Chronic Lead Poisoning.

by

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Note.
The numbers attached to the names of authors throughout this text have reference to a list which will be found at the end of this paper.
Since the publication of the valuable work by Fouquerel des Planches (1), the subject of chronic lead poisoning, previously but imperfectly known, has attracted great attention, both from the serious nature of the lesions produced in the course of the malady, and on account of its not unfrequent occurrence. Dairy from this time very numerous contributions to the literature of the subject have appeared, the majority dealing with the disease from a purely clinical point of view, while some contained the results of experimental investigation.

The scope of the work, the results of which are here given, was, from unavoidable circumstances, confined entirely to the latter category; and where in the course of the following pages the results of clinical study are appealed to, it will only be for the purpose of illustrating some point noticed in the course of experimentation, or to supply a link in a chain of reasoning, which observations on the lower animals are not capable of furnishing. Here, then, no detailed description of the history of Saburine poisoning, as it affects man, or of its etiology, or its
symptoms, of its diagnosis, or of its treatment. On such points the ordinary literature of the subject is sufficiently complete, to refer to them more than is necessary would only prolong this Thesis beyond reasonable limits.

The greater number of the experiments here recorded were performed on the Pharmacological Laboratory of the University of Berlin, to which I am much indebted to Professor Oscar Liebreich, for many kind and valuable suggestions during the whole course of my work.

Without further preface we may proceed to consider.

I. The various channels by which Lead may be introduced into the bodies of animals, for the purpose of studying its effects.

In most, if not in all such experiments, which have been previously made, the lead salt has been introduced into the stomach; and doubtless this plan has much to be said in its favour, imitating as it does the most usual manner of absorption met with in the human subject. But on the other hand it has certain disadvantages, as, in the first place,
it is not possible to estimate exactly the quantity which is absorbed, & secondly, the unabsorbed portion, mixing with the contents of the intestine, becomes excreted along with the feces, & thus entirely prevents us from ascertaining whether the lead which has been absorbed has been secreted through this channel.

In no experiment of the following series has the poison been as introduced. The solution was, in the case of rabbits, either injected directly into the external jugular vein, or subcutaneously; while in those frogs which were used, the fluid was introduced into the posterior lymph-sac.

The preparation of lead made use of, was in some cases the ordinary acetate, in others the subacetate in the form of the Liquor Alumbei subacetato of the Prussian Pharmacopoea. The former salt was dissolved in distilled water, sometimes with the aid of a minute quantity of acetic acid.

The rabbits experimented upon were placed in wooden cages, the floor of which were constructed of a series of glass rods running parallel to each other, & so arranged as to retain the feces, while the urine passed through. It was received in a glass vessel placed below. In this way all risk of accidental contamination with lead was avoided.
II Methods of Analysis.

The detection of salts of lead, in the fluids or solids of the animal body, has been made in various ways, differing in their details, but all agreeing in estimating the metal either in the form of the sulphide or the sulphate.

Some experimentors have asked the tissues alone (Berulardt ²), or mixed with nitrate of potassum and bicarbonate of soda. Others have performed this operation before the blow-pipe, adding small quantities of nitric acid to the charred mass, from time to time (Rouclier ³). The charring process has been at other times performed by means of strong sulphuric acid (Berulard, Hurban, and Leger ⁴) or nitric acid (Rosenstein ⁵). But by whatever method the end aimed at was reached, the charred or ashen mass was next dissolved in acid, the lead precipitated as sulphide or sulphate, in which condition its quantity was estimated.

As a general rule however the process adopted has been to destroy the animal matter by means of chlorine, precipitate the lead present as the sulphide, by passing in a stream of Sulphuretated Hydrogen Gas, and finally change this salt into the sulphate, in which condition the amount of lead present, was estimated.
Guiselewsky proceeded in a somewhat different manner. After having destroyed the organic matter by prolonging heating or boiling along with hydrochloric acid and chlorate of potassium, he placed the fluid in a dialyzing apparatus, and passed a constant current of electricity through it. The negative pole (platinum) lying in this fluid close to the dialyzing membrane, while the positive electrode, also of platinum, was suspended in the surrounding acidulated water. In the course of eight to fifteen hours, the lead separated out on the negative electrode as a dark deposit. It was then dissolved in acid, precipitated, and estimated in the form of sulphate of lead.

In a somewhat similar manner Magencou and Bergeret have been able to detect the presence of this metal in the animal fluids. They seem however to have been able to arrive at greater delicacy by substituting aluminium for platinum, as the negative electrode.

It was in the hope of being able to detect salt of lead, when present in the tissues, in even smaller quantities than the usual methods allow of, that, at the kind suggestion of Professor Oscar Liebreich, I made a few observations to ascertain whether zinc dust would, when introduced into a solution of
lead, cause a deposition of that substance in a metallic form, in a manner similar to its action on solutions of mercury (Ludwig?). Thence we have an entire elimination of the necessity of employing an electric battery. The difficulty of procuring fine dust in a sufficient state of purity, lead to magnesium being substituted in its stead, and all the analyses were performed with this metal, in the manner about to be described, with the exception of a few where the quantity of lead present was so great as to allow the ordinary method of being made use of.

If a small piece of magnesium ribbon be placed in a moderately strong solution of any ordinary lead salt, the lead separates out, and is deposited in a metallic form on the magnesium. This separation takes place very rapidly, especially if the solution be slightly warmed. Though not completely hindered by the alkalinity of the fluid, it is much better seen when the reaction is neutral or faintly acid.

Such is the reaction on which depends the method of analysis made use of in the following experiments. The finer details of the process can best be explained by giving one out of a considerable number of observations on solutions of lead of various
strengths, made for the purpose of ascertaining the accuracy of the method.

Ten cubic centimetres of a solution of acetate of lead in distilled water, containing 0.000005 gramme in each cubic centimetre, were placed in a test-tube, and a small piece of magnesium ribbon was added. The fluid, after being gently warmed over the flame of a Bunsen's burner, was allowed to stand at rest for a few minutes. The solution was then poured away, the magnesium left in the tube carefully washed with a stream of distilled water, and allowed to fall on the centre of a watch-glass. With the aid of one or two drops of nitric acid the magnesium was dissolved, the glass was then placed on a water-bath. When evaporation was complete a few drops of strong hydrochloric acid were added, allowed to evaporate, this last process was repeated five or six times, until all the nitric acid had been driven off. The residue was then dissolved in distilled water slightly acidulated with hydrochloric acid, and the watch-glass transferred to the bottom of a large beaker. Into this vessel a stream of Sulphurated Hydrogen was passed through a glass tube which reached to the bottom of the beaker, but which did not come in contact with the fluid con-
tained in the watch glass. After some time this fluid became saturated with sulphured Hydrogen, and on removing the watch glass the presence of lead was indicated by a faint, black precipitate.

