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Reprinted, with additions, from Occupational Medicine
January 1947, Vol. 3, pp. 13-19
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CONFERENCE ON LEAD POISONING

FACTS AND FALLACIES CONCERNING EXPOSURE TO LEAD

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A FEW years ago the *New York Daily News* (circulation 2,300,000) with the second largest newspaper circulation in the world, printed on its front page a photograph of some women lying prone in a factory loft and carrying the caption "Lead Fumes Victims." They had been working in a crowded room with closed windows while painting was going on. When I subsequently visited the editorial staff of the newspaper and protested the printing of this photograph I pointed out, as the investigation of the Lead Industries Association had indicated, and as one might have expected, that no lead paint was used at the point of the accident, but a lead-free paint, and that, furthermore, lead paint does not give off lead fumes. I was then informed that the newspaper reporter had merely followed the physician's conclusions and that, anyway, the lead industries should be proud to have made the front page of the *New York Daily News* and to have received such widespread publicity. Unfortunately, this is not the type of publicity relished by the lead mining and fabricating industries. They do not mind reading items describing the indispensable tasks performed by lead from day to day in making civilized life comfortable, but they do object to the unfavorable publicity that lead receives occasionally when it is absolutely innocent of any wrongdoing.

The *Daily News* episode typifies a mistake frequently made. I venture to say that a common but erroneous impression among many in the medical profession, and laymen alike, is that all paint contains lead and, consequently, that any one exposed to paint is exposed to lead poisoning. This is far from being true. That is why I should like to tell you a bit about paint as helpful to physicians.

Not so long ago white lead was the principal paint pigment consumed in the United States, but today the amount of white lead con-

Presented in a Conference on Lead Poisoning at the Seventh Annual Congress on Industrial Health, Boston, Sept. 30, 1946.

sumed in the United States is well below some other paint pigments, as the following table indicates:

Estimated Annual Consumption of Paint Pigments in the United States (in Short Tons)

White lead, dry and in oil	80,000
Zinc oxide	25,000
Leaded zinc oxide	60,000
Lithopone	115,000
Titanium	125,000

Moreover, white lead is relatively expensive. Manufacturers of prepared paint, therefore, are generally inclined to use as little of it as they can in their finished product. Prepared interior paints, furniture paints and enamels are usually altogether free of lead; at times they may contain minute quantities or traces from coloring tint used or from the drier. On the other hand exterior paint contains lead almost invariably because, when all is said and done, white lead is necessary to make a satisfactory durable exterior paint.

THE USES OF LEAD

Lead is a common metal of wide and important application, and the illness resulting from its use is largely occupational. For the record, roughly 1,000,000 tons (907,184,000 Kg.) of lead are used in the United States annually, or 2,000,000,000 pounds. In milligrams of exposure this figure would become astronomic.

The largest single use of lead in the United States is that of the storage battery industry. The exposure here is primarily occupational, but the improper disposal of old storage battery casings and their use for fuel have resulted in cases of lead poisoning, especially among children. Altogether too many cases of this type have occurred, of which many have been reported in medical literature. The industry is strongly condemnatory of the practice. I hope that physicians and public alike will help to stamp it out.

The second largest use of lead is in the sheathing of telephone and power cables. Here, again, the hazard of lead poisoning is occupational and occurs mainly in the melting of the lead. I know of no poisoning of the public from lead sheathing.

The third largest use of lead is in the manufacture of paint pigments such as white lead and red lead, where there is considerable occupational exposure, but because of increasingly effective method of control, the incidence of serious occupational lead poisoning is declining. Considering the thousands on thousands of homes painted and protected with white lead and the rare and doubtful occurrence of any lead poisoning to the public because of its use, I think that the record here is also in favor of lead.

The next largest use of lead is that involved in the manufacture of tetraethyl lead for use in gasoline. An outstanding job of prevention of lead poisoning in the manufacture and use of this lead compound has been accomplished. Then there were a host of other uses, too numerous to record here, comprising such well known products as ammunition, foil, collapsible tubes, pipe, sheet, solder, bearing metals, insecticides and type metal. This wide diversity of familiar lead products helps to make everyday life comfortable, but at the same time few physicians can be expected to have comprehensive data on their composition, lead content and chemical characteristics.

It is quite understandable that the average practicing physician can easily make diagnostic errors about lead. As Dr. Mayers has pointed out[1]:

> Again and again, for example, a diagnosis of occupational lead poisoning is made in a person who works in a lead pencil factory even though the material known as "lead" is actually graphite and there is no exposure to lead. Similarly, a painter's complaints are very apt to be interpreted as lead poisoning even though he is a spray painter using no lead materials whatever. In a painter who uses lead paint, a diagnosis of lead poisoning is almost inevitable regardless of what is wrong with him.

This point of view I find echoed by Teleky, who wrote[2]:

> Numerous mistakes in diagnosis have been made when the diagnosis depended on occupational history alone. I have seen about a dozen appendectomies performed on lead-poisoned persons, because lead was not recognized in the occupational history. On the other hand, one sees appendical abscesses diagnosed as lead poisoning because the patient was a lead worker. I have also seen a worker with lead encephalopathy, paresis and colic in whom the diagnosis of lead poisoning was not made because nobody knew that a red paste used by him contained red lead.

Recently a lead-mining company engaging in the collateral activity of producing house insulation material from waste slag was sued by a home owner who maintained that its insulation, though buried in the walls, had given him lead poisoning. And he offered medical testimony in support of his claim. The slag contained only a minute amount of lead in an essentially harmless form.

During the war when tin was scarce and lead plentiful it was necessay to advocate the substitution of lead for tin wherever possible. One such opportunity was the substitution of lead for tin in shaving cream tubes! Yet when I spoke to one government official on the subject, not a physician, he told me, in all seriousness, that if the shaver cut his face lead poisoning might result from the lead in the soap!

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1. Mayers, M. R.: Lead Poisoning and Compensation, Compens. Med. 1:13 (Jan.) 1946.

2. Teleky, L.: Compensation of Occupational Diseases, Compens. Med. 1: 8 (Feb.) 1946.

It is interesting to note that during the war lead was substituted rather widely for tin and aluminum in collapsible tubes for both shaving cream and tooth paste without, so far as I know, a single case of lead poisoning charged to this packaging practice. I must in all honesty report, however, that the tube manufacturers had developed a lead tube lined with a practically impervious or synthetic lining to insulate the contents from the wall of the tube.

For many years the Lead Industries Association has supported, in part, medical research on lead at Harvard having only one objective, to learn more and more about the toxicology of lead and to make the results freely available to public and industry without reservation of any kind. At the same time, important medical studies on lead in other institutions, particularly the University of Cincinnati, Yale University and the United States Public Health Service, have contributed immeasurably to a better understanding of lead hygiene.

As a result of all these investigations, which extend over a period of twenty years, it is apparent today that despite the large amounts of lead used in everyday life (1) the lead hazard in industry and to the public is relatively small and can be effectively controlled when it cannot entirely be eliminated, and (2) it is not difficult but it requires careful work to determine whether or not a person has been leaded.

PHYSIOLOGIC EFFECTS OF LEAD

A long time ago, the lead industry realized that, in addition to the responsibility of producing lead and its derivatives, it had an additional responsibility, the development of competent medical and hygienic information about lead and its proper uses.

It has had to recognize frankly the hygienic problems inherent in lead and its many products. The lead industry is determined to continue the progress which it has made and to overcome its difficulties through adequate medical and engineering preventive measures.

Even though lead has long been known as one of a group of many metals with toxic properties, little attempt had been made to understand the biochemical significances of lead absorption until the work of Dr. Aub and his associates was conceived and carried out.[3] In succeeding years, many other able workers have contributed to a better understanding of lead in its physiologic and related implications.

The culmination of current medical knowledge of lead can be found summarized in a recent (1943) excellent publication of the American Public Health Association,[4] prepared by a committee of distinguished specialists on the subject. Unfortunately, publications such as this one

3. Aub, J.: Lead Poisoning, Baltimore, Williams & Wilkins Company, 1925.

4. Occupational Lead Exposure and Lead Poisoning: Report Prepared by the Committee on Lead Poisoning of the Industrial Hygiene Section, New York, American Public Health Association, 1943.

are not read by the general public or even by all members of the medical profession, with the result that there is still a definite tendency to blame lead for almost any condition that cannot readily be explained by some other cause.

Apparently, two schools of thought on lead are found among members of the medical profession today. School A feels that inasmuch as lead is a cumulative poison—a word which needs careful defining—the effects on the body are ultimately disastrous no matter how small the amount ingested. On the other hand, school B refuses to accept this theory without scientific confirmation and is constantly accumulating data to disprove it. I shall try to give a few examples of the two schools.

My first illustration of school A is an article [5] which appeared in *The Journal of the American Medical Association* under the title, "Chronic Lead Poisoning." My observation is intended to be purely impersonal. In this article, the author described how he had difficulty in maintaining his balance while walking on a rough road in the dark. A year later, his Airedale dog acted queerly. During the following winter his wife noticed an incoordination of the house cat, which lost its footing in trying to jump a short distance. For all of which he concluded that he had contracted severe lead poisoning! Then the author had considerable difficulty in finding any lead exposure other than from amounts used as solder in the hot water system. The available analytic data on the excreta of the persons in this group were not convincing.

I considered the article questionable and was not surprised to learn that several medical experts dismissed it as inacceptable.

The trend of thinking shown in this article was carried a bit further in a paper in which the authors described an alleged case of lead poisoning in an infant who drank some orange juice squeezed in a toy *aluminum* cup! [6] They attempted to prove that even the extremely small amounts of lead they stated that they were able to find in the aluminum, running to spectroscopic quantities, caused the lead poisoning. And in support of this position one of the authors told me the observations in the case of the man, the dog, and the cat which I just described, apparently accepting it as proved.

Dealing with children, this paper was given alarming newspaper publicity over the nation, through Dr. Dafoe's syndicated medical column, and by others. Once again, lead was an easy target. These two articles caused the publication of a letter [7] to *The Journal of the American Medical Association*, which is so significant that I reproduce it here:

5. Williams, H. B.: Chronic Lead Poisoning, J. A. M. A. **112**:534 (Feb. 11) 1939.

6. Rathmell, T. K., and Smith, F. L., Jr.: Toy Dishes and Acute Plumbism, J. A. M. A. **114**:242 (Jan. 20) 1940.

7. Aub, J. C.: Lead as a Hazard, Correspondence, J. A. M. A. **114**:2237 (June 1) 1940.

To the Editor:—Two months ago, in the January 20 issue of THE JOURNAL, you published an article by Drs. Rathmell and Smith to which I must take exception, particularly as it followed so soon after a paper by Dr. H. B. Williams in which also many experts doubt the diagnosis. In this article the child is supposed to have had acute lead poisoning due to only an infinitesimal quantity of lead obtained from orange juice put into an aluminum container. It seems to me unwise to give great publicity to a so-called established case of lead poisoning in a child who is said to have ingested less than 0.02 mg. of lead. Most persons ingest more than that every day in their drinking water, with absolutely no known deleterious effects. An analysis of the dishes was mentioned but no report on this was made, and it is obvious that no accusation can be made without that, particularly as aluminum dishes should contain practically no lead. Besides, lead does not usually give the acute symptoms ascribed to it in this article. One substance that I know of, namely antimony, may give gastrointestinal symptoms such as vomiting, but to incriminate an infinitesimal amount of lead without knowing whether antimony was present in the juice is distinctly unscientific.

I write this vigorous letter because too much publicity is being given to minor exposures to lead these days. This is particularly true with regard to lead taken by mouth, which is so much less toxic than inhaled lead. That lead may produce deleterious effects there can be no question, but there is no evidence that a small fraction of a milligram can produce the effects ascribed to it in this article.

JOSEPH C. AUB, M.D., Boston.

The obvious inference is that children should not drink orange juice or use aluminum utensils if they wish to avoid trouble from lead. Desirable as it is to do everything possible to protect children from injury by lead, I am here completely stymied. Countless thousands of women must have been made unnecessarily apprehensive by the widespread publicity given this item in the public press.

So much, briefly, for the theory of one medical group which gives the human body little or no credit for any ability to handle infinitesimal amounts of ingested lead.

The other group believes differently and has actually tried out the effects of small amounts of lead on human beings for extended periods. Witness the painstaking studies of Kehoe[7a] on human subjects fed regular quantities of lead over years (1 and 2 mg. daily in addition to their normal intake) without ill effects. Or witness the scientific approach of the United States Public Health Service in experiments described by Fairhall and Neal,[8] in which 2 subjects lived on a simple diet to which 10 mg. of lead arsenate was added every day for ten days without any ill effects. So far as I know, no nationwide publicity

7a. Kehoe, R. A., and others: Experimental Studies on Lead Absorption and Excretion and Their Relation to Diagnosis and Treatment of Lead Poisoning, J. Indust. Hyg. & Toxicol. **25**:71 (Feb.) 1943.

8. Fairhall, L. T., and Neal, P. A.: Absorption and Excretion of Lead Arsenate in Man, Pub. Health Rep. **53**:1231 (July 22) 1938.

was given to any of these significant investigations. It is always the sensational which makes the front page.

Lead has long been recognized by the industry as essentially an industrial hazard, and increasingly effective precautions are taken in mines and factories to safeguard employees and to reduce the incidence of lead poisoning. It is a never ending battle in which, although great progress has been made, there is still room for improvement.

RESULTS OF INVESTIGATION INTO THE SAFETY OF CERTAIN USES OF LEAD

It is the position of lead as a public hazard, however, that has intrigued me most, for the lead industry needs the good will of the public to continue developing the necessary lead resources of the world. The observations and experiences of the industry indicate that various lead-consuming industries have been criticized for injuring public health only to have subsequent careful scientific investigation show the criticism to be undeserved. Incidentally, whenever criticisms are brought to the attention of the Lead Industries Association, its policy has been to recommend an impartial scientific investigation, with full publicity to the conclusions no matter what the outcome. I cite briefly a few examples:

Solder in Milk Cans.—One small drop of solder is generally used to close cans of evaporated milk. This use of lead was attacked as being possibly a dangerous contaminant of the milk. Careful investigation at the Harvard School of Public Health was made, and the results gave lead a completely clean bill of health.[9] Since the appearance of this study, the subject apparently is a closed one.

Lead-Weighted Silk.—A few years ago, when the use of lead for weighted silk was first proposed, at least one large department store was apprehensive about the health of the public in using it. Here, again, the subject was investigated at the Harvard School of Public Health, and the facts disclosed to the world.[10] Lead was given a clean bill of health.

