observation. Perhaps you remember that Joseph Bell of Edinburgh, the physician who was the original of Sherlock Holmes, used to have patients pass rapidly through his consulting rooms, asking them no questions and permitting his students only that fleeting look at them. Then he would demand that the diagnosis be made on the basis of what had been seen in that single cursory examination. This patient would have made a great story for Conan Doyle. He could not wear his old hat, and from that simple fact Dr. Cutting made a perfect diagnosis, and we have had the privilege of seeing the earliest case of Paget's disease I, at least, have ever encountered.

*Note.*—Excision of the mass in the neck for biopsy was done December 20, 1932, the pathologist returning a diagnosis of carcinoma. Deep-ray therapy was instituted, with fair immediate results. The patient has since disappeared from the clinic and cannot be located.

RABIN

# Pediatrics

## Lead Poisoning in Children*

By H. B. CUSHING, M.D., A. E. CHILDE, M.D., L. J. RHEA, M.D., I. M. RABINOWITCH, M.D., H. S. MITCHELL, M.D., and S. G. ROSS, M.D.



### LEAD POISONING IN CHILDREN

#### Introductory Remarks

By H. B. CUSHING, M.D.

Clinical Professor of Pediatrics, McGill Medical College, Montreal, Canada

During the past year the staff of the Children's Memorial Hospital, in which this meeting is being held, has been considerably perturbed by the large number of cases of lead poisoning in children admitted to the wards.

In a year there have been seventeen children admitted with lead poisoning of whom two died in convulsions within a few hours after admission. After much inquiry and discussion we concluded that the increase was partly real, from new sources of lead poisoning in the community, and partly apparent, due to improved methods of diagnosis.

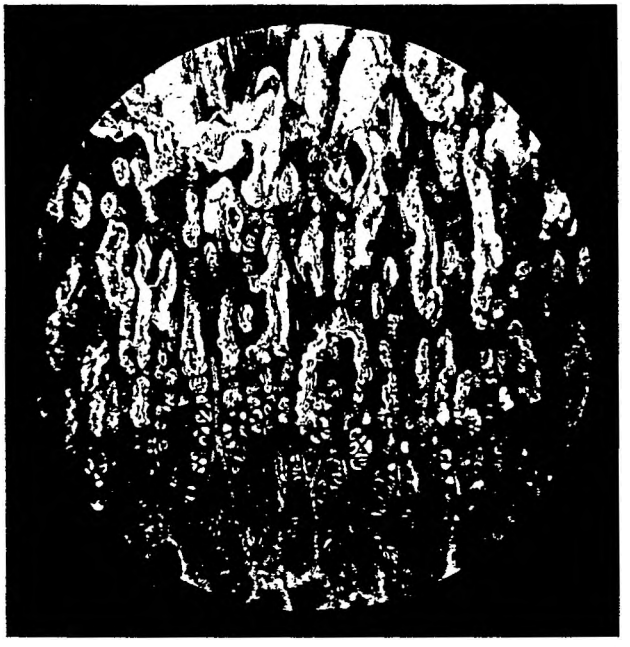
Let us take first the question of diagnosis. The diagnosis of lead poisoning has always been one of the famous pitfalls of medicine. The poisoning shows itself in such unexpected places, from such diverse sources, and with such manifold clinical manifestations that everyone is sure to overlook it at times. In children the diag-

* A Symposium delivered at the Annual Meeting of the American College of Physicians at Montreal, February 9th, 1933. Observations made at the Children's Memorial Hospital, Montreal.



1934

FIG. 3.



Lead line. Note dense calcified parallel trabeculae and abnormal inter-trabecular tissue.

FIG. 4.

Lead line oil immersion. Note dense trabeculae, cartilage cells and inter-trabecular connective tissue.

Meninges showing edema and lymphocytes.

FIG. 5.

Meninges showing thickening and many infiltrating lymphocytes.

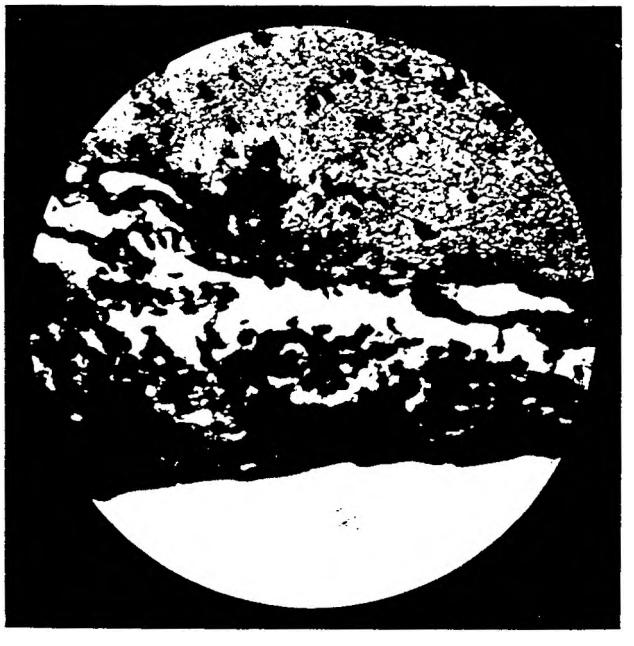


FIG. 6.

nosis is peculiarly difficult from the tendency to unusual cerebral signs, and the common absence of such usual manifestations as the lead line on the gums, colic, and wrist drop. The new method of diagnosis, introduced two or three years ago by American observers, by the roentgen ray appearance of the rapidly growing ends of the long bones has greatly facilitated matters and it is this method which is responsible for the recognition of many of our cases. We are all quite convinced that before this roentgen ray method of diagnosis came into use, we failed to diagnose many cases of obscure nervous conditions, which were really due to lead poisoning.

Next as to the increase in cases due to the source. Practically all our cases in children this year came from one cause, i.e., from eating paint. The children were all young, mostly between one and three years of age. There was usually a history of chewing paint off their cribs, toys, pencils, etc. The country lately has been flooded with cheap wooden painted toys and this seems to have led to the increase in lead poisoning cases.

Naturally the next step was to ascertain if the paints used actually contained much lead. I went to several leading paint companies of the city and all assured me that none of their paints contained poison, in fact might even be used as infant food. However, by calling on different experts I gathered the following information.

Formerly white lead was used as a basis in most paints. In recent years this has been displaced by other substances. The outdoor paints always contain large quantities of white lead to give them greater durability, but the better paints used indoors do not contain any lead and are made of zinc or titanium. Also that the rapidly drying enamels do not contain lead at all, but usually aniline dyes. The use of red lead in sealing the joints by plumbers has now been mostly replaced by varnish but it is still used in outdoor paint for iron structures. Thirdly, the best yellow paint consists of chromate of lead and the greens are made up with chromate of lead.

The next step was to analyse the paint from various infants' cots and toys and ascertain if it contained lead. It was easily shown that the enamel used on all the better cots showed practically no lead but some of the cheaper ones, and especially those repainted at home, contained large quantities. Most toys, especially those

enamelled, showed no lead, but the cheaper wooden ones, especially if painted yellow or green, had very large amounts of lead.

Becoming interested in the subject, I got hold of my daughter's school bag and took a yellow pencil out of it from which, in the anxiety of her studies, she had chewed all the paint off the end. I had the paint analysed and found it contained large quantities of lead. So far she has not died of lead poisoning but I will see that she does not use any more painted pencils.

Every child from the time it gets its first teeth, tends to put everything in its mouth and chew it. It is obvious that most of those who do not exercise this habit excessively get no harm from it, for the better toys and indoor furniture are not dangerous. But it is also obvious that those who eat paint to excess, especially if supplied with cheaper toys and furniture are in serious danger of lead poisoning.

Many countries in different parts of the world prohibit the use of lead in indoor paints and paints for toys, etc., but I am not aware of any such laws in any country or state in North America.

We would be horrified if we saw a mother give a child a piece of broken glass or a sharp razor to play with, yet obviously these would be far less dangerous than to give them cheaply painted toys, or a cheap yellow pencil. With this in mind, we are wondering if some steps should not be taken to try and prevent this form of lead poisoning.

# THE ROENTGEN RAY DIAGNOSIS OF LEAD POISONING IN CHILDREN

By A. E. CHILDE, M.D.

Roentgenologist to Children's Memorial Hospital, Montreal, Canada

WHILST lead poisoning has been recognized clinically for many years, it was not until 1930 that the changes occurring in growing bones, as recognized by radiographs, were first described.[1] Roentgen rays of normal growing bones, show very narrow white lines at their growing ends. In lead poisoning these white lines are denser and wider than normal. Their width is dependent upon the amount of growth which has taken place during the ingestion of lead. If a large intake of lead has taken place over a short period of time, death may occur, and still the bones may show only narrow white lines. Conversely, if the amount of lead ingested has been comparatively small but taken over a long period of time, very wide lines may be present and the symptoms be mild.

These changes are seen at the ends of all the long growing bones in lead poisoning. For practical purposes an extensive examination is not necessary, and plates of one wrist and one knee usually give sufficient information. In the final analysis, the chemical, clinical and roentgen ray evidence, as well as the history must all be considered, but for rapid diagnosis, such as is frequently necessary, the roentgen ray is a very valuable adjunct.

The roentgenologist may be of service in the diagnosis of plumbism in two different ways:—

*Firstly:* He can usually substantiate or help disprove a tentative diagnosis of lead poisoning. All our definite cases with one exception have shown positive roentgen ray finding.

