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hours. The retching and vomiting are very obstinate, and continue for a long time; the vomitus is often milky with lead chloride and sometimes streaked with blood; there is pain in the abdomen of a colicky character, also thirst. The bowels are as a rule constipated, but occasionally there is diarrhea with black stools (lead sulphide). The urine is generally diminished. The breath has a foul odor, and the tongue is coated; the skin is dry, and the pulse small and frequent. In addition there may be present various nervous manifestations; such as, headache, shooting pains in the limbs, cramping in the legs and lead numbness. Fatal cases pass into coma and die without convulsions.

The characteristic symptoms of chronic lead poisoning are those of general ill health. The symptoms may at first be indefinite, coming on irregularly and often months after the individual has discontinued working with lead. There are general digestive disturbances, loss of appetite, nausea, vomiting, diarrhea or constipation. There are generally present certain blood changes, the number of red cells and the hemoglobin index being low. The red cells, when stained with methylene blue show basophilic granules. This "stippling" is one of the important and almost constant diagnostic signs. Schüster attributes these blood changes to injury of the bone-marrow. The skin assumes a peculiar yellowish hue, and in some cases the patient is distinctly jaundiced. This is due to the wide-spread destruction of the red corpuscles. The gums show a black line which has been demonstrated to be lead sulphide. The symptoms which often develop later are highly characteristic and assume various forms; in the order of their frequency there may appear colic, articular-gin, paralysis, nephritis, cerebral symptoms and anæsthesias. Of Tanquerell's cases there were 1217 of colic, 101 of paralysis and 72 of encephalopathy.

One of the best pieces of work ever done on experimental lead poisoning was that of Harnack¹ published in 1878. Harnack used lead in organic combination in the form of the triethyl lead acetate, and his observations were made on frogs, rabbits, cats and dogs. The work consisted mainly in administering the lead compound to these animals, either subcutaneously or intravenously, and observing the symptoms which developed. These observations represent a very valuable contribution to our knowledge of lead poisoning, and, considering the date at which the experiments were performed, it is indeed a splendid piece of work. There appear to be, however, many parts of Harnack's work of which further study would be exceedingly desirable. Therefore, I have continued the investigation of this subject, using the following preparations: *Triethyl lead, triethyl lead chloride, triethyl lead acetate, trimethyl lead, trimethyl lead chloride and triethyl antimony nitrate*.

PREPARATION OF COMPOUNDS

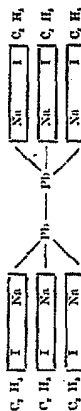
These preparations were first made by Löwig² (1858) who prepared the triethyl lead, and in addition the oxide, carbonate, sulphate, nitrate, chloride and bromide of the compound. The work of Löwig was repeated by Klippel³ (1860) who, in addition, made the following compounds: the phosphate, formate, acetate, butyrate, benzoate, tartrate, oxalate, sulphide, cyanide, sulphocyanate and also double salts with mercury chloride and with platinum chloride.

He also repeated some of the work, using amyl iodide instead of ethyl iodide. As previously stated, Harnack (1878) made the acetate and studied its action on frogs, rabbits, cats and dogs.

I have prepared these triethyl lead compounds according to the method used by Löwig and Klippel with various modifications.

As a starting point for the preparations, it is necessary to obtain a sodium-lead alloy. This alloy is made by melting 50 grams of lead, and introducing into the molten mass 16 grams of sodium, which has been previously cut into rather small pieces, about 1 cubic centimeter in size. The reason for selecting 50 grams of lead is that it gives a yield of a desirable amount, while the reason for combining lead and sodium in a ratio of 50 to 16 is based on their atomic weights (lead 206.2, sodium 23.05), the product desired being an atomic relation of $\text{Pb}(\text{Na})_2$.

After the sodium and molten lead are united, a short time should be allowed to elapse until the mass starts to form a crust over the surface. At this point it should be covered with hot, dry sand and allowed to cool. When cool the mass is best ground in an iron mortar, and when reasonably well powdered, it is put in an Erlenmeyer flask of about 200 c.c. capacity. The flask is connected with an upright, water-cooled condenser. Through the upper end of the condenser is introduced 50 c.c. of ethyl iodide or ethyl bromide. A reaction should take place, lasting for two or three hours. If reaction fails to take place, 1 or 2 c.c. of ethyl alcohol may be added. The reaction is as follows:

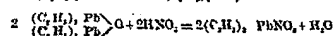
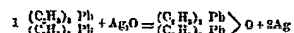


When the reaction is complete, the excess ethyl iodide or ethyl bromide is distilled off, and the contents of the flask is extracted with ether. This is best done by nearly filling the flask with ether and stirring the contents with a stirring rod. The mixture is then allowed to settle and the ether extract is poured into a graduated cylinder, which should be large enough to contain three such extractions. This extraction process is repeated twice. The extract, after the suspended matter has settled, should be clear and have a greenish-yellow color. It is then poured from the graduate into a distilling flask of one liter capacity, and about 200 c.c. of water is added to the contents. The ether is then distilled off on a water bath, and the compound, being insoluble in water, collects as an oily mass beneath the water in the flask.

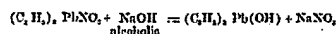
This oil has a specific gravity of 1.471 at 10° C., and corresponds to the formula of $(\text{C}_2\text{H}_5)_3\text{Pb}(\text{C}_2\text{H}_5)_2$. The compound is but slightly soluble in water, not very soluble in alcohol, but quite soluble in ether.

The salts of the compound may be made by one of two methods; first, by preparing the hydroxide and neutralizing with the acid, or, second, the method introduced by Klippel, which consists in making the desired salt from the carbomide. The first method is the one I have used. The oil is treated in a beaker (with enough alcohol to cover it well) with an alcohol solution of

silver oxide made acid by nitric acid. (The concentrated nitric acid should be diluted with one-half its volume of water, and this nitric acid solution is added until only a small amount of silver oxide is present as such in the alcohol solution.) This alcoholic solution of silver oxide and nitric acid is added to the alcoholic solution of the oil, slowly and with constant stirring until metallic silver no longer precipitates out. The alcoholic solution is then filtered and contains the nitrate of the compound in solution.

