Dr. Anderson Stark's Phases. Nickel and Cobalt.
NICKEL and COBALT

their

PHYSIOLOGICAL ACTION on the ANIMAL ORGANISM.

An Experimental Study) mainly) of their

TOXICOLOGY.

Presented to the University of Edinburgh
as a Thesis for the degree Medicinae Doctor
by
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Assistant to the Professor of Institutes of Medicine.

[1882]
Nickel.

The investigations, the results of which are contained in the following pages, were carried on during the winter 1880-81 and autumn of 1881 in the Pharmacological Laboratory of the University of Strassburg i. C. where a series of researches on the physiological actions of the metals on the animal organism had already been carried out. These metals were lead, platinum, mercury, antimony, tin, and iron. Bearing in mind how closely nickel & cobalt have always been associated with iron by materia-medica, chiefly because of their close chemical relationship, but doubtless also because there was no definite knowledge to the contrary, it naturally became a matter of interest and importance to test the soundness of this assumption experimentally.

To Professor Oswald Schmiedeberg
I am greatly indebted for the suggestion...
Nickel.

That I should take up the subject, and for his kindly encouragement during the carrying on of what has proved a long and tedious work.

The physiological action of the nickel compounds has hardly at all been studied, partly doubtless because of a tacit assumption on the part of pharmacologists that they acted to a great extent like iron compounds, and consequently even references to the action of nickel compounds are few and sparse in medico-scientific literature: they are the following:

Dr. G. Fuchs performed the following experiments—referred to by Buchner in 1827.

1) 10 grains crystallized sulphate of nickel injected into a dog's stomach produced only repeated vomiting, and as did 20 grains given 2 days later.

2) 10 grains given to a rabbit had no perceptible effect, but 20 grains killed the rabbit in a few hours with con-
Nickel

ulcers, and post mortem the gastric mucosa at the cardia was found covered with blackish-red spots.

3) 10 grams in water solution injected into the jugular vein of a small dog killed it immediately. The dissection was at once performed and the excitability of the cardiac muscle found to be completely abolished, on both sides was much fluid blood.

4) 5 grams of the same salt injected into the jugular vein, caused in half a minute vomiting which was repeated from time to time. Later diarrhoea appeared, and now only mucous fluid was passed. Even the dog feebly moved and lay motionless. In a few hours it began to recover; it remained dull and ill 4 days long, the apetite weak and short. The dog was freshly emaciated, and on the 14th day the eyes were covered
Nickel

with a purulent fluid. On the 6th day it was well again.
538-440 grains of the sulphate laid in the subcutaneous tissue of the neck of dogs, were absorbed without vomiting or other remarkable symptoms.

Thus (says Buchner) we see that the nickel salt only then is particularly dangerous, and by cardiac paralysis rapidly fatal, when it is injected into the vascular system, but that also by way of the stomach it may be fatal, death being accompanied by convulsions.

Orfella (op. cit. 15) merely quotes these experiments of Gmelin.

Hussmanns (op. cit. 17) says that the nickel and cobalt salts agree in their action with the chloride of manganese, and with potassium manganate and permanganate. In acute poisoning with 1-3 drms of the sulphate he says, there is said to be irritation and corrosion of the intestine, and death with
Nickel

Nausea and convulsions: also great secretion of bile.

Parrandent (cf. p. 19 + 20) assuring that the iron group of metals will have similar physiological actions, proceeds to prescribe manganese, nickel and even chromium in cases where iron is very generally used e.g. anaemia, menorrhagia, amenorrhoea, and hæmothoea and has seen beneficial results follow.

Buchheim (cf. p. 21) says that small doses of nickel and cobalt salts introduced into the alimentary canal do not induce symptoms of poisoning, but that with regard to their action in the blood, we do not possess as yet sufficiently exact knowledge.