Spray Residues.—Several years ago, representatives of the apple industry in the Northwest came to the Lead Industries Association greatly disturbed about the attacks made on the fruit industry by organizations of consumers which alleged that the American people were being used as guinea pigs and were being slowly poisoned by the lead arsenate spray on fruit. We urged a complete and impartial investigation to ascertain the facts, feeling that, if true, the apple industry ought

9. Fairhall, L. T.: Lead Content of Evaporated Milk, J. Indust. Hyg. & Toxicol. **19**:491 (Nov.) 1937.

10. Fairhall, L. T., and Heim, J. W.: Problem of Possible Health Hazard of Lead-Weighted Silk Fabric, J. Indust. Hyg. **14**:317 (Nov.) 1932.

to institute improved control measures, but if not true, the people should be told. Subsequently, the apple industry succeeded in procuring a Congressional appropriation which was given to the United States Public Health Service to make a painstaking survey. The results are probably well known to my audience and are to be found in a Public Health Bulletin of the United States Public Health Service.[11] It indicated, to say the least, that the fear expressed about spray residues was exaggerated. The report did not find a single case of lead poisoning among the 1,231 persons examined, some subjected to high exposures of the spray.

Paint on Cribs and Toys.—It is commonly believed that the eating of paint on cribs and toys has been a source of lead poisoning among children. Investigations of the Lead Industries Association cast grave doubts on most cases coming to its attention. This might be expected, as crib and toy manufacturers do not use lead paint on their products. Other paint pigments are cheaper and make a harder enamel than is obtainable with lead. Lead paint, because of its extraordinary durability, finds its chief application on exterior surfaces, not on furniture.

A few years ago, in bold type, an alarming article appeared in one of the safety journals of the National Safety Council entitled, "Lead Toys—Lead Paint—Lead Poisoning."[12] Fifty-five Chicago children were alleged in this article to have died from lead poisoning in five years in one hospital. On investigation by the Lead Industries Association, it was shown that there was no lead poisoning of the kind described, nor were lead toys or lead painted cribs involved, but that over the same period 5 children had taken some old lead battery boxes, used them as fuel and breathed the fumes, with fatal results. A year later a retraction was made.

It is unusual to find the results of the analysis of the paint in medical articles alleging lead poisoning in children which ascribe the source to the paint on the cribs or toys. And yet this simple step would seem so obvious and necessary, in proving exposure. Instead the roentgen ray, a diagnostic tool of limited value for lead, is often used as the main reliance to prove the presence of lead in children's bones.

Incidentally, may I say here that the members of the medical profession will do the lead industry a great favor if they will report to the industry the presence of lead paint on any crib or toy. The industry's own survey, conducted several years ago, showed no crib manufacturer in the United States using lead paint on children's cribs or toys. The industry would like to have your assistance in informing it where these leaded cribs or toys may be found so it may take remedial measures.

11. Neal, P. A., and others: A Study of the Effect of Lead Arsenate Exposure on Orchardists and Consumers of Sprayed Fruits, Public Health Bulletin 267. Federal Security Agency, United States Public Health Service, 1941.

12. Lead Toys—Lead Paint—Lead Poisoning, Safety Educ. **22**:74 (Oct.) 1942. Error in Report on Lead Poisoning, ibid. **23**:58 (Oct.) 1943.

Alleged After-Effects in Children Poisoned with Lead.—The subject was brought to a head by a report [13] in *Time* magazine of the results of a study made in Boston, alleging that serious mental impairment occurred in children several years after they had been leaded in infancy from chewing paint.

On examining the study by Byers and Lord [14] which served as the basis for the article in *Time*, I noted that in none of the 25 alleged cases of infant poisoning described had the paint from the cribs, toys or furniture chewed by the children been analyzed. Certainly there was no proof here of lead exposure.

Moreover, on investigation of the medical basis for concluding that these 25 cases were all of lead poisoning I discovered that the so-called shadow in growing bones disclosed by roentgen rays was given as the principal evidence for determining the presence of lead in the children. As the significance of lead concentrations in urine or in blood for diagnostic purposes did not become evident until comparatively recently, I do not think that physicians in general should be criticized seriously for depending on roentgen rays and subordinating more tedious analytic procedures.

I decided that I would make a deeper investigation of the use of roentgen rays in determining lead poisoning among children, as the practice had apparently grown popular in recent years. My trail led me back into the literature to studies of bone shadows recorded in Boston and Baltimore in 1933 and earlier. Being of an engineering turn of mind and desiring to get my teeth into something tangible to prove or disprove the presence of lead in bone shadows, I was seeking any analytic evidence procured by autopsy. I expected this to be rare, as few children had apparently died from lead poisoning. I found that in an article [15] appearing in the *Journal of Pediatrics* analytic evidence on which the conclusions were drawn, as reported by these authors, was secured by others and was open to serious questioning. The authors stated:

> The lead is the chief and probably the essential cause of the shadow, if the analysis of Aub in Vogt's case and the analyses in Caffey's case hold for others. In Vogt's case Aub found that in the dense areas at the ends of the bones the lead per gram of bone was 0.527 and the calcium 0.124 grams. The ratio of lead to calcium was greater than 4 to 1. In Caffey's case 1 gram of dry bone taken from the dense zone yielded 0.7 grams of lead.

A glance at these analyses is sufficient to show that any infant having a concentration of lead in bone to the order of 53 per cent or

13. Paint Eaters. Time **42**:49 (Dec. 20) 1943.

14. Byers, R. K., and Lord, E. E.: Late Effects of Lead Poisoning on Mental Development, Am. J. Dis. Child. **66**:471 (Nov.) 1943.

15. Park, E. A.; Jackson, D.; Goodwin, T. C., and Kajdi, L.: X-Ray Shadows in Growing Bones Produced by Lead, J. Pediat. **3**:265 (Aug.) 1933.

70 per cent is heavily leaded—indeed the concentration is better than any lead ore found in American mines!

I then went back to the original source of these analyses and found that, unfortunately, the authors had reported and used, for their interpretation, grams of lead instead of the milligrams which were actually disclosed by the earlier work. Hence, instead of 0.527 Gm. of lead, they should have reported 0.527 mg. in the dense area at the end of the bones. Consequently, they had shown one thousand times as much lead as was actually discovered in the "lead" lines in the bones of children.

The ability of the roentgen rays to detect lead in the bones comes down then to this proposition. Can a roentgenogram distinguish between the density of a piece of bone 1 Gm. in weight completely uncontaminated and another piece of bone of the same size containing only 0.0006 Gm. of lead? The best evidence which I can find, the opinion of the manufacturer of the x-ray equipment himself, is that the difference is too small to be detectable in a photographic plate. The United States Public Health Service in its experiments on the same subject, where samples of bone were actually leaded and compared with unleaded bone, confirmed this conclusion.

Proponents of the use of roentgen rays on children now tell me that the growth factor is responsible for the bone shadow phenomenon in children (not in adults) and that, even though the concentration of lead in the epiphesis of the bone may not be enough to be detectable, the presence of lead in the body manifests itself through the shadow. I shall be anxious to hear Dr. Caffey's paper on this subject.[16]

I am pleased to report that as an aftermath of this investigation and through the cooperation of physicians in Boston and Baltimore several recent cases of alleged lead poisoning in children have been shown to be nothing of the kind.

CONCLUSION

In closing, I wish to take this opportunity to pay my deep respect to the members of the medical and associated professions who have done so much for the metal I represent. Admittedly the job is not yet completed. There is still much to learn about lead. Moreover, newer products and applications will be found for it. Just now at the dawn of the atomic power age it appears that lead will be in especially strong demand as a shield from harmful rays. Indeed, I do not know where the lead will be found to supply known uses and those in prospect. But I do know that the close cooperation between the members of your profession and the lead industry will mark further steady progress in meeting any health problems involved, industrial or public.

16. Caffey, J.: Radiology in Diagnosis of Lead Poisoning, read before the Conference on Lead Poisoning at the Seventh Annual Congress on Industrial Health, Boston, Sept. 30, 1946.

PUBLIC EXPOSURE TO LEAD

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LEAD poisoning results from absorption of more lead than normal body processes can handle. Industrially, the most important route is via the air breathed, but that is not the only route. In ordinary life, however, one is more apt to be poisoned by taking lead through food or drink than by other means.

The standard for lead in drinking water is 0.1 part per million or 0.1 mg. per liter,[1] a figure applicable to all beverages. The only standard for foods is the figure set by the United States Government for lead in spray residues on fruit, 7.1 parts per million.[2] It is important to realize that this standard is not generally applicable to all foods, as it is not sufficiently severe.

There seems good reason to believe that the daily ingestion of about 0.5 mg. of lead in food or drink, and the intermittent ingestion of somewhat more, is safe, but that daily ingestion of much more than 0.5 mg. is apt to cause trouble.

Permissible lead dustiness in United States industries is 1.5 mg. per 10 cubic meters,[3] which might be compared with the British figure, 5 mg., suggested some years ago by Legge and Duckering. Ten cubic meters is chosen as the volume of air supposedly breathed in an eight hour working day.

What opportunities are there for the public to have such exposures? I will try to enumerate the more important, but will touch only lightly on the industrial exposures which are the subject of Dr. Mayers' paper.[4]

LEAD POISONING FROM PAINTING

As to lead poisoning from painting, I would say that in these days the average person often is forced to do his own minor and even major

1. Hoskins, J. R.: Proposed Revisions in Chemical Standards for Drinking Water. J. Am. Chem. Soc. (News Ed.) 19:1138, 1941.

2. Letter to Fruit Growers and Shippers. Administrator of Federal Security Agency, Aug. 10, 1940.

3. Allowable Concentration of Lead and Certain of Its Inorganic Compounds, New York, American Standards Association, Sept. 16, 1943. Kehoe, R. A., and others: Occupational Lead Exposure and Lead Poisoning: Report of Committee on Lead Poisoning, New York, American Public Health Association, 1943.

4. Mayers, M.: Industrial Exposure to Lead. Occup. Med. 3:77 (Jan.) 1947.

household repairs. If one attempts to buy paint, one takes what is offered. It probably will not be lead paint unless it is asked for specifically. For outside work, lead is usually preferred, but inside paints need not be lead.

Sandpapering old lead paint indoors or burning it off with a torch certainly causes enough dust for the worker, whether householder or professional painter, to breathe more than 1.5 mg. per 10 cubic meters, but the amateur probably does not work long or often at the job, and trouble from such work is extremely rare.

Most persons renew their own broken window panes, including the cleaning off of the old frame, resetting and puttying in the new pane. They use white lead putty—if they can get it—but they do not get lead poisoning because the exposures are too brief.

Thousands of square feet of Liberty ships were paint sprayed by the Maritime Commission during the last war. By specification, most of this paint contained lead as the important pigment, especially for the priming coats on steel hulls. Working conditions were not perfect, because of the great demand for ships and fast launchings, but lead poisoning among painters in American shipyards was virtually unknown.

Severe lead poisoning of children who have chewed lead-painted objects has occurred in various parts of the world.[5] In the United States, it is becoming rare because lead-painted toys and furniture are rare—toy manufacturers are advised not to use lead paint for these purposes, and compliance with this advice is good. Certainly such poisoning today is not common.

LEAD POISONING FROM LEADED GASOLINE

When gasoline containing minute amounts of tetraethyl lead was first suggested for motor fuel, considerable apprehension was felt lest the public, especially in garages and filling stations, acquire lead poisoning. Tetraethyl lead is a good solvent for lipids, but it is significantly volatile, so that spillage of leaded gasoline might present a serious health hazard. Also, the particles of lead appearing as fume in exhaust gases are in the ideal condition to be breathed—extremely small particles which are not irritating to the respiratory tract.

It was known that violent encephalopathies had occurred in the early period of the manufacture of lead tetraethyl. There was inadequate but highly suggestive industrial experience to indicate that the use of leaded gasoline was safe to the general public. Time and extensive investigation have proved the original fears to have been groundless—warning labels appear on all containers for this special motor fuel and

5. Blackfan, K. D.: Lead Poisoning in Children with Especial Reference to Lead as a Cause of Convulsions, Am. J. M. Sc. **153**:877, 1917.

on all pumps at filling stations. In general, the public follows directions, showing that a fine job of education has been accomplished.

Cases of serious lead poisoning have appeared here and there in connection with prolonged and careless use of leaded gasoline for dry cleaning. A foreign-born patient, in broken English, once told a physician of my acquaintance that the leaded gasoline was the best there was for the car, so he thought it would be best for cleaning. Doubtless such cases will continue to appear, but most persons would think twice before they used leaded gasoline for dry cleaning.

During the war, the military personnel of this and other countries used gasoline stoves for cooking and for many other purposes. Since only leaded gasoline was available to American and British armed forces outside of the United States, these stoves used leaded gasoline as fuel. The American forces employed a cookstove fitted with filters that removed most of the lead before the gasoline entered the burners, but no such stoves were available elsewhere, and other types of heaters were not so equipped. Careful inquiry has not established the occurrence of lead poisoning among the military personnel under these conditions, despite certain reports to the contrary. However, it seems probable that safety lay in the intermittency of the exposure. The public should use nonleaded gasoline in household or camp stoves unless they are designed to control the potential lead hazard.

LEAD POISONING FROM SALVAGING SCRAP

As to lead poisoning from salvaging scrap, old automobile batteries today are sold to the junk man who, in turn, sells them to the scrap metal dealer. The junk man breaks off the casing, which may be combustible and which contains considerable lead. These casings are likely to be found in city dumps, and have been used as household fuel during hard times. Some lead has escaped into the air breathed in the household and has caused severe lead poisoning.[6] Other instances of poisoning have occurred among poor persons who salvaged lead scrap from town and city dumps.

Scrap metal dealers have not been subject to any important amount of lead poisoning, so far as I know, probably because they do little handling and shoveling of the battery plates or the dust that comes from them. In most of the smelters where the lead is ultimately recovered, they can handle the plate scrap by mechanical means and undue exposures to dust can thus be avoided.

LEAD POISONING FROM PLUMBING

As to lead poisoning from plumbing, the word "plumbing" implies the use of lead. In days gone by, a plumber came to one's house, made

6. Williams, H., and others: Lead Poisoning from the Burning of Battery Casings, J. A. M. A. **100**:1485 (May 13) 1933.

or "wiped" lead joints and connected up lead pipe. The supply pipe for drinking water might even have been lead, or at least contained a considerable section of lead. One can still find plenty of such installations in old houses, especially in New England, but the modern household pipe is of iron, copper or brass, and water mains are of iron. Water tanks generally are galvanized iron or steel painted with zinc dust Through the years, developments have been such that today's plumber is primarily a pipefitter, a steamfitter and a heating contractor. He has little contact with lead. He does some soldering, but does little lead burning or joint wiping. He uses better tools than his predecessors, and, in this country at least, circumstances or industrial developments have simply removed him from serious risks of lead poisoning.

