COMMENT-Dr. Michael Utidjian

I have some comfort, possibly for Dr. Frost. In the course of a telephone conference with Dr. Krop of FDA, I raised this question of the common idea that there is prejudice on the part of the FDA against arsenical pharmaceuticals at this time. He agreed that there was such a feeling abroad but that it was unfounded. I specifically asked about Mapharsen. Some years earlier at the University of Pittsburgh, I was involved in a veneral disease prophylaxis development project and Mapharsen was one of the ideas that we had looked into and then dropped because of the belief that the FDA would never license a new application; a new type of use for it. Dr. Krop informed me, and he asked that I convey to the conference the information, that the FDA has no blanket proscription or prohibition on arsenicals and that future new drug applications for arsenicals will be decided on their individual merits.

COMMENT-Dr. John R. Goldsmith

I do not know whether this ought to come up this afternoon, and I will leave that to you Dr. Lloyd, but when occupational groups are exposed to arsenic and some of them ultimately develop cancer, they also show other

manifestations which are present and evidence of high arsenical exposure. When I received my medical education we learned quite a lot about the ability to detect keratotic lesions or warts in places where they should not occur, as well as other skin reactions. I think it is most important for workmen exposed to this type of occupational carcinogen to at least know about any premonitory things that need to be checked out. In many types of environmental cancer, the exposed workers are not given any information. I would like to ask of those having experience in clinical occupational medicine with arsenical workers if observations being made in such groups are consistent with what has been seen in those patients given arsenic clinically for treatment of disease.

MODERATOR-Dr. William Lloyd

We are so short of time and can only consider this speaker's comment and Dr. Hine who can respond to Dr. Goldsmith's question.

QUESTION-Dr. John Bundy

I would like to ask Dr. Kraybill about his reference to the clarification of how these studies will be used in regard to particle size, molecular form and impurities. Have you considered particle size and shape in any investigations with regard to macrophage integrity or functionality?

ANSWER-Dr. Herman Kraybill

We have not. Some people here are more familiar with studies on inhalation and particle size than I. I just raised the point. My view is that particle size may play a role here. Dr. Goldsmith is shaking his head, so I guess there is not very much, if any.

MODERATOR-Dr. William Lloyd

Dr. Hine, would you like to say a few words about other manifestations of arsenic exposure?

ANSWER-Dr. Charles Hine

Dr. Goldsmith, in answer to your question, unfortunately, there are no easily recognized signs in persons with unusual exposure to arsenic from industrial sources. None of the cases of bronchogenic cancer which we have studied, some of which may have been associated with arsenic exposure, had keratosis or neuritis. Most of them, but not all, had irritation of the conjunctiva of the eyes and of the upper respiratory tract. Now the reason they probably did not have the symptoms (though the experience may have been different at Allied and Dow) is that the ASARCO personnel, as you noted in the slides, were completely protected

with special clothing and equipment. You just do not have unexposed areas. I think it is true that keratosis can develop from systemic administration or from contact. However, the amount of arsenic absorbed was not sufficient to give rise to keratosis in our cases. There were no skin cancers in the small numbers of workers employed. Obviously, we do not see this skin cancer as a cause of death. The medical observations are, and I am quoting Dr. Pinto, that these were rare and no different than in the unexposed areas in the plant with personnel working in different places.

QUESTION-Dr. John Bundy

Dr. Hine, were these all bronchogenic or were there any adenocarcinomas or oat cells?

ANSWER-Dr. Charles Hine

I think we have at the present time reviewed none of the slides. We would have to take the diagnoses from the death certificates. I think that out of 36 which we have on hand at present and have reviewed, 35 or so were bronchogenic.

MODERATOR-Dr. William Lloyd

I would like to thank our speakers again and the audience for their participation. If you will wait for just a moment, several announcements by Dr. Carnow.

CONFERENCE CHAIRMAN-Dr. Bertram Carnow

The meeting will end promptly at 4:00 pm. Those of you who want to make plane reservations should allow at least an hour to get to the airport.

Dr. Russell Peterson is in and had an opportunity to observe our fair city for an hour and a half while he circled the airport this morning before landing. He will be addressing us during lunch.

Lunch, as you will note, is at 11:30, because we started early and everyone had an early breakfast. This will permit us to get out in time for those of you who wish to do so can return home this evening.

LUNCHEON SPEAKER INTRODUCTION

Dr. Paul Peterson, Dean
University of Illinois School of Public Health

I would like to share with you that it has been impossible for me to establish that our luncheon speaker, Dr. Russell Peterson, and I are relatives; I have tried awfully hard. All of us Petersons like to feel that somewhere back in Scandinavia our forefathers were related.

Dr. Peterson earned his doctoral degree in chemistry at the University of Wisconsin and has had a long distinguished career in research and development in industry. He not only brings to us this unusual scientific and research background, he also moved into the political arena, formerly serving as Governor of Delaware. He now brings this rich background to the President's Council as the principal advisor on policy with reference to environmental issues. As he has indicated, when one speaks of occupational health problems, one is also dealing in a very intimate way with problems of health that result from our environment.

It is a great privilege and pleasure for me to present to you, Dr. Russell Peterson, Chairman of the President's Council on Environmental Quality.

CHEMICALS ON TRIAL: THE CASE FOR BETTER CONTROL

Dr. Russell Peterson
Council on Environmental Quality

A modern Rip Van Winkle awakening today after a 10-year sleep would, I am sure, be surprised by the growth of the environmental awareness in the United States. A decade ago, such concerns as air and water pollution, land use, and the preservation of wilderness areas worried a comparative few of us - and even those few were frequently regarded as cranks.

Today, by contrast, environmental concern is widespread, as evidenced, for example, by front-page reporting of plans for oil drilling on the Outer Continental Shelf, or for strip mining coal in the Northern Great Plains. Ten years ago we would have been concerned only with the energy that such developments would make available. Now, we are also concerned that such development proceed in a manner that minimizes the risk of damage to the environment. Our new attitudes about environmental matters present a remarkable case study in rapid social change. Yet, it is ironic that we should have made progress in some environmental matters so quickly and be so slow in other areas that directly affect human health. I refer of course to the regulation and control of hazardous chemicals.

In 1971, the Council on Environmental Quality (CEQ) issued a report on toxic substances. The report pointed out that about 2 million chemical compounds are known, and that thousands of new chemicals are discovered each year. Most new chemical compounds are laboratory curiosities that will never be produced commercially. However, several hundred of them do go into commercial production each year. Although most of these substances are not toxic, the sheer number of them, the increasing diversity of their use, and the environmental problems already encountered in connection with some warn us that we are dealing with a major problem. The report further concluded that the environmental impact of most substances is not well understood. Of those compounds studied, testing has largely been confined to acute effects - those which show up quickly and are easily perceived; but our knowledge of chronic, long-term effects is inadequate. We know that cancer, genetic alteration, and various sorts of mental, physical, and physiological change can be chemically induced. In general, however, we find it difficult to pinpoint the chemicals which cause such effects.

On the basis of this study, CEQ concluded that there was an urgent need for a program to screen toxic substances before they went into commercial use. The report conceded that our understanding of environmental threats, our skill at testing substances for adverse effects, and our ability to monitor and predict these effects were not fully adequate. Nevertheless, it concluded that our knowledge in these areas was sufficiently developed to justify immediate action. No longer did we have

to maintain a purely reactive posture with respect to toxic substances to limit ourselves to attempting to repair the damage after it has been done. Nor should we, the report stated, "continue to allow the entire population or the entire environment to be used as a laboratory."

The council recommended new legal authority in February, 1971, on the basis of the Council's recommendations, the President submitted to Congress a proposed Toxic Substances Control Act.

It is now February, 1975, four years since the initial submission of that proposed legislation. Each year since 1971, the CEQ Annual Report has cited new instances of health crises caused by chemicals such as PCB's, mercury, haloethers, and vinyl chloride. Each year since 1971 versions of the Toxic Substances Control Act have been debated in Congress, but none of them has been voted into law.

I repeat that in connection with the commercial production, distribution and use of chemical compounds, we are dealing with a major problem. More accurately, we are *failing* to deal with it. This important legislation was badly needed four years ago; we need it even more today. I want to urge you, therefore, as individuals and as members of a new but "influential society" to join me in urging passage of legislation which will meet the goals of the Toxic Substances Control Act. Such legislation has formidable opposition, principally, but not entirely, on economic grounds. Understanding those objections and their validity, or lack of it, requires some basic understanding of the proposed bill.

What should a Toxic Substances Control Act do? It should meet three major needs. First, it should provide for reporting to the government of chemical production and intended use. Second, it should permit the government to require testing of chemicals so an assessment of their potential for human and environmental risk can be made. Third, it should give the Administrator of the EPA the authority to regulate the production, distribution, and use of all chemical substances not currently regulated under other authorities.

In addition, the legislation should take a new approach to two aspects of the regulatory process. The first of these is *responsibility for safety and health testing* for commercially produced chemicals. Under present regulatory patterns, this responsibility is assumed entirely by government. Over the years the FDA, the NCI, the NIEHS, and the EPA have spent millions of tax dollars annually to test commercially produced chemicals. The thrust of proposed Toxic Substances Control legislation, however, is to require industry to test both new and existing compounds at its own expense.

I strongly support this latter approach. Testing to assure the safety of a chemical for the workers who will be involved in its

production, for the public who uses or consumes the chemical, and for the environment itself, is a proper developmental cost. We can no longer afford in fact, we could never afford to allow the production each year of thousands of chemicals whose consequences are vaguely understood or totally unknown.

The second issue arising from past efforts to regulate chemicals involves *information access*. In some cases, individuals and organizations that have information pertinent to the regulatory process withhold it. Sometimes data are held back in the name of protecting trade secrets; this is a legitimate concern, and proposed Toxic Substances Control legislation is written to safeguard such secrets. In other cases, regulatory agencies have been hampered by the suppression of health data--or by the submission of data which, by accident or design, tell a misleading story.

You are all aware of one, far-reaching example of this in the arsenic field. Inorganic arsenic, a by-product of smelting, is processed by only one plant in the United States. This plant ships the processed arsenic to companies in more than 40 major industries for subsequent use. We now know, thanks to disclosures in 1974 by Allied Chemical and Dow Chemical, that workers who had handled inorganic arsenic have been contracting lung and lymph cancers at dramatically higher rates than workers who were not exposed--from 3 times as high to 60 times as high. We also know (now that we have started digging back in the files) that reports suggesting a link between arsenic and cancer date back to the turn of the century.

Arsenic levels in industrial plants are regulated by Federal standards; why did we not know (until the Allied and Dow studies told us) that these standards were much too high?

Federal standards for arsenic exposure in industrial sites are based on a single study, performed in 1963 by an employee of the one and only arsenic processor in this country. In essence, that study compared cancer rates between two groups of workers in the plant: one group regularly exposed to arsenic, and another group that supposedly was not. The study found no significant difference in cancer rates between the two groups and concluded, therefore, that regular exposure to arsenic did not result in any excessive incidence of cancer.

In 1969, however, Drs. Frederick Lee and Joseph Fraumeni of the NCI pointed out an astonishing gap in this study--investigators had not compared the plant workers with people who worked outside the plant, that is, with those who definitely were not exposed, day in and day out, to inorganic arsenic. In their own study, Drs. Lee and Fraumeni found that lung cancer rates for smelter workers, whether supposedly "exposed" to arsenic or not, were three times higher than rates for the general

population.

As a result of this and subsequent studies, the government will propose a dramatic reduction in Federal exposure standards for inorganic arsenic. On the basis of the original study, those standards were set at 500 µg/cu m of air. In 1973, NIOSH, research arm of OSHA, recommended that exposure levels be cut to 50 µg-1/10 the old standard- and now, largely as a result of the Dow and Allied studies, OSHA will propose a new standard of 4 µg.

All of the returns are not in on arsenic studies, so no comment on the causes of the awareness of what appears to be bias in the original can be made. However, a proposed reduction from 500 µg to 4 µg is comment enough. This history of arsenic exposure standards supports the argument that Federal regulatory agencies cannot be restricted to filtered information.

The final issue that arises in connection with proposed Toxic Substances Control legislation is perhaps the most important; that is *burden of proof* in the decision making process. Where does that burden lie? Before a chemical is approved or rejected for mass production, should the government be required to prove that the compound presents an unacceptable risk to public health, or should the manufacturer or processor be required to demonstrate that it does not? I believe that the proposed Toxic Substances Control legislation is correct in placing the burden of proof on the manufacturer.