Pigey (cf. p. 24) does not separate the actions of the nitrates of nickel and cobalt, but found in acute cases stupor, action lowered, temperature, the heart's action and peristalsis slower and weaker, pupils dilated. In chronic cases, emaciation, urine increased 3–4 times, dark brown, bring when cool, etc.
Nickel.

may exceed 1049, may contain albumen and hyaline coats. The first heart first is slowed then ceases to beat. In the dog the pulse first is accelerated and the blood pressure rises, then the pulse slows, the blood pressure falls, and the heart ceases to beat. This is by a purely local action affecting its muscle and its automatic ganglia. An affection of the vagi or accelerating fibres was not observed. The haemocytes swell up, lose their pigment and become transparent sacs, and in some they may fall to pieces. Simpson (p. 267) used nickel sulphate, 1-2 grms, as a gentle metallic tonic: found doses to produce sickness and nausea. believed nickel and manganere to correspond in their action with iron that these three metals might be substituted the one for the other. He found nickel completely successful in a case of severe periodic headache where quinine and other medicines had failed, and thought that he had seen it beneficial in chlorosis and amenorrhoea.
Nickel

Palmer (Op. Cit. 18) used sulphate of nickel as a sedative in painful affections, e.g. neuralgia, or as a specific where opium was not tolerated, and always successfully. Its use is not followed by disagreeable sensations nor by alimentary derangement.

As is well known many simple salts of the metals have an acid reaction in watery solution and have a strong affinity for the albumin of the tissues which they may coagulate (although in deed coagulation is not necessary for the destruction of the constitution of the tissues. [Hermann Op. Cit. 257] and thus locally destroy tissue while little of the metallic compound is really absorbed into the system generally. Thus it is that many so-called "acute metallic poisonings" are really not specific, but are simply the results of
The local action of caustic substances.

In order to obtain the general action of a metallic oxide, the combination in which it is administered,

1. Should be readily soluble in water, media, the solution neutral or just slightly alkaline.
2. Should not coagulate protein substances.
3. Should not be precipitated by solutions of the alkalies or of the alkaline carbonates.
4. Must not contain any active constituent other than the metallic oxide in question.
5. Locally it must not excite more than any other soluble, and pharmaceutically indifferent salt.

Many efforts have lately been made to produce preparations satisfying these conditions e.g., double salts of mineral acids and co-


odium with zinc, with copper, with platinum, with lead; then also compounds of the me-

tallie oxide with organic bodies, such as mercuric oxide with hyoscine, arsenic and Alum; first prepared by Peccei, fer-

bic oxide with triethyl acetate (Burt) ---

ferric oxide as ferric cadmium double tartrate; various oxides with peptone, and so on.
Nickel.

Some of these are good, some are not. e.g. lead triethyl acetate has a distinct action of its own wherein it acts as a complete compound only after some time it is broken up and then the lead oxide action commences.

In my first experiments, I used the double salt of sodium and nickelous oxide but found this unsuitable since it can be preserved in solution only if it be made acid or strongly alkaline. Then I tried the double salt made by dissolving nickelous carbonate in solution of pyrophosphate of soda, but this was too weak a solution and as I afterwards found was strongly active from its pyrophosphoric acid. Then a solution of simple nickelous citrate rendered alkaline with caustic soda also soon gave a rich precipitate. Finally I found the compound which I have used in my experiments and which satisfies completely all the before mentioned conditions. It was first prepared by Holdt as follows: Neutralize two parts of crystallized citric acid in syrupy solution
Nickel

with strong caustic soda solution and then add one part more of the acid, saturate this solution, gently warming then boiling it, with freshly precipitated and thoroughly washed nickelous carbonate. Let it cool and then filter. The filtrate is of a beautiful apple-green color, forms a glass on its evaporation, and may contain more than 10% of nickelous oxide. It is perfectly stable and may be administered in all the modes: mixed with blood serum no coagulation results and no destruction of the blood corpuscles is observed.

I have found this combination suitable also for the administration of iron, manganese and cobalt.

The chemicals used were obtained from Merck in Darmstadt, were always tested by the March method for arsenie, and always found to be arsenie-free.