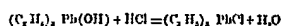


The solution is then neutralized with an alcoholic solution of sodium hydroxide. A precipitate often occurs at this point, which is probably a basic compound of the lead or silver and should be removed by filtration. The hydroxide of the compound remains in the alcoholic solution.



To obtain the hydroxide in a more purified form, one may treat this alcoholic solution with ether and much water. The water and alcohol are completely miscible which forces the compound into the ether layer. The ether layer is separated from the water by means of a separatory funnel, and the ether layer, after distillation, yields a thick mass, which, on standing, becomes somewhat crystalline.

If the alcoholic solution of the hydroxide is treated with dilute hydrochloric acid, the chloride of the compound will, in the course of time, crystallize in long, beautiful crystals, having a silky luster.



In the course of the analysis of these compounds, they were heated, as is the usual custom, to 105° C. to drive off the moisture. However, it was found impossible to obtain a constant weight, and for that reason it was supposed that decomposition was taking place. Therefore, instead of heating samples to 105° C., the temperature was maintained at 95° C. The following analysis will show the result of such heating:

Acetate No. III, dried over sulphuric acid for one month, was heated to 95 degrees.

2476 g. lost .0473 g. or 19.10 per cent.

2135 g. lost .0624 g. or 29.22 per cent. The heating was discontinued at this point and the samples analyzed.

Analysis of the Dried Acetate.

2003 g. gave .1708 g. Lead Sulphate or 58.31 per cent.

1511 g. gave .1283 g. Lead Sulphate or 55.00 per cent. Theoretical 55.62 per cent.

It is evident from the above figures that these compounds undergo sublimation when heated to such temperatures as those indicated. This analysis was made on a preparation which had been prepared in the early part of the

work, and which was not subjected to purification by recrystallization from alcohol. However, the analysis shows a fair degree of purity.

The lead in these compounds is in the masked or protected form, and prevents the lead from reacting with the usual precipitants, as, chlorides, sulphates, sulphides, and carbonates. Also leucine, when injected into the blood stream, will not precipitate. Therefore, I have been able to inject these compounds in .5 per cent aqueous solution. The results of such injections are given in the following paragraphs.

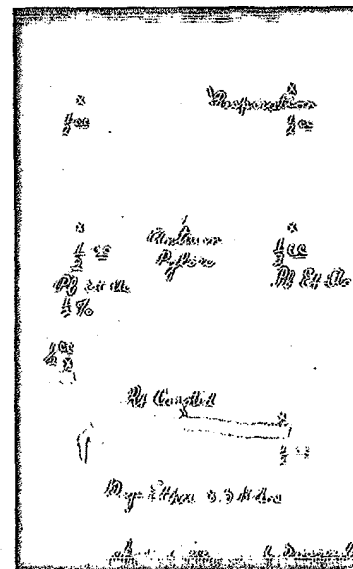


Fig. 1.

EXPERIMENTAL

Fig. 1 shows respiration, pyloric contractions, and blood pressure recorded in a dog of 8.5 kilos under ether anesthesia. At the beginning of the record (the side of the record) there was injected .5 c.c. of a .5 per cent solution of the triethyl lead acetate. It will be noted that the respiration

stopped. There is a marked increase in tone and activity of the pylorus, and a prompt, pronounced and prolonged fall in blood pressure.

The dose, 5 c.c. of 5 per cent triethyl lead acetate, figured in grams of substance injected, is found to be 0.025 grams or about 0.015 grams of lead.

The quantity of lead necessary to produce poisoning is not definitely known. Brouncker¹⁸ states that poisoning may result from 1 mg. of lead per day while others give higher figures. Gieringer¹⁹ claims that symptoms will occur in man only after several months with the daily ingestion of from 4 to

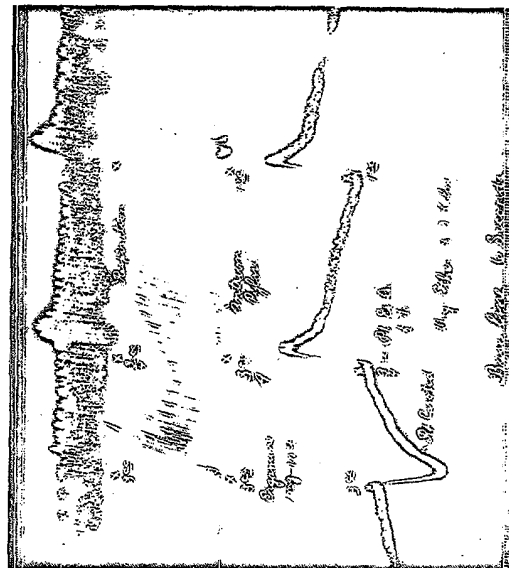


Fig. 2. According to Phlegge and Heffter¹⁸ such symptoms will occur in three or four weeks with the daily ingestion of 60 mg.

The objective symptoms occurring after the first injection of the compound have been recorded by Harnack²⁰ and are the observations made on an unanesthetized animal. However, they are, for the most part, quite similar to the present observations made on anesthetized animals.

According to Harnack, "the first symptoms following immediately after the injection are doubtless due to the action of the intact compound. The animal yelps loudly and falls in a faint, as if partially narcotized, during which the respiration is completely stopped. If one introduces artificial respira-

tion, the animal will, in the course of a few minutes, breathe and awake from the faint. It is still somewhat dazed and weak and there appears to be psychic irritation, hallucinations, loss of higher functions of the brain, etc. There is also pronounced salivation with a flowing from the nose and a condition of nausea is present; however, without any vomiting."

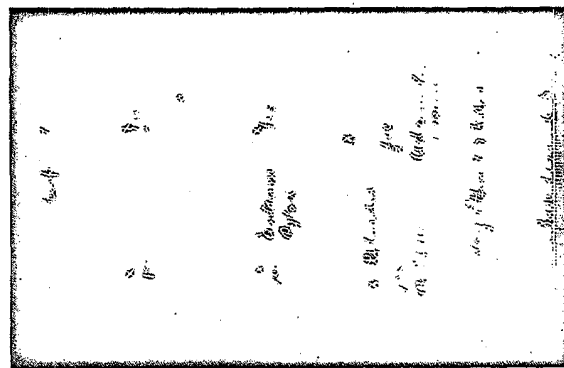


Fig. 1.