Just last month, as you know, the United States Court of Appeals for the District of Columbia, in a three-judge decision, overturned an EPA regulation governing the content of lead in gasoline. Last year, the Eighth United States Circuit Court of Appeals in St. Louis issued a stay of a District Court ruling which, in effect, would have shut down the Reserve Mining Company. The implication in both cases was that the government bears the burden of demonstrating a definitive link between chemical use and a health hazard.

In my view, these decisions constitute precedents which are not only major, but dangerous. The reason is that these rulings, with their perspective on burden of proof, fail to address a critical phenomenon--delayed health effects.

In the Reserve Mining Case, the Justice Department asserted the following:

1. Reserve Mining opened its plant and began dumping into Lake Superior eighteen years ago.

2. The corporation was processing 100,000 tons of taconite (low-grade iron ore) daily, and dumping 67,000 tons of taconite waste in Lake Superior.

3. Asbestos fibers averaging less than 2μ in length were found in concentrations ranging up to 100 million/liter in the drinking water of Duluth and nearby communities.

4. These fibers were directly traceable to the taconite dumping.

5. Over the last 18 years, approximately 200,000 people have ingested considerable amounts of asbestos fibers in their drinking water.

6. In addition, levels of asbestos in the air near the plant range from about 100,000 to 10 million fibers/cu m. Besides drinking asbestos fibers, therefore, the residents of the community have been inhaling them.

7. Asbestos, finally, is a known carcinogen.

These assertions were all demonstrable. What the Federal Government, 3 states, 5 environmental organizations, and 3 cities (all plaintiffs in the suit) could not demonstrate, however, is that anybody had actually contracted cancer from the asbestos.

Of course, they could not. With asbestos-induced cancer, the average period from first exposure to initial symptoms is 20 to 40 years. Reserve Mining has not been in business long enough for any one to prove that its waste is hazardous to human life.

But in 5 to 10 years, we should start accumulating enough evidence to know for sure. It may be that the exposure to asbestos in the area will not induce cancer and the Reserve Mining Company and the Eighth U.S. Circuit Court of Appeals will be vindicated in their gamble that this is the case. If those levels are proven high enough, however, it will be 20 years too late for those who contract cancer to do anything about it.

Reversing the burden of proof would, I realize, invert a cherished legal principle, one that has been a fixture in Anglo-Saxon jurisprudence for over a thousand years--the accused is innocent until proven guilty. In connection with health hazards whose effects do not show up for years, however, it is questionable whether we should apply the presumption of innocence to chemicals.

Reversing the burden of proof would, in some cases, result in major economic loss. This would be expecially true in situations where this

approach were applied after the fact. The Reserve Mining case is an example in which about 3,200 employees would have lost their jobs until Reserve devised an alternate means for disposing of its waste. Certainly, all of us whose professional actions and personal concerns involve occupational health must maintain a prudent concern for the economic impact of our decisions.

However, our present inability to demand proof of safety with many new chemicals, and our recognition of the prospect of economic loss, create a circular process. Today we cannot prohibit production of a new chemical because its health hazards are not yet proven. By the time the health hazard is proven, however, production of the chemical may involve the investment of millions of dollars and the employment of thousands of people. So, when and if the chemical becomes a proven health hazard, it is very expensive to prohibit. More important, by that time many citizens may be suffering from cancer or other long-term effects which, had the chemical been tested, might never have occurred.

Those opposed to the Toxic Substances Control Act have put forward a number of objections to the concepts in the proposed legislation. Their primary argument is that the process of regulation would be time consuming and would keep promising new chemicals out of use for many years, thereby stultifying the process of research and development.

There is, undoubtedly, some validity to this argument. It will take a certain amount of time to properly test a number of chemicals, particularly those similar in structure to other chemicals that have proven toxic, of those that are entirely new. But, this is a necessary price to pay. The only alternative is to permit the continued use of our environment as a testing ground, and of ourselves as guinea pigs (a form of Russian roulette unacceptable to ourselves and to our children).

Chemicals are on trial in the United States. We cannot afford to hold them innocent until they are proven guilty.

CONFERENCE CHAIRMAN-Dr. Bertram Carnow

I want to thank Dr. Russell Peterson for an inspiring talk. I think it really serves to give focus to all of the things that we are trying to do here and the things that we will have to continue to do in the future. So, with renewed zeal, I suggest that we retire to the working room and go back to our deliberations.

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CONFERENCE CHAIRMAN-Dr. Bertram Carnow

I now would like to introduce the Moderator for the Session on the Epidemiology of Arsenic, Mr. Gerald Ott, Corporate Medical Biostatistician at the Dow Chemical Corporation. Mr. Ott.

EPIDEMIOLOGY OF ARSENIC
SOME COMMENTS ON LONG-TERM HEALTH EFFECTS OF ARSENIC EXPOSURE

Mr. Gerald Ott, Moderator
Dow Chemical Company

A B S T R A C T

Objectives of the Conference on Arsenic pertaining to the Epidemiology of Arsenic will be discussed. Improved methods for developing occupational health data to enable more rapid identification of adverse health effects related to chemical exposure will be suggested. Also, a model for linking industrial hygiene and medical records will be outlined.

Before introducing the speakers in this session I would like to briefly emphasize several of the stated purposes of this conference. The participants have been asked to evaluate the extent and reliability of available information on the health effects of arsenic. Dr. Russell Peterson's remarks* at the luncheon today attest to the seriousness with which we should approach this subject.

Since a variety of modes of occupational exposure to compounds containing arsenic have long been recognized, the literature available for review is fairly extensive and involves the use of numerous epidemiologic approaches. In evaluating long-term health effects, the following will be discussed by the speakers.

1. An assessment of characterization of work exposure, which may be composed of identification of compounds in the environment, measurement of exposed intensities, including peak exposures, and duration of employee exposure at specific exposure levels, will be reviewed.

2. There should be an acceptable method of defining exposed and control populations.

3. The assessment of health parameters should consider such problems as latency and include a description of the methods used to determine the presence or absence of the health characteristics of interest.

4. Analysis should specify and use co-factors such as age, cigarette smoking history and exposure to other chemicals in defining health risks.

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*See page 285 for Dr. Peterson's remarks

This type of information may be difficult to obtain in many cases; however, the results of studies must be interpreted in view of these kinds of considerations.

Participants have been called upon to discuss the additional data which may be needed in order to make further judgments with respect to the health effects of arsenic and necessary programs for obtaining these data. In this context, I would like to briefly sketch a strategy that has enabled the Dow Medical Department to more efficiently conduct observational studies.

A problem that has received much of our attention is the linking of industrial hygiene data to individual employees, since characterization of the work environment is so important in occupational health studies. Figure 1 diagrams the flow of information between industrial hygiene and medical functions through the personnel system in our company.

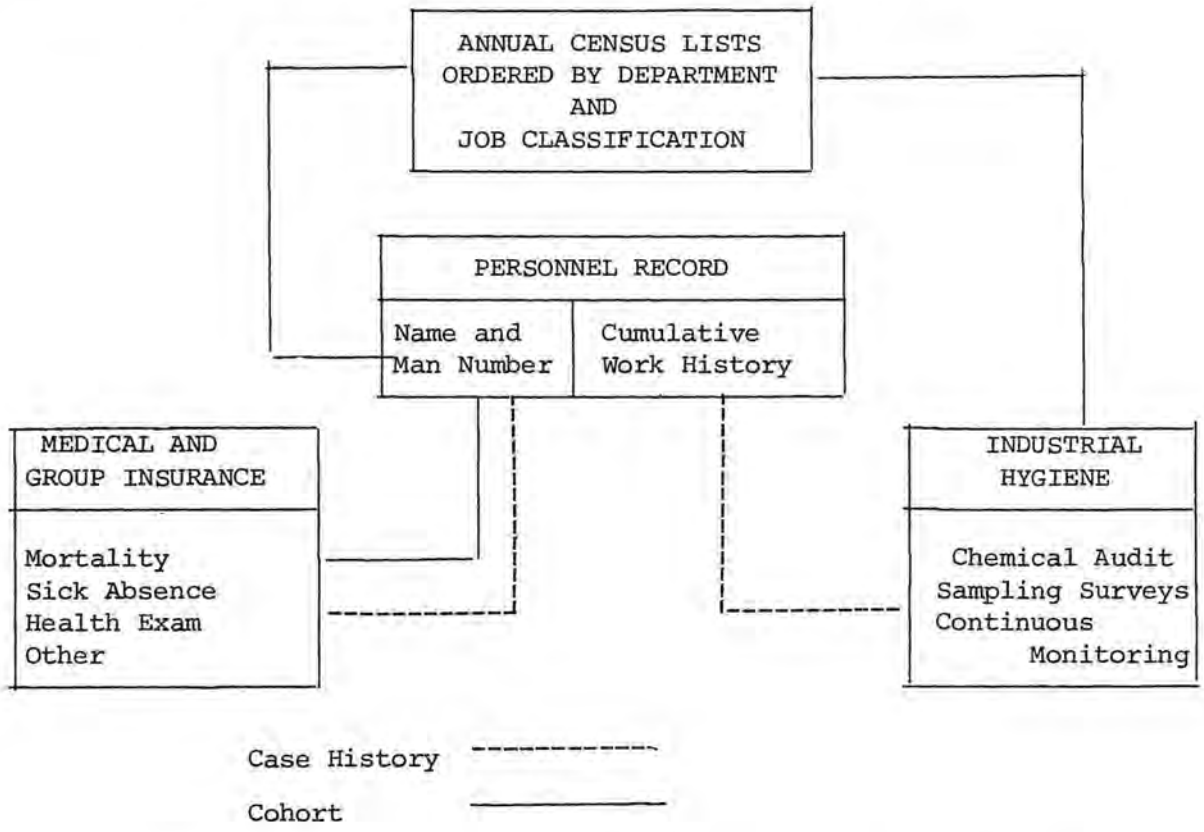

Figure 1 Flow of industrial hygiene and medical information for cohort and case history studies

Personnel records are fundamental to the linking process and two source documents have been particularly important, the periodic census lists prepared for each department and the personnel work record containing the employee's cumulative work history. In carrying out medical surveillance studies, the first step was a thorough review of the existing and planned industrial hygiene work. This usually leads to the identification of areas of concern from which the exposed population can be drawn, using the personnel system. Once the population is defined, work histories and industrial hygiene reports are obtained so that individual exposure histories can be reconstructed. The procedure that I have outlined here has been included in a publication on exposure to arsenicals.

Once exposure data have been linked to the individual, it is generally not difficult to obtain appropriate health data from medical department files, which, in this case, have been partially computerized. Major obstacles limiting our accomplishments to date have been the lack of computerized industrial hygiene information and personnel files, and limited industrial hygiene resources.

Two steps are being initiated to overcome these difficulties. The first step is the involvement of plant personnel in the measurement and evaluation of exposures, and this is being enlarged. It is expected that more complete coverage of the workplace will result if personnel can be called upon to monitor their own operations under the guidance of trained industrial hygienists. Computerization of the monitoring results will be necessary to insure that the data generated will be of maximum use to the medical department in years to come. The second step will consist of computerizing the cumulative work histories of all former and current job changes for each individual during his employment with the company.

The net result of these steps will:

1. Eliminate the tedious manual extraction of work history and exposure information.

2. Provide a mechanism for identifying cohort populations directly from the data base.

3. Provide clinicians with a summary of the exposure history for each employee.

These approaches merit the consideration of industry and will be of value in dealing with many problems of occupational interest. At the same time, it is most important to realize that medical surveillance systems should not be considered a primary line of defense against occupational health hazards. Animal toxicology, good engineering practices, and employee education are fundamental to assure a safe work environment.

With these remarks, I would like to introduce the first speaker, Mr. Warren Ferguson, Director of Occupational Safety and Health at the Allied Chemical Company. Mr. Ferguson.

EPIDEMIOLOGY OF ARSENIC

Mr. Warren Ferguson
Allied Chemical Corporation

A B S T R A C T

A proportionate mortality analysis of retired arsenical workers at a small agricultural chemical plant showed that 17 or 22 deaths between 1961 and 1973 inclusive, were due to cancer. Exact probabilities, calculated from SMR's, revealed statistically significant excesses in cancers of the lung and the lymphatic system. The median induction period was 33 years. Longevity, below age 70 years, appeared not to be affected. No common etiological factors, other than exposure to arsenicals and city of residence, have been identified.