The purity of the Magnesium ribbon was most carefully tested on numerous occasions the above process being followed out in all its details, distilled water acting as a substitute for the lead solution, and the absence of any reaction indicating the presence of lead not only established the purity of the magnesium, but also showed that no source of contamination existed in the various reagents or pieces of apparatus made use of in the process of testing.

After a considerable number of observations made on simple solutions of lead acetate, it was found possible to detect the presence of the metal in solutions which contained 0.000005 grm. in each cubic centimetre, when 10 c.c. were used for analysis, and even smaller proportion when larger quantities of the solution were employed.

Where the lead is present in the form of an albuminate this reaction cannot be relied upon, and on this account all organic materii...
in the fluids & tissues to be examined must be destroyed before magnesium is made use of.

In the case of urine, while in many instances lead may be recognized without any further process, yet it is desirable for the sake of certainty to submit it also to the same preliminary manipulation as the other tissues & fluids, & this process becomes absolutely necessary in cases of albuminuria. When lead (acetate) is added to human urine it can be detected even in very small quantity by means of magnesium, but we have no certainty as to whether the metal, when being excreted, is under the same conditions as after artificial addition.

In the observations recorded here, the organic matter was destroyed either by the action of Chlorine (a much prolonged process), or more rapidly by direct cooking along with Potassium Nitrate, & Sodium Bicarbonate. In either case a neutral solution of the inorganic residue was made, & to this the Magnesiumribend was added. The further details of the process have already been given.

While this method was only used here for qualitative analysis, it would probably also be of service in quantitative researches,
The aim of these experiments was not to determine the quantity of lead present in the different tissues (the results of Reubel being sufficiently reliable) but solely to discover its presence when in very small quantity, and for this purpose the above method was well suited.
III. The absorption of lead after subcutaneous injection.

When a solution of a lead salt is mixed with a solution of albumen, there is formed an albuminate of lead which, unless the solution be much diluted, separates out, and falls as a flocculent precipitate.

This formation of lead albuminate also takes place in the living tissues. This can be best seen in the tongue of the frog, where this structure is spread out in the manner usually adopted for microscopic examination, or a drop of a solution of lead acetate injected into its substance, one can readily observe the formation of this albuminate, as an opaque deposit, best seen by reflected light. A similar deposit is found under the thigh of the rabbit after subcutaneous injection of a lead salt. This albuminate also forms on the surface in the epithelial layer of mucous membranes to which lead in a soluble form has been applied. (Nottmagen 8.)

Although the albuminate of lead is, to a slight extent, soluble in water, yet these deposits remain for a long time apparently but little altered, and in the case of rabbits they may be seen many days or even
weeks after the subcutaneous injections have been made.

After hypodermic injection, that portion of lead which is absorbed, passes along the lymphatic vessels, and in sections of the skin and subcutaneous tissue made after death the metal can readily be detected there as the black sulphide by means of sulphuretted hydrogen. In preparations so stained it can be observed that the lead is present not only in the various lymphatics (particularly around the blood vessels) but also in the deeper layers of the epithelium.

This reaction can also be seen in the tongue of the frog during life, as the following observation shows. —
Experiment I.  

March 26th, 1878.

Frog. The animal was secured on a board & the tongue examined microscopically in the usual manner.

11.45 a.m. Injection into the tissue of the tongue of two drops of a saturated solution of acetate of lead. In a few seconds the opaque white albumen-like formed, well seen by reflected light.

11.53 a.m. Injection of 1 c.c. Sulphuretted Hydrogen water into the posterior lymph-sac.

11.58 a.m. A slight brown juice in the deposit can now be observed.

From this time onwards the precipitate became more & more brown, until it assumed the well marked characters of the sulphide of lead. The brown staining stretched along the lines of the vessels.

(Vide also Exp. XIII. given at the end of the text.)

This result may also be obtained in the case of warm-blooded animals, as the following observation shows, where the deposition was caused during life by sulphide of sodium absorbed into & circulating in the blood.
Exp. II. Young rabbit.

Dec. 13th. 2 pm. Injection of two drops of a solution of acetate of lead (containing 5 gm. in 50 c.c.) into the left ear, & the same quantity into the loose subconjunctival tissue at the outer angle of the left eye. At the same time 2 c.c. of a strong solution of sulfide of sodium were injected below the skin of the right dorsal region.

14th. 11:30 pm. Animal apparently well.

12 noon. Injection into the right ear of 6 drops of the lead solution, & the same quantity into the left conjunctiva.

12:15 pm. Injection of 2 c.c. of solution of sulfide of sodium into the left dorsal region.

Animal died during the night.

Post-mortem examination showed that some degree of brown coloration had taken place in the right ear at the point where the subcutaneous injection had been made, & also in the left conjunctival tissue; but no change was to be seen in the left ear. In both situations the albuminate of lead remained in great measure unabsorbed, whilst the tissues were brought in contact with sulfured hydrated hydroxide there was marked blackening.
The time required for the absorption of lead, from other than mucous surfaces, is a difficult matter to ascertain. We do not here deal with the question of how long any given quantity of the salt takes to pass into the blood stream, but only seek for an indication which will enable us to say with certainty that some, unknown, part of the whole has been absorbed.

The most rapid absorption has been observed in frogs, where the solution of lead was injected into the lymph-sac, where evident indications of its action showed themselves in twenty minutes or half an hour. The doses were, as will be noticed, large. (See also Exp. XII. at the end of the text.)

Experiment III. Frog. March 11-1379.
1:45 pm. Injection of 0.2 gm. Acetate of lead in 1 c.c. distilled water (with a drop or two of acetic acid) into the posterior lymph-sac.

2:5 pm. Animal torpid. If laid on its back it remained in that position, made no effort to regain its normal posture. There was no paralysis nor any loss of reflex irritability.