FOOD AND DRINK AS A SOURCE OF LEAD

As to food and drink as a source of lead poisoning, the lead limit set for drinking water, as I have stated, is low—0.1 mg. per liter. Probably the same figure would be demanded for all beverages. During the struggles with prohibition and all its attending ills, many of the large city hospitals received patients, often foreign born, who had drunk wine made in containers from which lead dissolved. Others experienced serious lead colic from drinking home brews distilled and condensed in lead coils—coils which were easy to make and easy to get. Happily, these troubles are largely in the past.

An extensive study by Neal and others,[7] of the United States Public Health Service, has shown that spray residue on apples is an unlikely source of lead poisoning. The men doing the spraying of both fruit trees and common shade trees all over the country can be subjected to considerable lead exposures. If a number of men travel about as a contract spraying team, the exposures over a period of a couple of months can become serious, and such men have been poisoned. The lead in such sprays is generally in the form of lead arsenate. Most large orchards today wash off with suitable chemicals excess spray residues. Obviously, the tolerance figure of 7.1 parts per million for lead in spray residues looks high, compared to that for drinking water, but it should be remembered that the lead occurs on the fruit skins only, and the standard is based on the maximum amount of fruit expected to be eaten by one person.

LEAD POISONING FROM WELDING

Machine shops and garages in most villages and towns today can handle small welding repair jobs. Large establishments may have portable

7. Neal, P. A., and others: A Study of the Effect of Lead Arsenate Exposures on Orchardists and Consumers of Spray Fruit, National Institute of Health Bulletin 267, Federal Security Agency, United States Public Health Service, 1941.

electric welders, but all have gas welding outfits and know how to use them. The mechanics all know that the torch furnishes an excellent method of cleaning off old paint prior to welding. The welding or cutting of lead-painted steel with gas or electric torches caused some famous lead poisoning troubles in the dismantling of Navy ships after the first World War.[8] Serious lead exposures have occurred in the building, wrecking and repair of steel structures, on which many coats of lead paint had been applied.[9]

Whether or not lead poisoning can result to the welder or burner engaged in such work depends mostly on the length and severity of his exposure. Fortunately, it is generally short, but concentrations of lead in the air breathed, from results obtained in practical trials in the laboratory of the Harvard School of Public Health, are apt to be far in excess of the recommended figure of 1.5 mg. per 10 cubic meters. But there were some one hundred and fifty thousand welders in the Maritime yards during the last war, and lead poisoning was virtually unknown among them.

CONCLUSION

Lead poisoning among the population at large is rare, but it was not rare fifty years ago. Industry knows what industrial lead poisoning means. It does not belittle the toxicity of lead, but it resents unsubstantiated accusations against lead.

Mr. Wormser has given some good examples of carelessness by physicians in studying the origin of supposed lead poisoning;[10] Industry suffers frequently from incorrect diagnoses in which lead is blamed for something which it has not done. I know of one large zinc smelter handling ore containing only traces of lead among whose workers the local physicians repeatedly have claimed lead poisoning simply because the name of the company had the word "lead" in it. This, then, is a plea for better and more careful diagnoses of lead poisoning, both in industry and in ordinary life.

I have one more critical suggestion: There are enough data now on industrial lead poisoning to permit a reconsideration of the present standards of lead dustiness in air, now 1.5 mg. per 10 cubic meters. That figure was derived from a study of lead battery manufacture and has been applied indiscriminately to all lead dust exposures; it makes no distinction between the different chemical forms of lead and lead compounds and their known differences in toxicity.

8. Brown, E. W.: A Study of Lead Poisoning Among Oxyacetalene Welders in the Scrapping of Naval Vessels, J. Indust. Hyg. 8:113, 1926.

9. Tabershaw, I. R.; Tuotolo, B. P. W., and Gleason, R. P.: Plumbism Resulting from Oxyacetalene Cutting of Painted Structural Steel, J. Indust. Hyg. & Toxicol. 25:189, 1943.

10. Wormser, F.: Facts and Fallacies of Lead Exposure, Occup. Med. this issue, p. 135.

INDUSTRIAL EXPOSURE TO LEAD

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IN PRESENTING the subject of industrial lead poisoning to this audience, I assume that no one is interested in a listing of industries where lead is used, or even in a discussion of new or unusual uses of lead in industry. For what matters it to the practicing physician where in industry lead is used? What he wants to know is whether the particular patient under his care is working with lead. But, more than that, he wants to know whether this exposure is such as to create a lead hazard. To many physicians, work with lead presupposes a lead hazard. Unfortunately, it is not so simple as that.

Exposure to lead in industry presents some special and interesting medical problems. Some of them derive from the peculiar toxicologic properties of lead, its physical and chemical properties and the processes and operations involved in its use. Other problems are of a more general character, those which are common to all cumulative industrial poisons which, once absorbed into the body, tend to remain there. Still other problems arise from the fact that exposure to lead in industry tends to be a long-drawn-out affair. It thus becomes intricately involved in a variety of unrelated medical entities which develop during the long period or periods of exposure. Beyond all that are some public health problems. A sense of civic responsibility on the part of the public and of public agencies has become crystallized into a variety of legal concepts and requirements the objectives of which are prevention—such as labor laws to provide safe and healthful working conditions, compensation for the injured, legal requirements with reference to reporting such cases to official agencies and attempts by these and other methods to develop accurate statistics on morbidity and mortality. Hence the physician who acquires a patient who says that he works with lead finds himself in a somewhat unfamiliar environment, one which involves many considerations and responsibilities beyond the purely medical problem, as he knows it, of making a correct diagnosis and treating his patient. That it tends to make him uneasy is understandable.

Perhaps one of the physician's greatest problems is to find out accurately about the occupational exposure of his patient. A visit to

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the plant is not only an unfamiliar and time-consuming operation, but it is apt to be unproductive. Certainly those of us who are specialists in industrial hygiene realize that it takes a skilled observer to understand plant operations. Moreover, it may be necessary to make chemical analyses of the air in order adequately to determine whether or not a lead hazard exists. This the practicing physician is obviously not equipped to do.

Fortunately, there has been a great expansion during the war of divisions of industrial hygiene in departments of health and labor in the various states, and the practicing physician who is in doubt can call on them for investigation and report concerning the occupational exposure of his patient. The more experienced physician will be in doubt far more often than the one who is inexperienced, and he will avail himself of these services more freely.

The report which he receives from such an agency must, however, be critically analyzed. It may not be a physician's report at all. Frequently it comes from the industrial hygiene chemist or engineer and is limited to data as to the concentrations found, frequently presented as an "average" and accompanied by a statement (in the case of lead) that the accepted maximum permissible concentration is 1.5 mg. per 10 cubic meters of air.

One should beware of evaluating occupational exposure to lead—or exposure to any other potentially toxic chemical for that matter—in terms of "average" exposure. We all know that there may be great variations in the intensity of exposure in the course of the day's work. When the degree of exposure is ironed out into a flat "average," however, there is an oversimplification which is not only unrealistic but may even, on occasion, be dangerous in leading to complacency when urgent control measures are required. In reality these "surges," if plotted, may well resemble a septic temperature chart.

While "surges" are perhaps less serious in industrial exposure to lead than in exposure to carbon monoxide gas in garages, for example, or exposure to volatile solvents, any information presented as an "average" must be looked on askance. Intermittent and periodic exposures to "surges" of sufficient degree in certain industries have produced poisoning even though the line representing the day's average exposure fell within accepted safe limits.

In the Division of Industrial Hygiene in the New York State Department of Labor my colleagues and I are much interested not only in this matter of "surges" but in the whole question of occasional or intermittent exposure in relation to our ideas as to permissible concentrations. We recognize the limits of our knowledge in this field. We

know little enough about toxic limits for exposure to occupational disease hazards in general. We know far less about the results of occasional or intermittent exposure to the presence of "surges." We are setting out study this problem.

However, despite all the limits to the knowledge in this field it is necessary, as a practical matter, to find out as much as possible about the extent of a patient's exposure to lead—in terms of hours per day, days per week, months per year and intermittent or periodic exposure over a period of many years, perhaps. This last is again more difficult than it sounds because what we find today is not necessarily representative of previous exposures. Industrial processes may have materially changed. Particularly housekeeping has improved, and good housekeeping is still one of the principal means for preventing lead poisoning.

It is the older worker who has spent many years of his life working with lead—whether continuously or intermittently—who presents some of the most difficult problems, for in the course of a long life many pathologic and functional changes have occurred in various tissues or organs of his body. These the physician may be capable of evaluating. However, in the case of a lead worker he finds himself put to it all along the line to dissociate those elements in the clinical picture which may properly be attributed to lead from those which are due to other causes. This is a major stumbling block, for what is "normal" for a given age group in a given social and economic segment of a community? What incidence is there, within each group, of enlarged livers, arteriosclerosis, anemia or hepatic dysfunctions? "Normal standards" are strikingly absent.

It is an old medical concept, for example, that prolonged exposure to lead accelerates the development of arteriosclerosis or chronic nephritis or both. Recent work, however, has not substantiated this. Similarly, the finding of such an obscure neurologic condition as multiple sclerosis in a lead worker, always gives rise to speculation as to the possibility of causal relation. Cases in this category are periodically reported in the literature as due to absorption of lead. Unfortunately, however, there are few data available as to either the general causation of these conditions or the role played by lead in their production. No opinion, therefore, is possible at the present time with reference to causal relation in these cases.

Whenever, indeed, one is dealing with any obscure disease entity, regardless of what it is, the medical picture as a whole must show some concrete evidence that there has been significant exposure to lead, absorption of lead or intoxication with lead before lead can be considered as a possible causal factor. There must also be some pertinent relationship *in time* to the onset of the particular disease in question. One can-

not assume because an obscure disease has occurred in a lead worker that it is necessarily due to lead.

In industrial exposure to lead, nowadays, when exposure is usually to relatively low concentrations for long periods of time, one is dealing with cumulative absorption which in itself presents special diagnostic problems. The patient is not necessarily acutely ill with colic. His symptoms of constipation, headache, nervousness or insomnia are in no way pathognomonic of any particular disease, certainly not of lead poisoning. Perhaps he has come with an infection of one of his toes, and the examining physician observes that he has a wrist drop. The wrist drop is an old story as far as the patient is concerned, and he has not come to be treated for it. What about lead poisoning in such a case? Why are there not abnormal numbers of stippled cells in his blood and no unusual quantity of lead in his urine?

A medical understanding of such a case is not acquired by checking over the symptoms, physical signs and laboratory data listed in textbooks against those presented by the patient. It lies, rather, in trying to understand the dynamics of the situation. Lead is absorbed into the body; some of it is stored, and some is excreted. Time is an important factor not only as it relates to duration of exposure, but to the length of time which may have elapsed since exposure ceased. The intensity of exposure in relation to time is also important. In other words, what one finds at any given time on physical examination is the resultant of a series of biochemical and physiologic activities in the body which have been affected by the introduction into the body of varying amounts of lead over given periods of time.

The man with the wrist drop referred to may or may not be found to have an abnormal concentration of lead in his urine at a given physical examination. Whether he does or does not has little if anything to do with the wrist drop, which probably developed years ago. The lead found in his urine at this stage gives information primarily as to the extent of his present exposure to lead or absorption, if any. He has probably not been working with lead for years—because of the wrist drop—in which case one would not expect to find abnormal amounts of lead in his urine at this late date. On the other hand, his wrist drop may never have been due to lead in the first place. This requires investigation of his occupation at the time the wrist drop developed. Investigation of the extent of exposure to lead in his present occupation will not necessarily contribute an answer.

For convenience, one commonly talks about three characteristic clinical syndromes in lead poisoning: (1) a group having predominantly gastroenteric disturbances including lead colic; (2) one having predominantly neuromuscular disturbances including peripheral neuritis and wrist drop, and (3) one characterized by disturbances of the central

nervous system, including lead encephalopathy. Actually, most cases of exposure to lead under the more or less controlled industrial conditions prevalent in this country at the present time are mixed cases of a relatively mild character. In general, a more intensive exposure to lead over a longer period of time is required to produce lead neuritis than to produce lead colic, and neuritis is likely to be associated with a history of one or more prior attacks of colic in a worker who has continued his work with lead. Cases of acute encephalopathy are extremely rare nowadays because exposure is rarely intense enough to produce this condition. One of the outstanding exceptions is that of exposure to organic lead compounds such as tetrethyl lead, if conditions of exposure are not adequately controlled.

The indispensable role of the laboratory in the differential diagnosis of lead poisoning is well recognized. Since, however, the medical practitioner is not always entirely conversant with laboratory procedures and technics used in lead poisoning, a word might be said with reference to some of the pitfalls: 1. Laboratory evidences of lead absorption tend to disappear after discontinuance of the exposure. Such tests, should, therefore, be made at the earliest possible moment. 2. When quantitative analysis of biologic materials such as urine, blood or feces is contemplated, their collection should be carefully supervised or controlled to insure against contamination with lead from hands, clothing, glassware, etc., and extreme care should be exercised to insure the use of laboratory reagents free from lead impurities or contaminants. 3. Laboratory tests should be performed only by reliable and experienced persons. 4. Lead is excreted by so-called normal persons who have had no known exposure to lead. 5. It is essential to be familiar with accepted standards for "normal" persons as a basis of comparison, in determining "excessive absorption" or "excessive excretion." 6. Laboratory data provide information primarily with reference to exposure to and absorption of lead. It is thus an aid to clinical diagnosis, but not a substitute therefor.

The importance of differentiating between lead "absorption" and lead "poisoning" cannot be overemphasized. Indeed, the lack of any accepted definition for these terms adds seriously to the inherent difficulties in the medical interpretation of these cases. Common agreement, however arbitrary, as to the definitions of lead "poisoning" and lead "absorption" is an essential, especially when litigation is involved.

"Lead absorption" actually means nothing more than the absorption of lead into the body. It implies nothing as regards toxicity. When lead absorption is sufficiently great, however, to disturb the person's sense of well-being, i. e., when lead absorption reaches the stage of toxicity, it results in true "lead poisoning." Such a worker does not have to have the characteristic symptoms brought to his attention by careful history taking. He complains of troublesome symptoms which interfere with

his sense of well-being and for which he seeks relief. "Lead poisoning" is thus the toxic stage of lead absorption.

Differences in the susceptibility of individual workers to lead poisoning must be taken into account. Such differences are not confined to lead workers but seem to characterize all occupational exposures to toxic chemicals. While no satisfactory scientific explanation is as yet available, the existence of this phenomenon is strikingly evident. In the field of epidemiology, all physicians are familiar with the fact that when there is an epidemic of poliomyelitis in a community, for example, certain persons succumb to the disease while others do not.