The findings, as developed in the study by Baetjer, Lilienfeld, and Levin, have more meaning when they are viewed in historical perspective. The Baltimore Agricultural Chemical Plant is a small one. The population year round was traditionally 75 people and is now about 50. To this permanent force, temporary seasonal workers were added -- about 50 in the spring, somewhat fewer in the fall.

The plant was established in 1897 as an independent company and purchased by Allied prior to World War II. It comprised three major activities: 1) manufacture of arsenic acid from arsenic trioxide and nitric acid; 2) manufacture of arsenical pesticides and herbicides; and 3) blending and formulation of a wide variety of agricultural chemicals.

We were dissatisfied from the outset with the hygiene control in the arsenic acid plant, not only because of its failure to meet generally recommended TLV's, but also because the workers involved were developing keratosis and other indications of toxic effects. Immediately after the war we began planning for reconstruction and in 1952 the present plant was completed. This reconstruction, together with improved personal hygiene practices (daily showers and clothing change, for instance) seemed at the time to have eliminated our toxic risk.

We did not have the same obvious effects in the plant area which produced lead and calcium arsenates and paris green (copper aceto-arsenite). Skin irritation was a problem at times, and over the years we were able to minimize this factor by a series of progressive improvements in our packaging system.

Exposure levels were not recorded in the old arsenic acid operation. However, by analogy with other systems still operating in bulk handling of mineral dusts, we feel entitled to assume that the pre-1952 exposures were at or above 5 mg/cu m at least on a peak basis.

In the insecticide area, 1972 data indicated that we were operating at about 0.5 mg/cu m as a TWA. A reasonable assumption is that exposures in the 1950's were equally twice this number.

Of the observed cancer deaths, almost all were found in three population clusters: the operators in the old arsenic acid plant, warehouse laborers who charged the old arsenic acid reaction kettles, and operators and packers in the insecticide plant. Among the cancer cases (Baetjer *et al*) a significant excess among total cancer, pulmonary cancer, and lymphatic cancer, when calculated as strict probabilities on an SMR basis was reported.

Interestingly, longevity statistics are not as depressing. The cancer group shows a median survival of 67.2 years, survival past age 70 of 35 percent and survival past 75 years of 5 percent, Table I. These values are almost identical to the longevities of the noncancer group at this plant. Except for survival past 75, they also fall within the range of values for other populations whose proportionate mortalities fall within the normal range.

TABLE I
LONGEVITY OF ARSENICAL WORKERS VERSUS TYPICAL "CLEAN" POPULATIONS

	Arsenic Plant CA Group	Alkali Plant "A"	Limestone Quarry "B"	Acid Plant "C"	Nationwide White Collar & Professional
Median Age at Death	67.7	68.1	67.5	66.5	66.1
Percent Survivors Past 70 years	33.0	43.1	35.0	29.7	34.0
Percent Survivors Past 75 years	3.7	22.8	24.0	16.8	16.5

Tabulation of years from first exposure to death from cancer yields another unusual population characteristic as shown in Table II. This is indeed a long incubation period, even in the face of truly massive past exposures.

TABLE II
ARSENIC WORKERS YEARS FROM FIRST EXPOSURE TO DEATH FROM CANCER

Exposure	Time
Minimum	10 years
First Quartile	22 years
Second Quartile (median)	33 years
Third Quartile	48 years
Maximum	56 years

The following questions frequently are asked and deserve some brief comment:

1. Is there prior work history to known carcinogens, such as asbestos or coke ovens?

We have reviewed this factor and can find neither coke or asbestos in the prior work histories.

2. What co-factors might be present?

Other than smoking (and most smoking habits were unknown) the arsenic acid workers may have been exposed to NO_x. The laborers had presumptive exposure to common clays used as diluents. The insecticide workers were only exposed to the other raw materials formulated as copper acetate, lead oxide and calcium hydroxide.

3. Do you intend to publish your findings?

As a corporation, we do not intend to publish our findings because the work mainly corroborates the Dow studies. We have agreed that our consultants may publish any aspects of the study which they feel represent original contributions to the literature, subject to normal legal review.

4. Do you intend to continue your studies?

We have delivered to our consultants all personnel records, name lists, and medical records required for a complete prospective/retrospective study. We would hope to receive this report in late 1976 or early 1977.

MODERATOR-Mr. Gerald Ott

Thank you Mr. Ferguson for your presentation.

Our next speaker is Dr. Samuel Milham, Chronic Disease Epidemiologist in the Washington State Department of Social and Health Services. Dr. Milham.

COMMUNITY EXPOSURE STUDIES AND SMELTER WORKER MORTALITY STUDIES AS RELATED TO A COPPER SMELTER

Dr. Samuel Milham, Jr.
Washington State Department of Social and Health Services

A B S T R A C T

Studies in Tacoma, Washington, were conducted to investigate arsenic exposure in children living near a copper smelter and to test the Lee-Fraumeni hypothesis that copper smelter workers have increased incidence of respiratory cancer. Community exposure studies showed increased arsenic levels in hair and urine of children residing near the smelter. Urinary arsenic levels decreased as residential distance from the smelter increased. Younger children were found to have higher levels of urinary arsenic than older children. Worker mortality studies showed that smelter workers have increased mortality from respiratory cancer. No other causes of death showed a statistically significant excess mortality.

Since may, 1972, the Washington State Department of Social and Health Services Division, has been involved in studies on environmental contamination related to the American Smelting and Refining Company copper smelter in Ruston, Washington (adjoining Tacoma). The studies have been of 2 types: community exposure studies, and smelter worker mortality studies.

The community studies have been summarized in a recent publication.[1] Briefly, children who lived near the smelter were shown to have increased levels of arsenic in hair and urine. The urinary arsenic level decreased with distance of residence from the smelter stack, and house vacuum cleaner dust arsenic levels showed a similar distance relationship. Younger children showed higher average levels of urinary arsenic than older children, and urinary arsenic levels in young children living close to the smelter varied synchronously over a five week period.

Since this report, further analysis of urine and hair sampling from children living near the smelter revealed that:

1. No urinary mercury was detected in 45 samples (detection limit = 1.9 μg/l).

2. Urinary arsenic levels in 1974 sampling were essentially the same as those found in 1972 and 1973 (further sampling will be done in the summer of 1975 to assess the impact of environmental control steps currently being taken by the smelter).

3. Hair arsenic levels were seen to be lower than those done initially. Maximum levels of hair arsenic are now about 40 ppm, as compared with initial levels of 100 ppm. This difference is due to a change in the way the samples are handled before analysis. The initial samples were analyzed for arsenic without any pre-treatment. The current samples are washed to remove absorbed arsenic.

4. Hair samples, from 20 long-haired school girls (18 Ruston girls and 2 non-resident controls) for segmental analysis of heavy metal concentration, indicated the maximum concentrations as copper 164 ppm, lead 36 ppm, mercury 7.1 ppm, cadmium 43 ppm. Neither control showed any arsenic, antimony or cadium. Results of the segmental analysis will be published later.

5. In the summer of 1974, the smelter was closed by a strike and during the strike, the average urinary arsenic level was .08 ppm for 18 specimens. After the strike, the average for 19 specimens from the same children was .16 ppm. Ten children were sampled twice during and twice after the strike. Eight of the 10 showed increased urinary arsenic excretion after the strike (1 stayed the same and 1 decreased). Since normal values of urinary arsenic are <.02 ppm, the elevated excretion of urinary arsenic seen during the strike means that children are exposed to arsenic from secondary sources (ingested or inhaled house dust) as well as from the smelter directly.

The smelter worker mortality study was based on occupational and cause-of-death information contained on death certificates in the Washington State Vital Statistics file. Three parallel studies focused on learning whether the Tacoma smelter employees showed increased mortality from respiratory cancer as reported by Lee and Fraumeni[2] for other smelters.

In the first study, applying U.S. mortality rates to published populations at risk at the smelter[3] yielded 18 expected respiratory cancer deaths. Examination of all Pierce County, Washington (location of the smelter) resident male deaths in the years 1950-1971 due to respiratory cancer revealed 39 with stated employment at the smelter. The smelter employment records verified that all 39 men actually had been smelter employees. Another out-of-county case was discovered later.

Since there was an apparent discrepancy between the number of respiratory cancer cases reported in a smelter mortality study[3] and that discovered through death certificates, a record overlap study was done with the cooperation of the smelter.

Table I, COMPARISON OF SOURCE OF ASCERTAINMENT
TACOMA SMELTER RECORDS *VERSUS* DEATH CERTIFICATES
RESPIRATORY CANCER DEATHS 1961-1972

Source of Ascertainment	Number of Deaths
Smelter Records only	1
Smelter Records and Death Certificates	18
Death Certificates only	6
Total	25

Table I shows that in the years 1961-1972, there were 25 respiratory cancer deaths in smelter employees. Eighteen cases were ascertained through both record sources; 6 on death certificates only, and 4 on smelter records only. The discrepancy resulted from the method used in the smelter study of ascribing deaths to immediate cause of death rather than to underlying cause.

As part of a general occupational mortality study, proportional mortality rates were computed for detailed causes of death in smelter workers. This method uses all other male deaths in the State as controls. Table II shows, again, that smelter workers have increased mortality from respiratory cancer. No other causes of death showed a statistically significant excess mortality.

In summary, this work supports the Lee-Fraumeni study and the hypothesis that workers in copper smelters have an increased incidence of respiratory cancer. This study cannot speak directly to the question of etiology, but the smelter worker population affords a unique opportunity to examine the whole question of arsenical carcinogenesis in man.

TABLE II

PROPORTIONATE MORTALITY RATIOS, WHITE MALE DEATHS IN WASHINGTON STATE, 1950-1971

435 SMELTER WORKERS, HEAT TREATERS, ANNEALERS, TEMPERERS

CAUSE OF DEATH	ICD #		1950-1960	1951-1971	1950-1971	AGE AT DEATH 20-64	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80+
Malignant Neoplasm Respiratory System	160-165	OBS	23	30	53	27	0	0	0	2	2	2	4	7	10	11	8	6	1
		EXP	12	21	32	15	0	0	0	0	1	1	3	5	6	7	5	3	2
		PMR	197*	146*	164*	176	0	0	0	R	R	162	154	143	181	165	157	179	58
Nose, Middle Ear, Accessory Sinuses	160	OBS	1	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0
		EXP	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		PMR	R	0	R	0	0	0	0	0	0	0	0	0	0	R	0	0	0
Larynx	161	OBS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		EXP	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
		PMR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Bronchus, Trachea, Lung (Primary)	152	OBS	13	23	36	21	-	-	-	2	2	2	3	6	6	7	4	3	1
		EXP	7	15	22	11	0	0	0	0	0	1	2	4	4	5	4	2	1
		PMR	178*	152*	161*	196	0	0	0	R	R	R	164	168	164	155	105	133	90
Bronchus and Lung	162.1	OBS	7	23	30	19	0	0	0	2	2	1	3	6	5	4	3	3	1
		EXP	4	15	19	8	0	0	0	0	0	1	1	3	3	4	3	2	1
		PMR	197	153*	162*	226	0	0	0	R	R	R	248	202	170	111	88	145	95
Pleura	162.2	OBS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		EXP	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		PMR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lung, Unspecified Primary- Secondary	163	OBS	8	7	15	6	0	0	0	0	0	0	1	1	4	3	4	2	0
		EXP	3	4	8	4	0	0	0	0	0	0	1	1	2	2	1	1	0
		PMR	245*	159	195*	165	0	0	0	0	0	0	R	99	262	170	R	R	0
Thoracic Organs Secondary	165	OBS	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0
		EXP	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		PMR	R	0	R	0	0	0	0	0	0	0	0	0	0	0	0	R	0

CONTINUED

TABLE II *CONTINUED*

CAUSE OF DEATH	ICD #		1950-1960	1951-1971	1950-1971	AGE AT DEATH 20-64	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80+
Malignant Neoplasm Prostate	177	OBS	9	5	14	3	0	0	0	0	0	0	0	1	2	3	4	1	5
		EXP	6	8	14	2	0	0	0	0	0	0	0	0	1	2	3	3	4
		PMR	151	62	100	187	0	0	0	0	0	0	0	R	198	135	69	30	125
Testis	178	OBS	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1
		EXP	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
		PMR	0	R	R	0	0	0	0	0	0	0	0	0	0	0	0	0	R
Other Male Genital Organs	179	OBS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		EXP	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		PMR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Kidney	180	OBS	2	2	4	3	0	0	0	0	0	0	1	1	1	0	0	1	0
		EXP	1	2	3	1	0	0	0	0	0	0	0	0	0	1	0	0	0
		PMR	146	118	130	210	0	0	0	0	0	0	R	R	R	0	0	R	0
Bladder and Other Urinary Organs	181	OBS	0	1	1	1	0	0	0	0	0	0	0	1	0	0	0	0	0
		EXP	2	3	5	1	0	0	0	0	0	0	0	0	1	1	1	1	1
		PMR	0	34	20	80	0	0	0	0	0	0	0	R	0	0	0	0	0
Malignant Melanoma of Skin	190	OBS	1	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0
		EXP	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
		PMR	R	0	R	R	0	0	0	0	R	0	0	0	0	0	0	0	0

*Statistically Significant at 5 percent
PMR - R Expected Value less than 1

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MODERATOR-Mr. Gerald Ott

Thank you Dr. Milham for your interesting presentation.