(The rest of this observation has no bearing on the subject of chronic lead poisoning.)

In the rabbit, lead was found in various internal organs after four hours (Exp. IV.), five hours (Exp. V.) and twelve hours (Exp. VII.), probably
absorption does not take place to any appreciable extent within the shortest of these periods.

The marked increase in the rate of absorption which obtains when the lead salt is introduced in the stomach instead of being injected under the skin, is seen when one compares the results recently obtained by Ammoschat 14 with those already given. In Ammoschat's experiments not only was the absorption very rapid, but the amount of lead detected in the liver & bile formed a considerable proportion of the total substance injected into the stomach.

It is unnecessary to do more than allude to the other ways by which Lead may be introduced into the body. In addition to the Alimentary & genital urinary tracts, this substance may be absorbed through the mucous membrane of the lungs & bronchi (W. Rosenthal 9), through the conjunctiva, or from the surface of ulcers. It seems very doubtful whether the salts of lead ever pass through the uninjured skin.

Why?
IV  The Destination of Lead.

By whatsoever channel the metal is absorbed it reaches the blood and circulates with that fluid through all parts of the body. It has already been said that the absorption of lead, though beginning instantly, is very slow, only minute quantities entering the circulation at any given time. It cannot therefore be a matter of surprise to find that the blood seldom contains more than a mere trace of the metal, so that not infrequently no lead at all can be detected in that fluid.

As an example of this the following experiment may be given: where the lead, while recognisable in the liver, could not be discovered in the blood after a most careful analysis.

Experiment IV. White rabbit 1510 grammes in weight.

Jan. 22, 1878.

12.45 p.m. Injection of 0.05 gram of lead acetate dissolved in 2 c.c. water, one half into the right, the other half into the left lumbar region.

4.45 p.m. Animal killed. Blood vessels washed out as well as possible with distilled water. Organs analysed after the method already described. The liver contained lead, but no trace of the metal was to be found.
in the kidneys, blood, or muscles of the hind legs.

The following experiment will suffice to show that under certain circumstances lead may be detected in the blood as well as in other organs. It will be noticed that in this case the dose of lead was considerably larger than in the observation just given, so this circumstance may account for the difference of result.

Experiment V. White rabbit. Weight 1160 grammes.
11 gm. Weight 1150 gm. Quantity of urine for the last 24 hrs. was 3000 cc. normal—no lead present.
10 am. Injection under the skin of the back of 0.3 gm. acetate of lead in 1200 cc. water.
3 pm. Animal killed. Arteries washed out. Urine found in the bladder contains a trace of lead.
Bile & Liver
Kidneys
Blood

All contain lead.

The results of Henbuli's analyses agree with those given above, in so far as the blood is concerned— for though in one case (No. 1) he found some considerable quantity of lead in that fluid, yet as a
rule he was only able to detect its presence, and
estimate it, and in some instances he entirely failed
to obtain any indications of its metal.

So long as the lead in the blood remains in
a soluble condition it probably passes out of
that fluid as rapidly as it enters it, but under
certain circumstances it may be subjected to
influences which determine its precipitation
in an insoluble form within or around the
capillaries.

One of the symptoms of lead poisoning most
relied upon for diagnosis in the earlier stages
of the malady is the peculiar Blue Line which
appears on the gums close to the alveolar
margin, which closely follows the line of
the teeth. This appearance which has been
investigated by Milton Figge, and later perfected
by Otis, consists of a black deposit in and
around the capillaries of the gums. These
writers attribute the appearance to a deposit
of Sulphide of Lead produced by the Sulphuric
Hydrogen, generated from the accompanying food
which accumulates on the teeth, acting on the
lead circulating in the blood, and is often
conclusion at which Garrod, and most other
authors have arrived.

It has been already noticed (Exp. I. p. 13.)
that a similar deposit can readily be pro-
duced in the living tissues. I have endeavoured
to imitate still more exactly this reaction by
injecting sulphuretted Hydrogen into the frog's
foreskin, & then administering lead subcuta-
neously, but have failed to obtain a like
result. The reason seems to be that owing
To the small amount of lead present in the
blood at any given moment, it requires
a considerable time, probably days, before any
distinct deposit can form; & long before this
period has elapsed the sulphuretted Hydrogen
must have disappeared from its position by
absorption.

Leaving the blood with considerable rapidity
the Lead becomes deposited in the various
vessels of the body, chiefly in the liver, but
also in the kidneys, lungs, spleen, brain,
splenic cord, muscles, bones &c.; but it
appears impossible to attach much weight
to these observations as the comparative
alterations in function of different organs
caused by the presence of the metal must
depend far more on their function than
on the quantity of Lead which they in-
dividually contain, a fact which appears
to have been lost sight of by some
writers.
These experiments do not bear out the opinion of Heubel (loc. cit.) that the kidneys as well as the liver contain a large proportion of lead, but on the contrary they tend to show that such is not the case; at all events when the vessels have been emptied of blood by the injection through them of distilled water a proceeding which probably also washes out the winiform tubules.

Heubel 10 has found that in animals poisoned with lead the proportion which the blood corpuscles bear to the serum is altered, the watery portion of the blood increasing along with a proportionate decrease of its corpuscles,

and more recently Brodie 13 has shown that in one case of chronic lead poisoning the coloured corpuscles fell in number from 1,843,000 to 1,087,000 in each cubic millimetre.

The coincident emaciation was well marked in the case of the rabbit experimented upon, it usually began immediately after the first dose of lead had been administered, continuing steadily to increase during the whole course of the disease, although the appetite of the animals did not seem to be affected.

The mode of death met with in certain of these observations forces upon our consider-
the action of intravenous injection of soluble salts of lead, which, although somewhat foreign to the subject of chronic lead poisoning, cannot be entirely passed over.

It is evident that the very slow absorption of lead after hypodermic injection is fitted to determine a wide difference in effect between that method of administration and the direct injection of the solution into the veins, and in point of fact one encounters, after the latter procedure, a train of perfectly new symptoms. If the dose be a large one, the result is that the animal passes into a convulsion and dies almost instantly, but with smaller quantities recovery from the immediate symptoms takes place.