In the industrial field, an important contribution along these lines may be in the making as a result of recent experimental work with toxic hepatitis. Here it is being shown that the liver can be protected against toxic doses of such hepatotoxic agents as carbon tetrachloride or chloroform by the administration of sulfur-containing amino acids, particularly methionine. It is also known that alcohol and vitamin deficiencies (especially a deficiency in vitamin C) appear to increase susceptibility to certain toxic chemicals. Biochemical and metabolic differences between individuals may play determining roles.

Whatever the cause, these differences in individual susceptibility do exist and must be taken into account. Each case of lead poisoning must be examined on its own merits, and cannot be evaluated in the light of whether or not the patient's co-worker has or has not also contracted this disease.

Most disturbing, perhaps, to the practicing physician is the need to prove his diagnosis in court, frequently to a lay referee, for, as a practical matter, compensation is available not to persons who are suffering from an occupational disease but to persons who can prove that they have it. It is the physician's task, therefore, to prove it, and this disturbs him considerably. He is not in the habit of approaching diagnosis with this in mind. In his regular practice, he makes a diagnosis solely for his own use in the treatment of his patient. If at any time, in the course of such treatment, he has reason to reconsider the correctness of his diagnosis, he is at perfect liberty to do so in the light of his patient's response to therapy or any other experience which has developed in the case.

In dealing with occupational diseases, however—or suspected occupational diseases—the fact that his diagnosis will be the subject of legal adjudication tends to make the physician look for short cuts such as he would never think of otherwise. Thus, in discussing lead poisoning, physicians constantly ask for a few specific criteria on which to make the diagnosis. They are particularly partial to laboratory data which carry something of the magic of numbers. Needless to say, such short

cuts are not to be found in medicine, whether one is dealing with the occupational diseases or with those which are nonoccupational in origin.

Not uncommonly in industrial lead poisoning a patient continues to show "occasional stippled cells," possibly no more than one or two per 10 fields examined, with or without a slight increase in the amount of lead excreted in the urine. This situation almost invariably leads to the practice of repeating the laboratory tests periodically, almost ad infinitum, in the vain hope that perhaps a definite laboratory report, one way or the other, will ultimately be obtained, and the diagnosis then made in accordance with it. Actually, in these cases, conclusive laboratory tests are not often obtained; the patient becomes the despair of every one, and the result is that no proper investigation is ever made to determine what really is the matter with him. What he needs is a completely fresh and detached reevaluation of his condition by a good clinician.

It is rare in medicine to find a patient who presents a classical picture of any disease. Good diagnosis is necessarily a synthesis on the part of the examining physician of many observations, all interpreted in the light of his experience. It is dependent not only on his knowledge and experience with the particular disease in question, but on his knowledge of the whole gamut of diseases, because every diagnosis is in the last analysis a differential diagnosis. There is great need at the present time for the application of good clinical medicine to the diagnosis of lead poisoning.

In closing, I want to say just a word about prevention. Production methods and engineering technics for the control of lead poisoning in industry have developed to a point where theoretically, at least, one can hope for complete control in the not too distant future. Actually, however, most lead plants are not in this happy state at the present time. Medical supervision is as necessary as ever and should be extended so far as possible to include every person who works with lead.

CLINICAL SIGNIFICANCE OF HEMATOLOGIC CHANGES IN LEAD ABSORPTION AND LEAD POISONING

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ANY discussion of the clinical significance of changes in the blood in relation to absorption of lead and lead intoxication can be kept brief for two reasons: First, the facts as to clinical significance have been established and confirmed,[1] and second, the status of knowledge as to pathogenesis of the changes is so equivocal and ill defined as to be of limited general interest. Any merit which added discussion may have, therefore, will be that of emphasis by restatement, in an endeavor to direct the clinical effort to the patient himself and to the more definitive analytic data.

Recent studies of Kench, Gillam and Lane [2] and the observations of Falconer [3] are in support of the thesis that the basic hematologic disturbance in lead poisoning is an interference in the formation of protoporphyrin brought about by depression in cellular activity rather than by blocking of the formation of the iron-porphyrin complex. This interference results in nonutilization of protoporphyrin and consequent porphyrinuria, disturbed synthesis of hemoglobin with hypochromic anemia and an increased hemoglobin metabolism.[4]

At one time or another almost all elements of the blood picture have been studied for their possible significance as criteria of lead intoxication. All deviations were found to be nonspecific. Two changes, however, occur with sufficient frequency and of such an order of magnitude as to be useful, though not definitive, diagnostic aids. These are punctate basophilia (or stippling) and reduction in hemoglobin.

STIPPLING

Stippling, the hematologic change most commonly thought of in connection with plumbism, is, like polychromasia, essentially an abnor-

1 Kehoe, R. A., and others: Report of the Committee on Lead Poisoning, New York, American Public Health Association, 1943.

2. Kench, J. E.; Gillam, A. E., and Lane, R. E.: Biochem. J. **36**:384, 1942.

3. Falconer, E. H.: Am. J. M. Sc. **203**:857, 1942.

4. (*a*) Pfeil, E.: Ang. Chem. **53**:374, 1940. (*b*) Mangeri, S.: Med. d. lavoro **31**:97, 1940. (*c*) Robscheit-Robbins, F. S., and Whipple, G. H.: J. Exper. Med. **63**:767, 1936.

mality in the behavior of the erythrocytes to stains. That both polychromasia and stippling are manifestations of reticulation has been fairly well established by the fact that the proportions of polychromatophilic cells and stippled cells are largely determined by the method of staining,[5] while the sum of the two elements parallels the reticulocyte count. It appears probable,[6] though not certain, that persistence of the same reticular substance is responsible for all three types of cells, since the form of the reticular material in supravital specimens does not indicate whether the fixed, stained cell will be stippled or polychromatophilic. Toxic agents, such as lead and phenylhydrazine, influence the basic reticulum in some unknown fashion, this alteration being evidenced in the abnormal staining reactions.[5c]

Significance of Stippling.—Since stippling is not a specific change in the blood unique in lead absorption and is commonly present in the normal, nonexposed population[7] and since no characteristic morphologic differences in stippling occur, it is evident that any clinical significance that obtains will be determined by quantitative relationships. The first requisite for this is a method of measurement that will give reproducible results characteristic for the method. No standardized method is yet established. It is known that the stain, the time, the p_H, etc., will affect the counts,[8] and there is, moreover, good evidence[9] that the manner of preparation of specimens, the temperature, the humidity and the time of drying will influence the results profoundly. This status of affairs is responsible in large part for the divergence in values that have been reported for nonexposed groups and greatly limits the practical value of what can be a useful tool. For example, in table 1 are given a number of values reported for nonexposed normal and diseased persons and exposed groups. It may be seen that the ranges in values are extremely wide. Similar, smaller, differences in magnitude are evident in the proposals for threshold values for lead intoxication. A few such are given in table 2. The authors' comments reflect the uncertainty which exists when one attempts the establishment of any threshold value.

It follows that the clinical significance of a single stippled cell count must be interpreted in the light of method, associated disease, etc. With

5. (*a*) Schmidt, P., and Weyrauch, F.: Ueber die Diagnostic der Bleivergiftung, Jena, Gustav Fischer, 1933. (*b*) Pappenheim, A.: Folia haemat. **24**:1, 1919. (*c*) Whitby, L. E. H., and Britten, C. J. C.: Lancet **1**:1173, 1933.

6. Rosegger, H.: Klin. Wchnschr. **15**:158, 1936.

7. (*a*) Kehoe and others.[1] (*b*) Footnote 5. (*c*) Rosegger.[6] (*d*) Falconer, E. H.: Ann. Int. Med. **12**:1429, 1939. (*e*) Teleky, L.: München. med. Wchnschr. **71**:266, 1924. (*f*) Kehoe, R. A.; Thamann, F., and Cholak, J.: J. Indust. Hyg. **15**:257, 1933. (*g*) Sanders, L. W.: ibid. **25**:38, 1943.

8. Kehoe.[1] Pappenheim.[5b] Whitby and Britten.[5c]

9. Bruckner, H.: Arch. Hyg. **98**:95, 1927.

the same method, however, repeated counts on persons and groups are useful indexes of magnitude of lead absorption, especially when sudden and progressive increases in counts occur. The erratic character of the

TABLE 1.—*Means and Ranges in Values of Stippled Cells per Million Erythrocytes*

Author	Stain	Number	Mean	Ranges	Sample
Brown, E. W.: J. Indust. Hyg. 8 : 113, 1926	Wright	55	0	.....	Normal subjects
Kogan and Smirnowa [19g]	M-B*	...	0	.....	Nonexposed workmen: stippling only with anemia
Mayers [19f]	M-B	250	0	0-1	Normal subjects: only 1 stippled cell found
Falconer [7d]	J-G†	206	92	0-400	Normal subjects: 25% had no stippling
Falconer [7d]	J-G	254	363	.....	Nonexposed patients
Sanders [7g]	M-B	2,231	374	0-5,000	Nonexposed oil refinery workers: 67% had no stippling
Sanders [7g]	M-B	82	416	0-2,500	Medical students: 46% had no stippling
Nelson, Lockwood and Mackay [16]	M-B	255	937	0-7,000	Nonexposed workers
Lane [10a]	M-B	223	...	0-2,000	Normal subjects: 50% had no stippling
Nelson, W. T.: M. J. Australia 1 : 310, 1931	M-B	...	...	0-4,000	Healthy men: 15% had no stippling
Nelson, W. T.: M. J. Australia 1 : 310, 1931	M-B	...	...	0-7,200	Nonexposed clerks: 24% had no stippling
Kehoe, Thamann and Cholak [7c]	M-B	60	960	0-6,000	Native Indians, men, women and children
Falconer [7d]	J-G	5	2,000+	.....	Patient without lead exposure
Falconer [7d]	J-G	1	27,000	—52,000	Patient without lead exposure
Sanders [7g]	M-B	20	480	0-1,400	Hazardous exposure: 45% had no stippling
Falconer [7d]	J-G	8	2,100	.....	Paint manufacture
Sanders [7g]	M-B	20	2,912	0-7,200	Hazardous exposure: 100% had stippling
Nelson, Lockwood and Mackay [16]	M-B	59	4,335	0-20,000	Slight exposure to lead
Nelson, Lockwood and Mackay [16]	M-B	41	14,220	0-20,000	Storage battery workers
Nelson, Lockwood and Mackay [16]	M-B	12	36,382	.....	Persons with lead poisoning

* Methylene blue.
† Jenner-Giemsa counterstain.

TABLE 2.—*Proposed Threshold Values for Stippled Cells per Million Erythrocytes*

Author	Value	Note
Schmidt, cited by Falconer [7d]		
Schmidt and Weyrauch [6a]	100	"Indicative of intoxication"
Schnitter, cited by Falconer [7d]	500	"Pathognomonic for intoxication"
Kehoe and others [1]	800-1,000	"Suggests increased absorption"
Sanders [7g]	1,000	"Suggests increased absorption by groups"
Sanders [7g]	5,000	"Requires additional evidence to attain diagnostic significance"
Sanders [7g]	9,000	"Defines lead intoxication"
Falconer [7d]	16,000-22,000	"High probability of being due to lead intoxication"

stippled cell response and the dangers of relying on results of a single sampling, even in groups, have been well demonstrated by Sanders,[7g] who found a normal mean value (480 per million) and ranges, for one

month, in a group of 20 men with hazardous exposure (as evidenced by a mean urinary concentration of lead for the group of 0.128 mg. per liter). These results may be compared with mean stippled cell counts of 2,912 per million (ranges 6 to 7,200) obtained eight months before, when the urinary excretion of lead for the group was 0.191 mg. per liter.

Critical evaluation of the best information at hand [10] makes it possible to elaborate certain statements as to the validity and clinical significance of stippling.

(*a*) Stippling and polychromasia are the result of the reactions of reticular substance to stains, and are indications of activity of the marrow.

(*b*) Alterations of the reticular substance, especially the alteration caused by lead, will lead to increases in stippling.

(*c*) Stippled cells are present in nonexposed, normal persons at times in numbers up to 7,000 per million. In diseases other than lead poisoning (hepatic cirrhosis, pulmonary disease) and especially in the blood dyscrasias, stippled cell counts as high as 50,000 per million may occur without associated lead exposure. Single counts therefore may have value only when critically applied.

(*d*) Hazardous lead absorption usually but not always causes elevations in stippled cell counts; when it does, the relationship is general and direct but erratic and with wide ranges of variation for single observations.

(*e*) The greatest value of stippled cell counts derives from recurring observations on groups of exposed workmen and comparison of these results with previous values for the group and with values for nonexposed controls. Repeated observations in individuals are of more limited usefulness when used as an index of hazardous absorption or as a diagnostic or prognostic criterion in lead intoxication.

(*f*) No critical stippled cell level for hazardous lead exposure can be set. Considerable experience with a uniform method in a given situation may enable prediction of likelihood of occurrence of cases of intoxication in groups. Any threshold value, however, cannot be applied elsewhere owing to the pronounced influence of technic on the counts.

(*g*) High stippled cell counts occur with great frequency in active lead poisoning. Absence of stippling in cases of suspected poisoning is good evidence that some agent other than lead is responsible.

10. (*a*) Kehoe.[1] (*b*) Schmidt and Weyrauch.[5a] (*c*) Whitby and Britten.[5e] (*d*) Falconer.[7d] (*e*) Sanders.[7g] (*f*) Mayers, M. R.: J. Indust Hyg. **8**:222, 1926. (*g*) Kogan, B., and Smirnowa, L.: ibid. **9**:435, 1927. (*h*) Lane, R. E.: ibid. **13**:276, 1931. (*i*) Nelson, W. T.; Lockwood, L., and Mackay, K.: M. J. Australia **2**:317, 1932.

(*h*) There is urgent need for a standardized method for quantitation of the altered reticular substance.

HYPOCHROMIC ANEMIA

Hypochromic anemia, with reduction in mean corpuscular hemoglobin and porphyrinuria, is believed by some [4a, b] to be the most sensitive index of hazardous lead exposure, and where it is possible to repeat examinations at frequent intervals it is undoubtedly an excellent index of the general health of the worker. Despite this, the consensus leads one to the conclusion that hypochromic anemia is even less specific than stippling, since it so frequently results from environmental factors, undernutrition and disease. Moreover, the degree of reduction in hemoglobin is never great, and the mean levels for groups do not always relate well to the magnitudes of exposure.[11] Even in cases of lead intoxication during the acute episode, individual hemoglobin and erythrocyte values fall within ranges like those of nonexposed workmen.[12] I may state, then, that though reduction in the hemoglobin content of erythrocytes may be an early index of hazardous lead absorption, the reductions which occur are usually slight, not closely related to magnitude of exposure and not differentiated from hypochromic anemia arising from other common causes. Hemoglobin concentration, like weight, is best employed as an index of the general state of health and nutrition.