CASE No. I.—This presents the typical picture seen in lead poisoning, (Fig. 1). The bones are those of a child aged two and a half years. The white line at the distal end of the femur is wider than those at the proximal ends of the tibia and fibula as growth is more rapid in the former location. Growth at the wrist is also less rapid than at the lower end of the femur and narrower bands are present at the distal ends of the radius and ulna.

CASE No. II.—Plates of the long bones of a boy of five and a half years showed very little evidence of lead lines (Fig. 2). This child was an idiot, who was not growing. His gums showed a lead line, and stippled cells were

present in his blood. Lead lines appear only in growing bones, and consequently were not seen in this case.

*Secondly:* The diagnosis of lead poisoning may be suggested in obscure cases in which it has not previously been considered. In this respect the changes at the costochondral junctions are often of value.

CASE NO. III.—This was a little girl of four years of age who was referred for a plate of the chest. White lines were noted at the costochondral junctions (Fig. 3). The examination of the long bones was suggested and typical lead lines were found. Stippled cells were later demonstrated in her blood and a history of eating paint from her toys and bed was obtained.

Particularly in young children, these white lines are never normally present at the costochondral junctions. In older children of ten years or more, narrow white lines in these regions may be of no significance.

CASE NO. IV.—This was a boy, age six years, with symptoms resembling those of appendicitis. In the course of a barium series, the plates of the stomach showed white lines at the costochondral junctions (Fig. 4). Again in this case, plates of the long bones were advised, and they showed the usual changes as seen in lead poisoning. A subsequent blood smear revealed stippled cells. The pain was due to lead colic.

CASE NO. V.—A flat plate of the abdomen of a child of two years showed numerous small dense particles. White lines were present at the costochondral junctions (Fig. 5). These small particles were probably paint which had been eaten. The symptoms were very violent and examination of the long bones showed only narrow white lines, indicating a large intake of lead over a short period of time.

CASE NO. VI.—A flat plate of the abdomen of another child, age four and a half years, showed a few particles similar to those seen in the previous case. In addition a number of opaque foreign bodies were present in the large bowel, giving further evidence of the perverted appetite of this child (Fig. 6). They consisted of glass buttons and beads.

Findings such as shown in the last two cases, will sometimes help diagnose an otherwise obscure case, particularly when the gastro-intestinal symptoms of lead poisoning predominate. It is interesting to follow the later course of these "lead lines."

CASE NO. VII.—This child is four years old. Fifteen months ago, she was in this hospital suffering from acute lead poisoning. At that time she showed typical bony changes. Now she returns with a history of renewed pica. Her recent plates show two sets of white lines (Fig. 7). Thin lines are present in the shafts of the long bones some little distance from their growing ends. These are the old lines which appear to have moved up the shaft. Actually they are in

**the same position as before, but normal bone has grown beyond them in the last fifteen months. New lead lines are present at the ends of the shafts of the bone as a result of the recent intake of lead.**

At least some of the transverse white lines, which are seen in the shafts of many long bones, are actually old lead lines. Until recently they have all been considered due to cessation of growth, and of course, this is often the explanation.

It must be emphasized that dense white lines at the ends of the shafts of the bones are not diagnostic of lead poisoning, as there are other conditions in which similar or identical lines appear. They are merely confirmatory evidence of plumbism. Amongst other conditions which must be excluded, the following are the more important:—

1. *Healing Rickets.*—In the past it is probable that when lead lines were seen they were usually mistaken for healed or healing rickets.

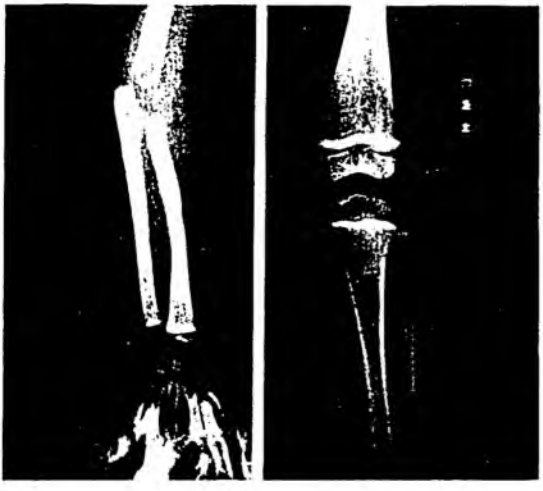
2. *Bismuth Lines*[2] *Case No. VIII.*—A boy of ten years of age was found to have congenital lues. A plate of the knee taken before antiluetic treatment was instituted, showed no departure from the normal (Fig. 8). Nine months later, following treatment with bismuth, wide white lines had appeared, due to deposition of bismuth (Fig. 9).

3. *Cessation of Growth: Case No. IX.*—Plates of an infant of nineteen months revealed no ossified carpal centres. No ossification was present in the epiphysis for the upper end of the tibia and only a very tiny ossified centre was present at the lower end of the femur. The child was a cretin and was not growing. This explained the white lines at the ends of the shafts of the long bones (Fig. 10). Thyroid extract was administered, growth commenced, and the white lines disappeared.

Similar white lines are frequently seen in infants following an acute illness, and they disappear when recovery takes place, often leaving a faint transverse line in the shafts of the bones. They are quite dense but very narrow. The history of illness or failure to gain weight, helps differentiate them from narrow lead lines such as may occur when there is a rapid intake of lead.

4. *Marble Bones.*—Cases of early marble bones show lines which

FIG. 1.

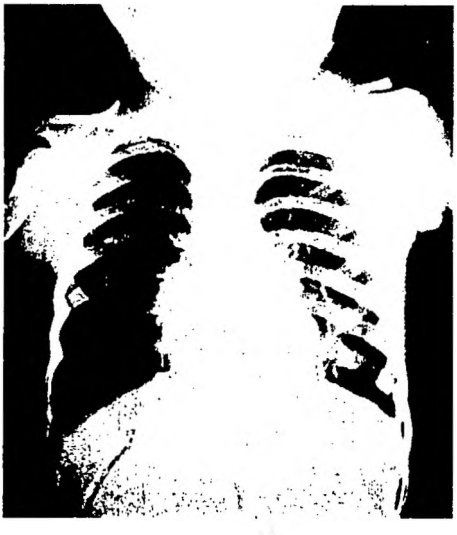


CASE 1. Typical lead lines as seen in the long bones of a child of 2½ years.

FIG. 2.


CASE 2. The bones of an idiot of 5½ years, w had a lead line on the gums, lead in the urine a many stippled R. B. C's. No definite lead li present in the bones, as the child was not growi

FIG. 3.



CASE 3. Chest plate of a girl of four years showing white lines at the costochondral junctions. Lead poisoning was suspected from this finding, and subsequently proved.

FIG. 4.

CASE 4. Plate of stomach of boy of six years, showi white lines at the costochondral junctions. The abdomin pain was really lead colic.

closely simulate lead lines,[3, 4]. This condition is rare and can be excluded clinically.

5. *Scurvy.*—The lines are more irregular and the clinical picture is entirely different.

6. *Strontium & Phosphorus*[5, 6].—Similar lines may be produced by an intake of these substances.

## SUMMARY

1. Radiographs of growing bones are of value in lead poisoning as confirmatory evidence.

2. It is sometimes possible to suspect lead poisoning in children from radiographs of the chest and abdomen. In cases with obscure symptoms, when the diagnosis of lead poisoning has not been considered previously, this may be of considerable value.

3. Lead lines form only in growing bones and if growth does not take place no definite lines will be seen, even though lead poisoning is present.

4. Lines identical with those seen in lead poisoning may be present in other conditions. Hence white lines are not by themselves diagnostic of lead poisoning, but must be considered only as confirmatory evidence.

## REFERENCES

[1] VOGT, E. C.: "A Roentgen Sign of Plumbism," *Am.J.Roentgenol.*, 24:550, November, 1930.

[2] VOGT, E. C.: "Roentgenologic Diagnosis of Lead Poisoning," *J.A.M.A.*, 98:125, January, 1932.

[3] PIRIE, A. H.: "The Development of Marble Bones," *Am.J.Roentgenol.*, 24:147, August, 1930.

[4] PIRIE, A. H.: Personal Communication.

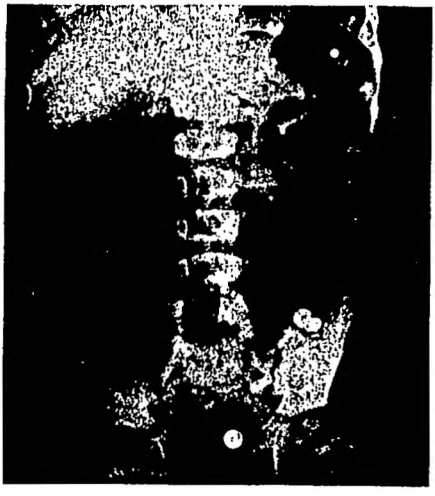
[5] PHEMISTER, D. E.: "The Effect of Phosphorus on Growing Normal and Diseased Bones," *J.A.M.A.*, 70:1737, June 8, 1918.

[6] PARK, E. A., JACKSON, DEBORAH, AND KAJDI, LASLO: "Shadows Produced by Lead in the Roentgen-ray Picture of the Growing Skeleton," *Am.J.Dis.Child.*, 41:485, March, 1931.

Fig. 5.