It will further be observed in Fig. 1 that the second injection of the same amount of the compound is followed by an entirely different result. The blood pressure, instead of falling, rises and remains quite as high as it originally was. Intestinal activity is again somewhat increased and respiration, although poorly shown here, is stimulated instead of being stopped. This striking reversal of conditions apparently completely escaped the attention of Harnack.

Fig. 2 is another record made on the same animal as used in Fig. 1. It shows the result of: first, the injection of 3 c.c. of ergamine solution (1 mg. per 10 c.c.) giving a normal effect for ergantine. The second injection is

3% c.c. of the .5 per cent triethyl lead acetate solution. The effect on respiration is better shown than in the previous tracing. The third injection of 1 c.c. of the drug, which is the fourth injection of the compound, gives results similar to the previous injection.

Fig. 3 is the third tracing taken from the same animal and shows the result of injecting another cubic centimeter of the triethyl lead acetate solution,

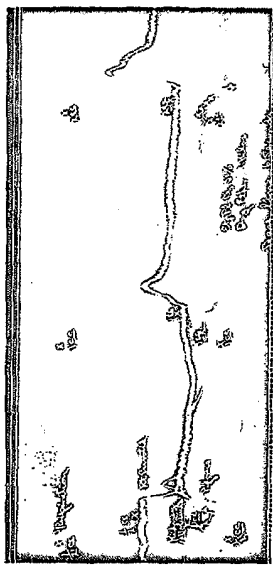


Fig. 3.

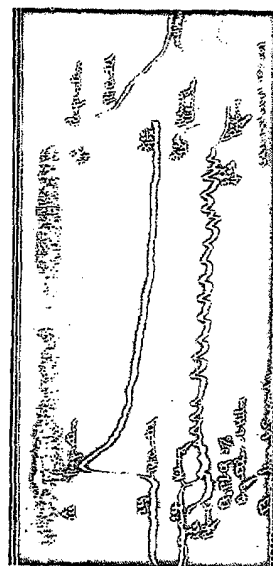


Fig. 4.

the respiration being stimulated, pyloric activity increased, and blood pressure markedly increased. The result of injecting $\frac{1}{2}$ c.c. of adrenalin (1:10,000) is also recorded and furnishes a comparison with the lead compound as well as a check on the technique.

Fig. 4 shows respiration, blood pressure, kidney volume, and pyloric contractions taken on a dog of 6 kilos under ether anesthesia. The first injection of .5 c.c. of .5 per cent triethyl lead chloride gave similar results to those obtained from the acetate salt, the respiration being stopped, blood pressure fal-

ling, and pyloric tone and activity increased. In addition, it will be seen that the kidney volume, although but slightly altered, did show the heart beat much more plainly than before the injection. The second injection of 1 c.c. of the drug showed practically the same results as those obtained from the second injection of the acetate, with the additional fact that the kidney is constricted. The third injection of 2 c.c. of the chloride shows the stimulation of the respiration and the marked rise in blood pressure, also a decrease in kidney volume.

Fig. 5 is a second record made from the same animal and shows the result

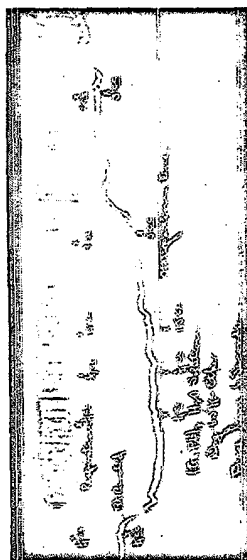


Fig. 5.

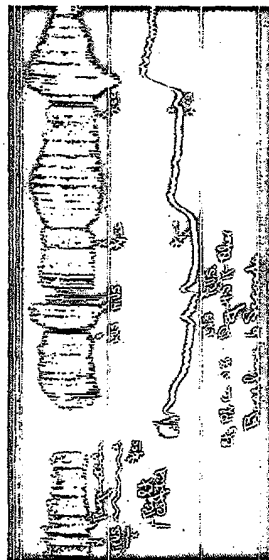


Fig. 6.

of the fourth injection of the chloride, and at the right hand side of the record is shown the result of injecting $\frac{1}{2}$ c.c. of 1:10,000 adrenalin.

Fig. 6 is a record made on an animal of 6.5 kilos under ether anesthesia, and shows the respiration and blood pressure with the result of injecting an aqueous solution of the triethyl lead. The water solubility of this compound has not been determined exactly; however, it appears to be but slightly soluble. The first injection of $\frac{1}{2}$ c.c. of such an aqueous solution gave a very similar result to those obtained from the use of the salts previously discussed.

With additional injections, the reversal of the first results did not occur so promptly, but this might be due to the size of the doses administered, and not to any marked difference in their action.

The characteristic fall in blood pressure following the first injection and the rise following the second injection, would suggest the possibility that the vagal action upon the heart was involved in producing the first fall and that

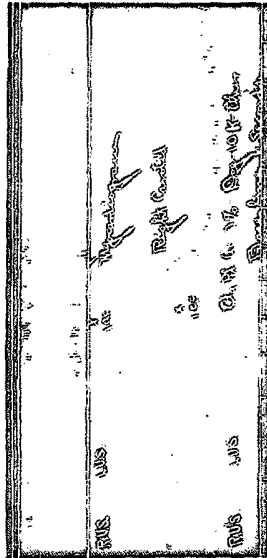


Fig. 7.

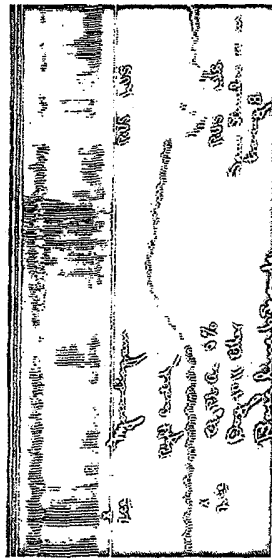


Fig. 8.

such action was not present at the time of the second injection. Fig. 7 is a record which apparently supports this suggestion. It shows the respiration and blood pressure in a small dog of 4.5 kilos under ether anesthesia. At the left side of the record at the point marked R.V.S., the right vagus was stimulated in the neck and the characteristic results of such stimulation are recorded. There was injected $\frac{1}{2}$ c.c. of triethyl lead acetate solution, and after about two minutes the left vagus was stimulated, causing a stoppage of respiration and an asphyxial rise in blood pressure. However, the vagal stimulation

showed no direct action on the heart. Stimulation of the right vagus gave similar results. These results would lead one to believe that the first action of the drug on blood pressure is due to vagal stimulation followed by paralysis.