In the latter case (as in Exp. XI. p. 58.) the animal passes through a series of tonic and clonic convulsions into a condition of complete paralysis, the respiratory muscles alone remaining intact. After some little time the power of movement begins to return, and recovery gradually takes place. As an example of rapid death following such intravenous injections the following observations may be given.

Experiment VI. Feb. 12, 1878.

Large brown rabbit. Weight 2000 grams.

External jugular vein laid bare and cannula inserted.
During the course of the operations little or no blood was lost. An ordinary hypodermic injection-syringe was filled to the loosen 10 cm. of the Vincentian Pharmacopeal solution of subacetate of lead was very slowly injected, the whole operation lasting about 4 minutes. Almost immediately after the conclusion of the injection, & before the syringe or cannula were removed, the animal was seized with a severe general convolution during which it died.

A careful post-mortem examination showed no embolic process, or any other appearance which might serve to account for death. The right side of the heart was distended with fluid blood, the left contracted. In the brain & spinal cord no lesions were found.

With regard to the pathology of this condition it can only be said that we have not at present sufficient data to enable us to make any definite statement, & to theorise on the subject is therefore useless.
V The Elimination of Lead.

The salts of Lead, which are circulating through the body or are deposited in the tissues, only pass out of the system by two channels, through the intestines, or through the kidney. It has been asserted that elimination takes place through the skin, but this is more than doubtful.

The experiments of Neubel, Accenschat, and others, clearly show that lead passes in considerable quantity from the liver into the bile, and is carried by that fluid into the intestines. This fact however does not by any means prove that the metal is excreted by this channel, for, as it is well known that lead in a soluble form is absorbed by the intestinal mucous membrane, so we may very fairly admit the possibility of reabsorption taking place to so great a degree as to prevent any elimination. As has been already said, experiments in which lead has been administered by the stomach are not capable of clearing up this important point, and it is unnecessary to add that the blackening of the feces, so often recorded, can have no weight as an argument, as we have no means of judging whether this lead is merely an
unabsorbed portion of the dose swallowed, or whether it has been excreted along with the bile.

On many occasions in the course of these experiments minute quantities of lead have been detected in the cecum, but the amount has always been too slight to cause blackening of the fecal masses. As however the metal was not invariably found we can only draw the conclusion that after hypodermic administration lead is frequently excreted by the intestines in rabbits.

Reasoning from the fact that while lead was present in considerable quantity in the bile, in liver substance, but was only recoverable in the feces with difficulty, it seems allowable to conclude that a degree of reabsorption does take place in the intestinal tract. (I do not mean to hold that all the lead excreted into the intestine is carried further by means of the bile, as it appears not improbable that the other glands which pour their secretion into the bowel may to a more or less marked extent assist in the process of lead excretion.)

To illustrate this excretion of lead the following observation may be given.
Experiment VII. Rabbit - weight 1800 grams.
Feb. 21. 9 p.m. Injection of 1 c.c. Leg. Plumbi Subacetici (Per. O.B.) mixed with 9 c.c. distilled water. The injection was made under the skin of the back & lower limbs, at eight different points (at each 1 c.c.)
Feb. 22. 9 a.m. Animal killed. Had passed no urine, but some was found in the bladder, black & albuminous. The following was the result of analysis.
Blood: No lead was discoverable.
Urine: A trace of lead.
Bile: A small quantity of lead.
Liver: A considerable quantity of lead.
Part of contents of Small Intestine (duodenum) - a trace of lead.
Part of contents of Large Intestine (descending colon) - No lead.

The kidneys, which when removed from the body were much congested, were hardened in alcoholicate of Potassium solutions. Microscopic sections showed very marked signs of congestion. Numerous haemorrhages had taken place in the cortical portion of both kidneys, many of the tubules contained blood corpuscles.

In this animal, then, lead was found, twelve hours after administration, in the liver, bile & small intestine, but was absent in the
Contents of the Large Intestine. This fact, it is capable of, at the least, two interpretations, either the lead, which had been excreted by the bile, was reabsorbed too rapidly by the intestinal mucous membrane to allow of its reaching the colon, or the absence thereof may have been due simply to the circumstance that sufficient time was not given to allow the intestinal contents to be forced on so far. There are, unfortunately, no facts which allow us to decide upon this point.

The second channel by which lead is excreted is the Urine.

I have been able to find no trustworthy series of observations on this point. Some scattered facts there are indeed, derived apparently from clinical observation, but these are very contradictory. Some writers (Taylor, Orfila) holding that lead is found in the urine in saturnine poisoning, while others (Touquet, les Claudes. etc.) deny the fact. So much doubt surrounds the subject that MacDougall 15 has recently said: "It must be allowed that nothing positive is as yet known regarding the excretion of lead in the urine in cases of chronic lead poisoning."
In the course of the observations recorded here, the urine was very frequently analysed, and lead, in small quantity, was proved to be present in a considerable number of instances (as in Experiments VII, VIII, IX, X, XI). A glance at the details of these observations will show that the metal was by no means invariably met with, and that, though in one experiment (No. IX) it appeared only during the last twenty-four hours of life, yet as a general rule it manifested its presence shortly after administration.

One of the most general symptoms met with in these animals was albuminuria. It was seldom indeed that an injection of lead was not followed by the appearance of albumen in the urine, and it is impossible not to connect in some way the presence of lead in the urine with the appearance of this substance. When it is considered that lead present in the blood is in the form of an albuminurate (Maurer, 15) the reason of the simultaneous appearance of lead and albumen becomes more apparent. Though by no means proved, yet it may be held to be probable that these conditions of kidney tissue, which permit of the passage of albumen into the urine, are also those which offer the greatest
facilities for the transudation of albuminuric of lead (Koblenz &), & whatever may be the true explanation of the fact, it is certain that where in the course of these experiments lead was detected in the urine, albumen, when tested for, was never found absent. In addition, the simultaneous appearance & disappearance of these two substances was sometimes very striking. Of this the following observation will serve as an example.

**Experiment VIII. Rabbit. Weight 15 lb.**

Jan. 29 1 pm. Injection of 10 grm. acetate of lead under the skin of the back. The salt was dissolved in 4 c.cm. of water, with the aid of a trace of acetic acid, & the injection was made at four different points of the back (each 1 c.cm.)

Jan. 30. 1 pm. Quantity of urine passed in the last 24 hours is 100 c.cm. It contains a large quantity of blood (Corpuscles + bloody casts), & albumen.