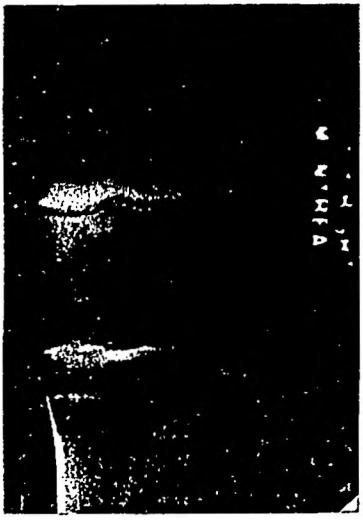
Flat plate of the abdomen showing many lead par- and also white lines at the costochondral junctions.

Fig. 6.



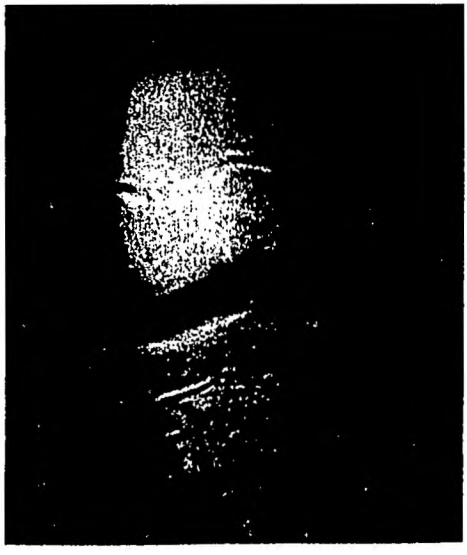
Case 6. A flat plate of the abdomen showing numerous foreign bodies in the large bowel. In the original film a few lead particles could be seen.

Fig. 7.



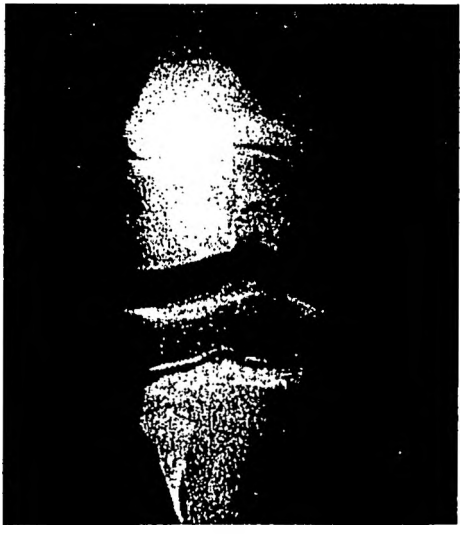
7. Bones of child of four years showing d lines and also old lines from acute lead fifteen months previously.

Fig. 8.



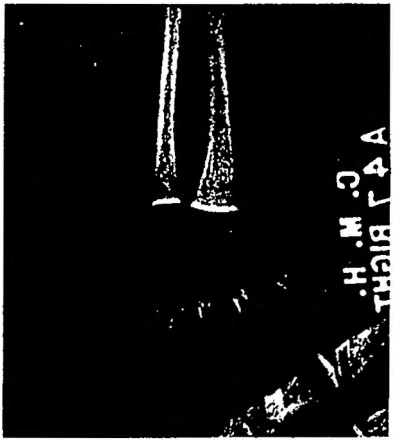
Case 8. Knee of boy aged 10 years taken before antiluetic treatment was instituted.

Fig. 9.



Case 8. Knee of the same boy as Fig. 8, taken nine months later, following treatment with bismuth. White lines have now appeared at the ends of the bones.

Fig. 10.




Case 9. White lines at the ends of the bones in a cretin who was not growing. These disappeared following the administration of thyroid extract.

# SOME OF THE BIOCHEMICAL ASPECTS OF LEAD POISONING

By I. M. RABINOWITCH, D.Sc., M.D., C.M.
Consulting Biochemist, The Children's Memorial Hospital, Montreal, Canada

THE history of the industrial use of lead dates back to antiquity. It is a long story and will not be dealt with now. Suffice it to say that the Egyptians knew how to isolate lead from its ores; lead plates and small statues of Egyptians Deities, Osiris and Anubis, were found in tombs dating to about 1200 B.C.

The ease with which lead may be isolated from its ores probably explains its early history. The older methods consisted of roasting lead sulphide—a common ore—in air at comparatively low temperatures and then mixing the products—oxide and sulphates—thus obtained with more ore and igniting it at a high temperature away from air. The reactions may be represented chemically as follows:—

First stage: $PbS + 3O = SO_2 + PbO$
$PbS + 4O = PbSO_4$

Second stage: $PbS + 2PbO = SO_2 + 3Pb$
$PbS + PbSO_4 = 2SO_2 + 2Pb$

By modern smelting, with the aid of coke, limestone and blast furnaces, ores containing much silica are made use of more economically than in the past, (the coke reduces the oxides formed and the limestone acts as a flux) but the process is fundamentally the same.

Is lead a poison? The answer to this question is simple. There is the incontestable clinical fact that when an individual is exposed to lead or its compounds there follows, under given conditions, colic, constipation, anaemia, palsies, encephalopathy and cardiovascular-renal changes. The vagaries of the action of lead are, however, many. Exposure to as little as one milligram of one form of lead for a few days may, at times, lead to all of the above mentioned signs and symptoms; whereas, a lead bullet weighing many thousands of milligrams may be quite harmless, though it may be in the body for many years. Lead, therefore, appears to resemble mercury. It is, for example, a well known fact that many grams of metallic

mercury may be taken by mouth without harm; mercurous chloride (calomel) is more harmful; and very small amounts of mercuric chloride (bichloride of mercury) may lead to signs of extreme intoxication in a very short time with vomiting, haematuria, melaena, anuria and death either from shock or uraemia.

A number of workers have reported on the relative toxicities of lead and its compounds and one of the striking features of the conclusions drawn is the general disagreement. This is largely due to the many factors which govern the action of lead and these are understandable only when consideration is given to some of the chemical and physical properties of lead and its compounds. One of these properties is solubility.

If ten or fifteen of the more common lead compounds are tabulated in order of their solubilities, much of the discrepancies between the above mentioned workers disappears, for it will be noted that toxicity is, in general, related to solubility. Therefore, with respect to solubility, the findings with lead agree in general with those of mercury. Metallic mercury is, as stated, relatively nontoxic and is quite insoluble in water; mercurous chloride is more toxic than the element, but is also more soluble, and mercuric chloride is much more soluble than the mercurous compound and is still more toxic.

There appears to be a number of objections to this view. For example, one worker has found that metallic lead is more toxic than lead sulphate and, in water at least, the latter is more soluble than the former. The incidence of encephalopathies has been found to be greater with the oxide than with the sulphate, yet, in water, the sulphate is more soluble than the oxide; and lead chromate, one of the most insoluble salts of lead, has been found to be more toxic than lead iodide which, in water, is about one hundred thousand times more soluble than the chromate.

One explanation of these apparent discrepancies is found in the fact that the solubilities of lead compounds in water differ from their solubilities in human serum. Metallic lead, for example, is about fifty times more soluble in serum than in water; lead chromate is eighteen times; and the oxide of lead is approximately seventeen times more soluble in serum than in water. In serum, metallic lead is about ten times and lead oxide is about twenty-five times more soluble than lead sulphate. The higher incidence of encephalopathies

with the oxide than with the sulphate is thus largely explained. The marked toxicity of lead chromate is also largely explained on this basis. Though this compound is the most insoluble salt of lead, in the lungs it readily unites with sodium bicarbonate to form lead carbonate, a compound about one hundred and seventy times more soluble than the chromate. Thus:—

$$PbCrO_4 + 2NaHCO_3 = PbCO_3 + NaCrO_4 + CO_2$$

| | |
|---|---|
| Sol. of $PbCrO_4$ in water | 0.00001 |
| Sol. of $PbCO_3$ in water | 0.0017 |

The above strengthen the view that the toxicity of lead and its compounds depends largely upon solubility. There are, however, still a number of phenomena to explain. For example, the different solubilities in serum and water do not explain the different toxicities noted with the same amounts of the same compounds; nor do they explain the development of widespread lesions in one case and localized lesions in another with the same compound. These discrepancies, however, become more apparent than real when due consideration is given to a number of chemical and physical factors which govern the mode of entry and distribution of lead in the body. Again, we note a relationship between toxicity and solubility.

Lead enters the human body through (a) the respiratory tract, (b) the gastrointestinal tract and (c) the skin. The order of clinical importance is in the order mentioned. Lead enters the lungs largely due to exposure of the individual to dust. In addition to direct filtration through the alveolar membranes, the dust particles may also reach the parenchyma by phagocytic action. Two important factors to consider with regard to the lungs, therefore, are (a) the size of the lead particles and (b) their solubility in the blood. After lead enters the lungs it readily reaches the general circulation. This accounts largely for the general distribution of lesions following this form of poisoning.

Lead enters the gastrointestinal tract largely by oral ingestion. An important factor to consider here, therefore, is alteration of solubility of lead compounds by gastric juice. This, for example, largely explains the extreme toxicity of lead chromate, one of the most insoluble salts of lead. Lead chromate may be quite insoluble in water, but dissolves readily in hydrochloric acid. When this compound, therefore, is taken by mouth, it unites with the hydrochloric

acid of the gastric juice and is converted into lead chloride—a compound about one hundred and eighty thousand times more soluble in water than lead chromate.