Harnack, in discussing the action of the triethyl lead acetate on the rabbit, says: "Also the heart muscle and the muscles of respiration take part in the paralysis, as is indicated by the weak pulse, the slow superficial respiration, the lowering of temperature of the peripheral parts and the weak filling of the blood vessels in the periphery of the body." Desiring to determine whether or not such a weakening of the heart muscle was responsible for the lowered blood pressure in the dog, I made myocardiograph records such as is shown in Fig. 8 which is a record of the blood pressure and direct heart muscle action.

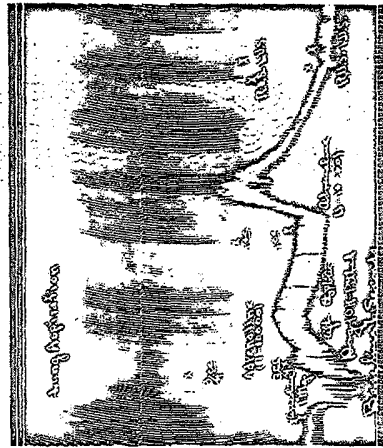


Fig. 9.

At the left side of the record, the right vagus was stimulated. This produced a slowing of the heart with a fall in blood pressure. Stimulation of the left vagus gave similar results. After a normal blood pressure was again established 1 c.c. of the .5 per cent triethyl lead acetate was injected. It will be noted that about 6 or 8 seconds later there occurred the characteristic fall in blood pressure, which was accompanied by a slowing and a weakening of the heart beat. Fig. 9 shows the result (taken on the same animal as was used in record 8) of injecting 2 c.c. of the solution. In about 24 seconds the blood pressure rose and the heart beat was more rapid and stronger. Stimulation of the right and left vagus, with the same strength stimulus as used in record 8, showed the vagus was still active, but not so strongly as in Fig. 8.

At this phase of the work it was thought important to determine whether the innervation of the bronchial musculature was also affected similarly to

that of the heart. Fig. 10 shows the result of such observations. This animal was pithed and, after receiving 20 c.c. of triethyl lead acetate solution, 2 c.c. at a time, the record (Fig. 10) was made. The first injection at the left was 1 mg. of arecoline. The normal action of arecoline on the lung volume and blood pressure is observed. After constriction of the lungs by the arecoline, $\frac{3}{4}$ c.c. of adrenaline 1:10,000 was given with the result that adrenaline dilated the lungs in the normal manner. Another c.c. of adrenaline was again injected, which produced a further dilatation. It will be noted that vagal stimulation (R. V. S. and L. V. S.) had no direct action on the heart. It would appear from this record that the drug does not paralyze the endings of the postganglionic fibers of the vagi, or of the sympathetics in the lungs.

In attempting to determine whether or not the sympathetic ganglia are acted upon by the drug, a series of experiments were carried out, using lobelin.

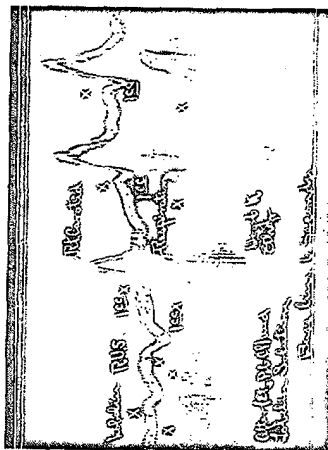


Fig. 11.

Lobelin is a drug which first stimulates and later paralyzes the sympathetic ganglia, an action quite similar to that of nicotine. Fig. 11 shows a record taken on an animal which had previously received three or four injections of triethyl lead chlorate, and had given a normal response to each. A small amount of lobelin solution was then injected and the usual reaction, due to stimulation of the sympathetic ganglia, was observed. The record shows the result of a second injection of lobelin, which by the lack of response, indicates that the ganglia are paralyzed. As a further check, the right vagus was stimulated with the result shown. It will be observed that, after the administration of lobelin, the results of administering triethyl lead are very similar to those obtained from a normal animal. In answer to the question as to whether or not a primary fall in blood pressure, following the first injection of triethyl lead salts is obtained after lobelin, we may refer to Fig. 12. This tracing shows the respiration and blood pressure as recorded in a dog

of 8.5 kilos under ether anesthesia. The blood pressure changes in this particular animal, following the injection of lobelin and triethyl lead solution, are not very pronounced. However, they are completely typical, and the record serves to show that the triethyl lead acts in its usual manner after the injection of lobelin.

Harnack, in discussing the fall in blood pressure, produced in rabbits, maintains that the vessel walls are not acted upon, and that the vasomotor center is not affected, but that the whole action is due to the weakened condition of the heart. As evidence he submits the following: "To decide this question, the following course of research was carried out: a rabbit which showed the action of triethyl lead decidedly, was, while in such condition, examined to note the state of the ear vessels. Such animals, if then subjected to elio-

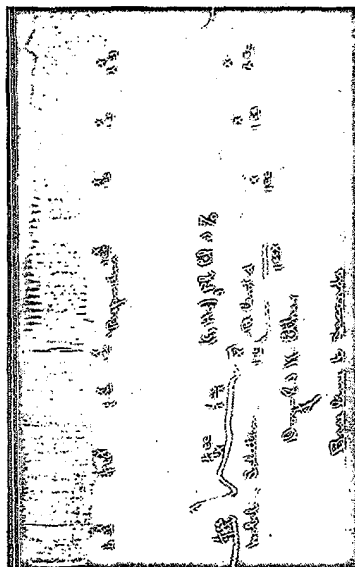


Fig. 12.