OTHER CHANGES

Significant changes in leukocytes and platelets do not occur except in severe acute intoxication and when large therapeutic doses of lead are given [13] and are neither noteworthy nor specific. In clinically active poisoning, leukocyte counts are usually within normal limits.[12]

Erythropoietic activity of the marrow is evidenced by the appearance of reticulocytes in the peripheral blood (normally from 0 to 2 per cent of erythrocytes). It is to be expected that any agent, such as lead, which affects hemoglobin metabolism will cause changes in reticulocytes. The qualitative changes (stippling and polychromasia) have been mentioned in a preceding section. In addition, increases in the absolute numbers of reticulocytes are commonly seen with lead absorption. Some reports suggest a rather close correlation between reticulocyte counts and order and duration of exposure when large groups are studied.[11] In individuals and small groups, however, reticulocyte counts appear to be a no more sensitive and significant index than does stippling. This is in keeping with the common observation of the erratic character of reticulocyte responses both after therapy and as a result of action of harmful agents.[14] Since

11. Dreesen, W. C.: J. Indust. Hyg. & Toxicol. **25**:60, 1943.
12. Ashe, W. F.: J. Indust. Hyg. & Toxicol. **25**:55, 1943.
13. Falconer.[8] Brookfield, R. W.: J. Path. & Bact. **31**:277, 1928.
14. Minot, G. R., and Castle, W. B.: Lancet **2**:319, 1935.

stippling is a manifestation of altered reticular material the vagaries of the two will be associated. Correspondingly, the technic for basophilic aggregation of McCord,[15] which enumerates reticulocytes as well as other basophilic material in the erythrocytes, would be expected to give related values, possibly more sensitive, but not more specific.

Corpuscular fragility in lead absorption at one time received considerable attention, and both increased [8a] and decreased fragility has been reported in cases of lead intoxication. No recent, well controlled studies have been reported. In view of the problems of interpretation of corpuscular fragility tests, and the varying criteria used for lead intoxication on which statements have been based, it is my opinion that determinations of corpuscular fragility are of less diagnostic value than are simpler technics such as the technic for stippled cell counts.

CONCLUSIONS

1. Lead interferes with synthesis of protoporphyrin and alters the reticular substance, but there are no specific hematologic changes in lead absorption.

2. Basophilic stippling becomes significant with respect to lead absorption when subject to the following conditions: (*a*) with employment of a uniform method for which normal ranges of values have been defined, (*b*) when repeated frequently on groups and used as an index of trends in exposure, (*c*) as supportive evidence in the diagnosis of lead intoxication and (*d*) in the exclusion of lead intoxication.

3. Other hematologic changes are more variable and less characteristic than is the stippling.

Room 714, Chrysler Building, 405 Lexington Avenue (17).

15. McCord, C. P.; Holden, F. R., and Johnston, J.: Am. J. Pub. Health 25:1089 1935.

ANALYTIC METHODS IN DIAGNOSIS

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IT IS NOT my purpose at this meeting to present any new method of lead analysis or any new procedure for the determination and detection of lead in biologic substances, but rather to discuss certain phases of the analytic problems which are presented inevitably by the type of material being analyzed for lead.

In the course of the last quarter of a century, an almost endless variety of methods for determination of lead with reference to the general problem of lead poisoning has been developed, and this healthy state of affairs has done much to clarify many of the obscure problems of lead poisoning. It is perhaps rather unfortunate that, in general, the tendency has been to emphasize ease of execution rather than accuracy of execution with reference to these methods, and, to my mind, this has been a detriment rather than a help. The main difficulty, of course, in the analysis of lead in body fluids and tissues has been the great disparity between the bulk of material analyzed and the minute amount of substance sought. When it is realized that the determination frequently revolves around a matter of millionths of a gram in 1,000 or 2,000 Gm. of fluid or substance and that the total amount of other inorganic constituents accompanying lead in such material may amount to 50 or 100 Gm., it is obvious that the separation and quantitative evaluation of these extremely minute amounts of lead is exceedingly difficult. However, the problem is further complicated by the fact that in addition to mere bulk of accompanying substances, lead is also accompanied by small amounts of other metals which are potentially difficult to separate from lead. It is indeed fortunate that the substance diphenylthiocarbazone, commonly known as dithizone, was brought to light several years ago and that the singular properties of this substance with respect to many metals were so thoroughly investigated by Fischer. With the aid of this substance it is possible to separate lead quantitatively and rapidly, even though it is present in extremely small amounts, from a large amount of material. It is true that a number of other substances are similarly separated, but the separation of these from lead is not too difficult a problem. It is unfortunate, however, that so much

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attention has been devoted to the further or final evaluation of lead by means of this reagent rather than to the effectiveness with which lead can be separated from other metals as has been described. This is understandable because an extremely small amount of lead gives a pronounced and deep color under certain conditions with this reagent and the facility with which colorimetric determinations are carried out in general makes such a procedure extremely inviting. To that end, long and elaborate procedures have been adapted in order to minimize the effects of interfering substances without too greatly affecting the precise evaluation of lead itself.

This brings up a point which I should now like to discuss more in detail. The analytic chemist is confronted in his laboratory work with a series of operations requiring the greatest care and delicacy of manipulation. Frequently, this requires a great deal of time and an exacting attention to detail which is almost unique. In this sense, each analysis represents a technical achievement of high order, and the intelligent analyst usually seeks means to shorten the arduous labor involved in the various steps of analysis by short-circuiting these steps in such a way that needless labor is avoided. It is this fact, largely, that is responsible for the development of "new" methods of analysis. As the need for by-passing needless work has grown, particularly in the industrial field, technologic advances have kept pace with the chemist and instruments have been developed which greatly simplify his work and perhaps produce a great increase in output.

At the same time, many of these instruments have permitted him to evaluate quantities of substances so small as to be undreamed of at an earlier day. The analytic chemist has, for instance, the quartz microbalance, the spectrograph and the Geiger counter, which respond to the presence of very small amounts of material. Such instruments are of the greatest utility and have tended not only to extend the field of activity of the analyst but, in many cases, to extend accuracy of observation. It is unfortunate, however, that with the acquired facility of operation and the widening horizon of application, as well as the extreme sensitivity, of such instruments, there is a tendency on the part of many analysts to short-circuit operations without too close an attempt to find whether such shortcuts are valid; to substitute, in other words, for the known delicacy of the instrument working under the best of conditions the application of the instrument to procedures of uncertain accuracy. It is simple to do this and to shift the responsibility from the analyst to the instrument, but no known procedure can be carried far without the analyst's assuming responsibility. The fact that an instrument of great delicacy and, under proper circumstances, of accuracy is used does not in itself effect the true solution of an analytic problem. The analyst must still accept responsibility, and the degree to which this

responsibility is important rests, of course, on the nature of his problem. As an instance of this, I can cite the application of the spectrograph and the polarograph to the determination of lead in biologic substances.

About twenty years ago, refinements began to appear in the quartz spectrograph which greatly increased its use and extended its range in the field of analytic chemistry, and quantitative applications of the spectrograph were rapidly developed. These developments have been facilitated by several means, perhaps the simplest of which is the comparison of the densities of a given line at various concentrations with reference to the density of a comparison substance in known concentration. Many modifications of this procedure have been introduced, depending on the nature of the material used for analysis. While at first approach this seems to be a method of solution of many analytic problems and, indeed, is of the greatest importance to many analytic problems, there are phases of this procedure which have natural limitations. The arc spectrum, for instance, is in general most suitable and most sensitive for many applications of the spectrograph, but there are factors which, when closely investigated, indicate that frequently there are difficulties in securing true analytic values by this means. The arc itself is not the simple thing that it first appears to be. There are gradations of temperature varying from the positive to the negative electrode and, as a metal boils off, there are variations with time in the amount of metal at various points between the electrodes. At the temperature of the arc, which is around 6,700 C., all the substances in the arc are partly ionized, and because of the electrical field these ions wander in the gas column. The metal ions migrate to the cathode and are neutralized there, diffusing away as vapor. The result is a concentration of neutral metal atoms and ions in a thin layer just above the cathode. This cathode layer effect is most notable when small amounts of substances are vaporized in the arc.

The types of lines emitted and their intensities are also affected by the presence of such easily ionized substances as sodium chloride. It is apparent, therefore, that the direct current arc is far more complex than it is customarily believed to be and that exacting quantitative work requires consideration of these factors.

However, in spite of the known difficulties of application of the spectrograph to the determination of lead and perhaps in total disregard of them, I have heard of determinations made of urinary lead with a single drop of urine. While this may be impressive to some, it is, to any one familiar with the field, merely ridiculous. Despite the many difficulties attached to the application of the spectrograph to determinations of this character, it is, in the hands of the conscientious analyst, an instrument of the greatest utility.

An interesting method for the determination of lead is that of the dropping mercury electrode which was first proposed for this purpose by Shikata, a Japanese student of Heyrovsky's, about 1927. The polarograph utilizing the dropping mercury electrode has been applied to the determination of small amounts of a variety of substances in addition to lead for a number of years. Its application depends on the interpretation of current-voltage curves obtained during electrolysis, and it employs a dropping mercury electrode in order to provide a fresh cathodic surface continuously. By the application of a small and steadily increasing voltage, a point is reached corresponding to the deposition potential of the ion sought. At this point, there is a sudden upsurge of current owing to the discharge of the ions at the cathode and the dissolution of mercury at the anode. The voltage at the onset of the surge of current represents a deposition potential characteristic of the ion. This surge of current reaches a limiting value depending on the ion concentration, and the proportion between the total rise in current and the concentration of the depositing ion is determined by calibration against known standards. The application of the polarograph to lead analysis of body fluids is invitingly simple, and if one is content to accept instrumental readings without further checks, the analytic throughput of the instrument is large. With extreme care one can, however, obtain analytic values, say for lead in urine, comparable with those obtained by other means.

In order to attain the desired accuracy, great care must be used in the purification of mercury and reagents, the calibration of the instrument and the interpretation of results, as well as attention paid to the constancy of salt content and acidity of the solutions analyzed. Organic material must be absent. Extraordinary precaution must be taken to remove oxygen from the nitrogen gas used as a bubbler to sweep oxygen from the cell before electrolysis. I mention the latter point since the impression appears to be somewhat prevalent that commercial nitrogen is sufficiently pure for this purpose. In fact, the accurate determination of urinary lead with this instrument is more or less of a research job and is so time consuming that it presents no advantages to the routine analyst whose interest lies beyond a quick value of any sort.

The colorimetric determination of lead by means of dithizone has perhaps received more attention than almost any other method. It also has the advantage of rapidity, and, when the amounts of lead are sufficiently large and in the absence of interfering substances, it is useful for this purpose. The principal difficulties that one encounters in the determination of minute amounts of lead by this method are, first of all, the presence of certain other metals and the tendency of dithizone to oxidize and give a slightly colored solution with certain oxidative substances. This becomes particularly pertinent in the determination

of lead in the blood, where an estimation is usually recorded in terms of 3 or 4 micrograms of lead in a 10 Gm. sample of blood. While lead is unquestionably present in the blood stream in extremely minute amounts, it is doubtful whether it is present to the extent that a number of persons have postulated as a result of measurements of this type. So far as I am aware, there are no published data in which the analytic values for the usual 10 Gm. of blood are compared with a sufficiently large quantity of the same blood to fix incontestably the value for normal lead. Instead, repeated "determinations" of lead made on 10 Gm. samples of blood have been used as the basis for fixing values for lead in the blood. It may be said that these values have been substantiated by spectrographic, polarographic and electrolytic methods and that they all are consistent. It is only when one attempts to make a serious study of lead in these concentrations of 3 or 4 micrograms per sample of blood and is confronted, not with the technics of investigation, which are sufficiently simple, but with the vagaries of the material sought and with readings attributable to other factors, that one is likely to revise one's opinion. I regard most values reported for lead in the blood with considerable reserve and suggest that more investigation be made of blood with reference to its intrinsic lead content. Certainly, it should not be difficult to test this by separating lead quantitatively from one hundred times the usual amount used for analysis, if analyses can be made of 10 Gm. samples with the great accuracy claimed for this small amount. Such analyses can be made with pooled lots of human blood, as my colleagues and I have done, or with animal blood, comparison then being made between 10 Gm. and 1 or 2 kilogram amounts of the same blood.

I bring up this point because there has been a certain tendency to have a blood lead determination made in cases of suspected lead poisoning and to rest the diagnosis on this analytic report as received. In cases of this type, a child with an apparent high level of lead in the blood is in the unfortunate position of being given possible treatment for lead poisoning when diagnosis of disease of an infectious nature is difficult or obscure. If values for lead in the blood are to be important in the diagnosis of lead poisoning, further investigation should be made of this subject in the interest of scientific accuracy.

I have referred to the question of lead in the blood somewhat at length because the disparity noted with reference to the actual amount present under ordinary conditions introduces an uncomfortable element in regard to data representing the amounts present in real cases of lead poisoning.

I might add parenthetically that the amount of lead normally present in the blood is of no particular interest to me, whether it is 1 microgram or 1,000 micrograms for 100 Gm. of blood. I am only interested in

the truth, and I should say that I am not relaying second hand information, but the results of my own observation and experimental findings. The investigation of this matter is time consuming and arduous, and perhaps thankless. The history of lead in the blood for the past decade or so shows a series of levels steadily revised downward, but each level at the time stoutly upheld as the acceptable value. I am not setting any value, but although our investigation was interrupted by war work, I have sufficient evidence to refuse to accept whole-heartedly the present situation with respect to lead in the blood.

There is one further point that I should refer to in connection with chemical data. To the nonscientific mind, positive results frequently carry more weight than low or negative results, and the greater the values reported, the more dramatic the effect. Perhaps it might be well to look behind the scenes more and study the source of technical errors. It would be unfortunate if, in the field of biochemistry, there is a situation analogous to that referred to by T. B. Smith in certain phases of commerce, in which professional analysts are classified as "high" analysts and "low" analysts, the sellers favoring one class and the buyers the other.

A great deal of responsibility is attached to the determination of lead as a diagnostic aid in lead poisoning. Instrumental readings of the greatest accuracy are obtainable from the modern apparatus available to the present day chemist. But the instrument itself cannot supply the intelligence necessary for accurate analysis. The conduct of an analytic operation should match in care the accuracy of the reading to which the instrument is susceptible. In other words, the chemist has a great responsibility in analytic work of this type, for so much depends on the outcome of his analysis. It is not sufficient for him to follow a routine procedure and to assume that, because he has followed the directions word by word, his analytic results must be correct. A poor chemist may obtain poor results with a good procedure; a competent chemist can, on the other hand, obtain fairly accurate results with an indifferent method.