Jan. 31. 1 pm. Urine passed in the last 24 hours is 35 c.cm. still contains some blood. Albuminuous - a trace of lead.

Feb. 2nd. Urine for the last 48 hours measures.
20 C.Cm. It is albuminous, acid, with a trace of lead.

Feb. 4. 1 p.m. Urine for the last 48 hours 70 C.Cm. acid no albumen or lead.

2 p.m. Injected subcutaneously 0.1 gram ofacetate of lead, dissolved as before in 4 C.Cm. water.

Feb. 6. Quantity of urine in last 24 hours 70 C.Cm. Trace of albumen + lead.

Feb. 7. Quantity of urine in last 48 hours 15 C.Cm. acid. No albumen or lead.

Feb. 9. Urine unfortunately lost.

2 p.m. External jugular vein laid bare +

0.2 gram Acetate of lead in 1 C.Cm. water was slowly injected. Animal immediately passed into convulsions + died.

In the above experiment it will be seen that not merely on one but on two occasions was there the simultaneous appearance + disappearance of lead + albumen.

Whether this relation holds good in all cases or not it is at least extremely probable that certain diseased conditions of the kidney are more favourable to the passage of lead through the walls of the capillaries than others, & on this supposition may perhaps
Leopoldo, the Ecuadorian physician, held as to the excretion of lead by the urine, which have been already referred to.

Lesions of the Kidney.

While the lead which is present in the liver causes no appreciable change in its structure or function, it is far otherwise in the case of the kidney. In all the rabbits used in these experiments (except the exception of No. II where a minimum quantity of lead was administered), there was found after death a more or less intense renal congestion. One of the symptoms which indicated the presence of this condition during life was albuminuria, to which reference has already been made, the other consisted in the appearance of blood in the urine. In two instances (Exp. VIII. v. XI) this was present in a high degree, and it is to be remarked that while in the latter animal the solution of lead was injected directly into the jugular vein (a method of procedure which Leopoldo has shown may itself produce such a symptom), in the former instance the lead was introduced by simple hypodermic injection. The presence of blood corporcles in the urine
showed that it was not merely a transmutation of serum tripled with blood-pigment
but a pure haematinia.
But in other instances through no blood
was observed in the urine, yet after death
blood corpuscles were found in the urinary
tubules. An example of this may be given.

**Experiment IX.**

Rabbit - 1070 grammes.

Feb. 11. 1878. 4 pm. Injection under the skin of the
cranial region of 20 C.C. Leq. Plumbi Subacetici (Per. Ql.)

Feb. 12. Quantities of urine 30 C.C. neutral
no albumen or lead.

Feb. 14. Weight 1016 gram. Quantity of urine
in the last 24 hours 900 C.C. no albumen
or lead

2 pm. Injection of 10 C.C. of the above
solution near the same point.

Feb. 15th. Weight 900 gram. Injection as on
yesterday.

Feb. 16. A slight degree of paralysia
manifest itself in the hind
legs.

Feb. 17. Animal died during the night.
Weight after death 820 gram.

Urine for the last 24 hours
100 C.C. slightly albuminous,
+ contains a trace of lead.
Post mortem examination.


Microscopical.

Sections made through the spinal cord & medulla at various points show nothing abnormal.

The sciatic nerves, stained in osmic acid, showed no degeneration of any part of the fibre either in the lower or upper part of their course.

In sections through the kidney substance, blood capillaries are seen in the uriniferous tubules, & in scattered extravasations through the renal substance. There is also in some parts a degree of cloudy swelling of the epithelium of the convoluted tubules.

From numerous sections made through the kidney, of Experiments VI, VII, IX, X, & XI, the following brief account of the microscopical anatomy of their conditions is derived.

The congestion was chiefly observable in the cortical substance, where the epithelium lining the Tubuli Contorti was in a
state of "cloudy swelling" (this condition is
however so commonly met with in rabbit
as to be of no practical importance) The
numerous blood corpuscles which
these sections show are disposed in
three positions; firstly, distending the
blood vessels; secondly, as scattered extrava-
asations in the renal substance; and thirdly,
occupying the lumen of the tubuli contorti and
passing onwards into the straight tubules.
The extravasations seemed in some cases to be
produced by the rupture of a small
arteriole, as a part of their boundary
was formed by a layer of connective tissue
which was anatomically continuous with
the adventitia of the arteriole. The extravasa-
tion had evidently taken place under the
adventitia.

It is a somewhat remarkable fact
that no corpuscles were to be found in
the capsule of Bowman, nor did the
glomeruli appear to take any prominent
part in the process. This is the more
noteworthy considering that (according to
Cornil & Deluyier 18) the acute congestion of
the kidney produced by Cauterization
chiefly affect the glomeruli, yet that it is
into the capsule of these tufts that the
escaped blood corpuscles first find their
way, passing from thence into the convoluted tubules. If, as seems probable, (though the possibility of another explanation must be admitted) the concentration and subsequent passage of the blood-corpuscles into the tubules are to be ascribed to the direct irritation of the lead, these observations would appear to indicate that the separation of salts of lead does not take place through the glomeruli, but by the way of the epithelium of the tubuli contorti, in the same manner as Heidenhain has shown obtains in the case of indigo.

With regard to the hemorrhages which occur from ruptured arteries it must be borne in mind that in all probability the walls of the blood-vessels are weakened by prolonged congestion (Colloidemia), so that, during certain periods of lead poisoning the blood-pressure is above normal, a fact which will be more fully considered presently.

The calcifications of the kidney so frequently met with in cases of lead poisoning in man, was not observed in the course of this inquiry, but it is
easy to see how a condition of
spurious elevation might arise as a
consequence of a continuation of such
a marked congestion as that here
observed.
Thus far we have been considering the conditions under which lead is absorbed into, retained in, or excreted from the body, but before we can arrive at any conclusive regarding its action on the economy, it is necessary to consider various other symptoms which manifest themselves in the course of saturnine poisoning.

1. Lead Colic.
2. Cerebral Symptoms.
3. Paralysis, anaesthesia, etc.
Lead Colic

Among the most prominent symptoms of saturnine intoxication must undoubtedly be placed the colic which attacks the patient somewhat early in the course of the malady, which, while frequently severe, sometimes reaches such a pitch of intensity as to urge the victim to suicide. The pain does not appear to differ except in degree from that met with in other varieties, but there are certain clinical facts in connection with it which may serve to throw some light on the general pathology of the disease, which must therefore be pointed out here.