form anesthesia, showed a widening and filling of the ear vessels, which were previously narrow and weakly injected. This shows that the vessel muscles are not directly stimulated by the lead." In order to show that it is not the vasomotor center which is affected, he carried out the following experiment. In a rabbit (1570 grams) he cut the sympathetic nerve on the right side of the neck and, after the vessels in the right ear dilated and increased in temperature, he injected .049 grams of triethyl lead acetate subcutaneously. The following morning there was only a slight beginning of paralysis. Therefore, another small quantity of the salt was given (amount not stated). Very soon the paralysis became greater, the heart beat weak, and the animal cool. The vessels in both ears were bloodless, and those in the right remained wider than in the left. Chloroform was then given, and the left ear vessels dilated. The animal died during the anesthesia from "heart paralysis." There were therefore no grounds, he decided, for supposing that the lead stimulated the vaso-

motor center in rabbits, or that the irritability of the vessel muscle was increased. I have studied a series of animals in order to determine whether injec-

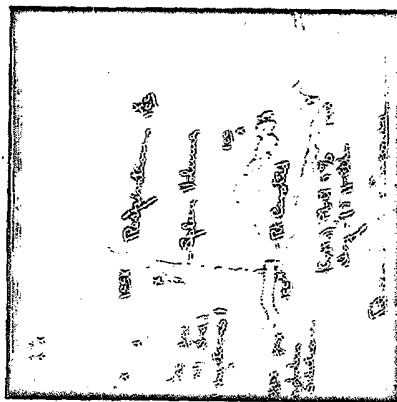


Fig. 14.

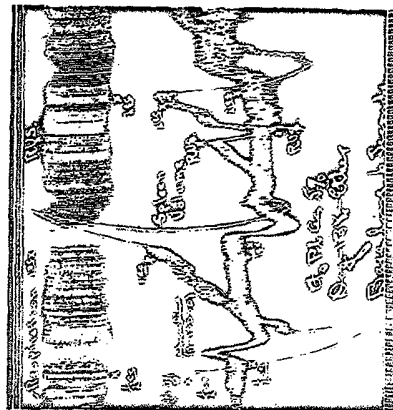


Fig. 15.

tion of the drug produced any volume change in the spleen or kidney. Fig. 13 is a record taken in the course of such work and shows respiration, spleen volume and blood pressure. The first two injections, shown on the record, are those of lobelin sulphate solution and are the second and third injections. It will be noted that the lobelin had no noticeable action, which means that the first injection (not shown in the tracing) was sufficient to paralyze the sympathetic ganglia. The injection of 1 c.c. of the 5 per cent triethyl lead chloride gave complete stoppage of respiration, an initial increase in spleen volume followed immediately by a decrease, and the blood pressure was lowered. The second injection of the drug stimulated respiration, decreased spleen volume, and increased blood pressure.

Fig. 14 shows respiration, spleen volume, and blood pressure. The injection of $\frac{1}{2}$ c.c. of 1:10,000 adrenalin solution gave the characteristic action

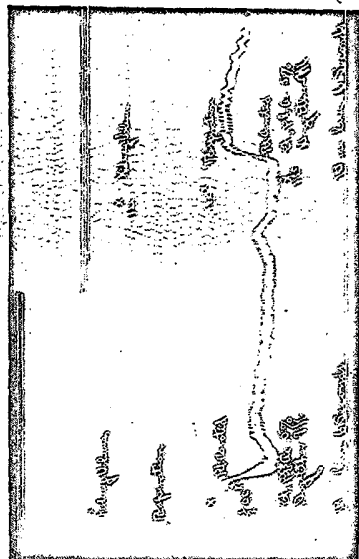


Fig. 16.

on the spleen volume and some increase in blood pressure. The injection of 1 c.c. of a 5 per cent solution of the lead salt gave stoppage of respiration, an increase in spleen volume followed immediately by a decrease, and the blood pressure fell as usual. The principal thing of interest in the second injection of lead (2 c.c.) is the marked constriction of the spleen without the preliminary dilatation.

Fig. 15 shows kidney volume, respiration and blood pressure. It will be noted that with the first injection the kidney volume increased. This increase in volume is followed by a not very marked, but prolonged decrease. The second injection of the drug gave only the decrease in kidney volume.

Fig. 16 is presented to show the initial increase in kidney volume, followed immediately by a pronounced decrease in volume. It will also be noted that, with this first injection of the drug, there is a marked increase in tonus activity

of the pylorus. In this connection, reference to Fig. 1 will show that intestinal activity was there also markedly increased.

In order to determine whether or not the vagus endings are the seat of action of the lead salts, the triethyl lead acetate was administered after atro-

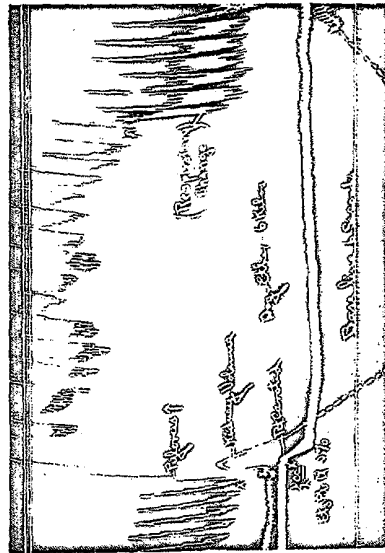


Fig. 14.

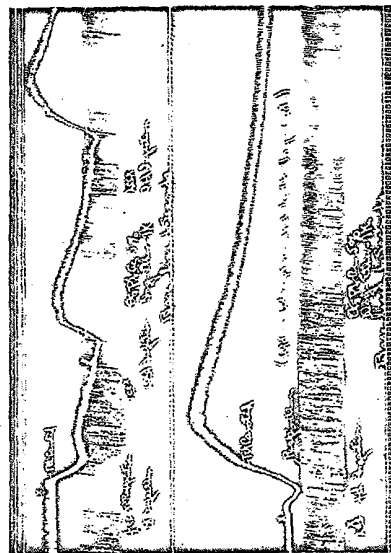


Fig. 17.

pine, and also after atropine and section of both vagi. Fig. 17 is a record of blood pressure and respiration recorded in an animal after the administration of atropine and section of both vagi. It will be noted that the first injection (upper half of tracing) produced a cessation of respiration and a fall in blood pressure, somewhat similar to the effect observed on animals with intact vagi; also the subsequent injections of the triethyl salt gave results similar to those obtained from normal animals. It is of interest to note the relative height and duration of the second and fourth injections.