These observations are offered, not in a critical spirit, but in order to focus attention on certain points that frequently arise with reference to analytic methods used as diagnostic aids in cases of suspected lead poisoning. A large number of investigators have been and are exploring much of this field, and through their perseverance and resourcefulness it is to be hoped that many of the obscure chapters in lead poisoning will become more completely clarified.

SUMMARY

Certain phases of the analytic problems presented by the type of material subjected to lead analysis are discussed. The difficulty of

separation and of quantitative evalution of extremely minute amounts of lead is indicated, as well as the exacting attention to detail necessary on the part of the analyst. Instruments of great delicacy have extended the range of observation, but responsibility for the analysis still rests with the chemist. Colorimetric, polarographic and spectrographic methods are discussed, and the difficulties in securing true quantitative values are pointed out. Many reported values for lead in the blood are regarded with reserve, and the need for further investigation in this field is indicated. The responsibility of the analyst in securing data of an incontrovertible nature and the importance of these data for diagnostic purposes are stressed.

EXPOSURE TO LEAD

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IN SPITE of the amount of time spent in this conference on the discussion of this problem, the subject has not been covered in such a manner as to provide for the practical application of the best and fullest information now available. This effort has illustrated the difficulties of covering such a many-sided subject in a session of this type.

It is my function at this point to try to summarize the information, to try to make certain factual interpretations of the information so far presented and to bring this discussion into a well rounded state so as to bear with greatest practical efficacy on the problems which we, as industrial physicians and practicing physicians and industrial hygienists, have to meet. That is an extremely difficult assignment, and I have not the slightest hope that I shall be able to do it. I shall have to exercise my own judgment in the addition of certain facts to the discussion, and shall try to emphasize what in my own mind are the high spots in the practical application of the huge mass of information, inadequate as it is, that is available on this subject.

In doing this I shall try to stick to three principal headings: (1) the significance of the exposure of the public to lead, (2) certain aspects of industrial exposure to lead and (3) the problem of diagnosis.

THE SIGNIFICANCE OF EXPOSURE OF THE PUBLIC TO LEAD

I call your attention to a group of data in table 1, obtained in an incomplete attempt to picture for one area, and for only a few spots in that area, the lead content of the air. I shall not draw any conclusions as to the applicability of these results to the quantities of lead inhaled generally by persons in the population, but these samples were taken within the breathing zone of persons within this area. A more comprehensive study of this problem will be carried out in the future, but these are a few of the data which bear on it. A person in Cincinnati may be exposed to quantities of lead in the air respired during twenty-four hours, to an extent which is of about twice the order of magnitude of the figures given. Presumably, therefore, in the course of one day one is breathing in about 0.1 mg. of lead. Much of this is extremely

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finely divided. The amount actually absorbed is entirely a matter of conjecture. In following certain persons in otherwise approximately balanced experiments on the intake and output of lead, my colleagues and I have been able to find evidence of an imbalance which is the result of this inhalation of lead in the course of the day. The quantities represented from day to day, however, cannot be determined by the methods so far employed. In order to be more explicit, let me state the case in other words. In carefully controlled experiments on human metabolism we have found that over a period of six or eight months or a year, the normal healthy adult puts out a little more lead than he ingests in his food and drink, and although the quantity is small, the

TABLE 1.—*Particulate Lead in the Atmosphere*
Cincinnati, 1941

Lead, Mg. per 10 Cu. M.	Frequencies of Occurrence of Quantities of Lead Indicated
0 - 0.019	18
0.020 - 0.039	37
0.040 - 0.059	11
0.060 - 0.079	5
0.080 - 0.099	6
0.100 - 0.119	2
0.12 and over	7
Total	84
Mean	0.051
Probable error	±0.004
Standard deviation	±0.051

consistency with which it occurs is such as to demonstrate that there is an additional source of lead intake and absorption. This source, obviously, is to be found in the inhalation of the lead that has been shown to be present in the atmosphere. The origin of such lead is manifold. Time will not permit discussion of this point.

The next set of data, in table 2, brings me to the subject of food and to a brief and cursory reference to the problem of public health related thereto. As we have shown previously in experiments involving lead intake by mouth and lead output in feces and urine, the quantities which appear in the feces from day to day bear a close relationship to those occurring in the food from day to day. It is obvious that only a small proportion of ingested lead is absorbed. The result depends, in some degree, on the solubility of lead in the alimentary tract. In experiments of this type in which solutions of lead salts have been administered in known quantities to human subjects, we have found that something like 10 per cent of the lead is absorbed. This represents a greater proportional absorption than would be anticipated under ordi-

nary circumstances. By and large, the degree of variability in the daily intake of lead in the food and drink and in the daily output in the feces, as shown in table 2, is fairly representative, and the mean values are characteristic of those found in the case of large groups of normal persons in the general population.

Now the point of these facts, for the purposes of present discussion, is that the situation illustrated by these data has existed for well over ten years with practically no change that could be demonstrated. It is about time to repeat our observations and to see whether anything has happened during and since the war to change this picture qualitatively or quantitatively, but it has been so stable for such a period of time that nothing remarkable is to be anticipated.

TABLE 2.—*Daily Occurrence of Lead in the Food and the Corresponding Feces of Three Normal American Adults with No Occupational Lead Exposure*

Lead, Mg. per 24 Hours	Frequencies of Occurrence of Quantities of Lead Indicated					
	In Food			In Feces		
	M. B.	E. B.	H. D.	M. B.	E. B.	H. D.
0 - 0.099	..	..	4	7	3	8
0.10 - 0.199	12	11	50	1	11	37
0.20 - 0.299	7	18	42	6	12	42
0.30 - 0.399	8	13	10	5	13	25
0.40 - 0.499	1	12	3	2	6	4
0.50 - 0.599	1	4	1	4	6	1
0.60 and over	2	3	2	6	5	4
Totals.....	31	56	121	31	56	121
Mean.....	0.270	0.352	0.220	0.377	0.338	0.247
Probable error.....	±0.017	±0.016	±0.007	±0.087	±0.016	±0.007
Standard deviation	±0.137	±0.181	±0.110	±0.301	±0.172	±0.121

It is important to recognize that these physiologic observations have provided a means of studying the population on a broad basis. It will not be difficult to establish the essential facts with reference to the alimentary lead exposure of representative groups in the population of any community through the proper application of these methods.

Table 3 shows a simple application of this method in that samples of feces, representing roughly twenty-four hour evacuations, have been obtained from a series of persons and the results tabulated according to the frequencies of their occurrence. The mean value for this large number of samples is a familiar figure, being about one third of 1 mg. The fact was mentioned this morning that the present limit for lead in certain specific items of food amounts to about 7 parts per million by weight. If all foods were contaminated with lead to this extent, adults would be taking in average amounts of 14 or 15 mg. per day.

This brings me to the question of permissible limits for the contamination of food materials with lead and how the safety of the community can be guarded by the acceptance and enforcement of such tolerances.

It is clear that if every producer of food materials were to exercise the right of having his product contaminated to the extent permitted in some instances, the community would be seriously endangered. The tolerance applies to apples, on the theory that lead-containing insecticides must be employed to secure a crop. The concentration of lead in

TABLE 3.—*Lead Content of Random Samples of Feces of Normal Persons from Ten Widely Scattered North American Cities*

Lead, Mg. per Sample of Feces	Frequencies of Occurrence of Quantities of Lead Indicated
0 - 0.199	26
0.20 - 0.399	48
0.40 - 0.599	17
0.60 - 0.799	7
0.80 - 0.999	2
1.00 - 1.199	4
1.20 - 1.399	2
2.00 and over	1
Total	108
Mean	0.398
Probable error	±0.021
Standard deviation	±0.310

most of the other foods and beverages is low. It is important to remember these facts in relation to this general problem.

The data of table 4 show the facts in relation to water and certain other beverages. The drinking water in most North American cities contains lead to the extent of about 0.02 to 0.03 mg. per liter. Excep-

TABLE 4.—*The Lead Content of Various Beverages in the United States*

Substance	Source	Range of Analytic Results, Mg. per Liter	Number of Samples
Water	36 scattered cities	0.008- 0.04 (mean 0.01)	37
Water	Cincinnati	0.01 - 0.05	10
Water	New building	0.37 - 0.92	3
Coffee	Prepared for use	0.01 - 0.03	2
Milk	Cincinnati market	0.02 - 0.04	3
Beer	Cincinnati market	0.01 - 0.09 (mean 0.04)	21
Beer	Cincinnati market	0.13 - 0.29	3
Grape juice	Cincinnati market	0.04 - 0.4	7
Wine	Domestic and imported	0.05 - 1.51	10

tions to this condition may be found by taking samples of water from the mains of new buildings, as is illustrated in the data. The hot and cold water lines in the building were of the usual type, with no lead pipe at any point. However, unwittingly, the joints of the pipe were luted with a lead-bearing compound. When water was allowed to stand overnight in these pipes, it was contaminated to the extent

of 0.39 to 0.92 mg. per liter. If the water flowed freely from the taps for ten or fifteen minutes the lead content dropped to 0.03 mg. per liter. This situation has probably occurred in connection with extensive building projects involving large numbers of houses, and under these conditions it may have more than minor or temporary importance. In general, however, the condition is fleeting and intermittent, and is not of great practical importance.

As to other beverages, only a few samples of many available have been given. The question of the generally accepted tolerance of 0.1 mg. of lead per liter arises. In my opinion, while this tolerance does not permit undue hazard under ordinary circumstances, it is too high for that segment of the population, wherever it may be, that is required to take in much larger than ordinary quantities of water per day in order to maintain water balance. Persons who must live and work at high temperatures may increase their water intake many-fold. Under these circumstances, if the situation were continued there might well be a potentially dangerous intake of lead. It is much better that drinking water should be as carefully controlled as it is at the present time and maintained within the limits which prevail commonly.

TABLE 5.—*Concentration of Lead in the Bones of Persons Believed to Have Had No Occupational or Unusual Lead Exposure*

Identification	Age, Years	Concentration of Lead in Mg. per 100 Gm. of Fresh Bone: Rib	Concentration of Lead in Mg. per 100 Gm. of Fresh Bone: Femur
E. S.	3	....	2.22
Girl	6	1.02	1.14
E. J.	20 ?	1.11	....
E. H.	31	0.47	....
N. B.	64	....	0.80
A. P.	70	0.39	3.59
J. W.	78	0.60	2.89
A. C.	86	0.56	1.36

There is one other point of some consequence in relation to this general problem. The idea has existed over a considerable period of time that lead accumulates in the body irrespective of the rate of daily absorption, as long as some exposure and absorption occur. The evidence of our experimental work over the last several years has been such as to indicate that under the conditions of the normal or incidental lead exposure which characterizes modern community life generally, outside the lead industries, no such accumulation occurs or it is so slight as to be insignificant in the course of a lifetime. This problem has been approached from several points of view. A few data that have been published previously are employed for illustration in table 5. The concentration of lead in the bones of persons of greatly differing ages at the time of death is shown. These cases were selected as

carefully as possible to avoid the inclusion of any instance of occupational or other unusual lead exposure. One can make no claim for certainty in that regard, but for the sake of additional assurance, most of these data relate to women whose occupational histories were simple and apparently dependable. One sees that, despite the wide range of the life span, there is no consistent evidence of progressive accumulation of lead in the skeleton. One would anticipate that such evidence would most certainly show up in a series of this type. The defect in the more extensive and less critically chosen data that have been published in support of the existence of progressive accumulation of lead during

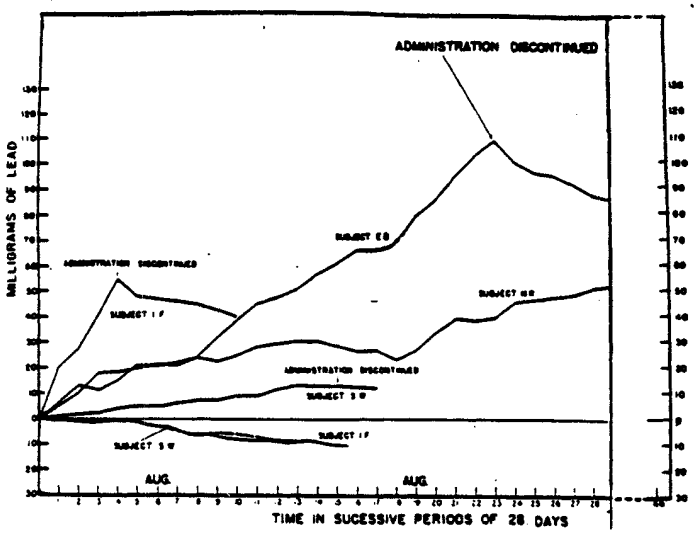

Chart 1.—Lead balance, retention and loss in normal adult human subjects under varying conditions of lead intake by ingestion. Points on the curves represent the cumulative total of the differences between the lead in duplicate samples of food and drink, plus that administered, and the lead output in the feces and the urine.

life can be appreciated, when one recognizes the great difficulty in the avoidance of persons who have been subjected to occupational or unusual types of lead exposure. Indeed our examination of Tompsett's data led us to suspect that some such unusual lead exposure had occurred in an appreciable number of his cases, a suspicion which was later confirmed by correspondence.

The next series of results illustrates a somewhat different approach to this problem. A series of curves is given in chart 1, each representing the facts in relation to one person studied under carefully controlled

laboratory conditions. The intake and output of lead day by day over a period of weeks, months and years were determined by analytic means. The difference between intake and output has been plotted in each instance in a cumulative manner, so that the total quantity of lead retained in the body at any time, as the result of the experimental conditions, is indicated. These experiments are based on the most recent and most accurate methods used in the Kettering Laboratory for studying the alimentary and urinary metabolism of lead, that which is absorbed by way of the respiratory tract being ignored.

There are several points of interest in chart 1, to which I shall refer briefly. Two of the subjects (I. F. and S. W., represented in the lowermost curves) took a normal diet of their own choosing and no additional lead. It will be observed that these persons, in accordance with my previous statements, put out slightly more than they took in. The interpretation of this fact has been made before. The correspondence in the behavior of these subjects over a period of about eighteen months in each instance is so striking and so clearly defined as to be convincing. The discrepancy between the total intake represented by ingested lead in the food and beverages and the output in the feces and the urine approximated 10 mg. in the eighteen months. It is a minute quantity and you will recognize, in all likelihood, as I do, that no significant difference between intake and output could have been found from day to day. Prolonged observations were required to reveal the fact, but the trend continued in such uniform fashion as to be improbable of explanation as experimental error, and therefore it is accepted as fact.