The heightened arterial tension along with the slowness of heart action which occur in cases of lead colic have been observed by many authors, among whom may be named Marey, Foster, Frank, and Riegel. The last named writer has studied the arterial changes in more than two hundred cases, and points out that not only does the arterial tension increase or decrease in proportion to the changes in severity of the pain, but that there is generally observed a coincident diminution of urine, which follows closely the changes in blood pressure. He has
found that on the one hand the removal of the pain by means of morphia does not affect the arterial tension, whereas, on the other, the exhibition of nitrate of silver not only reduces the arterial pressure, but also subsides the pain of the colic. (It must be remembered that, the theory which recognizes in the heightened blood tension only a reflex action set up by the pain of the colic, is not disapproved by these observations, for the influence of morphia may have been merely to prevent the pain from being felt, not to remove the irritation of which that pain was only an indication.)

The other symptoms of lead colic do not call for notice, with the exception of the constipation, which, though frequent, is not invariably present.

The pathological appearances on record are of too meagre a nature as to be of but little value. It is not even satisfactorily proved that the intestine is in a condition of spasmodic contraction, so much so that Vulpian has doubted the fact. Cullenburg & Landoir have maintained that there is, on the contrary, dilatation or relaxation.

Kausmann & Mayer found in one case atrophy of the gastric & intestinal walls, also
with induration of the coeliac ganglia. \footnote{Eulenburg \& Landouze} \footnote{Schröckmann} \footnote{Loc. cit.} \footnote{Riegel} \footnote{Other writers, which account for the intestinal, arterial \& neural phenomena by supposing that the action takes place through the medium of the vasomotor nerves, either inhibitory, developed by the irritation of the branches of the vagus supplying the intestines, or from a direct action of the poison on the vasomotor centres.}
arterial tension & pulse rate are not invariably associated with the attacks of colic, but frequently are present constantly during the progress of the disease.

No symptoms of colic were observed in these experiments.
II. Cerebral Symptoms.

Perhaps the proven symptoms met with in the course of lead poisoning are those which are comprised under this heading, and it is necessary very briefly to refer to them.

The conditions which are here alluded to present forms varying from slight alterations of function—such as melanrhythmia—to the most severe attacks of eclampsia.

These epileptiform convulsions are not merely seen in dogs to which lead has been administered (Henbel found eclampsia in four out of eight dogs experimented upon), but in rabbits I have failed to observe any unmistakable evidence of such a condition.

It seems probable that (in the human subject at least) some cases of eclampsia following may be of uraemic origin, consequent on the renal changes produced in the course of lead poisoning.

Of the various forms of uraemia we are entitled to suppose that that variety which is believed to result from hydreaemia is the one to which those persons who are under the influence of lead are most exposed. The observations
of Heubel on the increase of the watery part of the blood, already referred to, deem in any case to point to such a conclusion.

We have no reason, however, to suppose that all cases of Saturnine Eclampsia are merely examples of uræmia. The kidneys are not invariably so much diseased as to account for the symptom, nor writers seem very generally agreed that some other cause must be looked for.

Examination of the brain in fatal cases has not added anything of importance to our knowledge. One or two authors mention an anaemic condition of the hemispheres, and one observer, Brodie, noting a granular fatty degeneration of the walls of the cerebral bloodvessels. Rosenstein refers the various cerebral symptoms to anæmia of the brain substance, and, in admitting the strong probability of their vasomotor origin, we have probably gone as far as the facts, at present known, permit of.

This symptom is most commonly observed in the arms, the extensor muscles of the forearm becoming gradually paralyzed until they ultimately lose all power of contracting in answer to the will, and at the same time undergo considerable atrophy. Without attempting to enter into the many clinical details of the paralysis, which do not concern us here, we may be allowed to mention a few characteristics of this symptom which have a direct bearing on its pathology.

It will be noticed that while all the other muscles on the extensor surface of the forearm are involved in the paralysis, the *Extensor radii longus* almost invariably retains its contractile power to the last. In the upper arm the biceps & triceps may become added to the number of the affected muscles. Occasionally the extensor muscles of the foot may become paralyzed, and are facts wanting to show that even the muscles of the larynx are subject to attack (Sanguiniae des Pleures, Gerhardt).

In the experiments here recorded paralysis was noticed on three occasions, but it was never so well developed as to allow of specific statement as to which muscles were affected.
The first symptom noticed was a degree of awkwardness in the motions of the animal, accompanied by tremor in the muscles especially of the hind limbs. The paralysis then gradually became more apparent, while involving the fore feet was always better seen in the hind feet.

To return to the human subject. As regards the reaction of the paralyzed muscles to electricity, the facts observed are very precise. The contractions produced by Faradic currents, whether applied to the muscle or nerve, decline in their intensity very much in the same proportion as the muscles lose their power of moving in answer to the Will, unless still paralysis has set in and the Faradic irritability is lost. With respect to the galvanic current, we must carefully distinguish the result of exciting the nerve from that produced by passing the current through muscle. In the first instance, the conditions closely resemble those produced by the Faradic current i.e. the contractility diminishes in proportion as the loss of motion power. When the galvanic current is applied to diseased muscles, however, there is a considerable difference in effect. There may be at first a very slight decrease of irritability, but immediately a great increase
Other place so that the muscles contract with abnormal power, when thus stimulated. This symptom is the more remarkable seeing that it has been frequently observed before any muscular weakness gave an indication of the approaching paralysis (Crb. 3). This state of heightened irritability remains for a long time present, but in those cases where no recovery of power takes place in the paralyzed muscles, it is gradually lost.

But besides this "quantitative" change in the relation of the paralyzed muscles to the peripheral current, there is also a difference in what may be called "quality". This point can only be made out by means of the Polar method, it may be roughly expressed by saying that the Anodic closing contraction increases in intensity until it becomes equal to the Kathodic closing contraction, whereas the reverse holds good as regards the opening current. The contraction at the negative pole increases until it becomes equal to that at the positive.

We have thus, in a certain type of paralysis what may be taken as a typical example of the "Degeneration Reaction".
So far there are two important conclusions to be drawn from clinical observation of cases of tabetic paralysis:

(1) The paralysis has a marked tendency to affect groups of muscles according to their function.