From the gastrointestinal tract, the lead enters the portal circulation. This accounts largely for the local distribution of lesions in this type of poisoning and it also accounts for the relative infrequency of such poisoning, since the lead is readily excreted by the liver. Lead, like mercury, may be excreted by the intestinal mucosa. This accounts largely for local intestinal lesions. Following oral ingestion, some of the lead may eventually enter the general circulation. This accounts for the occasional finding of widespread lesions in this form of poisoning. Absence of poisoning, in spite of exposure to oral ingestion of lead may also be due to a characteristic property of proteins, namely, their precipitation by the salts of heavy metals. By combining with the protein secretions in the gastrointestinal tract the solubility of lead may be altered and thus become harmless not only because of its conversion into a new compound, but, also, because of the increase of the size of the particles. Lead chromate poisoning in the absence of hydrochloric acid in the stomach may be explained by the chromate uniting with the sodium carbonate of the pancreatic juice. The chromate is thus converted into a carbonate and the latter is, as stated, about thirty-three hundred times more soluble than the former. Thus:—

$$PbCrO_4 + Na_2CO_3 = PbCO_3 + Na_2CrO_4$$

Poisoning by absorption of lead through the intact skin is relatively uncommon, except when the lead is mixed with oils which, in turn, are readily insoluble in the skin lipoids. Important factors to be considered here are (a) reactions (acidity) of the sweat and (b) temperature of environment which influences the degree of contraction and dilatation of the skin capillaries; lead is more soluble in acid than in alkaline sweat and when the capillaries are dilated they permit entry of lead more readily than when they are contracted.

Other examples of the relationship between solubility and toxicity are the effects of lactic and tartaric acid. The solubility of lead in lactic acid explains largely the different effects of lead bullets. In areas with relatively little lactic acid, a bullet may remain harmless for years; whereas, when such a bullet is lodged in active muscle

where the concentrations of lactic acid may be large, signs of poisoning may appear. Herein is found the explanation of the relatively high incidence of palsy of active muscles, such as in small muscles of the hand. Here, also, is found an explanation of the sudden onset of poisoning following infection, cyanosis, etc.

Lead dissolves in tartaric acid. This explains the poisoning following ingestion of fruits, wines and other products rich in tartaric acid and stored in vessels lined with lead or alloys containing it (copper vessels, glazed surfaces of crockery and metal vessels containing solder).

Circulation and storage of lead in the body tissues is intimately related to solubility. It is, however, not entirely confined to this property. There is, for example, reason to believe that lead is carried not only in solution, but, also, in colloidal suspension. The relative insolubility of the phosphates of lead and the relatively minute amounts of lead which enter the blood at any one time compared with the amount of phosphates in the blood, suggest that lead is readily converted into lead phosphate in the blood stream and carried in this insoluble form. Storage and mobilization, however, are largely dependent upon solubility. Storage depends upon conversion of soluble into insoluble compounds, and mobilization depends largely upon conversion of insoluble into soluble forms. The whole mechanism of storage and mobilization is, however, as yet, imperfectly understood. From its position in the Table of Elements, one would, a priori, expect that the mechanism of storage of lead would somewhat resemble that of calcium and strontium and this has been found to be so by experiment.

In addition to the above factors, there are a number of others which must be considered in order to appreciate the many responses of the individual to exposure to lead. Duration of exposure; amount of substance to which the body is exposed; the general physical condition of the individual at the time of exposure; there are physiological factors such as muscular activity, etc. and pathological factors, such as cyanosis and infection; functional capacity of the excretory organs, liver, kidneys, intestines is an influencing factor and diet and medication are important. In general, it may be stated that wherever any of these conditions tends towards acidosis, the tendency is to liberate lead from its stores and conditions which tend to store calcium tend to store lead. This forms the basis of present-

day therapy. Calcium chloride, calcium lactate, milk, calcium-rich and alkaline ash diets are used to aid storage of lead; whereas, the therapeutic agents used to aid elimination include hydrochloric acid, phosphoric acid, ammonium chloride, di-ammonium phosphate, calcium-poor diets, acid-forming foods and parathyroid hormone. In treating acute lead poisoning, for example, where the immediate purpose is to store lead, the individual is given large quantities of milk or other calcium containing materials and every effort is made to combat acidosis. When the excretion of lead is considered advisable, efforts are made to produce acidosis; treatment is given so that there is a tendency towards acidosis and the excretion of calcium. The lead follows.

Spectrographic data indicate that lead is found universally in soils. Whether it is a contamination or at times has a biological value is not definitely known. Its widespread distribution, however, suggests that it must be present in all food materials, plant and animal. One would, therefore, a priori, expect that excreta, urinary and faeces, would normally contain lead without undue exposure, such as in industrial work. This has been found to be so. By present day methods, lead may be detected in extremely minute amounts and, according to this technique, urine of normal individuals with no undue exposure has been found to contain as much as 0.1 mg. per litre. It is the exception rather than the rule for urine to be entirely free of lead. The differences between health and disease are, therefore, quantitative and not qualitative. Though more lead is found in faeces than in urine, examination of urine is of greater diagnostic value than faeces; for when lead is found in urine, and careful attention is paid to technique and all possible sources of contamination during collection, it is reasonably certain that the lead was in the general circulation; whereas, lead found in faeces may never have been absorbed from the gastro-intestinal tract.

According to the many analyses of a variety of body tissues made in the Metabolism Laboratories of The Montreal General Hospital, it would appear that man affords no exception to the general rule with regard to the wide distribution of lead; though the amounts may be extremely small and detectable only by microchemical technique. Normal spinal fluid, however, appears to be comparatively free of lead.

# PATHOLOGY OF LEAD POISONING

## With Special Reference to the Lesions of Bones and Brain in Children

By LAWRENCE J. RHEA, B.S., M.D.

Director Department of Pathology, The Children's Memorial Hospital, Montreal, Canada

---

THERE has been an active interest in the pathology of lead poisoning in human beings for a long time and a great deal of work has been done upon various aspects of it. The interest in its pathology is in part due to the fact that lead is the most common cause of poisoning in those who work in manufacturing industries and it may result from such diverse sources as drinking water, drugs, cosmetics of various kinds and a number of other substances which may be contaminated with lead.

While lead poisoning has been known for a long time to be frequent in adults, its occurrence in infants and children has not been fully recognized until recently. The classical clinical manifestations of lead poisoning, such as paralysis and gastric disturbances, have long been recognized but only recently has it been established that lead is responsible for some of the obscure signs and symptoms referable to the central nervous system in infants and children, and that it may result in changes at the epiphyseal line in the young.

Japanese workers have shown that lead, acting upon the central nervous system, is responsible for a group of signs and symptoms in infants, the etiology of which had been unknown. These signs and symptoms were referable to the central nervous system and were in most instances due to lead which had absorbed directly or indirectly from lead-containing cosmetics used by mothers of nursing infants. These are but some of the reasons why the pathology of lead poisoning has been, and still is, of active interest.

Taken as a whole, the pathological changes in the human body that are due to the absorption of lead are not well established. This is illustrated in the comparatively long list of lesions that have been attributed to lead. Many of these lesions have not, however, been

proved to be due to the action of lead. In fact, there seem to be but two pathological lesions that can be said to be specific for lead —the lead line on the gums and the stippling of the red blood cells.

One of the reasons that confusion exists as to just what are the specific pathological lesions of lead poisoning is that the study of tissues has been largely limited to a microscopical examination. Such examinations have not been successful in most instances in proving that a given lesion is, or is not, due primarily to the action of lead.

The more recent biochemical studies of the changes in the human body that result from lead poisoning have already thrown light upon the pathology of the condition and lend hope for further progress.

Before describing the results of the examination of the central nervous system and the bones obtained from a postmortem made upon a child who died at the Children's Memorial Hospital, Montreal, it will be of interest very briefly to refer to some of the salient points about the biochemical properties of absorbed lead as well as its distribution in the human body. These have a direct bearing upon the pathological changes to be discussed. Dr. Rabinowitch in his contribution to this Symposium has said in regard to lead, "From its position in the table of elements, one would, a priori, expect that the mechanism of the storage of lead would somewhat resemble that of calcium or strontium and that has been found to be so by experiment."

Aub, Robb and Rossmeish emphasize the comparative metabolic relations between calcium and lead. They say, "In as much as lead metabolism runs parallel to that of calcium, the lead problem becomes essentially a problem of calcium metabolism." Aub, Fairhall, Minot and Reznikoff demonstrated, by experimentation, the very marked affinity of lead for bones. These workers state, "Since the skeleton is the only tissue to retain, permanently, any significant amount of lead, an ever increasing percentage of the total absorbed lead comes to be stored in the bones." In the living, lead is laid down especially in the area of active bone growth. These facts prepare us for the observations made by Park, Jackson and Kajdi as to the site and even the character of the changes produced in the growing bones of children with lead poisoning. This rather selective

property of ingested lead leads to a lesion in the bones of the young that can be well demonstrated by the roentgenray as a shadow at the epiphyseal line. Not only is the lead line demonstrated by roentgenray but it can easily be seen in the gross and leads to a very striking microscopical picture. The mechanism of the production of this lesion is not clear to me.

The very prominent clinical manifestations referable to the central nervous system in lead poisoning has been attributed to a rather long list of lesions. As in the more general pathology of lead, some of the lesions in the brain attributed to lead are certainly not due to it. In the more acute cases, the central nervous system does however show a meningo-encephalitis and it seems probable that the clinical signs and symptoms referable to the central nervous system are at least in part due to it.

Just how the lead reaches the nervous tissues and what is the mechanism of its action is not clear. Whatever the metabolism reactions may be, they result in pathological changes in the bones and in the central nervous system, which lead to very definite changes as will be shown in the following report.