Our last speaker is Dr. Charles Hine, who is the Medical Director of the American Smelting and Refining Company. Dr. Hine.

SOME OBSERVATIONS OF EMPLOYED PERSONS EXPOSED TO ARSENIC

Dr. Charles Hine*
American Smelting and Refining Company

A B S T R A C T

Systemic, occupational poisoning is a rare occurrence although increased body burden may occur among persons with certain occupational exposures. There is an increase in conjunctivitis in workers having contact with high concentrations (500 µg/cu m) of airborne arsenic and perforation of the nasal septa may occur on rare occasions. There is no evidence of adverse effects on the liver, kidneys or blood-producing organs, even at relatively heavy exposures to airborne arsenic. In observed workers, no systemic arsenic poisoning, as evidenced by neuritis or verruca, was noted and no changes were reported in sickness disability among exposed persons in a copper refinery. An increase in bronchogenic cancer may occur among workers exposed, in the past, to elevated concentrations of airborne arsenic.

In the last 20 years, out of approximately 62,500 autopsies in San Francisco, only 5,000 deaths were found to be due to chemical agents or drugs (generally suicidal).# Arsenic as a cause of death is involved relatively infrequently today. Approximately 1 death per year out of 2,400 autopsy cases was due to accidental or intentional ingestion of arsenic; so, as a cause of mortality in the general community, arsenic would not appear to be significant. Many disputed cases and those in which there is some question as to personal injury, morbidity, or mortality from chemicals were examined by the State Workmen's Compensation Appeal Board. During the last 10 years relatively few cases of industrially incurred arsenic poisoning were seen in the State of California. However, there are no primary smelters in this area.

There is, of course, a large agricultural industry and an industry which compounds and distributes arsenical compounds. In review of their compensation records, the order of magnitude is approximately 25 cases

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**Dr. Hine is presently serving as Medical Director for American Smelting and Refining Company, working with Mr. Nelson. In addition, he is a medical consultant to Shell Oil Company, working with Dr. Joyner.*

#Dr. Hine has been associated with the medical-legal jurisdiction in the County of San Francisco for the last 20 years and also serves as an independent medical examiner for the California Workmen's Compensation Board.

reported under the circumstances that were described as the "first report of work injuries." Most of these injuries were among applicators of arsenicals and were cases referred to as dermatitis. There was one case of a keratosis in a man who worked as a brick mason in a metal refinery in Nevada and one case of peripheral neuritis of a permanent nature in a custodian who accidently spilled 10 percent sodium arsenite on his foot. Unfortunately, he did not immediately remove this substance and he developed systemic arsenical poisoning. Other than this, in the general population occupational arsenical poisoning is extremely rare.

Asarco has 1,000 employed persons and only 100 are directly concerned with arsenic. The remaining employees are engaged in the operation of a copper smelter and refinery. The problem in defining the population is the mobility between the arsenic group and the group which is engaged elsewhere. There is also a considerable turn over, so there are no accurate records as to total number of exposed employees. The turnover has been as much as 100 percent in war years and the experience goes back 50 years. In the present economic situation, the turnover is about 10 percent. So, there were approximately 20,000 persons at risk who were exposed to arsenic during this period of time.

Studies have been made of this population and contrary to previously presented suggestions, there certainly was no filtering of data and Asarco's professional and medical observations were published in the literature. Dr. Pinto, an industrial physician, collaborated with an epidemiologist and the manuscript was reviewed by the editorial board of the journal in which the paper was published. This was a good presentation of the data. A comparison was made of what was considered to be a non-exposed group within the smelter, and a group which was exposed. These groups were defined through job category, by analysis of arsenic in the air, and by urinary excretion of arsenic. This resulted in a reasonable, though not entirely exclusive, separation. It is now recognized that the groups are not entirely non-exclusive because arsenic is detected in all areas of the plant where air samples have been taken. This has varied in the past from as high as 20 mg/cu m to an average of 4 µg/cu m. This gives a range of some 5,000 fold difference in air concentrations. The arsenic excretion of the employees also varies considerably.

In the San Francisco area, the average arsenic excretion expressed in whole numbers is about 50 ppb; in Tacoma, among the non-exposed groups, the excretion is about 100 ppb; and the excretion in the exposed areas will average 500 ppb and at times be considerably higher. Epidemiologically, the important characteristics of the group to which we refer as being exposed, or rather more exposed to arsenic include:

1. Increased dermatitis experience. Arsenic is an irritant material to the skin.

2. An increase in conjunctivitis among the workers coming to the first aid room.

3. Also, increased evidence of perforation of the nasal septa; that is, an erosion of the nasal mucosa. This has decreased with recent adequate control of nasal protection.

4. Increased arsenic excretion in this group.

The point where there is no difference is in the blood, liver and kidney chemistries reported on these people in terms of those defining adequate function. There showed no difference, nor was the hematological picture different in these two groups. No neuritis was encountered in any of the employees who have worked with arsenic. There was no evidence of systemic arsenic poisoning as indicated either by an increase in frequency of neurological diseases, frank neuritis itself, or an increase in kidney disease. There was no change in the sickness disability among these people or time loss from work, nor was there any change in the incidence of verucca among the exposed population. All of these findings have been reported in the past in other studies.

Death certificates were analyzed in persons who have worked at the Tacoma Plant and are presently pensioners. There has been a total accumulation of 298 deaths. The records up to the present time indicate 35 died of bronchogenic cancer. This indicates a rate of 11.8% which is approximately twice the expected in the community. It should be re-emphasized that there was no significant difference in standard mortality rate from all deaths and there was a deficit of deaths from some cancers. There was an excess of bronchogenic cancers. The distribution of death shows a median age of death among the group as 66 years from bronchogenic cancer as compared with the median age of death from this disease noted among other employed groups; there was no significant shortening of life span. The ages and occurrence of bronchogenic cancer range from 32 to 93 and the 32 age individual had worked 6 months in the plant in an area without an especially high exposure.

There is a current review of all these data being prepared by Drs. Enterline and Pinto; they are reviewing and re-classifying the death certificates. It is hoped to obtain a better identification of exposure risk by a method involving measurements of arsenic excretion of the groups in 35 different job classifications.

I would like to make a brief reference to a study called the "Brigham Young study" which is being distributed here. This study was requested by Kennicott Copper Company a few years ago, and was carried out by non-biological statisticians who did not work with an epidemiologist or have access to someone experienced in the nomenclature. There was adequate statistical analysis of the data, but, in reviewing it, some questions develop as to the proper classification of some of the cases that were considered as bronchogenic cancer. This lead to a decision to make a further study and Kennicott surpported a study at the University of California in which Dr. Milby and I participated. The cause of death among employees in all divisions of Kennicott was observed. There were some 2,000 persons

who qualified with 5-years experience, 1,900 having had 10-years experience. Briefly, in summary, we could find no trend by work classification in the frequency of death due to disease of the respiratory tract, overall cancer, or bronchogenic cancer. I have some suggestions as to what should be done further, but this light is blinking and I must stop.

QUESTIONS, ANSWERS, COMMENTS

MODERATOR-Mr. Gerald Ott

Thank you, Dr. Hine. We have time for a number of questions now if you would like to address the speakers. Please identify yourself and your affiliation.

QUESTION-Dr. William Lloyd

In reference to Mr. Ferguson's remarks about my objecting to his statistics, I would like to point out that the statistical material presented on longevity are completely inappropriate estimates of longevity for any defined population. If they want to talk about longevity, they have to talk about longevity of a defined cohort that starts out at a certain point in time. I would point out that the record they looked at are the records of deaths among a currently employed population and retirees. It is therefore loaded with long term survivors. Consequently, looking at the average age of death of this population tells you nothing about average life expectancy. You would have to start with a beginning cohort. This is not the way to look at that kind of data.

This is also true in looking at the latent period. If you begin with a group of people who by definition are long term survivors, your retirees predominantly, then you are going to have a longer latent period from initial exposure to death. In reference to what Dr. Hine said, something I would like to point out to you is Dr. Hine's comments on the investigators at Brigham Young and the way they classified their material. I have not seen anything yet that would tell me what it was that they did incorrectly in they way of classification and I would like to hear from Dr. Hine what was wrong. I would also reemphasize what Dr. Milham said, that Dr. Pinto, who should know better, was classifying death certificates by other than the usual accepted rule in the field. Consequently, deaths due to bronchogenic carcinoma were charged out to pneumonia.

ANSWER-Mr. Warren S. Ferguson

I knew Dr. Lloyd would object to our statistical handling but I think I gave him more grounds for objection than really exist. In the first place, we do not run either longevities or proportional mortalities on any plant which has not been in existence since 1935 or previous to that time, and we always compare these plants against each other. Secondly, the numbers relate to total body count and not to body count of retirees only. Whereas in the Hopkins study, because we asked for a statistically rigorous evaluation, we did select from a group of 27 deaths only 22 white male retirees for strict probability calculations. Does that set aside a little bit of

your reservation, Dr. Lloyd?

COMMENT-Dr. Charles Hine

In the Brigham Young study we just had the following questions and corrections, since we had recently reviewed these data. One, this was a study essentially of smelter workers; however, a non-smelter worker was included in the groups. Two had Greek death certificates from which the exact cause of death could not be ascertained. This was done because it was probable that there were two cases of undefined cancer included in the data, and there were several cases identified as metastatic cancer without definition of a primary site included. So when the data are corrected for this, I think there were less than 17, and in such a small number the significance becomes questionable. I am sorry I cannot recall the name of the trained nosologist that worked with Dr. Milby in his other studies. We can find this out if you wish.

ANSWER-Dr. Andrew Reeves

Epidemiological studies are fundamentally unsuitable to illuminate the real etiologic agent in a situation like this. I am reminded of my own undergraduate days 30 years ago when it was generally believed that naturally occurring potassium has a light degree of radioactivity. I believe some 10 or 15 years later, it was realized that it was due to a then undiscovered element, francium, which contaminated potassium to a minor degree with this apparent radioactivity. I was just thinking, has Dr. Ott or anyone else, among the epidemiologists, conducted any such investigations to find out if this arsenic to which people are exposed may contain a slight degree of radioactivity because it may be perhaps contaminated by something like polonium? If so, is this a possible explanantion for the puzzling carcinogenicity of arsenic in epidemiologic studies only, and not in the lab? In the lab, of course, one would use arsenic which is purified.

COMMENT-Dr. Charles Hine

We think that there is a very good point. Mr. Nelson could respond more accurately to the question concerning radioactivity content. This is being investigated further. It has been thought of as a contributing factor. We are confused because even though this is a unique plant with high exposures to arsenic, there are other things in the air from the ore. Mr. Nelson stated about five other trace metals which had been found to be present. In addition, Dr. Selikoff raised a very interesting question this morning about smoking history, and this is being gone into again by Dr. Pinto and Dr. Enderline. Our preliminary results show that most of the persons involved were smokers. Pointing toward asbestos as a carcinogen, I think Dr. Selikoff is of the same opinion, that asbestos is not a carcinogen in the absence of smoking. We feel that arsenic may be a co-carcinogen, may be associated with other materials, and this is an important point in consideration of carcinogenicity of this agent.

MODERATOR-Mr. Gerald Ott

We are developing a fairly long line of questioners. Would you like to continue, Dr. Carnow, and then maybe we can take a few from the back.