(2) The electrical conditions found in the paralyzed muscles are those which are typical of peripheral paralyses, although not with in one disease (essential paralysis of children) which is generally held to be of central origin.

In the great majority of instances the sensory nerves are also involved in the diseased process, though (in spite of Mononard's assertion 32 to the contrary), cases certainly do occur in which no changes in sensation or sensibility can be detected. The most usual condition met with is anaesthesia. Rosenfeld 9 has observed analgesia, i.e. the same writer states that the power of perceiving heat may remain while all other forms of sensibility are lost. Various neuralgic symptoms are also present in Lead Poisoning, 7 it may be remarked that these various symptoms are not confined to the paralyzed portions of the body, but distribute themselves in an apparently irregular fashion over the
Gubler seems to have been the first to call attention to a curious phenomenon which is occasionally manifested in such cases in connection with the extensor tendons of the forearm and hand. The lesion only develops itself when the paralysis is very pronounced, and consists in a transfiguration over the metacarpal bones, usually the second, third, or fourth. As a rule there is no change in the skin or subcutaneous tissue, but the sheaths of the tendons involved are thickened, the tendons themselves swollen and spindle-shaped. There is no exudation in the synovial cavity. This condition, which has since been frequently observed, was ascribed by Gubler to a strained position in which the tendons lay, or to trophic changes produced in the course of the malady. It has since been shown, by Touraine and others, that a similar swelling may be observed in certain cases of ordinary hemiplegia of cerebral origin, as well as in Traumatic Paralysis (Erb).
described by many writers (Boullande, Renaut, Lancereaux, Gombault). Unless the disease has lasted for some time there is but little change in the macroscopic character of the affected muscles, but after a long paralysis they are wasted, and later than normal. When examined with the microscope the transverse striæ are seen to be very indistinct, or to have disappeared. The nuclei of the sarcocylinder are present in increased numbers, the connective tissue is also proportionately increased. The nerve supplying the paralyzed muscles does not appear to have been examined with care during the earlier stages of the affection, but when the disease was well advanced many observers (Westphal, Mayor, Lancereaux, Gombault) have recorded the well-marked degeneration which was present. There was found nuclear proliferation & increase of connective tissue, with breaking up or disappearance of the axis cylinder (Gombault in particular mentions a case in which he found this degeneration strongly marked in the nerve, while the nerve root & spinal cord remained to all appearance healthy. The observations of Westphal are however the most interesting as he was able to convince himself that in the radial nerve of a patient.
who died suddenly during recovery from lead paralyzis, there were present fibres which had all the characters of the regenerated nerve fibres described by Remak.

On three occasions (in X, X, XI) the sciatic nerves, of rabbit, in whom paralysis of the hind legs had occurred, were carefully examined with the microscope after being stained with acetic acid, in no part of their course was any trace of degeneration seen.

In the same animals, sections of the spinal cord at various levels showed nothing abnormal; so far as I am aware, no pathological appearance has ever been shown to exist in the cord in cases of lead poisoning. (Bourlière, on one occasion, noticed a deposit of connection, but, on microscopic examination, he failed to find any abnormality.)

In considering the various theories which have been founded on these facts we are first of all confronted with the opinion that the cause of the Paralyzis lies in the muscular fibres themselves (Heide 39; Genexow 40) or in the conditions of their blood supply (Hetzig 41; Rinseinkel 42).

Such a theory appears to be entirely at variance with the clinical facts and is need hardly be discussed at length.
The cause of the paralysis must lie, then, in some part of the nervous system. It is clear that the poison may attack one or more of three situations, (1) the terminal nerve-endings in the affected muscles, (2) the nerves in their course, (3) the central ganglia of the nervous system which.

The pathological conditions which affect the end-plates of motor nerves in muscle are so entirely unknown, that it is not surprising that no facts bearing on this point have as yet been obtained. No writers have referred to the subject (with the exception of a doubtful indication given by Valpian), and it is merely alleged to here that the possibility of some such explanation of salverine paralysis may not be entirely forgotten.

The degenerative change in the radial nerve which appears undoubtedly to occur in certain cases of Lead paralysis, has led some writers to look upon this lesion as the primary cause of the paralysis. Another argument in favour of such a view may found in the relation of the affected muscles to the sympathetic current, which is admitted to be the same as that found in peripheral paralysis the result of traumatic injury of the radial nerve.

The observation of Gombault, already referred to
would seem to indicate that, the lesion of the radial nerve was proceeding from the periphery towards the spinal cord, & it must be remembered that in whatever manner the paralysis was produced, degeneration is likely to take place in the nerve & in that portion of the spinal cord which previously regulated the movements in the affected muscles, just as Bulpian has shown) the nerve & cord are subject to a certain amount of atrophic change after the amputation of a limb.

Without giving any undue weight to the observations, recorded in this paper, where the nerves were in all appearance healthy, it may at least be urged that before attributing tabesque paralysis to the degeneration of the radial nerve we must be put in possession of the results of a much more extended series of observations than have yet been made.

Now, as will be immediately shown, is the "degeneration reaction" strictly confined to peripheral paralysis; & finally, the involvement of muscles in respect to their function would incline us to look for some cause other than a mere lesion of the radial nerve in its course.

The argument which appears to have had most weight with those who hold that the
cause of lead paralysis lies in the spinal cord, is the resemblance which this condition bears to the Essential Paralysis of Children. This analogy, which has been pointed out by various authors, has of late found an able advocate in The younger Romanes, but although the argument is a seductive one, it must not be allowed too much weight. The points of resemblance between the two diseases need not be fully detailed here; it is only necessary to point out that (1) the groups of muscles involved in the Essential Paralysis are often the same as those affected in Lead paralysis, and (2) the reaction of the muscles to electric currents is similar in the two conditions.

But while in the Essential Paralysis there has been found a lesion in the anterior horns of the grey matter of the spinal cord, to which the disease is usually thought to be due, no such anatomical change has been observed in Lead poisoning.

On the whole, however, the weight of evidence seems to incline towards the theory of there being a spinal cause for Saturnine Paralysis.