The material upon which this report is based was obtained from a postmortem made upon a child who died in the Children's Memorial Hospital, Montreal. This death occurred in a series of cases of lead poisoning which has been studied in that institution during the past year.

CLINICAL HISTORY.—L. L. Hospital No. 6352; Age 4½ Years; Service—Dr. S. J. Usher.

The child had always been perfectly well until two days before admission to the hospital. At that time he developed vomiting, convulsions and the following day, coma. On admission the child was in deep coma, with conjugate deviation of the eyes to the right, horizontal nystagmus, unequal pupils and numerous stippled cells in the blood. An roentgenray of the long bones showed a dense white line at their epiphyseal ends. Dr. Childe, roentgenologist to the hospital recognized these changes as due to lead. Lumbar puncture showed increased pressure with seventeen cells and a positive Pandy Test.

The child had repeated convulsions while in the hospital and failed to regain consciousness. Death came three days after the onset of the first symptoms.

*Clinical Diagnosis.*—Toxic Encephalitis from Lead. Lead Line on the Gums.

The report upon the bone changes will be limited to the findings in the lower end of a femur, as this location illustrates best the points I wish to emphasize in this paper.

The lower end of the femur including the joint surface was carefully sawed through its entire length, fixed in formalin and decalcified in formic acid. In the gross, there was a very definite and striking change at the site of the epiphyseal line. There was here a wide, opaque, shiny, quite sharply outlined, compact area which had the general appearance of healing or comparatively recently healed rickets. The border of this area, however, was more regular than is generally seen in rickets. While the zone was quite hard, it was not as hard as the cortex of the femur. No blood could be squeezed from it and but a very little material was obtained from scraping. Sections were taken from several places and included a series which extended throughout the entire length of the specimen. These were imbedded in paraffin, cut very thin and stained with differential stains. The microscopical findings that I wish to emphasize especially were seen at the site of the epiphyseal line. The anatomical situation of this line had lost all the character of the normal. Instead of a spongy delicate tissue which blended with the adjacent parts there were compact, quite dense, longitudinal trabeculae, in which numerous cartilage cells were present. Between these trabeculae, there was deposited connective tissue of varying density which had almost completely replaced the normal intertrabecular tissues. The microscopical findings are illustrated in Figures 2, 3 and 4.

Fig. 1 shows the epiphyseal line of an infant of the same age as the one whose bone lesions are described above and illustrated in Figures 2, 3 and 4. The various stages in the development of the changes in the epiphyseal line are being investigated.

The brain showed edema of the meninges and dilation of the blood vessels of the brain substance. No gross haemorrhages or areas of softening were found. Sections were made from several locations and differential stains were employed including stain for fat. The meninges showed definite edema with an increase in lymphocytes. Both the edema and the degree of lymphocytic infiltration varied in different locations. The tissues of the meninges were in places separated by a fluid material in which there were a good many lymphocytes. This is illustrated in Figure 5. In other locations, there were great numbers of lymphocytes in the meninges and the edema was not so marked—Figure 6. Between these two

extremes, there were all gradations. I will refer to but four lesions of the brain substances—perivascular collection of cells, microscopical haemorrhages, hyperplasia of the vascular endothelium and areas of degeneration. The perivascular collection of cells occurred only in places and nowhere was it very marked—Figure 7. It was not found to be associated with thrombosis. There were not many haemorrhages and they were not regularly distributed—Figure 8. All of them were of comparatively recent origin. The vascular lesion from which they resulted was not demonstrated.

In some places, the vascular endothelium was hyperplastic—Figure 9. The amount varied, in some vessels, the lumen was almost obliterated.

By means of fat stains, focal areas of degeneration were found. There were a good many of them. They were irregularly distributed and all seemed to be of recent origin.

The lesions in the bones and the central nervous system described above are considered to be due to ingested lead. The roentgenological findings in the bones were certainly, and the symptoms referable to the central nervous system were, at least in part, due to the lesions described.

REFERENCES

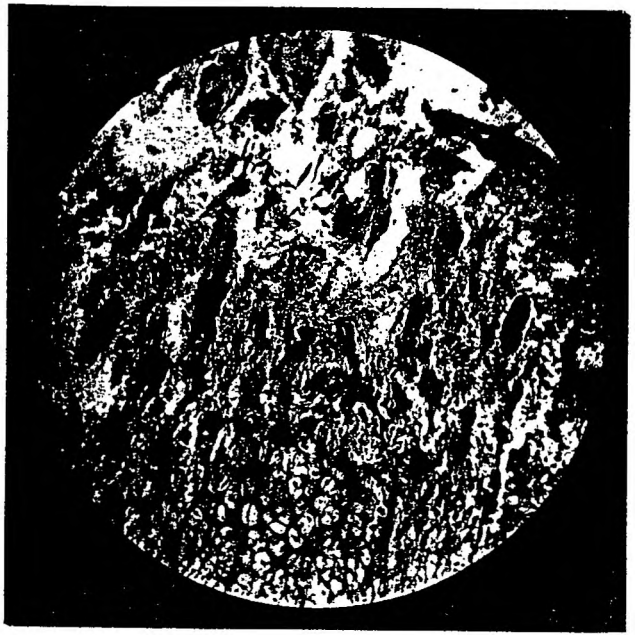
[1] KATO, KATSUJI: "Lead Meningitis in Infants. Résumé of Japanese Contributions on the Diagnosis of Lead Poisoning in Nurslings," *Am.J.Paediatrics*, 44:509, Chicago, September, 1932.

[2] AUB, JOSEPH C., ROBB, GEORGE P., AND ROSSMEISH, ELSIE: "Significance of Bone Trabeculae in the Treatment of Lead Poisoning; Lead Studies XVII," *Am.J.of Pub.Health*, 22:825–830, 1932.

[3] AUB, JOSEPH C., FAIRHALL, LAWRENCE T., MINOT, A. D., AND REZNIKOFF, PAUL: "Lead Poisoning," Medical Monograph, 12:129, The Williams and Wilkins Company Company, Baltimore, 1926.

[4] PARK, EDWARDS A., JACKSON, DEBORAH AND KAJDI, LASLO: "Shadows Produced by Lead in the X-Ray Pictures of the Growing Skeleton". *Am.J.Dis.of Child.*, 41, March, 1931.

FIG. 1.

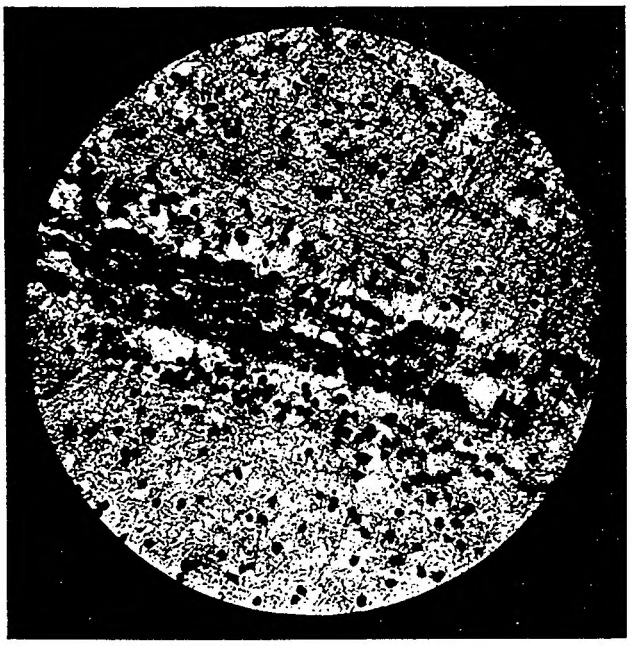


Normal epiphyseal region in a child.

FIG. 2.

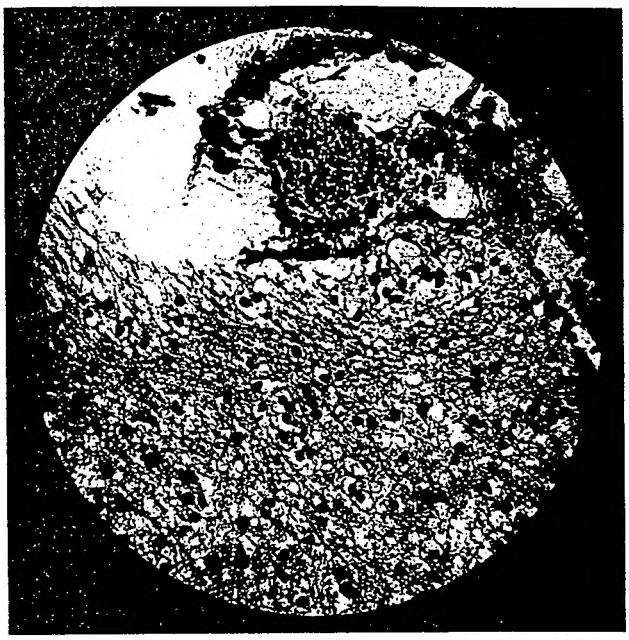
Longitudinal section lower end of femur showing "lead line."

FIG. 7.