Fig. 18 shows lung volume and blood pressure as recorded in a pithed dog of 6.5 kilos. Following the injection of .5 c.c. of .5 per cent triethyl lead chloride solution, the lungs show a slight but insignificant increase in volume. The blood pressure was gradually somewhat lowered and remained at a constant level regardless of the later injections of 1, 2 and 4 c.c. of the

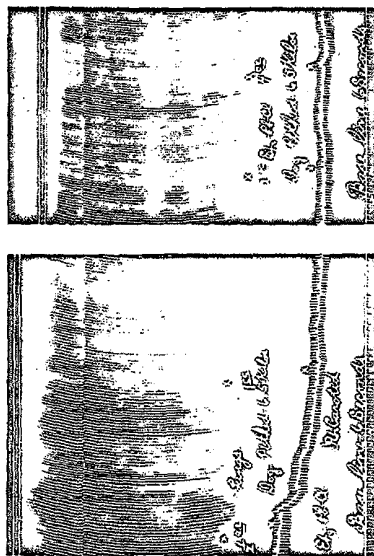


Fig. 18.

drug. It is evident that the drug has but little apparent action on a pithed animal. There are those who maintain that the dyspnea accompanying lead colic, is due to a spasm of the bronchial muscles.¹¹ However, it will be observed that lead, in such a form as here injected, does not cause a constriction of the bronchioles, but, if anything, a slight dilatation.

In order to further localize the seat of action on the central nervous system, the cord was sectioned below the origin of the phrenic nerves and the drug was then injected. Fig. 19 shows a record of such an experiment. The animal was breathing normally, as is shown by the record, and it will be observed that the respiration was greatly influenced by the drug, but that blood pressure shows only slight changes; the initial rise is possibly due to the action of the diaphragm. The injections following the first showed no significant ac-

tion on the blood pressure. Fig. 20 is a record made on a dog in which the record was sectioned at the seventh cervical and both vagi divided. The vagi were sectioned at the two crosses marked on the tracings as V. Following the section of the vagi, 1 c.c. of the acetate of the usual strength was injected. The respiration was stopped as usual, and it was found necessary to administer artificial respiration between the points marked with crosses as indicated.

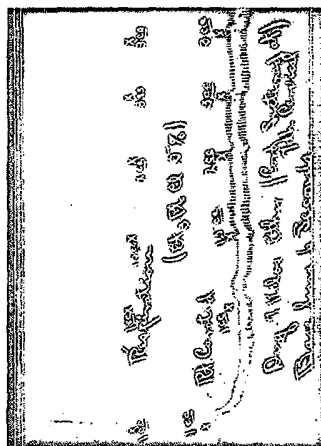
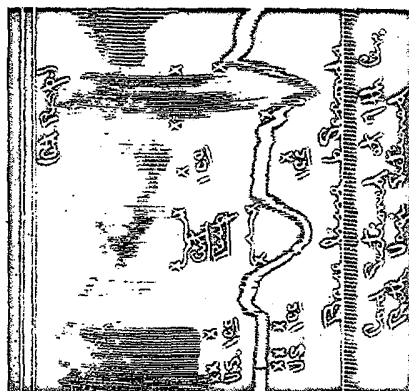


Fig. 13.



20

The most interesting part of the record is that the first injection produced a slight rise in blood pressure, and not a fall. The second injection of 1 c.c. did not alter the blood pressure, but did affect the respiration, making it necessary to introduce artificial respiration.

Desiring to determine whether the activity of the compound is due to the particular salt, or to the lead in the molecule, or to the special arrangement.

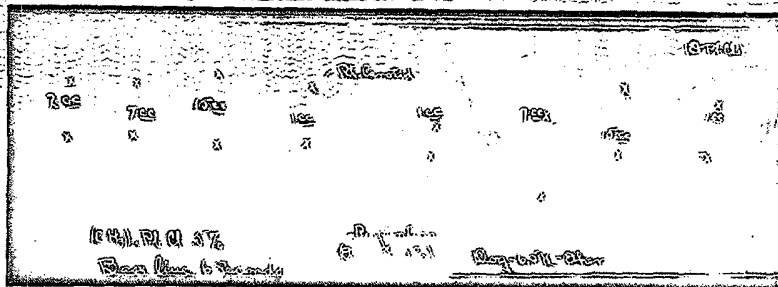


Fig. 21.

of the ethyl radicals in the molecule, I extended the work to include the preparation and use of the trimethyl lead, trimethyl lead chloride, and trimethyl antimony nitrate. That the action is not due to the particular salt of lead trimethyl is evidenced in the work already presented.

The preparation of trimethyl lead is described by Chabours;²¹ however, I prepared it in much the same way as the ethyl compounds, and for the chloride I obtained a preparation of white, thin, crystalline plates, having an odor not unlike the methyl amines. I did not run an analysis on the product, and for that reason, am not certain as to its absolute purity; however, as a check on the work, I used an aqueous solution of the oil, which is $(\text{CH}_3)_3\text{Pb-Pb}(\text{CH}_3)_3$, and later a 50 per cent alcoholic solution of the compound. The oil must necessarily be of a rather high degree of purity.

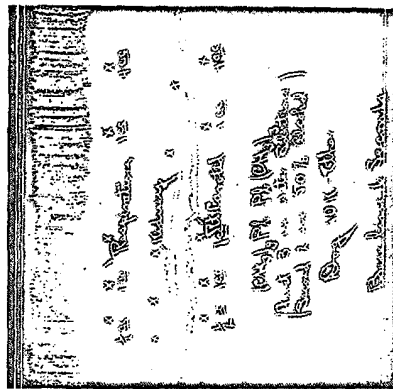


Fig. 21.