Other curves in this series or family of curves illustrate the facts obtained in the study of other healthy human subjects under conditions of increased oral intake of soluble lead. The upper curve marked S. W. is that obtained in the case of a subject who took an additional 0.3 mg. of lead per day, as a solution of lead acetate, thereby bringing the total (including that in his food) to somewhat less than 0.6 mg. per day. At that level of intake the metabolism was not balanced, for some accumulation of lead occurred. The accumulation was slight, however, so that it is apparent that it will be difficult if not impossible, by these experimental means, to arrive at a level of daily ingested lead which is just at the point of balance with output. Clearly, the point of balance in experiments of this type is to be found somewhere between 0.3 and 0.6 mg. of lead ingested per day.

Another curve (M. R.) gives the facts on the retention of lead when 1 mg. of lead per day was added to the dietary lead. This curve with some vagaries continues substantially as a straight line for four and one-half years. Another (E. B.) illustrates the effects of the addition of 2 mg. of lead per day to the dietary lead. This curve continues

straight or nearly so for two years. Another (I. F.) is the graphic result of the administration of 3 mg. per day, in addition to that in the diet. This experiment was terminated much sooner than it should have been, because of the fear, later found to be unwarranted, that the initial steep slope of the curve might be indicative of impending danger to the subject. It is apparent that over the periods represented in these observations the subjects failed to absorb quantities of lead which approach the point of saturation, so to speak, of the tissues in which lead is retained. Most of the retained lead found its way without undue delay into the skeleton, in which, obviously, the small quantities of lead were but traces in the bulk of minerals available. On this account, it is of the greatest physiologic significance to recognize that despite the substantially constant rate of absorption of lead from the alimentary tract in any individual experiment, there was a well defined progressive increase in the concentration of lead in the blood and the urine of every subject over the active period of administration of lead, with the single exception of the one whose lead intake was about 0.6 mg. per day. In view of the known facts concerning the distribution of lead in the tissues of the body over such periods of time, it is obvious that all or almost all of the lead absorbed into the tissues of these subjects, including that which found its way into their skeletons, exerted its effect in the maintenance of a state of dynamic equilibrium of the tissues with each other. Obviously little or none of the absorbed lead was stored in an inert form at any time, in the skeleton or elsewhere. In the case of the subject who ingested approximately 0.6 mg. per day for eighteen months, the total quantity of lead involved at any time during this entire period was too small to exert a demonstrable effect.

For practical purposes, these experiments demonstrate that the safe level for the ingestion of lead in food and drink, as determined by the establishment of a level of alimentary lead intake that will not result in the retention of lead on the part of normal healthy persons, is greater than 0.3 mg. and less than 0.6 mg. per day. It is fair to say that those of us who have interest in these matters in relation to the public health would like to see a situation maintained in which there is little likelihood of a practically significant amount of progressive accumulation of lead in the tissues of persons in the general population during their span of life.

INDUSTRIAL EXPOSURE TO LEAD

The foregoing facts and considerations have brought up the problem of industrial exposure to lead. It is clear that if the foregoing observations and concepts are valid, the degree of risk associated with occupational exposure to lead is the joint function of the severity of such exposure and its duration. The problem is to determine the limits

of safe occupational exposure to lead, by providing criteria which can be applied pragmatically and by determining the physiologic facts concerning the relative importance of duration versus intensity of exposure under a variety of conditions. Fortunately, to a considerable degree these tasks are susceptible of accomplishment, and to a practical extent they have been accomplished.

As a background for this discussion, certain facts with respect to normal persons, unexposed to lead compounds during their day's work, must be reviewed briefly. At this point, it is necessary for me to say that Dr. Fairhall's [1] skepticism concerning the validity of the more carefully collected data on the concentration of lead in the blood of normal persons should not be permitted to obscure the facts. In presenting the data in table 6, candor requires me to point out that

TABLE 6.—*Mean Concentration of Lead in Blood of Persons and Groups of Persons with No Occupational Lead Exposure* *

Identification of Group or Person	Number of Persons or Samples	Lead, Mg. per 100 Gm. of Whole Blood
Mexican Indians	30	0.023
American students	30	0.027
Subject E. B.	9	0.029
Subject M. R.	6	0.038
Subject H. D.	76	0.034
Subject I. F.	37	0.031
Number of analyses	188	0.030
Probable error		±0.0005
Standard deviation		±0.009

* Range of analytic results: 0.005 to 0.055.

the background of experience and technical proficiency which has brought forth these results has been tested somewhat by time and by the critical investigation of others. I do not take credit for their accuracy, for they represent the work of colleagues who have labored with skill and assiduity to develop methods that would yield precise and final results. I have examined these results as to their precision and reproducibility with a critique for which I am responsible, and I am convinced that they will stand the test of time. A similar skepticism, now resolved, once attached to our results on the lead content of the urine of normal persons, as I remember.

It seems apparent, if you will accept these figures, that the concentration of lead in the blood of the present day normal person varies between the limits of 0.01 or slightly less and 0.055 mg. per hundred grams of whole blood, only an occasional sample exceeding the value of 0.05 mg. per hundred grams. It is also an important physiologic fact

1. Fairhall, L. T.: Analytic Methods in Diagnosis, Occup. Med. 3:13 (Jan.) 1947.

that from 95 to 98 per cent of this lead is found in the erythrocytes in the blood. This circumstance is responsible for the existence of a first line of defense on the part of the human organism against a high concentration of highly reactive lead in the medium bathing the cells of the body.

In table 7 are given the mean values of the concentrations of lead in the blood of groups of persons whose occupations involve varying

TABLE 7.—*Variation of the Mean Concentration of Lead in the Blood of Groups of Persons in Accordance with the Severity of Their Occupational Lead Exposure*

Occupation	Occupational Lead Exposure	Number of Persons in Group	Lead, Mg. per 100 Gm. of Whole Blood
Miscellaneous	None	188	0.020
Installing insulation	Hypothetic only	27	0.037
Garage mechanic	Very slight	145	0.039
Paint manufacturing	Well controlled	20	0.048
Soldering	Well controlled	15	0.050
Manufacturing of lead shot	Potentially hazardous	13	0.062
Color manufacturing	Hazardous	7	0.086
White lead manufacturing	Hazardous	21	0.096
Lead smelting	Highly hazardous	78	0.153

degrees of severity of lead exposure. The total range of such values as we have seen them is not covered by these data, but they serve to illustrate the important fact that increasing severity of exposure is associated with increasing concentration of lead in the blood.

TABLE 8.—*Concentration of Lead in Urine of Groups of Normal Adults with No Occupational Lead Exposure*

Lead, Mg. per Liter	Frequencies of Occurrence of Quantities of Lead Indicated			
	Americans	Mexicans	Frenchmen	Germans
0 - 0.009	..	5	..	..
0.01 - 0.019	7	10	11	5
0.02 - 0.029	6	7	6	4
0.03 - 0.039	8	4	8	2
0.04 - 0.049	5	3	5	1
0.05 - 0.059	3	..	2	1
0.06 - 0.069	1	..	1	..
Totals	30	29	33	13
Mean	0.029*	0.022	0.030	0.027
Probable error	±0.002	±0.002	±0.002	±0.002
Standard deviation	±0.016	±0.017	±0.014	±0.012

* The mean concentration of lead in the urine in nine hundred and forty-seven twenty-four hour samples of the urine of 4 normal American adults studied under carefully controlled laboratory conditions was 0.027 ± 0.0003 mg. per liter.

The range of concentration of lead in samples of large volume of the urine of normal persons is illustrated in table 8. Here it is of interest to see that the subjects include Americans, Mexicans, Frenchmen and Germans, among whom the distribution of the results is substantially the same.

Tables 9, 10 and 11 illustrate facts which are amply supported by large numbers of observations made over prolonged periods of time in certain lead industries, and over a wide variety of industries with variable degrees of hazardous exposure to lead. The analytic data refer to samples of large volume. It is apparent that the classification of occupational exposure to lead according to its severity by this means is readily made.

In table 9 the levels of concentration of lead in the urine that are compatible with complete freedom from the risk of lead poisoning are shown. The evidence behind this statement as well as others that

TABLE 9.—*Concentration of Lead in Urine of Persons with Safe Occupational Lead Exposure*

	Frequencies of Occurrence of the Quantities of Lead Indicated			
Lead, Mg. per Liter of Urine	Random Samples from Workmen, Industry E. P.	Repeated Samples from Nine Men, Industry D. P. L.	Repeated Samples from Subject M. B. on Experimental Intake of 1 Mg. Daily Plus That in Diet	Random Samples from Workmen, Industry H. B.
0.0 - 0.019	8	8	..	0
0.02 - 0.039	6	110	34	5
0.04 - 0.059	3	239	82	6
0.06 - 0.079	3	104	65	11
0.08 - 0.099	2	15	14	5
0.10 - 0.119	..	..	2	2
0.12 - 0.139	..	..	..	4
0.14 and over	..	..	..	3
Totals	24	471	197	36
Mean	0.037	0.051	0.067	0.079
Probable error	±0.004	±0.0006	±0.0009	±0.004
Standard deviation	±0.025	±0.016	±0.018	±0.04

follow in similar vein is empiric, being based on careful clinical observations in a vain search for illness that could be regarded as relevant.

Table 10 presents data previously employed to designate the highest general level of urinary excretion of lead (as represented by large samples of urine) which, in our experience, was compatible with freedom from symptomatic plumbism. That is to say that men employed under conditions that gave rise to such levels of urinary excretion of lead remained free of symptoms and continued their work for years without complaint, illness or clinical evidence of plumbism. We were not sure in the past as to the margin of safety that was represented in this standard. As a consequence of experience during the war, when control of exposure was more difficult, we had the misfortune to establish the facts in this regard. Without going into details, suffice it to say that we have been conservative, without, I think, being overcautious, in the promulgation of this standard. Actually, the mean

values, without great increase in the over-all range of values, can go to 0.11 mg. or 0.12 mg. without incidence of lead intoxication, but when an occupational group exceeds the latter value, evidence of lead intoxication can be found among them before long, in our experience. Our error, therefore, if it be called an error, was on the side of safety. In my opinion, after years of experience, the safety factor included in our original standard is not too great, when one considers that most occupations should be safe for an indefinite period of employment, rather than for a relatively short period of years.

TABLE 10.—*Concentration of Lead in Urine of Persons with Occupational Lead Exposure Maintained for Years Near Threshold of Toxicity*

Lead, Mg. per Liter of Urine	Frequencies of Occurrence of Quantities of Lead Indicated *
0.000 - 0.019	..
0.020	3
0.040	14
0.060	17
0.080	10
0.100	9
0.120	6
0.140	9
0.160	4
0.200	1
0.220	1
Total	74
Mean	0.097
Probable error	±0.004
Standard deviation	±0.045

* These data represent one set of results obtained on one large sample of the urine of each workman chosen to represent a specific occupation. The group as a whole represents all the occupations in a plant. Comparable results were obtained at intervals over a period of years. Decreases in environmental lead exposure resulted in elimination of some of the higher values and lowering of the mean; increases in exposure caused opposite effects. So long as there was no significant increase above the level illustrated here, no clinical plumbism was evident, but when higher individual values were obtained and mean values exceeded 0.12 mg. per liter, signs and symptoms appeared.

Table 11 illustrates the excretory values obtainable under occupational conditions which result in the occurrence of cases of lead poisoning. Cases increase in number and severity as the mean urinary concentration of lead increases.

I should like at this time to emphasize the fact that the order of magnitude of the exposure of individuals can be determined by analytic means in such a way as largely to dispose of the bugbear of individual susceptibility. We have learned that the variation in the response of individuals to the conditions of a lead trade is not due to the factor of susceptibility to lead so much as to the generally unrecognized variability of the lead exposure from person to person and from time to time in the same occupation. I do not mean that there is not biologic variation

among workmen, but it operates within reasonable limits, and it definitely does not include the wide range of unpredictable susceptibility that is so commonly referred to in medical literature and comment. Our experience over a period of years has demonstrated clearly that if the lead exposure of a person is kept within certain reasonable limits he will not become ill. Admittedly, industrial employees are a somewhat selected group, and this, in itself, limits the factor of susceptibility, but within the limits of lead exposure which we have described as safe, individual susceptibility is not an important stumbling block to the accomplishment of satisfactory results.

TABLE 11.—*Concentration of Lead in the Urine of Persons with Demonstrably Dangerous Occupational Lead Exposure*

Lead, Mg. per Liter of Urine	Frequencies of Quantities of Lead Indicated		
	Random Samples from Workman, Industry C. S. B.	Random Samples from Workmen, Industry B. B.	Random Samples from Workmen, Industry E. P.
0 - 0.07	11	4	6
0.08 - 0.15	31	27	28
0.16 - 0.23	14	17	20
0.24 - 0.31	8	7	13
0.32 - 0.39	2	1	3
0.40 - 0.47	1	2	5
0.48 - 0.55	1	..	4
0.56 - 0.63	..	2	3
0.64 - 0.71	..	..	2
0.72 - 0.79	..	..	1
0.80 - 0.87	1	1	..
0.88 - 0.95	1	..	..
0.96	3	1	1
Totals	73	62	86
Mean *	0.155	0.172	0.194
Probable error	±0.0071	±0.0075	±0.0079
Standard deviation	±0.097	±0.095	±0.102

* The mean has been calculated on results above the dotted line.

In response to a request and in consideration of a practical problem, it seems necessary to say something about the matter of "spot" samples of urine, versus samples of large volume, as a means of measuring the lead absorption of individuals or groups. In chart 2 are shown the results of three sets of observations made at three different periods in the history of a person exposed experimentally to a given amount of lead over a long period of time. The dotted lines represent the concentrations of lead in the blood on these occasions, while the solid lines represent the concentrations of lead in the urine. Observations were made at intervals of two hours during each of the three twenty-four hour periods. As can be seen, the concentration of lead in the

blood is substantially constant throughout any one of the twenty-four hour periods, but it is higher at each successive period of the experiment, in response to the progressive retention of lead hitherto spoken of as occurring in such prolonged experiments. The variation in the concentration of lead in the urine on one of these days, which is the only present point of the demonstration, ranged from 0.07 mg. per liter at one time to a peak of 0.21 mg. per liter at a later time in the same day. This extreme degree of variation was a function of the volume of urine excreted at different times. When the volume was high, the urinary concentration was low, and vice versa. This illustrates the problem of sampling, so far as the physiologic principle is concerned. We have found it necessary to make use of spot samples under certain conditions, and such samples yield valuable information.

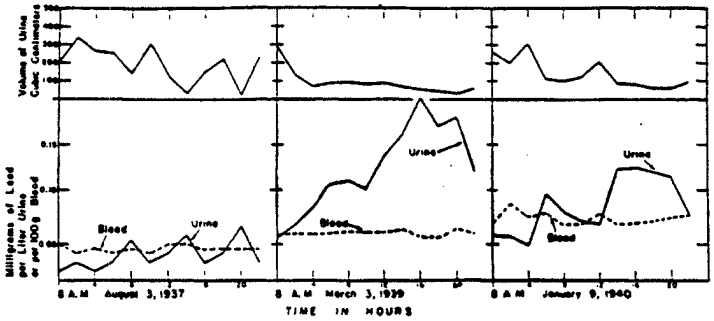

Chart 2.—Variations in concentration of lead in urine and blood during twenty-four hour periods (subject M. R.). The analytic results appearing as points on the lower section were obtained for the urine voided at two hour intervals and for samples of blood taken in duplicate at two hour intervals.