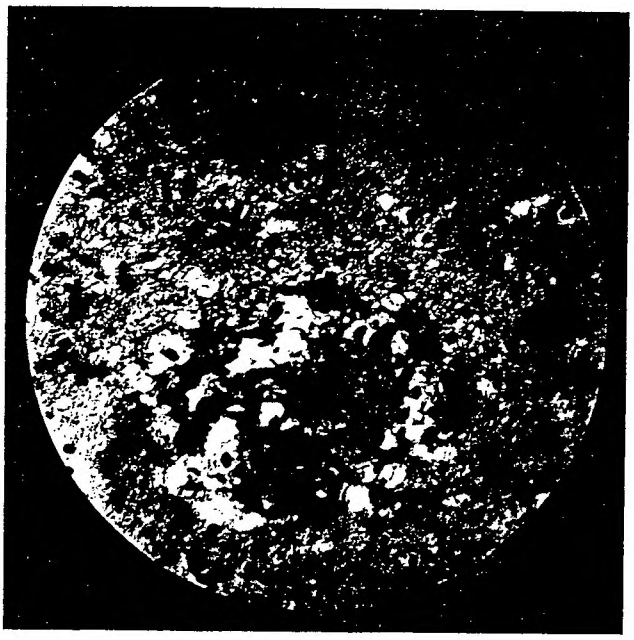


Perivascular collection of cells.

FIG. 8.



Focal area of haemorrhage in the brain.



Marked hyperplasia of vascular endothelium.

FIG. 9.

# LEAD POISONING IN CHILDREN

By H. S. MITCHELL, M.D.
Medical Superintendent, Children's Memorial Hospital, Montreal, Canada

THE following series of twelve cases was observed in the Children's Memorial Hospital, Montreal. The history is given more or less in detail in order to emphasize the variety of the clinical manifestations. A summary of the principal features is appended.

1. D. G., English Canadian, female, age four years. This child was admitted to hospital on June 7th, 1932 coming from a household in which an adult had open pulmonary tuberculosis. On account of persistent and increasing pallor and failure to gain weight, it was felt that the child was herself developing tuberculosis. She was accordingly referred to hospital for investigation along that line.

On physical examination, the only striking thing was moderate pallor of the mucous membranes and sallowness of the skin. She was slightly under weight but not remarkably so (33 pounds). More striking than anything else however (in view of the admission diagnosis), was the negative reaction to the tuberculin test in doses up to one milligram intradermally. There was no evidence of any glandular or peritoneal tuberculous disease. Roentgenrays of the chest failed to show any hilum glandular disease and there was no parenchymatous lesion. However, the costochondral junctions were noticed by the radiologist to be unusually dense and white. He accordingly raised the question of lead poisoning.

It was found that the child had large numbers of stippled red cells in her blood; that the long bones showed the characteristic roentgenray findings, and her urine contained 1.1 mg. of lead in a four-day specimen. Later, during therapeutically induced acidosis, a typical lead line appeared on the gums.

2. M. P., French Canadian, age six years, male. This child was admitted with the following history:—

he awoke at 8.00 a.m. August 24th, complaining that he had a "stomach ache." According to the mother, the pain was of a colicky nature. Throughout the day, this persisted and the boy ate nothing. A doctor was called in the forenoon of August 25th, who made a diagnosis of appendicitis and had the patient sent to hospital. There had been no vomiting, the bowels were constipated. On August 25th, the pain became more definite and localized in the right lower quadrant. In the meantime, it was determined that there had been three previous attacks of this character. The family history and previous medical history were both irrelevant.

On examination, it was found that the abdomen moved freely on respiration in all quadrants, there was no rigidity and no definite tenderness. No pain was elicited on coughing or straining. The liver and spleen were not enlarged. There was no costo-vertebral tenderness. Rectal examination was negative. Urinalysis was negative. W.B.C. 11,600. There was no fever, the pulse was not accelerated. In the absence of any definite signs, the condition was considered as very doubtfully of appendiceal origin.

After being kept under observation for a day, a barium series was performed, the only result of which was the demonstration of delay in emptying of the appendix. The radiologist however, reported a dense white line at the costochondral junctions, 1 mm. in width and raised the possibility of lead poisoning.

A blood smear done on September 3rd, revealed the presence of a large number of stippled red cells. A four-day specimen of urine contained .77 mg. of lead.

3. T. F., English Canadian, male, age four years. This child was brought to hospital because the parents noticed that from September 22nd, "the right side of the face and right eyelid were swollen and the right eye seemed twisted." It appeared that the child had been perfectly well until September 3rd, when he developed a respiratory infection. There was associated tonsillitis and fever with increased respiratory rate and cough. There had been no change in personality, there were no convulsions, no earache, no headache, no vomiting, no stiffness of the neck or back. Except for the right facial paralysis which was present on admission, physical examination was

entirely negative. There was no clinical or roentgen ray sign of mastoid involvement or otitis media.

It was considered that the facial paralysis was a peripheral neuritis and in an attempt to determine this factor, the child was examined for the presence of lead. A four-day specimen of urine contained in excess of 1 mg. of lead. There were several stippled red cells in the blood smear and roentgen rays of the long bones showed dense white lines at the epiphyses.

4. N. F., Greek, female, age three years. This patient was admitted at 2.00 p.m. on September 3rd, 1932 with the information supplied by the parents that she had been having convulsions. September 2nd, the child was perfectly well. At 3.00 a.m. September 3rd, she awoke and complained of not feeling well. The mother noticed that the child's skin was hot. At 3.30 a.m. there was a generalized convulsion lasting for three minutes. Vomiting followed, being non-projectile and the vomitus consisting of undigested food. From 3.00 a.m. until 2.00 p.m. there were four convulsions. The child had no cough and complained of no pain except for some questionable headache. The family history and the previous medical history were irrelevant.

Physical examination revealed a thin, pale, extremely lethargic child, almost unconscious, with frequent generalized convulsions and twitchings of the skeletal muscles. The only other findings were the presence of pharyngitis and signs of old rickets.

Sodium luminal was administered once intravenously to control the convulsions. The temperature was 104° F., pulse 140 per minute and respirations irregular. It was discovered that the child played in a neighbouring hardware store which dealt chiefly in paints and oils and that she had a well developed habit of pica.

Lead poisoning was suspected on this account and lumbar puncture was done with the finding of a normal spinal fluid. Roentgen rays of the epiphyses showed the characteristic dense white lines and a smear of the blood showed numerous stippled red cells. There was 1.2 mg. of lead in approximately four days' urine.

5. I. K., English Canadian, female, age four years. This patient was first admitted to the Children's Memorial Hospital on August 4th, 1932, at which time she was having repeated convulsions. It

was discovered that she had bronchopneumonia as a complication of whooping cough, and it was felt that this was enough to account for the convulsions. The convulsions were controlled by sodium luminal and other sedatives. The fever fell gradually, the bronchopneumonia cleared, she recovered and was discharged on August 17th, 1932. The parents were told that the convulsions were probably due to the associated bronchopneumonia and whooping cough, and that they were unlikely to recur.

Considerably to our chagrin, she returned on August 22nd, with convulsions as bad as before and the history that on August 21st, she developed a high fever followed by vomiting. On the evening of August 21st, convulsions re-appeared and continued at intervals until time of re-admission on August 22nd.

General physical examination was entirely negative except for acute nasopharyngitis and tonsillitis accompanied by a fever of 102° F. which later rose to 105° F. There were no abnormal neurological signs. The possibility of this being a case of unrecognized lead poisoning was brought forth and a blood smear showed numerous stippled red cells. A four-day specimen of urine contained 1.2 mg. of lead. Roentgenrays of the long bones revealed dense white lines at the epiphyses.

6. T. S., French Canadian, female, aged two and a half years. On September 27th, the child was referred to hospital by her family doctor as a case of infantile paralysis, with the history that there had been fever followed by weakness of the leg for seventy-two hours. The history on admission brought out the fact that the temperature had never actually been taken with a thermometer but that it was surmised that the child had fever. In addition, it was stated that the child had been "out of sorts" since September 22nd. On September 22nd, the parents noticed a staggering gait. There had been no vomiting or complaint of pain. September 25th, the child became quite drowsy and irritable when disturbed. On admission, the outstanding findings were retraction of the neck, stiffness of the neck, stiffness of the back, bilateral Kernig's sign, weakness of the extensor muscles of the left foot, extreme irritability and hyperesthesia of the extremities. On lumbar puncture a clear fluid was obtained with a positive Pandy's test and cell count of thirty

per millimeter, principally lymphocytes. The diagnosis of infantile paralysis was considered substantiated and convalescent poliomyelitis serum was given.

On ward rounds the following morning, it was discovered that the paralysis had practically disappeared from the left leg; the right, which had previously been sound, now showed partial involvement of the extensors of the foot. The deltoids on both sides were quite weak. A striking feature was the complete absence of any fever. It was decided that this was sufficient to temporarily at least, discredit the diagnosis of poliomyelitis, as in our experience, the progression of paralysis in poliomyelitis is usually accompanied by fever. It was further noticed that the child's colour, which had previously been examined in artificial light, was very poor and that the mucous membranes were pale. There was a very definite lead line (Burtonian Line) on the gums about several of the teeth. Roentgen ray examination of the long bones showed a dense white line at the epiphyses and blood smear showed large numbers of stippled red cells. A four day specimen of urine contained in excess of 0.5 mg. of lead.

7. M. H., English Canadian, male, age six years. On August 17th, an older brother of this child became ill with acute anterior poliomyelitis and died within two days. There was no question of the diagnosis of acute anterior poliomyelitis as it was fully corroborated clinically and proven by autopsy. August 17th, the patient M. H. received 25 cc. of convalescent poliomyelitis serum intramuscularly. The following day he was irritable and had a temperature of 100° F. with a slightly inflamed throat.