COMMENT-Dr. Bertram W. Carnow

One of the things that was not noted was the age of onset. It would seem that age of onset of exposure may be very important with carcinogens and should be duly noted, because someone starting to work in this plant at age 35, might have a very different exposure history, even though the duration of exposure is the same as someone who started in the plant at the age of 18. In regard to that, I think it might be important to examine other cohorts. We did not look at arsenic in the El Paso children but were unable to study whether it had caused any toxic effects. That smelter has been operating for some 70 years, as have many other smelters. It would seem to me that there may have been a large community outside the plant where exposure to arsenic could occur. A number of such community populations in these smelter areas might also be studied to some purpose.

We received a study carried out for the Canadian government in Yellow Knife, located in the Northwest Territory. This was a community of about 3,500 people exposed to large amounts of arsenic in the water and in the air. A significant increase in deaths was noted, particularly in the area of cardiovascular diseases. There was also some references to lymphoma and leukemia. I asked Dr. Milham to look at this paper and we agreed that the number in the sample was so small that conclusions cannot be drawn from this. We suggest, however, that this and other studies be examined and perhaps added to in the future.

QUESTION-Mr. Robert Arsenault

My questions are for Dr. Ott and Dr. Milham. Dr. Ott, in the Dow paper, which has not been discussed here, it was mentioned that the raw material was arsenic acid; however, in the Federal Register, arsenic trioxide was mentioned as one of the raw materials. Can you clarify this?

ANSWER-Mr. Gerald Ott

Arsenic trioxide was a starting material.

QUESTION-Mr. Robert Arsenault

So that was present in the Dow plant?

ANSWER-Mr. Gerald Ott

Arsenic trioxide was present in one building which was apart from the packaging building where most of the employees worked. Lead oxide was mixed with arsenic trioxide and the arsenic was converted to pentavalent form in

the first building. The material was then pumped over to the finishing building in a slurry and dried and processed for packaging.

QUESTION-Mr. Robert Arsenault

You also made the statement in that paper that the only common denominator that could be found was exposure to arsenicals. How were the other chemicals these workers were exposed to evaluated, and if they were evaluated, why wasn't the data put in the paper?

ANSWER-Mr. Gerald Ott

We have evaluated, using proportionate mortality techniques, every production unit in that location. The judgment was made, based on having looked at all these production units in relation to the arsenicals one, that the experience in the arsenicals area was unique to that unit. This is not to say that those people did not have other observed chemical exposure and I donot think we attributed all the effects to arsenicals. It was felt that regardless of whether there was some synergism present or not, the experience we were seeing was unique and not duplicated in any other production.

COMMENT-Mr. Robert Arsenault

One of the points that particularly impressed me was your equation wherein you described a dose-response relationship. For the basis of the data you used the air intake of 4 cu m a day. Was this your basis for ingestion in the lung or ingestion by swallowing? Most of the literature indicated the use of 10 cu m, which would have given you a cumulative exposure of 2 1/2 times what was reported in the paper. If you use the same method, the log to the bases of exposure, based on 10 cu m/day exposure, you get a straight line relationship which crosses the no effect level or unity at about 1000 µg of arsenic exposure. The curve does not come down in the parabola that you had in your paper. So, I would submit that your exposure for dose-response relationship is much too low by about 2 1/2 times.

I have a question for Dr. Milham with regard to the orchardists. In re-evaluation of the EPA study by Nelson, where the EPA showed no increase in lung cancer in a very well done statistical paper, the re-evaluation of the data by subdividing the population into counties showed, as you said, a 28 percent increase in Chelan County. However, Okanagon County showed an equal amount of decrease. This, in my mind, nullifies the effect of Chelan County, because you subdivide to the point where your variance exceeds its statistical reliance.

ANSWER-Dr. Samuel Milham

The study I talked about today is a statewide study, irregardless of county. Most of the orchard people in the state work or live in the orchard

areas: Chelan, Yakima and Okanogan Counties. I have not done a county by county breakdown for these people, but orchard workers in general in our state have 30 percent excess of lung cancer. As I said, farmers in general, (there are 24,000 of them) have a 20 percent deficit. I think this might speak to the smoking question, too. I cannot conceive of the fact that orchard workers are heavier smokers than strawberry farmers.

COMMENT-Mr. Robert Arsenault

As I recall your numbers, you had, over a 20-year period, a 19 percent increase which was not statistically significant.

COMMENT-Dr. Samuel Milham

Oh, but it is.

QUESTION-Mr. Robert Arsenault

If you took the last 11-year period, there is where you got your 27 percent. I would like to know how many numbers of orchardists were involved in that 11-year period.

ANSWER-Dr. Samuel Milham

I do not remember, but drop me a note and I will give you the exact numbers. I have got a stack of tables that thick. I will xerox a sheet off for you.

MODERATOR-Mr. Gerald Ott

May we have another question from the back of the room?

QUESTION-To Dr. Milham

Dr. Milham made a comment that I think should not go unnoticed by this group which related itself a little bit to some of the discussion that occurred yesterday as well. He said, in some instances in the children, the levels tended to go up or tended to go down, all of them at the same time. I wonder how much of this is due to laboratory quality control? That raises one other question, notwithstanding all of the emotion that may be packed into anyone's view for or against any particular subject, it goes something like, how precise we try to be with such imprecise measurements.

ANSWER-Dr. Samuel Milham

We split samples, and the lab that tested the arsenics has been doing them for about 40 years. It is in the pesticide region, and they did urinary arsenics for the old lead arsenate studies. The split samples were sent to two labs. The University of Washington did some arsenics for us, as

did the Tacoma Smelter. We shared some of our samples with Asarco. I submitted them blinded, coded, and frozen, so they did not know when the sampling was done or from who it was taken; if it was a case sample or from a control, there was no identity except a number. I am fairly confident that the secular changes are real. The case-control differences are just so beautiful that you cannot believe it. There was one little girl in the case school that had a normal urinary arsenic. It turned out that she lived in the central area of Tacoma and was bussed in. We noticed this after we examined our data.

MODERATOR-Mr. Gerald Ott

Mr. Nelson, would you like to comment?

COMMENT-Mr. Kenneth Nelson

I want to corroborate what Dr. Bundy said, that certainly there are analytical analomies that occur in any laboratory. I have raised the same question about the beautiful periodicity of Dr. Milham's data. Furthermore, if you look into the arithmetic of the situation, you see some questions are in order. For example, the highest outdoor, outplant concentration of arsenic measured by the University of Washington (they made a number of measurements) was, as I recall, 4 µg of arsenic/cu m of air, a maximum concentration over a 24-hour period. There is no particle size separation, just total arsenic, irrespirable and respirable. If one calculates that a child would breathe, say a maximum of 10 to 20 cu m in 24 hours, the intake would only be on the order of 40 to 80 µg. This hardly accounts for a level of arsenic in about a liter of urine or perhaps a little more in a 24-hour period, of 300 µg/cu m, .3 mg. Now obviously, there must be arsenic intake from other sources if the analyses are valid, and that is a good question. We know that one portion of seafood, salmon, taken from that area will elevate the urinary arsenic content to about that level. We have shown this repeatedly in adults and children. One portion of seafood, salmon lobster, shrimp, etc. So I cannot quite accept the arsenic data that you have accumulated, Dr. Milham. One other point, you said before and after the strike there were marked differences in the urinary arsenic content of the children you sampled. We obtained the results of those urine samples and we could find no differences, no statistically significant differences between the two groups of samples.

MODERATOR-Mr. Gerald Ott

We have really run out of time. The fact is we have gone over. Thank you very much.

CONFERENCE CHAIRMAN-Dr. Bertram Carnow

I would like to introduce Dr. Joseph Wagoner, Director of the Division of Field Studies and Clinical Investigation at NIOSH, who will be the Discussion Leader in the Panel Discussion on TLV'S.

SECSION X - PANEL DISCUSSION OF TLV'S
DISCUSSION OF NIOSH' POSITION ON TLV'S

Dr. Joseph Wagoner, Discussion Leader
National Institute for Occupational Safety and Health

Before turning the session over to the panelists, I would like to give an overview and some background on the NIOSH position as a lead point from which to depart in this discussion. In the sense that we have made our recommendations and since we are the funding agency for the convening of this conference, we are looking for some guidance and, hopefully, some concensus by the members of the panel.

The dimensions of occupational and environmental health are rather staggering. The WHO has estimated that 75 to 85 percent of all cancers may well be related to the environment. Dr. Robert Stone, Past Director of NIH, recently made the statement that most known environmental cancers result from increased agricultural and industrial technology

I would like to just sort of digress for a moment to where we have been, because I think this is instrumental in the determination of where we are going. Over the last four years, since the passage of the Occupational Safety and Health Act, there have been three standards recommended by NIOSH which have undergone review and been promulgated by OSHA. I think it is also noteworthy that all three of these standards were initiated as the result of litigation and all three dealt with carcinogens.

With regard to asbestos, we had both animal data and human data, so a TLV was set; although, NIOSH indicated in the preamble to the Criteria Document that there was no assurance that this would prevent asbestos induced neoplasia. Subsequent to this, fourteen substances were identified as suspected carcinogens, including betanaphthylamine, benzidine, bischloromethyl ether and a variety of others. Many such were identified from animal research data only. I bring this point out because I think we are on the other side of the coin today. These agents were referred to as being only animal carcinogens. We had to look at man, as we have repeatedly heard we must do. In other instances we already had both animal and human data. It was the concensus of both NIOSH and the Advisory Council that, indeed, there should be no detectable level for carcinogens. Vinyl chloride is the third carcinogen which has recently been addressed. We have the animal data, we have data in humans, and, once again, we took the position that we were unable to define a safe level.

I think that this provides us with some background as to where NIOSH has gone, what our recommendations are, and how we feel about TLV's. Today we have seen that our animal bioassay models have failed us. We have been unable to demonstrate that, arsenic is, indeed, a carcinogen. However, we do have the most definitive species of all, man, and the

preponderance of evidence from the epidemiologic studies in a diversity of environments, be they copper smelting industries or industries using arsenic trioxide, repeatedly has shown an excess of lung cancers to be a manifestation among individuals exposed to arsenic.

Two or three other issues were repeatedly addressed. One, the need for cigarette smoking as an integral agent in the introduction of neoplasia. We have recently seen data which now lead us to believe that, had we acted on the basis of this assumption with regard to uranium mining, we now would be seeing an epidemic in greater proportions than those being experienced among the non-white uranium miners (an excess in lung cancer risk is demonstrated among Indians who do not smoke but are working in the uranium industry). The inference that, in the absence of cigarette smoking, arsenic or asbestos is not carcinogenic certainly has no basis for mesothelioma or for cancers of the gastrointestinal tract. There are those who would also believe that, although there are fewer available data on this, smoking is not a necessary element in the induction of lung cancer among asbestos workers.

Is there some other material that might be in the ore which might lead to the manifestation of lung cancer and cause a bias in interpretation of the data? Some two or three years ago, Dr. Selikoff requested that an evaluation be made of ores going into the copper smelting operations for potential contact or contamination of asbestos. Indeed, NIOSH surveys indicate that asbestos is not a contaminant that we need worry about. Furthermore, unpublished data, which will be presented at the New York Academy of Sciences Meeting on Occupational Carcinogenisis by Dr. Newman and Dr. Archer, demonstrate that lung cancers in copper smelting industry workers in the Butte area have an over preponderance of adencarcinoma histologic type. A blind evaluation of 143 lung cancers, from both workers and the general community, was conducted by a panel of pathologists consisting of Drs. Aurbach, Cushner, Sokomano and Newman.

Based on the available evidence, what then is NISOH's position with regard to arsenic? First, NIOSH considers that the overwhelming evidence in man cannot be negated and arsenic is to be considered as a carcinogen. Second, we maintain that the present state of art, certainly with regard to epidemiology and most certainly in reference to experimental bioassay, is insufficient to demonstrate a safe level for carcinogenisis. Third, we agree, and it was instrumental in our decision making and our recommendation, that the worker should bear no additional carcinogenic burden as a result of his workplace, over and above that experienced by the members of the general community. On this basis, NIOSH took the position that the level we would recommend is .002 mg/cu m. This permits us to make a distinction, analytically, different from the ambient natural background, and still equate levels low enough so there was little difference, if any, between worker exposures and those of the general population.