Fig. 21 is a record of blood pressure and respiration taken on a dog under ether anesthesia. The first injection is that of 2 c.c. of 5 per cent trimethyl lead chloride. There is no apparent change in the respiration, and the blood pressure shows only a slight fall immediately followed by a greater rise. The next two injections of 7 and 15 c.c. correspond quite closely to the first injection. The injection of 1 c.c. of trimethyl lead chloride solution at this point gave the characteristic fall in blood pressure and a stoppage of respiration, followed after a brief interval by a pronounced stimulation. The second injection of 1 c.c. of trimethyl lead salt acted in the usual manner. The next two injections of 7 and 15 c.c. are of the methyl compound and show nothing very striking. The last injection of the ethyl compound gave a very pronounced result.

As a further check, the aqueous solution of the trimethyl lead was used. It will be noted in Fig. 22 that such a solution did not show any action on respiration or blood pressure. The kidney volume did show that filling of the kidney was not so good as time went on; this may be due to the action of the compound. Not knowing the solubility of the compound in water, a saturated solution in 50 per cent alcohol was used, which shows no pronounced changes. Fig. 23 is another record taken on the same animal as used in Fig. 22. It will be noted that a water solution of the trimethyl lead was very active. The third injection of 3 c.c. proved to be a fatal dose.

These records imply that either one or the other of two things is responsible for the activity of trimethyl lead compounds; either that the lead radical in that particular combination is responsible; or that the activity is due to

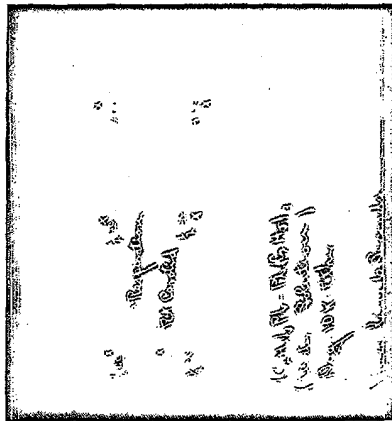


Fig. 22.

the peculiar combination of the ethyl radicals with the lead. Apparently trimethyl lead does not act in the body as the trimethyl lead compounds do. This point is not so startling when one considers that there are many substances which differ chemically much less than trimethyl lead and trimethyl lead differ (for example, some of the sugars), but which, when taken into the body, vary greatly in their assimilability by the tissues (as occurs with levulose and dextrose).

To determine whether the activity of the trimethyl compounds is due mainly to the particular grouping of the ethyl radicals, I have prepared and used trimethyl antimony nitrate. The trimethyl antimony is obtained by the action of ethyl iodide on an alloy of antimony and sodium in a manner similar to that used in the preparation of the trimethyl lead.²² It is a colorless liquid having an

odor of onions, and on coming in contact with the air, oxidizes instantly and burns with a white flame. Triethyl stibine oxide is obtained by shaking an alcoholic solution of the triethyl stibine with finely divided mercuric oxide. Mercury is set free, and the oxide of the radical is produced.

The nitrate can be prepared by: First, the action of nitric acid on the triethyl stibine oxide; or, second, the action of dilute nitric acid on the triethyl stibine. The nitrate crystallizes out in well defined, rhomboidal crystals with a melting point of 62.5° C. It is very soluble in water and has a bitter taste.

Fig. 24 shows respiration and blood pressure as recorded in an animal of 10 kilos under ether. Triethyl antimony nitrate was injected in a 1 per cent water solution. It will be noted that the results of the injection in no way correspond to those obtained through the use of the triethyl lead salts. It is

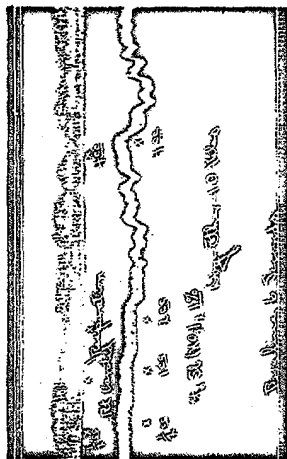


Fig. 24.

of interest that, after this tracing was made, the lead salt was injected and the characteristic results obtained. From this, it appears that the ethyl radical is not chiefly responsible for the activity of the triethyl lead compounds.

EXCRETION

Lead is excreted mainly by the feces (small and large intestine and bile) and to a minor degree in the urine; also traces appear in the saliva, sweat and milk.²⁵ After ingestion all is excreted in organic combination, except the unabsorbed fraction in the feces.²⁴

Danwe²⁶ states that lead injected intravenously disappears rapidly from the blood, the greater part disappearing in less than two minutes. Kobari²⁷ claims that the main deposition of lead in the body occurs in the kidneys, the bones, liver and other glands, a minor amount in the brain, striped and smooth muscle, and blood.

In attempting to determine the mode and rate of excretion of the triethyl lead compounds, Harnack failed²⁸ after numerous attempts, to show the presence of any undecomposed triethyl lead in the urine of animals poisoned with the compound. He maintained that, if such a radical should be present,

it would be easy to isolate it and to demonstrate its presence. He presents the following data obtained from large samples of urine, collected for long periods of time:

Three and one-half liters of urine, collected from a rabbit which had received during the period (48 days) a total of 0.3 grams triethyl lead acetate administered subcutaneously, gave a yield of .0077 grams of lead. There was therefore about 4 per cent of the lead excreted in the urine. The feces were not analyzed.

In the present work, I have, on several occasions, tested for the presence of lead in the samples of urine obtained from the animal at the end of the experiment. These animals would often receive a total injection of 125 grams during the experiment, and occasionally as much as .250 grams have been given, the duration of the experiment often being two hours or more. However, I have not, in any case, been able to detect the lead in the urine, either by applying the test to the urine directly, or by evaporating it to dryness in the presence of concentrated nitric acid and testing for the lead salt. However, I do not maintain from these findings that lead is not to a certain degree excreted in the urine.

DISCUSSION

With the foregoing experimental data at hand, it is very interesting to review the conclusions formulated by Harnack. He considers that interpretation of his results justify the following conclusions,²⁹ translated somewhat freely:

(1) That lead affects the substance of all cross striated muscle; not that it primarily makes each contraction impossible, but that it causes the active muscle to become quickly exhausted; also the muscle finally loses its irritability and dies; yet the lead does not interfere with rigor mortis. This action of lead is more pronounced in the frog and rabbit than in other animals.