Careful examination by two members of the staff at this time could elicit no indication of the presence of poliomyelitis.

August 19th, the parents returned with the child. His temperature was elevated and he had a reddened throat. There was some uncertainty about stiffness of the neck. Lumbar puncture was performed which showed a very definitely positive Pandy with thirteen cells per cubic millimeter, principally lymphocytes. There was no hyperesthesia of the extremities, there was no cerebral tache, Kernig's sign was not positive. Vomiting had occurred on August 19th. There had been increasing pallor for the preceding week and

the child had become rather drowsy during the same time. On account of the absence of definite evidence of poliomyelitis, this diagnosis was not thought tenable and the parents were asked if the child was in the habit of eating paint or gnawing its toys. They promptly replied, "he has eaten most of the furniture in the house and is particularly fond of the white paint on the window sills."

A stained smear of blood showed large numbers of stippled red cells. Roentgenray of the long bones showed the characteristic white lines at the epiphyses and a four-day specimen of urine contained 3.07 mg. of lead.

8. P. L., French Canadian, male, age three years. For the past year, the child had been very nervous and irritable. On the evening of August 24th, he felt feverish. During the night he was sleepless and had two generalized convulsions. The convulsions were followed by vomiting after which the child went to sleep. A doctor was called the following day who was of the opinion that the child might have poliomyelitis. A lumbar puncture was done which revealed normal fluid.

On August 27th, he was brought to the Children's Memorial Hospital where nothing striking was found in the general examination, except that there was marked constipation. There was pain in the lower back which seemed rather stiff but it was thought that this was accounted for by the lumbar puncture performed a few days before. The family history and the previous medical history were irrelevant.

The child, however, did not improve, and he returned September 7th, when he was referred for admission. At this time, it was noted that there was moderate lethargy and the colour of the mucous membranes was poor.

Examination of the chest and abdomen was negative but the tenderness in the back was still present and there appeared to be some hyperesthesia of the muscles. There was an acute nasopharyngitis with slight enlargement of the cervical lymph glands. The temperature was normal, pulse 100 per minute, respirations 20 per minute. Lumbar puncture revealed a clear spinal fluid with a cell count of four per millimeter and a negative Pandy's test. The presence of the pallor, constipation, lethargy and history of convulsions suggested the possibility of lead poisoning. Roentgen rays of the

long bones showed dense white lines at the epiphyses and there were many stippled red cells in a stained smear of the blood. A four-day specimen of urine contained 2.2 mg. of lead.

9. F. A., English Canadian, female, age two and a half years. This child was admitted on June 28th with a previous diagnosis of cerebral tumor. Antecedent history and previous medical history were irrelevant. She began to walk at a little over a year of age, she talked at eighteen months. The mother stated that the child previously was right-handed but now used her left hand entirely and refused to use the right. In walking, the gait was unsteady and the right leg was dragged.

Physical examination was entirely negative except for diminished deep reflexes on the right side. We were never able to demonstrate Babinski's reflex, muscular power was very much diminished in both the right upper and the right lower extremities as compared with the left, and while the left arm and leg did not seem to be impaired in any way, the right arm and leg were scarcely used at all by the child. The optic fundi were normal. The Wassermann was negative, the tuberculin test was negative and spinal fluid examination was negative. An encephalogram was attempted by the lumbar route without introducing any air into the ventricles. An attempt was made to introduce air into the ventricles by ventricular puncture but this also failed. At this time, it was thought advisable to discharge the child and have her re-admitted after an interval for further study.

Accordingly she was re-admitted six weeks later rather against the wishes of the parents, on account of the fact that she had entirely recovered spontaneously. The cause of this spontaneous improvement was the subject of a good deal of conjecture. The parents would not admit that she had ever been a paint-eater or that she had ever suffered from pica, but smears of the blood showed numerous stippled red cells; roentgen rays of the long bones revealed the typical findings of dense white lines at all the epiphyseal margins and a four day specimen of urine contained .76 mg. of lead.

It was later discovered that shortly before the onset of her symptoms in the Spring, she had been allowed to play most of the time in a room which the mother had recently painted.

10. B. A., English Canadian, female, age five years. This child was a microcephalic idiot who was admitted through the Neurological Out-Door to determine, if possible the cause of her idiocy.

When she was put into the crib on the ward, the most striking thing in her actions was the avidity with which she thrust into her mouth any article on which she could lay her hands. A lead line—the typical Burtonian stippled line of lead poisoning—was present about several of the teeth at the margins of the gums. She had a few stippled red cells in her blood smear. Roentgen rays of the epiphyses did not show any white line, which we believe is due to the fact that the child's growth is practically stationary, as she weighs only twenty-two pounds at about five and a half years of age, and her stature has scarcely altered in the last several months.

11. M. G., French Canadian, male, age three years, ten months. This child was admitted on August 13th, 1932. For the past two weeks the child had not been as well as usual. On August 10th, vomiting occurred at intervals during the night. The following day, there was considerable drowsiness. On the night of August 11th, a convulsion occurred following which there was more vomiting and the child went into a series of convulsions, after which it was unconscious.

On admission on August 13th, the child was very drowsy and could not be aroused. Generalized convulsions occurred at intervals. The deep reflexes were exaggerated, superficial reflexes were diminished but there were no pathological reflexes. There was no stiffness of the neck and no Kernig's sign. The colour was very pale, both of the skin and mucous membranes and it was later discovered that constipation had been present for some time. A lumbar puncture revealed a clear spinal fluid with a very strongly positive Pandy's test and fourteen cells, per millimeter. There was slight choking of the optic discs. A stained blood smear showed large numbers of stippled red cells. Roentgen ray of the long bones showed dense white narrow lines at the epiphyses, and a plate of the abdomen demonstrated small opaque particles within the bowel. The temperature which was normal on admission rose rapidly to 103° F. and the child died twenty hours after admission in a moribund state without responding to treatment.

12. L. L., French Canadian, male, four and a half years. This child was admitted to hospital 9.30 a.m., September 22nd, for convulsions, unconsciousness and vomiting. The history as given by the parents was to the effect that the child had been well until about noon September 1st, when he vomited. During the afternoon he felt fairly well and ran around and played. At 6.00 a.m., September 22nd, he again vomited. There was no fever and no pain and the child was rational; however, he felt drowsy. At 7.20 a.m. he suddenly went into a generalized convulsion which lasted about three minutes. From 7.20 a.m. to 9.30 p.m. the child had been unconscious and was having repeated convulsions all day. The family history was irrelevant. The child itself had been a normal baby, born of an instrumental labour and had never had any convulsions before. There was no possibility of the child having swallowed any poison as far as the parents knew. The only previous illness was at the age of two years, when there was a moderately severe respiratory infection.

The father was a painter and kept some of his stock-in-trade in the shed at the rear of the house. The child played here a good deal and during the last month had been noticed to have developed a habit of putting things in its mouth. On one particular occasion, he was seen to be eating both paint and wood on the balcony railing.

On physical examination, the striking points were:—That the child was totally unconscious, very pale, the skin was warm and sweating and there were frequent convulsive movements of the extremities. The fundi were negative, ears and mastoids were normal, there was a slight infection of the pharynx, the chest and abdomen were negative. All deep reflexes were grossly exaggerated. There was no Babinski reflex. The superficial reflexes were diminished in activity. The temperature was 102° F. There was no stiffness of the neck but a lumbar puncture revealed clear spinal fluid with seventeen cells per millimeter and a very strongly positive Pandy's test. A smear of the blood showed large numbers of stippled cells and roentgenray of the long bones showed dense white lines at the epiphyses. There were also many small opaque foreign bodies in the intestines. The child became moribund and died twelve hours after admission.

| Case No. | Age | Sex | Symptoms | Diagnostic Signs Present | Differential Diagnosis | Source | Ultimate Result |
|---|---|---|---|---|---|---|---|
| 1 | 4 | F | Pallor<br>Loss of weight | Stippled cells<br>Lead line (gums)<br>X-ray signs<br>Lead in urine | Juvenile tuberculosis | Pica | Recovery |
| 2 | 6 | M | Constipation<br>Abdominal colic<br>Pallor | Stippled cells<br>Lead in urine<br>X-ray signs | Appendicitis | Unknown | Recovery |
| 3 | 4 | M | Facial paralysis | Stippled cells<br>X-ray signs<br>Lead in urine | Peripheral neuritis<br>Intracranial tumor | Pica | Recovery |
| 4 | 3 | F | Convulsions<br>Vomiting<br>Headache | Stippled cells<br>X-ray signs<br>Lead in urine | Cause of convulsions? | Pica | Recovery |
| 5 | 4 | F | Convulsions<br>Vomiting | Stippled cells<br>X-ray signs<br>Lead in urine | Cause of convulsions? | Pica | Recovery |
| 6 | 2½ | F | Paralysis<br>Irritability<br>Pallor<br>Signs of meningeal irritation<br>Drowsiness | Stippled cells<br>X-ray signs<br>Lead in urine<br>Lead line on gums | Acute anterior poliomyelitis | Pica | Recovery |
| 7 | 6 | M | Irritability<br>Vomiting<br>Pallor<br>Drowsiness | X-ray signs<br>Lead in urine<br>Stippled cells | Acute anterior poliomyelitis | Pica | Recovery |
| 8 | 3 | M | Irritability<br>Convulsions<br>Drowsiness<br>Constipation | X-ray signs<br>Lead in urine<br>Stippled cells | Acute anterior poliomyelitis<br>Tuberculous meningitis | Pica | Recovery |
| 9 | 2½ | F | Muscular incoordination and weakness<br>Pallor | Stippled cells<br>X-rny signs<br>Lead in urine | Brain tumor | Unknown | Recovery |
| 10 | 5 | F | Convulsions<br>Idiocy<br>Pallor<br>Constipation | Stippled cells<br>Lead line on gums<br>Lead in urine | Cause of idiocy? | Pica | Gradual progressive mental deterioration and muscular weakness |
| 11 | 4 | M | Convulsions<br>Vomiting<br>Drowsiness<br>Unconsciousness<br>Constipation<br>Pallor | Stippled cells<br>X-ray signs | Tuberculous meningitis<br>Encephalitis | Pica | Death |
| 12 | 4½ | M | Convulsions<br>Unconsciousness<br>Vomiting | Stippled cells<br>X-ray signs | Tuberculous meningitis<br>Encephalitis | Pica | Death |

# THE TREATMENT OF LEAD POISONING

By S. G. ROSS, M.D.