I would like to charge this committee to address five issues:

1. Do they consider arsenic trioxide to be a carcinogen?

2. Is the present state of art sufficient to define a safe level and a threshold limit value?

3. Can we assess risk with level of exposure with the data we have in hand?

4. Where do we go from here for controls?

5. What medical surveillance is required or recommended for current employees, based on the assumption and the fact that a great proportion of current employees are bearing risk factors resulting from past inadequacies?

With these thoughts I will now turn the discussion over to the first member of the panel, Dr. Michael Utidjian, Director of Occupational Medicine and Toxicology at Tabershaw-Cooper Associates. Dr. Utidjian was introduced to you earlier in the conference. Dr. Utidjian.

BRIEF HISTORY OF THE CHANGES IN TLV'S FOR ARSENIC

Dr. Michael Utidjian
Tabershaw-Cooper Associates, Incorporated

Before answering those five points, I'd like to give a brief historical review of the gyrations that the arsenic standard has undergone over the years. As far as we know, the earliest standard in this country for inorganic arsenic was an emergency war standard, and it was suprisingly low, 0.015 mg/cu m. This was promulgated by the American Standards Association as it then was called; it is now ANSI. We do not know the basis for this proposed standard. It was a very low standard for that time and it may have been a reflection of the general fear of arsenic as a highly potent poison.

By 1945, when Warren Cook published a very useful list of the current standards in some individual states and with the U.S. Public Health Service, the recommended standard for arsenic had crept up to 0.15 mg/cu m. The basis then was analogous with lead, a toxic heavy metal about which it was felt more was known at that time. The standard for lead was also 0.15 as a TLV. In the article, Warren Cook commented that representations had been made by a single large concern involved in the manufacture of arsenic trioxide who claimed that on the basis of their experience, a level of 0.5 mg/cu m was safe, as it appears in Cook's paper, 5.0 mg/cu m. (I have often wondered whether this is actually a misprint for 0.5 or whether 5 mg was, in fact, the suggestion for a safe level in this industry.)

For one year, the standard was 0.1 and then by 1947 it was raised to 0.5, which is still the legal standard on the Federal Register today. This was also, for many years, the American Conference of Governmental Industrial Hygienists' TLV. When we got involved, about 18 months or 2 years ago, in the preparation of the original NIOSH Criteria Document, the big issue that we as contractors had to debate with NIOSH officials and the External Review Committee was whether the evidence was irrefutable that arsenic was, indeed, an occupational carcinogen. This was a more hotly debated issue than it might be today, or has been during this Conference.

The conclusions of NIOSH at that time (prior to the Allied and Dow disclosures) was that arsenic was a carcinogen. I say this because of the wording of the NIOSH document. At the end of the recommendation, the last few lines state, "However, more recent reports associate inorganic arsenic with occupational cancer. The Lee and Fraumeni report (about which we have heard today) strongly suggests that exposure at or around 0.2 mg of arsenic per cubic meter can result in an increased incidence of cancer. Because of the seriousness of the disease, prudence dictates the standards should be set at least as low as .05 mg of arsenic per cubic meter. It is believed that exposure at this level should, at the

at the minimum, significantly reduce the incidence of arsenic-induced cancer."

With this recognition of carcinogenic potential, there was an attempt to suggest, if not an absolute threshold, at least a feasible or reasonable one. A threshold of 0.5 mg/cu m is the current recommendation of NIOSH. This was made prior to the latest proposal that has been defined by Dr. Joseph Wagoner. I think this puts NIOSH in a curious and equivocal position, because we have this situation in which there seems to be numerous carcinogens; asbestos with a numerical standard, although this has been under heavy attack; 14 carcinogens, which have essentially a zero tolerance standard, and for a few months arsenic seemed to occupy an intermediate position.

After that brief historical review of the vacillations of the standards, I will try to address myself to Dr. Wagoner's questions. After extensive review of the literature, I feel that the evidence is incontrovertible, that arsenic is a carcinogen to man. I am not, for all the reasons that have been discussed today, discouraged from taking that position by the lack of animal model for the time being. I am confident that sooner or later an animal model will be found.

I think there are not sufficient data to set a numerical threshold. There are sufficient data to state that there is a level below which cancer will not occur. However, the position is reasonable that if there is a certain amount of arsenic in the total environment, the ambient air, in our water and food, etc., it would be ridiculous to propose a zero standard for occupational exposures to arsenic at this time. This is apart from the legal and technical difficulties of measurement and definition. I think the current proposal is a most reasonable one.

I think the only thing I want to contribute concerning medical surveillance is that sputum cytology should be added to, or even take precedence over, chest x-ray as a means of monitoring. There is growing evidence that sputum cytology will make a valuable contribution in early detection of lung cancer.

DISCUSSION LEADER-Dr. Joseph Wagoner

Thank you,Dr. Utidjian.

Dr. Warren Ferguson, Director of Occupational Health and Product Safety at the Allied Chemical Corporation, also presented earlier today, is the next discussant on the panel. Dr. Ferguson.

PROBLEMS IN SETTING TLV'S FOR ARSENIC

Dr. Warren Ferguson
Allied Chemical Corporation

It should be obvious that we have been asked to address a question which amounts to unscrewing the inscrutable. Obviously, when you only know the exposures for arsenic by gross estimates and you do not have the exposure estimates from such places as coke oven operations, which share the lung cancer problem, phosphoric acid manufacturers, which apparently do not share the lung cancer problem, phosphate mining, borax mining, and a whole host of other activities, including carpentry; it becomes difficult to develop a data base that statistically indicates a certain amount of arsenic from a specific activity does or does not result in an excess of cancer.

We are again faced with a problem in which arsenic is used in the gross term. Arsenic is a material whose alleged properties are defined "because it is an element." We know this is not true in reference to chromium and I question if it is true in reference to arsenic. Our company has never said that any and all arsenicals are carcinogens, merely that among certain arsenicals there seems to be one or more materials that exhibit carcinogenic properties. We do not know the answer to this problem and expect that, by the time we do know the answer, the engineers and hygienists will have already solved it and the debate will have become academic.

I offer the following in response to Dr. Wagoner's 5 questions.

1. Arsenic in some forms is a carcinogen.

2. In the present state of the arts we cannot prescribe a safe value. A combination of engineering and hygienistic approaches might indicate a level and the types of operating constraints and precautions which might bring us to a "zone of acceptable risk," especially if we look at some of the analogies we have in other known carcinogens.

3. We cannot assess the risk. Perhaps if one takes a square root function or a fourth power function or a log function and extrapolates a lifetime dose and comes out with an induction period of 95 years, it can be assumed that the risk is not too great.

4. Dr. Wagoner asked, "Where do we go for controls?" I am not sure if he is talking about statistical controls or engineering controls. Again, arsenic is ubiquitous. Any control population is going to have a body burden of arsenic that was obtained through the food, water supply, inhalation, gardening activities, and other individual exposures. So, this is not an exact analogue to a definite substance, such as vinyl chloride. Vinyl chloride can be presumed not to be present in clean

air, up-wind from a vinyl plant. This presumption cannot be made with reference to arsenic.

5. Concerning medical surveillance, we are currently concentrating on chest x-rays, skin examinations, urinalysis, and blood cell examination. We are also,on a one-time basis, going to use sputum cytology. I might tell you that in past decades we have had serious adverse psychological effects with sputum cytology. We have some emotional cripples in one of our plants, people who were told 20 years ago that they probably were going to get lung cancer within the next couple of years. These people still do not have lung cancer, but they have psychotic problems which have destroyed their usefulness. We have tended to use sputum cytology more diagnostically than as a screening mechanism; but, in this particular case, we are going to use it on a one time basis for screening just to see what develops.

I believe that we can estimate an acceptable risk and come up with a number, other than the lower limit of detection or twice the lower limit of detection, because we are talking in terms of our partial documentation and Dow's documentation, not only of persons with high daily doses, but episodic doses in people who obviously were literally covered with dust on a repeated basis. Some of the numbers are as high as 20 mg/cu m. This is a large amount of any agent. It does not matter if it is starch, talcum powder, or anything else. This is actually more than we should have from so-called non-toxic dusts.

There is an excellent chance that part of what happened in these isolated populations was not necessarily due to the daily burden but repeated, episodic, overwhelming exposures which we no longer tolerate. Such exposure does not happen anymore. This is one reason we feel some degree of security that our plant is currently safe. This is why we elected to close down our insecticide plant and keep the arsenic acid plant operating. The acid plant operates at between 6 and 15 µg/cu m, more or less consistently, and frankly, this is about the best we can do. Compared to situations which previously occurred on an episodic basis, we have come a long way since 1951.

Another reason for feeling that there is room for hope in the arsenic business is simply by comparison of arsenic with our experience with the chromates and benzidine. We have had experience in controlling chromates and benzidine at a non-zero level for a sufficient number of years and if we had not maintained essentially complete control, we would most certainly be seeing the leading edge of cancers in the current cohorts. We are not seeing this. In my opinion, arsenic is considerably less potent as an agent than the insoluble chromates.

In the first place, the recorded peak exposures of the affected populations are far higher than they ever were in the chromate business, and the recorded latent periods are much longer. The longevities are

much better. Check the 1948 reports and see how long these unfortunate people in the chromate business lived. The proportionate mortalities were about the same. I think we have demonstrated over 25-years experience that, if we truly observe a ceiling of .1 µg/cu m of chrome and a TWA of about half that, we can lick the chrome problem or certainly control it 95 percent. This is why I feel there is a number relating to arsenic, my guess would be 50 µg and 10 µg, which will give acceptable protection, provided we have a good ceiling control

DISCUSSION LEADER-Dr. Joseph Wagoner

Thank you for your comments, Dr. Ferguson.

Our last panel discussant also has been presented to you earlier today. I again introduce Dr. Samuel Milham, who is from the Washington State Department of Social and Health Services. Dr. Milham.

COMMENTS ON ARSENIC TLV'S

Dr. Samuel Milham
Washington State Dept. Social and Health Services

I shall answer Dr. Wagoner's five question quiz simply in a one, yes; two, no; three, maybe. In all seriousness, I do not have any doubt, or have very little doubt, in my mind that from epidemiological evidence as presented here and previously in the literature, that inorganic arsenic is carcinogenic. I would like to second Dr. Utidjian's remarks about sputum cytology. I would like to see in high risk environments, at least a one-shot screening of the population, just to see what the status of sputum cytology is. If, indeed, we do have a lung cancer excess, I think we are going to see some abnormalities in sputum cytology.

In other such industries we have taken a look, and have seen abnormalities. I would be willing to predict that if ASARCO examined sputum cytology at the Tacoma smelter, they would find a high prevalence of frank abnormality.

In terms of TLV's, this is not my area of specialization, but I think a realistic factor must enter in here. We saw a slide this morning of two men shoveling arsenic trioxide with white dust all over them. From what I know of the Tacoma smelter, and from my talks with smelter workers and discussions with the medical staff, I do not see anyway on earth that the new standard could be met, short of demolishing the plant and rebuilding. I think that sort of reality factor has to be considered. Basically these are my sentiments.

PANEL DISCUSSION ON TLV'S - ARSENIC

QUESTIONS, ANSWERS, COMMENTS

DISCUSSION LEADER-Dr. Joseph Wagoner

I would like to thank the panel discussants. Since the questioning session for the previous panel was interrupted, we will also answer carry over questions from that session as well as the session on TLV's.

COMMENT-

I have some information in answer to the question raised earlier about Wentachee Valley lung cancer experience. The question concerned lung cancer mortality rates of the counties that are included in the Valley. There is considerable variation in the lung cancer rates. The county which shows a significant excess of lung cancer is Chelan County. Approximately 70 percent of the population included in the Wentachee Valley Orchard workers come from that county.

COMMENT-Dr. Clark Cooper

I want to speak a moment on sputum cytology to which my co-worker, Dr. Utidjian, referred. I think the way it has been handled in the proposed guidelines for medical surveillance of arsenic workers is appropriate. I approve of recommending sputum cytological analysis as a supplementary procedure for early detection of lung cancer, rather than making it a required examination procedure. We must increase and strengthen our resources for sputum cytologic examination before we embark upon a widespread examination program of suspected high risk groups. There are few laboratories equipped and really prepared to do first class sputum cytology analyses. The uranium study has depended upon Dr. Saccomanno in Grand Junction. These are good laboratories, but there are not enough of them.