(2) That lead affects certain central motor nerve mechanisms; the action consists of a stimulation, from which originate peculiar ataxic movements, also a continuous trembling and twitching, and finally convulsions; yet, consciousness remains and sensibility is not lost. The seat of action is probably the mid-brain or cerebellum. The action is especially marked in the dog, but is also noted in cats and pigeons.

(3) That lead irritates certain nerve structures, located in the intestinal wall, which control the intestinal movements. This stimulation therefore causes general contraction and increased peristalsis of the intestines, producing colic and causing an increased irritability of the whole body, also diarrhea. The action is clearly outspoken in all mammals which were studied. An action on the smooth muscle of the intestine, of the blood vessels, etc., is not demonstrable. Respiration and circulation are not directly influenced, except that in animals in which the muscle paralysis is very prominent, then also the heart and respiratory muscles take part in the paralysis.

Although the records which I have presented do, to a certain degree, confirm some of Harnack's observations, there are, however, many points on which we differ widely. One of the most striking differences deals with the questions of respiration and circulation. Harnack was of the opinion that these were not primarily affected; however, there seems to be no doubt that, as

shown by my experiments, both respiration and circulation are greatly affected by the administration of the triethyl lead compounds. To determine the manner in which respiration and circulation are affected has been the object of a great deal of the present work.

It is generally assumed that chronic lead poisoning is accompanied clinically by a rise in blood pressure and vasoconstriction. Riegel and Frank²⁰ stated that, during the attacks of colic, the blood pressure was increased, and it has therefore been suggested that the hypertension may be due to the violent contraction of the intestines which produce mechanical displacement of blood, or to the pain reflexes. The pallor of the skin has been considered an indication of vasoconstriction. Quellien²¹ believes that even in acute poisoning the blood pressure is raised.

That the blood pressure changes as produced with lead triethyl salts are not due to the increased activity of the intestines with the forcing out of the blood from the intestinal area is clearly shown in Fig. 1 and again in Fig. 16, in which it will be observed that, regardless of the violent intestinal activity produced by the injection of the first dose, the blood pressure falls and remains low until the second injection of the compound. At this time peristalsis is not any more active, if even as vigorous, as following the first injection; yet the blood pressure is strikingly increased.

That the blood pressure changes are not wholly due to muscular activity resulting from central nervous stimulation is evident, for there is present as much or more, muscular activity following the first injection as there is after the second; yet, a fall in pressure is produced by the first injection instead of a rise. Also, if an animal is deeply under anesthesia so that no muscular activity is observed, the fall and rise are produced in the usual order.

That the cessation of respiration in the first case and the stimulation in the second are not directly responsible for the blood pressure change is especially well shown in Fig. 17 and others, where it will be observed that the intensity of the blood pressure change does not, in any degree, correspond to the respiratory changes.

One factor which appears to be quite active in producing alterations in the blood pressure is the variation produced in the rate and volume output of the heart following the first and subsequent injections. This point is shown in Figs. 8 and 9. After the first injection of the compound, the heart beats more slowly and the amplitude of the beat is considerably less. This action appears to be partly due to stimulation of the vagus. But Fig. 9 shows that, following the second injections, the heart rate and amplitude are considerably increased. It appears that the cardiac vagal action present at first has disappeared, and it was found in several animals, the tracing from one of which is shown in Fig. 7, that stimulation of the vagus with the electric current was either without action, or the action was much less, after the administration of the drug. From the records presented one is likely to doubt this proposed explanation of vagal stimulation and paralysis, since Fig. 17 was obtained after atropine and Fig. 13 after lobelin, and both show changes somewhat similar to those obtained from animals with intact vagi. However, a more careful consideration will show that the fall in blood pressure in both

of these cases was not a sudden fall such as results from electrical stimulation of the vagus, or, as that observed in Figs. 1 and 7.

The sudden dilatation of the spleen and kidney, following the first injection might also play some part in the fall of blood pressure, while the constriction of these organs evidently plays an important part in the rise following the subsequent injections.

Animals injected with the triethyl lead compounds, unless deeply under anesthesia, showed a marked stimulation of the higher centers, at times the stimulation being so intense that the animal would wink its eyes and apparently regain consciousness, although it was completely under the anesthetic just at the time of injection. These results and the violent action on the respiration prove that the drug acts on the higher centers and the medulla.

It is very interesting that triethyl lead and its compounds should be so active in stimulating the higher centers and the medulla, for it would be expected that, if the ethyl radicals exerted any action, this would be in the nature of depression, for such is the property of most of the ethyl compounds; for example, ether, ethyl bromide, etc. And again, it would severely be expected from the general character of chronic lead intoxications that the metal possessed strongly stimulating properties; therefore, it is rather surprising to find the compound so extremely active.

This violent stimulation of the medulla and basal ganglia is, beyond all doubt, responsible for most of the symptoms resulting from the administration of lead in such a combination. It will be observed that the drug has practically no action on blood pressure when administered to a pithed animal. Also in a dog with the cord sectioned at the seventh cervical vertebra, the result is practically the same, while after section of the cord and both vagi, the blood pressure shows a slight, but insignificant rise.

A pithed animal (lamin and medulla), or an animal in which the cord has been sectioned at the seventh cervical vertebra shows no signs of convulsions. This means that the medulla and possibly the higher centers are responsible for the convulsions.

The violent stimulation of the respiratory center in the medulla explains the changes produced in respiration. It seems possible that the stoppage of respiration following the first injection is due to extreme stimulation of the center, (or, of some higher controlling and inhibiting mechanism,) and that the increased respiration following subsequent injections is the result of direct stimulation of the center itself after its normal hypersusceptibility to the compound has been slightly depressed by the first injection of the substance.

The kidney and spleen volume changes also strongly suggest stimulation of the visomotor centers. The primary dilatation is apparently of central origin. But I have suspected many times that, in addition to this action, there might be some peripheral mechanism concerned, possibly in the nature of a brief primary stimulation of vasodilator nerve endings. The marked shrinkage in volume of the kidney and spleen which comes on secondarily is certainly due mainly, and perhaps entirely, to stimulation of the medullary vasoconstrictor center. It is exceedingly probable that this same action is the