Lecturer of Pediatrics, McGill Medical College, Montreal, Canada

No ATTEMPT will be made here to discuss the prevention of this disease. The treatment of the disease may be conveniently divided into two headings:

1. Treatment of toxic symptoms arising from the disease;
2. Removal of lead from the body—"deleading".

If we will recall to mind that in lead poisoning the lead produces symptoms only when in circulation in the blood, it follows that in treating this disease symptomatically our aim should be to remove the lead from the circulation. Lead circulates in the blood possibly as a phosphate, or in some other soluble form, and it has a natural tendency to be removed from the blood stream by being deposited in bone as lead phosphate. In cases of lead poisoning, especially the chronic cases, most of the lead will be found in the bones, and when stored there it is harmless. When lead has been absorbed through the gastrointestinal tract, some of it tends to be held in storage in the liver and to be excreted thence by the bile.

There are two methods by which lead may be removed from the circulation: (1) by increased elimination of the substance through the gastrointestinal tract and kidneys; (2) by storage in bone.

Catharsis is valuable at all stages as it tends to remove lead excreted from the liver, and also lead excreted by the intestine, and thus prevent its reabsorption.

During the acute stage, it is inadvisable to try to "delead" the patient, that is, to remove lead from the body, by increasing elimination by way of the kidney and gastrointestinal tract. The reason is that, inasmuch as in cases of lead poisoning there is practically always lead stored in the bones, and inasmuch as any process of elimination withdraws lead from the bones into the circulation where it is noxious, the probable result of such treatment would be to cause a continuation or exacerbation of the toxic symptoms.

For the above reasons, it is advisable in any case of lead poison-

ing where symptoms—such as cerebral complications, palsies, anaemia, colic—are present, to adopt measures for the removal of the lead from the circulation by promoting the storage in the bone, where it is innocuous.

Now, it has been observed that the metabolism of lead corresponds to the metabolism of calcium to this extent, that any measures which increase the retention of calcium in the body, with resulting deposition in bone, seem to favor also the storage of lead in bone. Up to a certain point, an increase in the intake of calcium causes an increased retention of calcium and lead in the bony calcium depots; therefore these patients should receive a high calcium diet. The simplest method is to give large quantities of milk. A quart of milk contains over 1 Gm. of calcium. At least this amount should be given to a child daily. To this, a soluble calcium salt, such as calcium gluconate or calcium lactate, may be added—average dose 2 to 4 Gm. daily—but not calcium chloride, as this causes an acidosis which would set free more lead into the circulating blood. Under this treatment, the acute cases often respond rapidly. The colic disappears, the anaemia improves, and the stippling of the red cells disappears. The nervous manifestations also clear up, provided the disease has not progressed too far before treatment was begun. In the acute cases, where the cerebral symptoms endanger life—and these are relatively frequent in early childhood—more radical treatment is necessary. In these cases, calcium gluconate should be given intravenously or intramuscularly, or calcium chloride intravenously. The usual dosage is 5 to 10 cc. of a 10 per cent. solution of these salts. This may be repeated in twelve to twenty-four hours. McKhann of Boston has recommended the use of a 25 per cent. solution of magnesium sulphate in 5 cc. doses, given intramuscularly, to relieve convulsions which, in some cases at least, are due to cerebral oedema. The use of hypertonic glucose intravenously has also been recommended to relieve the cerebral symptoms. For the associated colic of lead poisoning atropine has also been recommended.

### "DELEADING" TREATMENT

Once the patient has recovered from the acute symptoms of the disease, the problem of "deleading" must be faced. One is naturally tempted, especially where cerebral symptoms have been present,

to be satisfied to have the intake of lead stopped and the lead in the body stored in a harmless state in the bones. This condition can usually be maintained by suitable diet. In such cases, however, the lead is a potential danger. It is the "skeleton in the cupboard" or the "lead in the skeleton", ready to appear in the blood stream and become toxic when favorable conditions arise. Any condition causing diminution of the calcium balance in the body with resulting withdrawal of calcium from the bone favors an accompanying withdrawal of lead from the bones into the blood stream. The work of Aub and others has shown that it is the trabeculae near the ends of the long bones which give up their calcium reserve first under the conditions, and this also is the part of the bone where lead is stored in greater concentration than in the cortex of the bone. A low calcium diet, a diminished food intake such as would occur in acute infections, an acidosis from any cause, the osteomalacia which may accompany pregnancy or lactation—any of these might cause a reappearance of the toxic symptoms.

It is probably advisable, then, in the majority of cases, to attempt to "delead" once all the toxic symptoms have cleared up. I am still of an open mind as to whether, in cases where dangerous cerebral manifestations have been present, we should risk another exacerbation. The "deleading" should be done under careful supervision. It is a hospital procedure and takes a long time, depending of course upon the amount of lead stored. If toxic symptoms reappear, it must be discontinued, at least temporarily.

### MEASURE OF "DELEADING"

The popular method of deleading, based upon the work of Aub and his associates, is to give the patient a low calcium diet which will favor a withdrawal of calcium from the bones and also of lead—and resulting excretion of lead by the kidney and intestinal tract. This diet consists of such foods as milk, bread, potatoes, rice, tomatoes, bananas, apples, corn meal, tea or coffee. In addition, acids such as dilute hydrochloric or dilute phosphoric acid, 10–15 minims five times daily, or better still, acid-producing substances like ammonium chloride (given after meals) in doses of 3 to 5 Gm. in water daily, in divided doses. The patient should be given this treatment for a period of about a week at a time, with rest intervals.

Careful watch must be kept for symptoms of lead poisoning and of acidosis. When possible, the excretion of lead by the urine should be checked. In this way, after two or three courses, the readily available lead is removed and the remainder may be left stored permanently without much fear of future exacerbations.

I shall conclude by giving a short résumé of the results of treatment in a series of fifteen consecutive cases of lead poisoning in children. The ages of these children ranged between twenty-one months and six years. Two of these patients died both within twenty-four hours after admission—and both from lead encephalopathy. Ten of these patients had cerebral manifestations, four had cranial nerve palsies, three had peripheral nerve palsies, and four had gastrointestinal symptoms. They practically all showed a varying degree of anaemia.

The treatment in all cases consisted in the initial attempt to cause the lead to be stored in the bones. The patients were placed on a high calcium diet and the administration of calcium lactate by mouth. In cases with acute cerebral symptoms, calcium gluconate in a 10 per cent. solution was also given in doses of 10 cc. intravenously or intramuscularly, and repeated, if necessary, within twelve to twenty-four hours. Several of these patients were also given sodium luminal intravenously for the convulsions. In one cases, hypertonic glucose was given intravenously to control the convulsions by reducing the cerebral oedema.

In only two cases was a systematic attempt made to "delead" the patient. In one of these the treatment had to be discontinued, as cerebral symptoms—drowsiness, developed. The results of treatment were that in all the cerebral cases, except the two who died, the symptoms cleared up rapidly. The patients with cranial and peripheral nerve palsies all showed definite improvement; and the gastrointestinal symptoms disappeared in all cases.

# Recent Progress in Medicine and Surgery

## PROGRESS IN MEDICINE

By A. CANTAROW, M.D.

Biochemist, Jefferson Hospital; Demonstrator of Medicine, Jefferson Medical College, Philadelphia, Pennsylvania

### PROGRESS IN MEDICINE

The past decade has witnessed the emergence of many well-established facts from the obscure maze of theoretical speculation which formerly clouded the field of endocrinology. Following the discovery of insulin, which constitutes one of the greatest therapeutic achievements of all time, the coordination of improved surgical technic with improved physiological and biochemical methods has resulted in the elevation of endocrinologic research to a degree of exactitude from which it was previously far removed. Although the practical applications of many recent observations are not immediately apparent, certain advances in our knowledge of the functions of the glands of internal secretion are of such outstanding importance as to merit careful consideration by every clinician, regardless of his field of special interest. Unquestionably, the physiology of to-day is the medicine of to-morrow; increasing recognition of this fact is perhaps responsible, more than any other single factor, for the remarkable advances made in clinical medicine in recent years.

### PITUITARY GLAND

As stated by Evans,[1] "one of the most dramatic chapters in the progress of modern medicine is the story of the evolution of our knowledge of the pituitary body, that minute glandule situated almost in the mathematical center of the head, regulating as it does those fundamental mechanisms of growth, reproduction and even the power of the body to conduct its normal metabolic machinery." Evidence is accumulating which strongly suggests that the functional activity of the pituitary gland exerts an important influence