One not only has to deal with the questions involved in classification, but also must decide what is to be done with the results when they are obtained. Mr. Ferguson also mentioned some of these problems. Proper management of an individual who is sputum-positive and x-ray negative is a major problem. What should be recommended to a person with atypical cells but who does not have cancer? Should he be removed from the work force? These are serious questions that need epidemiologic study. I strongly suggest that either the National Cancer Institute, which is supporting the excellent work being done at Johns Hopkins and Minnesota, or some other group, do whatever is necessary to make resources available for adequate sputum cytology programs in this country. While agreeing with Dr. Utidjian I also think this has to be handled with caution, recognizing the real difficulties that may ensue.

DISCUSSION LEADER-Dr. Joseph Wagoner

We share your concern with the inadequacies in terms of the facilities to undertake sputum cytology, Dr. Cooper. I think the state of art

is beginning to be developed with the study of the Tyler, Texas population, some of our observations on the uranium populations, and Dr. Frost's observations with the chloromethyl ether. All point toward an over-riding fact that repeat sputa and induced sputa pick up abnormal cells in the absence of radiological evidence, which subsequently turns out to be frank neoplasia

COMMENT-Dr. Herman Kraybill

At the Cancer Institute, we have been evaluating the importance of sputum cytology. The procedure, I think, is best described as being on trial for its usefulness, but it is also a questionable procedure because even when frank malignant cells are found in the sputum, it does not indicate the location of the cancer, what might be done about it, or if something is done, whether it will be curative. However, it is a very important procedure, and it should be approached systematically on the same basis on which you would use a clinical trial of a new drug or a new diagnostic test to determine the net health benefits of the procedure. Sputum cytology should be one of the things that is done, but it is not as satisfactory a protection of workers' health as keeping down occupational exposures to known carcinogens.

COMMENT-Mr. Kenneth Nelson

There is one thing about the proposed arsenic standards that puzzles me greatly, and that is the seemingly inconsistent approach. For example, the vinyl chloride standard, I believe, is one ppm of vinyl chloride vapor, and that translates into about 2600 mg of vinyl chloride/cu m of air. The asbestos standard, I think, is 2 or 5 fibers/ml. This translates into 2 or 5 million fibers/cu m, which conservatively would weigh about 200 µg. So now we come down to arsenic and the TLV differences among these numbers.

DISCUSSION LEADER-Dr. Joseph Wagoner

You share the concern as we at the Institute share, the concern of the differential piecemeal approach that has been used in the past in handling carcinogens. I think we at the Institute are trying to grapple with that problem and coming up with a more uniform rational consistent policy on it. In fact, I know we are.

COMMENT-Dr. Douglas Frost

I want to underline what Dr. Ferguson said, that in dealing with arsenic, we are not dealing with anything like vinyl chloride. Arsenic is an ubiquitous element. It is a part of all of us, in all foods and everything we encounter, and it may be an essential nutrient. Klaus Schwarz has been trying to show this for years now and I think part of the reason for the failure to do this is that arsenic is so very ubiquitous in nature. It is in the air and is most difficult to eliminate completely, particularly in phosphates. That is why we have not been able to show that it is essential.

I keep looking for alternative causes of cancer. You have all agreed that arsenic is a carcinogen. I have corresponded with people in England who questioned this years ago. Sir Ernest Kennaway never did agree that this is true. Through correspondence in 1966 with J. M. Barnes of the British Research Council, I learned that in a factory where lead and calcium arsenate products were manufactured, it finally was concluded that "the experience of our work which extends over a period of 43 years, is that none of our employees who regularly processed arsenicals over long periods, up to 30 or 50 years, ever developed cancer. In fact, eight of them lived to reach their mid-eighties and were all active to near the end of their days."

In a letter, R. S. F. Schilling of the London School of Hygiene, Department of Occupational Health, wrote, "I have sometimes wondered if the powdered sulfur, which is the main ingredient in dip in percentage, played any part. A day spent working in it produced very much the appearance and sensation of the mild sunburn on exposed skin. It would be well known if it were carcinogenic (I hope) but it may have complicated the picture."

One thing that Mr. Ott and others at Dow overlooked was that their workers were exposed to elemental sulfur. According to the work of Horton and others, elemental sulfur was shown to be carcinogenic. The Lee-Fraumeni paper implicated the known carcinogenicity of sulfur dioxide, but we always come back to arsenic. I think it is the power of the word-- the power of arsenophobia.

DISCUSSION LEADER-Dr. Joseph Wagoner

We would be glad to share with you any of the data which you got from across the ocean in terms of our decision making. Would you care to make them available?

ANSWER-Dr. Douglas Frost

It would be well to bring England into this because they have had a century-long misunderstanding about arsenic. I think the British tolerance for arsenic was set in error, and arsenophobia, I think, is the most virulent of all the phobias by far. We do need to get straight about "arsenic" and arsenicals.

COMMENT-Dr. Merle Bundy

I would like to second Clark Cooper's concern about the use of sputum cytology because of the following difficulties:

1. The reading of the specimen: Do we have enough trained people to read the slides?

2. The technique in obtaining the specimen. In the experience of one of our doctors, the technique of obtaining a specimen leaves a lot to be desired.

He thinks that a process which is no more effective than what we have been able to demonstrate so far is useless and we may also lose ground with the employees. I would suggest that NIOSH or someone should be thinking about developing expertise across the country wherein facilities for sputum reading would be available. There are some proposed studies not yet under way, to investigate the usefulness of sputum cytology in the coke oven population.

DISCUSSION LEADER-Dr. Joseph Wagoner

With regard to that, we do have the session at the New York Meeting on Occupational Carcinogenesis where we are attempting to at least bring out some of the current state of arts, and I recognize your concern and do share it also, as a blanket across the board.

COMMENT-Dr. Merle Bundy

One other thing, Dr. Wagoner. In all of the pronouncements, noon has ever said anything about the age at which this should be started. Even Dr. Saccomano, I think, said that in a smoker there is no need to start under the age of 32 and in a non-smoker, under the age of 35.

DISCUSSION LEADER-Dr. Joseph Wagoner

As we use sputum cytology in the uranium industrial populations, I am unable and unwilling to come up with a blanket statement on the utilization of sputum cytology. Just as I maintain with regard to the routine use of x-ray in asbestos exposure, this is complete misutilization of medical care available in the United States for routine x-ray during the first, second, and third years after onset of asbestos exposure.

COMMENT-Dr. Samuel Epstein

In addition to the reservations expressed by Dr. Bundy and others on the utility of cytology, I would like again to stress the fact that cytology is merely an early method of diagnosing a generally incurable cancer. I submit that, in terms of our limited resources, it does not make very much practical difference if an incurable cancer is detected slightly earlier than would otherwise be the case. I would like to suggest that our resources should preferably be directed to prevention of exposure to carcinogens rather than to early diagnosis of incurable cancers.

If I may bring England into the discussion, there has been reference to Sir Ernest Kennaway, who is a very close personal friend of mine and with whom I had the privilege of working with for some time. Sir Ernest Kennaway, in fact, wrote a paper on arsenic as a contaminant of tobacco in which he suggested that one of the reasons why tobacco smoke could be carcinogenic was due to its content of arsenical insecticides.

There has so far been a very proper concern, almost exclusively so, with problems of occupational exposure to arsenicals. I would like to suggest that there is also a large human population that has been subjected to fairly heavy exposures of high concentrations of arsenicals. I am talking about the Vietnamese, particularly the Montanyards, who have been deluged periodically with a wide range of herbicides, including cacodylic acid, an organic arsenical. While I am not aware of the exact rates of degradation of organics to inorganic arsenicals, nevertheless, it appears that soil levels in parts of Vietnam would be extraordinarily high. I would recommend consideration of prospective studies on these populations in relation to arsenical conamination of the soil and argicultural products and possible carcinogenic effects. Finally, I question whether some of the more recent data on carcinogenicity of arsenic has relevance to the common custom of use of arsenic as a feed additive, particularly for poultry and swine.

COMMENT-Dr. Bertram Carnow

I would like to make one final comment on cytology. In 1960, we carried out a pulmonary cytology study using the ultra-sonic nebulizer with 5 percent saline and 10 percent propylene glycol in a heated aerosol to induce deep cough and obtain cytologic specimens. We examined a thousand smokers at the Union Health Center, looking for Papanicolaou's class IV and V cells. We did indeed find some abnormalities and found two people who had class V (malignant) pap smears. In one person, we were unable to find X-ray evidence of cancer. We followed him at frequent intervals and took comparative chest x-rays every 2-4 weeks. After 3 months, the x-ray revealed a density which was pneumonitis. Behind it, in a tertiary bronchus, a very small malignant tumor was found and a pneumonectomy was performed. We were pleased with this until he died of metastases 18 months later. This kind of exercise brought me to preventive medicine. Cytologic screening to monitor people who have already been exposed may be helpful. To think of it as tool for determining the nature or extent of exposure of workers is dangerous.

QUESTION-Dr. Emanuel Landau

If our concern is with environmental as well as occupational exposure, would it not be desirable to look at the incidence of cancer and cardiovascular disease among the wives and children of smelter workers and, if so, should not the roster of workers be used as a possible starting point for such a study?

ANSWER-Dr. Joseph Wagoner

Yes, I think it would be desirable. There can be inter-agency agreement. We are currently attempting to do some of this ourselves.

QUESTION-Mr. James Woodring

I understand the proposed TLV would be applied to all forms of inorganic arsenic. I am wondering, would there be value in trying to determine the exposure to various valence states and if in fact there are recommended methods for doing this?

ANSWER-Dr. Michael Utidjian

As far as I know, this issue came up again when we were discussing the possibility of monitoring the urine as a means of biological monitoring with the almost cerainty that there would be a very real distinction in the toxicity of the two forms, and the belief that most of the arsenic from seafood and other dietary items is in the pentavalent form. It was thought it would be rather difficult. One of the objections to doing urinalysis as a monitoring procedure is that every now and then you get very high levels in either unexposed people or people whose occupational exposure has not gone up, and it turns out that they have eaten a lobster tail within the last few days or some oysters or some other seafood. We investigated the possibility of some analytical method which would differentiate pentavalent from trivalent arsenic in the urine, but there was a negative response. There are macroscopic wet methods for differentiating different valency forms, conventional quantitative analysis, but they cannot be applied on the microscale. This whole issue again was presupposing that if the arsenic entered the body in pentavalent form it would stay in that form and this is by no means a certainty. I would like to move on and just comment on Dr. Carnow's point as we talk about monitoring. I think there is a very real distinction between sputum cytology as a monitoring procedure (which we have never used and I know of no recommendations for such monitoring), and the point that Dr. Carnow made for sputum cytology as a means of monitoring for early detection for those who have already been exposed, possibly to a critical carcinogenic dose. If there is only one or a handful in whom the cancer could be successfully treated, they certainly deserve every known means of monitoring for early detection. I understand that at Johns Hopkins now, by doing brush biopsy of individual bronchi, they have been able to specifically locate starting from sputum cytologic evidence alone. I just feel that everything possible should be done for those who have already been over-exposed, but I can only endorse the philosophic point that in this, as in all other areas of prevention, prevention by environmental engineering controls is the way to go.

DISCUSSION LEADER-Dr. Joseph Wagoner

May we close the session now so we can get back on schedule? I think Dr. Carnow has some closing remarks for us.

CONFERENCE SUMMARY

Dr. Bertram Carnow
Conference Chairman

This is the first conference I remember which finished fifteen minutes ahead of schedule, and we will try to complete this session as quickly as possible.

Summarization of the conference is relatively easy. I believe that there is a consensus among participants that inorganic arsenic is a carcinogen and that we are now dealing with a quantitative question regarding the level for arsenic which should be set to safeguard the health of workers. There is no longer a need to question whether or not arsenic is a dangerous material that workers should not inhale or ingest.

There are questions that still remain to be answered regarding appropriate animal models, carcinogenic co-factors, etc.; however, the safeguarding of the health of workers cannot wait for the final resolution of these questions. Some comments about the limitations of cytology and x-ray have been expressed. It is a most frustrating experience to find cancers in asymptomatic, x-ray negative, individuals and not be able to help them. The point that Dr. Utidjian made, that we must use every opportunity to diagnose those that have already been overexposed in the hope of early surgery and an increased salvage rate, is certainly valid. This is a reasonable course for those already imperiled, but it should not be used for mass screening for those who may be exposed in the future.