However, it is necessary to control the factor of diurnal variation. This can be accomplished in at least two ways, both of which are usually feasible. One consists in the determination of the specific gravity of the urine, making some allowance for the extent of the concentration of solids therein, while the other, more valuable, is that of taking a sample or samples of blood at the time the urine is collected, so as to be able to appraise the significance of the urinary concentration of lead on the background of the concentration of lead in the blood. By the combination of these procedures one is usually able to picture the physiologic situation, while at the same time one need not rely on one analytic determination. The advantages of this type of cross checking are great indeed, especially in medicolegal practice.

If one is studying a group of persons in a torrid climate and another in a cool one, one will find that the concentrations of lead representing

tolerable conditions of lead exposure will be higher in the hot area than in the cool. Likewise there will be differences in the results obtained in the summer as compared with the winter, in temperate or semitropical areas. These factors have to be taken into account in the interpretation of results and in establishing standards of safety.

Another aspect of the problem of sampling is that of the contamination of samples in the process of their collection. This, above all factors, has contributed to the confusion which has tended to surround this subject. It is still not sufficiently well known that the handling of such samples by procedures that are customary and satisfactory in relation to many other analyses will result badly in almost every instance in the case of lead analysis. Blood must be collected in chemically clean containers, preferably of glass of extremely low lead content, and must be drawn through a needle that is fabricated and cleaned so as to be devoid of any lead. The brass hub which is a usual part of the structure of standard hypodermic needles will contaminate blood samples with lead and will give rise to high results. Moreover, the likelihood of contaminating samples of urine with dust or other foreign material is such that one must exercise the utmost care against contact of the hands or clothes of the individual with the sample. Personal advice and supervision is often required to avoid the mishandling of the stopper or cover of the container. Samples of blood, urine, spinal fluid or tissues collected for lead analysis in ordinary hospitals by ordinary orthodox methods are almost always seriously contaminated. It is this which has accounted for the publication of impossibly high results for the urine and of certain equally fantastic results for blood and tissues. When samples of urine exceed 0.6 mg. per liter in their reported lead content, it is well to ignore them unless the results are confirmed by the most careful technic. Except in the rarest instance of most unusually rapid absorption of lead, such results convict themselves of error. I have seen concentrations as high as 1.5 mg. per liter, but they are most rare, and concentrations of 2 mg. or more per liter are almost certainly incorrect.

THE DIAGNOSIS OF LEAD POISONING

I come now to the problem of diagnosis, with which, obviously, I cannot deal at this time in any satisfactory fashion. Most of what I have to say on this subject has been said in some detail and published where it is readily available. However, I want to make two comments. One of them is that the diagnosis of lead intoxication is made on presumptive or definite evidence of significant absorption of lead, together with the existence of a clinical syndrome which, when carefully studied by acceptable clinical methods, is found to be in keeping with the known

toxic effects of lead on the human organism and is not more readily accounted for on the basis of other clinical considerations. My second comment, which to some degree is a corollary of the first, is that the known toxic effects of lead on the human organism are now susceptible of critical study and interpretation in a manner not previously possible. There is now available specific and fairly precise knowledge of the physiologic background by which one can estimate the significance of lead exposure and absorption. Persons do not get lead poisoning without having absorbed abnormal quantities of lead. When a person is suspected of having lead poisoning, it is well to establish that he has had a significant exposure to lead—not by his story or by casual observation of the conditions of his employment, but by physiologic means. The evidence, so far as it is entirely acceptable and not presumptive, resides in the man himself at the time of his illness, and can be obtained. It often becomes necessary in controversial and medicolegal cases to establish the order of magnitude of the exposure beyond presumption, and this can generally be done by suitable means. Such means should be used. Admittedly, such means call for difficult and precise procedures and unusual skill, as compared with most technics of the diagnostic laboratory. Thus there is a handicap to be overcome. Physicians have overcome handicaps in the past and they can overcome them in the future. Obviously, when the diagnosis cannot be proved by the most acceptable means, one must do the best that one can without proof. Such circumstances do not provide the proper basis for certainty, but they are often the background for dogmatic decisions. Unfortunately, medical procedure in relation to this problem is brought into disrepute by the exercise of arbitrary clinical judgments on the part of physicians who have not had or made use of the means of substantiating their opinions. It becomes increasingly important that physicians make use of the methods available for this purpose.

DISCUSSION

Dr. John McDonald, Baltimore, Md.: Some of us have been responsible for contributing a considerable number of statistics to various journals on lead poisoning in children, and have talked about cribs as a possible source of exposure.

We know that the brand new cribs coming from the manufacturers do not contain lead at all. They are perfectly safe to use. We have never had a case of lead poisoning in a crib from the original paint. What happens is that the paint wears off, and it is in the re-painting that danger occurs.

When a case of children's lead poisoning is reported to us, we make an effort to get a sample of that which the child has been nibbling. We bring it into our laboratory and we have it analyzed for the presence of lead.

The next time Mr. Wormser comes to Baltimore, I will show him a re-painted crib which caused at least three cases of lead poisoning.

Mr. Felix Wormser, New York City: I have taken into consideration, the danger from re-paint jobs. So far as white inside paint is concerned, there is no lead in it.

Dr. Robert A. Kehoe, Cincinnati: More lead poisoning in children has occurred than we like to think about. The number that are actually reported in medical literature have very little relationship to the number that actually occur.

Lead poisoning in a child is a serious disease. A fair proportion of them do not recover. We have on record in our own files from 1935 to 1946 twenty-eight proved cases of lead poisoning in children, with six fatalities. In four of those six fatalities, we have analytical data from necropsy material demonstrating without possibility of a doubt that they were due to lead. One is not able to say in each of the instances the source, but in most of them, one can.

It is not fair on the basis of a poor hearsay history to convict lead on cribs, toys and the like. But there have been instances of children who were sick and who died as a consequence of chewing paint off toys. Of the rather high-colored Japanese toys that flooded the American market in considerable numbers some years ago, those in yellow and red almost uniformly had a high lead content in paint.

Another instance of lead poisoning in children which should be remembered is molding sets.

The burning of lead battery casings in the household has been mentioned, and it should be remembered that these have taken the toll of a sizeable number of children in various parts of the United States—and not only children, but some few adults.

Dr. Ronald Lane, Manchester, England: May I first thank you for your invitation to attend this Congress on Industrial Health, and for the hospitality which you have extended to me. I also want to convey to this Association and to this meeting the greetings of the Association of Industrial Medical Officers in England. They are very anxious that we should keep close together for the betterment of this important branch of work.

May I support Dr. Mayers in her delightful paper that she gave this morning in the importance of the clinical side of diagnosis, and the importance of the really good physician's part in these cases of lead poisoning. I feel that all too frequently when young physicians, or perhaps the experienced physicians try to make diagnoses without that general, clinical knowledge which is essential, then there is trouble.

I should also like to support her in the doubt that she expresses on some of the spot checks taken and which may give reassuring figures, when perhaps a dangerous condition is in existence. I should like to conclude that a much more prolonged collection of specimens is necessary than is becoming popular at the present time.

One further point I should like to emphasize is that of susceptibility. About fifteen years ago, I recorded a case of familial susceptibility, in which three brothers in successive years came to work in the same factory and went off with lead poisoning with an exposure which we should have regarded as minimal. The presence of susceptibility in families has to be guarded against.

Dr. Alice Hamilton, Hadlyme, Conn.: I have often told people that I belonged to the covered-wagon stage and came here only to hear what the newest authorities have to say on lead poisoning. I must say that I am enormously gratified when I see the strides that have been made in what was for thirty years my specialty. Those strides have been made especially in the past twenty-seven years, because I date the forward move just after the first world war, and I think it ought to be a matter of great gratification to the American medical profession that they have caught up with the rest of the world, and in some respect, have gone ahead in that short period of time. I hope that industrial medicine will begin at least to have its appropriate and proper place in the curriculum, facing the fact that we are an industrial nation, and that it is a very great mistake to neglect the opportunity to turn the minds of the medical students towards that phase of the science.

Mr. Herbert Weber, Chicago: Lead becomes hazardous to us in making brass castings. One of our employees regularly shows 1,000 gamma lead per liter, and

his partner who moulds with him, while in the high range, shows no ill effects and no signs or symptoms of lead intoxication. Of course, this man with the high range does have definite signs of lead intoxication.

A superintendent at the same plant was exposed to high concentrations of lead for twenty years, before he developed wrist drop and paralysis of the eyelids, the latter unheard of in our previous experience.

Our company has plants scattered throughout the United States, and we keep control of the lead hazard by spot urine samples. We analyze 4,000 urine samples a year, and 200 to 300 blood samples. When a man comes to us for employment, we immediately request a spot urine and blood sample, to determine any previous exposure. We have had claims of lead intoxication after eighty hours of exposure stretched over a six-week period with the concentration of lead at 1.2 mg. If following monthly spot samples of our men, in some cases weekly, we notice a rise in lead content in the urine we request immediate check samples and a blood sample. We also determine what the air exposure is.

We send this information to our doctor, ask him to withhold his diagnosis until laboratory reports are available. In this way we have supplied him with better tools to make a diagnosis.

In our experience we have never been able to correlate stippling and urine excretion rates. Also, our experience is somewhat at variance with the published findings of the Committee on Lead Intoxication, in that we never have found any symptoms of lead intoxication when the excretion rate for spot samples was below 200 micrograms per liter.

We do find that new men, when exposed, show a rapid rise in lead excretion rates, but these seem to remain steady for a good many years, without any definite physical signs.

We find also a high variation in rates. For example, in the normal man, we have found variations from 30 to 220 gamma lead per liter. Therefore, we have long learned not to place any importance on one urinalysis, but only on the results of many of them, in conjunction with the physical findings of the physician, the actual plant exposure and blood analysis.

Dr. Elston Belknap, Milwaukee: I have gained experience with a fairly large number of men employed in the manufacture of storage batteries. A lead level of 1.5 mg. per 10 cubic meters of air is safe and might well be elevated. I have rarely seen cases of true clinical lead poisoning where the level of lead in the air has not been well over 3 mg.

The patient should be studied as a whole. Early study is definitely of advantage in selected cases. Is it not our present responsibility to point out to the practicing physician that there are several proved techniques with which he can meet the emergency of preventable disability in workers exposed to toxic materials. These procedures are not difficult. They embrace principles of clinical medicine with which he is already familiar in his practical experience.

I. Every physician is able to take a brief but thorough occupational history if its importance is emphasized. The clinical picture of an acute lead colic is just as typical in a full-blown instance as it was in the days of Hippocrates. Such a history makes up the majority of the cases of true lead intoxication, lead colic or lead poisoning seen in modern industry. Lead palsy and lead encephalopathy are very rare in adults.

II. In a case of suspected lead absorption before the stage of lead intoxication, every practitioner of medicine should master the skill needed to study the gums for lead line under a lens with proper illumination. The lead line if found is almost as conclusive evidence of lead absorption as is the level of lead in the urine, and much more easily determined. The finding of a lead line or lead in the urine does not by itself spell lead poisoning though it may warn of dangerous lead absorption.

III. Most important of all, every physician is able to make and study a blood smear. Such blood study is often the most definite indication of actual physiological response of the adult tissues to absorbed lead. A controlled serial study of the

stippled cell curve in lead-exposed workers is a practical yardstick available to every physician. Further, after ruling out other causes of stippled cells, the finding of 800 to 1,000 stippled cells per million, or 10 to 12 per 50 fields is quite definite indication of at least potential lead intoxication, in the face of known lead exposure. Usually an abrupt rise of the stippled cells to a level of 35,000 or 40,000 per million red cells (35-50 per 50 fields) is coincident with and frequently diagnostic of the onset of clinical lead intoxication, of the lead colic type.

However, the finding of only 300 to 500 stippled cells per million red cells (3-5 per 50 fields) raises the question of whether lead is responsible for the symptoms under investigation. I agree that the lowering of hemoglobin is a late finding in lead intoxication, much later than stippled cells and much too late for any practical control. I have heard men say they could control lead exposure by watching the hemoglobin. My experience has been that if they waited for that time the man would be in the hospital and not only would they be treating him for clinical symptoms and pain but probably severe anaemia.

Thus within the course of an hour's examination, the family physician, using history, physical examination and blood studies, all techniques long familiar to him, can in most instances make a tentative diagnosis of clinical lead poisoning. This must be backed up, of course, with further studies of lead exposure and actual lead absorption.

While we admit the great value of specialized study of lead absorption for purposes of research, the Council of Industrial Health should emphasize to the non-specialized member of the A. M. A. that the professional skill with which he is already familiar can be effectively used to meet the immediate necessity of keeping the worker safely at work.

Professor Ronald Lane, Manchester, England: As a means of connoting trouble the blue line is of considerable value, not as a diagnostic measure for the individual, but applied to the group. I have figures which show quite clearly that as lead exposure rises, so will the number of blue lines per hundred appear. It does indicate a rising absorption.

We in England have for many years said that we believe lead absorbed in large quantities over a number of years will give rise to a real anaemia. The old observers who made that statement were not at fault and I have in my own practice a number of cases which bear this contention out. I have had a group of some 300 lead workers exposed for something like thirty years. Of that group about 70 have been heavily exposed and among that 70 I have had no less than 8 men who have shown between the ages of 45 and 50 a rapidly-rising blood pressure. The picture is similar to a malignant type of tension except that it occurs later in life.

We should take the very greatest care in keeping lead concentration at a safe level. I should look askance at leniency in standards. It is not easy to assess what is going to happen in thirty years' time and I should certainly deprecate any suggestion we should raise the 1.5 mg. lead level. We have a standard of 2 in England. I would rather keep it where it is.

Dr. Grant Cunningham, Toronto: How far is one justified in depending upon blood examination of smears as supplementary to general physical examination as compared with more dependence on the quantity of lead. We have used the examination of blood smear, supplementing general physical examination in an effort to control poisoning in lead plants, the work carried out, of course, by the same technicians under supervision.

Dr. Machle: There is great and serious need for standardization of stippled cell counts. We not only have two or three methods in general use today, but we have, regrettably, a great deal of evidence which suggests that handling the slide prior to stain has an influence upon the stippled cells which are formed. I think it would be a tremendously valuable undertaking for someone to investigate a standardized technique, applicable to smears as well as staining.

Printed and Published in the United States of America