Before attempting to form any theory regarding the actual cause of the various phenomena which are met with in the course of Saturnine
Intoxication, let us frankly admit that the present state of our knowledge on the subject is not sufficiently ample to justify anything but very guarded statements. It appears nevertheless permissible to indicate, in what is perforce a very indefinite manner, the direction in which what facts we have point.

It would seem desirable to discard the habit of considering every symptom of the disease separately, or of attempting to assign a different cause to each one. Let us rather look at the malady in its entirety.

If we extend the theory which Weil 39, Rosenstein 40, and others have held in relation to eclampsia, viz. that lead has a specific action on the smooth muscular fibre of the blood vessels, we can imagine that such irritation would be capable of causing an anaemic condition in certain regions of the spinal cord, and so leading to the various symptoms of paralyses, neuralgia, anaesthesia, &c. Thus poison might attack the smooth muscular fibre of the intestines and cause colic (by the mere strain of which might be due the increased arterial tension), by the contraction of the cerebral arteries, so produced, might be due the eclamptic attacks, and finally the same condition in the epigastric arteries generally. Throughout the body would give rise to the heightened arterial tension which is sometimes
met with entirely independently of Colic.

Again, (to give a theory which appears to recommend itself more than the last), we may imagine that the metal has some specific action on those nervous tissues contained in the Medulla Oblongata and Spinal cord which govern the vasomotor nerves of the body, producing thereby changes in the calibre of the blood vessels of various organs. Such vasomotor changes taking place in certain regions of the anterior horns of the spinal cord might be credited with the various paralytic, neuralgic and anaesthetic symptoms already referred to.

Possibly changes might be due to a certain proportion, at all events, of the eclampsic attacks, and it is not difficult to imagine that vasomotor changes in the blood vessels of theplexus which governs intestinal movements might result in the phenomena of Lead colic; it is whether such condition be due to constriction or relaxation of the intestine. Variations of rate and of tension in the radial pulse, even if in some cases caused in a reflex manner by the pain of the colic, might well be supposed to be frequently caused by such vasomotor changes.

With such theories, founded on a very inadequate number of facts, we must in the mean time be content, feeling that it is left to the
future to determine with certainty the fundamental cause for the very various phenomena which are seen in the course of Saturiine Poisoning.

J. Graham Brown, M.B. C.M.
Expt. X.

Albino rabbit. Weight. 1690 grammes.

Feb. 14. 2 p.m. Injections of 0.1 c.c. of 1:1000 silver nitrate into the external jugular vein. No immediate symptoms.

Feb. 15. 1 p.m. Urine 5 c.c. urine after injection. Albumen.

Feb. 19. Weight 1570 grammes. Subcutaneous injection of 1 c.c. of the above solution. The urine collected for the next 48 hours gives no albumen reaction.

Feb. 20. Injection repeated, as yesterday.

Feb. 22. Weight. 1470 grammes.


Injection of 1 c.c. of the above solution under the skin of the back.


Mar. 2. Weight 1370 grammes. There is marked stiffness of the hind legs. The animal cannot move very slowly.

March 5. Weight 1190 grammes. Both fore and hind legs are distinctly paralysed.

March 6. Weight 1080 grammes. Animal is now so completely paralysed in both fore and hind legs that he can neither walk nor stand. If laid on his side he is unable to raise himself.

March 7. Died during the night.

Post mortem appearances.

The liver, foreshortened, all sign indications of
The presence of lead.
The kidneys are much congested, their microscopic character, are those already indicated in connection with Exp. IX.
The sciatic nerves showed no trace of degeneration or sections through the spinal cord, after careful hardening, were of normal appearance.

Experiment XI

Rabbit. Weight 1480 grams.
Feb. 20. 2.30 p.m. Injection into the external jugular vein of 0.25 C.C. of Liqu. Plumbi Sulph. (Brun. 7%) diluted to 2 C.C. with Ag. Bichlorid. The injection was made very slowly and regularly, and occupied from beginning to end about 10 minutes. At the end of the injection, convulsive symptoms began to manifest themselves, and the animal was at once removed from the “holder.”
A series of convulsions now took place, each lasting only a few seconds, but following each other with short intervals. This condition lasted about 8 minutes, and then all convulsive movements ceased. Here was now a complete paralysis of all the voluntary muscles. Respiration was unaffected. This paralysis gradually passed off (remaining longest in the fore leg) and at the end of 20 minutes the animal lead regained its normal condition.

Feb. 21st. Animal apparently well. Weight 1480. Only a few drops of urine have been passed, and they consist chiefly of blood. Microscope shows the
Presence of large numbers of blood corpuscles.
Feb. 23. Weight 1320.

Mar. 2. 1270. Subcutaneous injection of 10 cc. of the same solution.
Mar. 4. 1220.
Mar. 5. 1230. Tremor & Paralysis in both fore & hind legs.
Mar. 6. 1380. Paralysis seems to be more marked on the left than on the right side.
Mar. 8. 1220.
Mar. 11. 1200.
Mar. 12. 1250. Injection repeated (subcutaneous 10 cc.)
Mar. 15. Died during the night. Weight after death 950 grammes. Urine & feces during last week of life both contained lead.

Post Mortem.
Nervous cord & sciatic nerves both normal.
Kidneys showed the lesions already described.

Experiment XII
March 2. 1878. 11 a.m. Injection in the posterior lymphatic sac of 0.5 gr. Acetate of lead in 10 cc. distilled water. In the course of half an hour the animal became
sluggish would remain on its back if placed in this position without attempting to move. There was no paralysis. In the course of an hour these symptoms became more marked and the animal appeared to have lost all consciousness.

K. V. C. (The remainder of the experiment does not concern us here.)

Experiment XIII. Prof.

March 25, 1878.

Tongue fastened out in the usual manner for microscopic examination.

1:15 p.m. Injection of about 1 drop of a saturated solution of acetate of lead into the thin of the tongue. An opaque white precipitate at once formed.

1:25 p.m. Inj. into posterior lymphatics of 0.5 c.c. strong sulphuretted hydrogen water. In the course of 1 minute the sputum of albuminoid in the tongue became brownish and gradually deepened. The black colour spread far some distance along the sheath of the vessel.
A list of the chief references given in the text.

The necessity for writing this Thesis in Berlin, has prevented me from getting access to more than a very small number of English works. This want is perhaps the less to be regretted since British and American Authors have almost entirely confined their attention to the clinical aspect of Lead-Poisoning.

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