In commenting on Dr. Reeves' statement that we cannot, because of the multiple factors involved, use epidemiology as a way of diagnosing or establishing a causal relationship; epidemiology is probably the only way to ultimately arrive at a reasonable conclusion about the causal relationships of a material in a complex environmental system. This appears to apply particularly with arsenic, since there have been multiple studies on a variety of people, all of whom were also exposed to other materials.

If one observes the total picture, one sees that in cohorts, as well as in people exposed to a host of different materials, there is a common exposure to a material which results in lung cancer. This common material is arsenic. We must continue with epidemiologic studies, because this may be the only way in which a more complete picture will ultimately emerge (i.e. dose-response relationships, latent periods, and co-factors). This in no way permits us to delay in taking strong measures to protect workers. We cannot afford the luxury of waiting to act while determining how many people are dying now and speculating about how many people are going to die in the future.

I should like to deal with one additional factor in my closing remarks. During these sessions results of a number of studies were quoted from the literature which may not have been methodologically sound; these studies, however, were used to make assessments of risk. Important studies, such as these, should not have to wait for a criteria document to be established. There should be ongoing peer review and it is hoped that our Society will take the lead in carrying out such reviews to determine soundness of data and the data base, when important studies emerge.

Since this will be my last appearance, I would like to thank all of you for coming and urge those of you who have made presentations to send us a copy of any documentation of your presentation. If you have not written the material, at least send copies of the diagrams, figures, etc., so that we can make an accurate transcript. The transcript will be made available by NIOSH, I believe for a fee. I doubt if admission to this meeting was adequate to insure a copy of the proceedings for everyone at no cost.

I would like now to turn this conference over to Dr. John Goldsmith of the National Cancer Institute of the National Institute of Health. He will serve to put the conference in perspective.

CONFERENCE IN PERSPECTIVE

Dr. John R. Goldsmith
National Institute of Health

The first order of my business is to ask the conference to join me in expressing to Dr. Carnow and the staff our appreciation by a round of applause. I think they have done a superb job of organizing the meeting and I feel very grateful to them to have had a chance to participate.

At the Council Meeting of the Society before this conference started, it was agreed that one of the problems in the general field of occupational and environmental health is that too little of the scientific content of our meetings is communicated in easily understood language. In my remarks, I will attempt to put into plain language my sense of what has been said and the thoughts that have been expressed at this meeting.

Lead and arsenic have been mined, used, and occasionally have poisoned people who work with them for a very,very long time. The people who own and the workers in smelters and factories using lead and arsenic are processing materials the rest of us need and are willing to purchase. We have been discussing a social process and not merely participating in a polarized debate among technicians and scientists. If the workplace or the community near a mining or processing facility is polluted by the operation, the people who live near and workers in the processes may become ill, and this is too costly.

Measuring air levels, dust levels, or water levels can determine how dirty an operation is and an estimate can be made of the likelihood of sickness by measuring the blood, urine, hair, nails, etc. of the exposed population. Both environmental and human tests are necessary to do an adequate job of prevention of disease. The environmental measures are guides to how and where to be more careful and the tests on the people provide information to determine if something has been overlooked or if the job has been done right. One thing that has not been stressed during this conference, and I feel it is very important; that is the whole idea of the body burden.

The body burden for lead and arsenic can be estimated by tests, and we can arrive at a relative exposure value for different groups of people by adequate testing. The measurement is not precise, but you can rank groups of people who live and work in different places by this set of tests. This is very useful and is one of the basic tools of epidemiologic work in this field.

How and in what way can lead make people who are exposed ill? I am, again, stressing lead in these remarks because we have just finished a session concerning arsenic, however, some of my remarks apply to both.

Enough lead can cause convulsions, especially in children; and, long periods of exposure can cause paralysis in adults. While there are warning signs of these central nervous system effects, there is not, as yet, a simple, cheap, well standardized method for early detection of these unfavorable changes. Children who have had lead poisoning have emotional problems and brain damage. One of the effects is the inability to concentrate on school work and, hence, to profit less from schooling than they might. This condition, called "minimal brain damage" by Dr. Silbergeld, is helped by drugs which ordinarily are stimulants. However, in these children such drugs have a calming effect.

There are, of course, other causes of minimal brain damage. Not every case of childhood minimal brain damage is the responsibility of users or producers of lead products. Dr. Silbergeld, by giving doses of lead which are not otherwise toxic to immature rats and other animals, demonstrated that these animals become hyperactive and, like brain damaged children, were calmed by drugs which ordinarily are stimulants. Such research, a by-product really of environmental health, can also help children who have other types of brain damage. I am stressing this because sciences, especially the health sciences, do not come in neat packages where what you are studying can only help the problem you are investigating.

Lead can cause kidney damage if the exposure continues long enough. Smelter and battery plant workers have been shown to have higher than expected chances of dying from hypertension, high blood pressure and kidney disease. According to the blood lead level found and reported to us, these workers were, by present standards, over exposed for many years.

Lead can cause anemia because it interferes with the body's system for making red cells. A material which is produced in the body called aminolevulinic acid (ALA) is a building block for making hemeglobin and similar material. This process is activated by an enzyme called amino-levulinic acid dehydratase (ALAD) in the blood. This enzyme has a concentration which decreases with increasing blood lead. This means that with increased lead exposure, the enzyme is less active or there is less of it around. When it goes down enough, the ALA made by the body cannot be utilized and it spills over into the urine. This process occurs earlier in the progress of lead exposure than anemia and is one of the earliest toxic findings. ALA in the urine, in my opinion, is probably at present the simplest, cheapest, and most valid test for lead exposure that is higher than it should be. There are many other opinions, so I am not suggesting that this was agreed to by all at this meeting. ALA increases in adults fairly early in the process of continuing lead exposure. Thus, it is a useful, dependable guide to environmental exposure and blood lead tests should be made when ALA increases in the urine. The light shifts from green to yellow in testing and if it keeps on going up it should shift through orange and other tests will indicate when it has arrived at the red level.

Dr. Joselow presented preliminary data about a very promising new test which may, in fact, be far more useful; however, there are only a few places using this test and it is premature to say the test should be recommended, although its advantages seem very great.

Spilling a little sugar into the urine is generally accepted by physicians as a warning sign that diabetes may develop if one does not watch one's diet or weight. Similarly, spilling a little ALA in the urine is a warning sign that lead toxicity may develop if one does not clean up the workplace or the community, especially if the subject is a child living in an exposed community.

Women who are exposed to lead are probably as vulnerable to lead poisoning as men; however, women who are pregnant should not be occupationally exposed to lead because the growing fetus is extremely sensitive to lead exposure. It is possible also that the lead exposures in men can effect the likelihood of abortion and miscarriages in their wives. This is another subject which needs further investigation.

Most of the lead in the body is stored in bone, from which it can be released by metabolic changes, such as those that occur in chronic alcoholism. There was much discussion about drugs called versenate, EDTA, or penicillamine. This group of drugs can, if injected, pick up lead from the non-bony tissues and transport it to the kidneys for excretion. Treatment with such drugs in persons who have large amounts of tissue lead will lead to high levels of excretion in the urine. In some cases this is used as a test for excess lead exposure. This same drug has minimal activity when given orally but it may make blood lead levels appear low when exposure may, in fact, be at dangerous levels. Dr. Robinson, Medical Director of the Ethyl Corporation, summarized the views of some physicians and industrial spokesmen when he said, and I think this is a direct quote, "Doctors who use this type of drug by mouth to obscure the hazard of lead toxicity should be sued for malpractice."

Now concerning arsenic, which is the oldest and best known example of a cumulative poison. There are many metals which are more toxic. Arsenic causes skin irritation, pigmentation of the skin and a large variety of other symptoms. Warts on the palm and soles, if they occur in people exposed to arsenic, certainly require medical attention and decrease in the exposure. Excessive cancer risks are also found among smelter workers and among orchard workers, at least in one location. Children living near an arsenic smelter were found to have excess arsenic excretion and higher hair levels, with excesses increasing with nearness of their homes to the smelter source. Dr. Peterson of the Council on Environmental Quality spoke to us about chemicals which are on trial and which, in the absence of a toxic substances control program, were conventionally assumed innocent until proven guilty.

Lead and arsenic, the substances being discussed here, are no longer innocent. Our approach in dealing with them should not assume this. They have been proven, in sufficient exposures, to be guilty. Lead may produce excess kidney fatalities, anemia, and neurologic deficits in adults and children, and lead is indicated in the crippling of the mental and intellectual development and neurologic diseases of children. If, as a court of scientists, concerned citizens, industrialists, and advisors to industrial firms, we parole this guilty substance, I recommend that it be on the condition that no interference with the metabolism of workers occurs and that no increase in the body burden of children in the community be allowed to occur.

As far as arsenic is concerned, I think the previous session gave evidence that, with sufficient exposures, arsenic is a carcinogen. It is also an irritant and causes conjuctivitis, perforated septa, and probably other changes in the mucous membrane. We have agreed, or at least members of the previous panel agreed, that there is not sufficient data for setting a threshold. The sentence for arsenic which I would suggest to this court is the same as the sentence that should be given for other environmental or occupational carcinogens; that is for confinement. I think this is a reasonable sentence, under the circumstances.

I want to restate one thing that was mentioned fairly early by Dr. Paul Caplan and has not been restressed. That is the so-called principle of adminstrative controls which was thrown out of the court when proposed under OSHA legislation. I do not know the details of this. I am simply passing on something which I think rounds out the analogy of things that possibly should be tried and what should be done with the results of these trials. Administrative controls mean that people are only permitted to work for a certain period of time and then are laid off because the exposure is too high. The thing to do is to keep the exposure within a safe level so that workers can be continuously employed without over exposure.

There are a lot of known facts about these two substances. We have the tools to prevent people from becoming ill and we have a responsibility to take action in various ways which cannot be ignored. There are some unresolved problems which cry out for answers. We need a better understanding of the meaning of the body burden. Better evaluating and utilization of testing methods is desired. If the new testing method, the zinc protoporphyrin test which uses fluorescence for detecting excessive exposure to lead is favorable, it should be utilized. Research in "minimal brain damage" needs to be carried out for many reasons. The effects of exposures on fertility and reproductivity should be evaluated. We must better define the various other materials which can contribute to co-carcinogenicity of arsenic.

My own feeling is that there are a couple of general principles to be followed in the future evolution of occupational health. We want to

bring the tools for the protection of the worker as near to his use, his understanding, and his application, as we can. I feel uncomfortable professionally, in requiring a worker to have an elaborate test that requires a specially trained technician to take a sample of this or that. when the laboratory procedure is such that the samples' usefulness is in doubt. These workers are troubled, stuck with a needle, and then given an ambiguous answer. I think we need to concentrate on the objective of giving the worker the tools, the information, the access to laboratory tests, and make available information from experts. We want to keep this in the hands of workers who can help in protection of themselves. It is the knowledge that they have this responsibility and know how to use it which will make it pleasanter, less fearsome, and more productive to work in many industries where occupational hazards occur.

There is another problem; that is secret files of information, some of which must be opened. There have been several references to things that are not generally known or available. We must make sure that we are dealing with an open information system and this is everybody's job. It is my job to ask questions if I am working for the state or federal government and to find out who has the answers. It is the job of a person working in an occupational health plant to have records that are useful. It is the job of the worker to see that his exposure information is accessible and stable. This is a big job! A job we have not been doing very well.

I must say that I am delighted that, when various people whom I have met here were asked for copies of things referred to in their discussions, most responded in the affirmative. Sometimes I received the copy before my back was turned, practically. Still, there are files which are not open enough. There are types of information which are needed and as long as there are such secret files, the confidence of the worker and the ability of our profession to provide adequate protection are going to be impaired.

The second and final remark I wish to make is that we must provide a decent level of support for the studies that are needed. We do know a lot, but there are many things we need to find out. We have provided support and regulation for things like vinyl chloride, asbestos, etc. The treatment of cancer is supported; however, the field of occupational health has been most stringently treated at all levels, and we cannot afford this. This penny-pinching kind of approach has, if you will forgive my badly mixed metaphor, produced a hemorrhage, a hemorrhage of dollars. We know how to do the needed work; we have people who are trained; and we know how to apply the results.

Finally, I have enjoyed being here. I have learned a great deal. I hope that the rest of you have too.

☆ U. S. GOVERNMENT PRINTING OFFICE: 1976-660-258/45 Region No. 5-11

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HEW 399

HEW Publication No. (NIOSH) 76-134