The dose is always reckoned as "Nickelous oxide per kilogram" animal.

Post-mortem examinations were made in all cases. Frogs, fish, pheons, rats, Germa pigs, rabbits, cats and dogs were the
Experiments on Frogs.

A description of the general action of the salt—

The action is best seen when a large dose is injected subcutaneously into the dorsal lymph sac, but the phenomena are seen long before all the dose is absorbed. By the large dose the needful tension of the poison is sooner reached. First the colour of the skin all over the body becomes darker and more uniformly coloured and not unfrequently there is great production of a white froth, like a soap lather, all over the integument. Hereupon follows an interval, often of about 20 minutes, during which the frog sits quite quietly with the eyes retracted and shut. If it be injected now, it moves but in a clumsy manner, for the fore limbs seem weak, and the hind legs are drawn up in a peculiar fashion - the hind is altogether too much drawn up, the thigh is so pinioned up against the body as to lie on the dorsal aspect of
Nickel

The animal side, and the leg is as much flexed that the foot lies on the animal's back, quite internal to the plane of the thigh. Soon some fibrillar twitchings are observed in the muscles of the abdominal walls, then feeble twitchings of the flexors and muscles of the sole limbs generally. Lastly the toes are seen to twitch and then the muscles of the hind limbs generally. These twitchings become more and more pronounced and are followed by distinct oraments, and most often the mouth is opened widely and spasmodically.

In this stage the condition is outwardly at least, not unlike that produced by picrotoxin. Between the cramps the twitchings persist. In a short time and suddenly true and absolutely tonic attacks supervene in which sometimes impropothons, sometimes opisthontes in the more marked: now the outward appearance of the condition is that of strychnine poisoning, and even good pharmacologists have not been able to distinguish the two conditions.

The tonic tonic attacks now cease and a
Nichel

Superscription of the animal, set in
In this condition either it will retain
the dorsal position indefinitely long, or if
it tries to turn round it cannot do so,
making only feeble and shamig attempts.
Seemingly a voluntary motor paresis has
come on, while the reflex motion called
for by percussing the toes is decidedly
increased. The respiratory movements
of the pharyngeal floor are extremely ir-
regular. The paresis becomes complete
paralytic, the heart beats more slowly and
more feebly, the respiratory movements cease
altogether and death gradually and unpercep-
tibly supervenes.

Post mortem examination - rigor mortis;
at most a slight congestion of intestinal
tract; heart with auricles dilated by dark
blood, ventricles mostly small, pale and
semi-contracted. For some time after death
the nerve trunks and muscles react to the
paradice current, and other stimuli.
Records

of some experiments on frogs.

Ranae Temporariae

Each with 0.050 \( \text{KCl} \) per kg., frog subcutaneously.

Ex. 1. Male: weight = 45.0 and a Gravid female wt. 70.0

Jan. 14th Injection.

22nd They have both been examined and reported on from day to day, but having never shown noteworthy symptoms are killed to prevent confusion.

Ranae Temporariae

Each with 0.066 \( \text{KCl} \) per kg., frog subcutaneously.

Ex. 3. Male wt. 49.0

Gravid Female wt. 55.0

Jan. 14th Nickel solution injected under the dorsal integument.

Jan. 17th. To day the first manifestation of symptoms viz.: legs a little extended and weak and incoordinated on movement. 10th. Still affected, will lie on its back when so placed but can turn round. Seems stupefied


Jan. 14th. Symptoms now end slightly marked.

15th. Totally apparently dying.

17th. Found dead and stiff.

The slight congestion of the lungs.
Nickel.

Ranae Temporariae.

Each with 100 CuO per kilo foot subcutaneously.

Ex. 5 Male Wt. = 37.0  6 Gland Female Wt. = 80.0

Jan. 15 Injection of nickel solution under the dorsal integument.

Both are paralized show incoordinated movements particularly of the hind leg, can walk but not jump, nor can they turn round when laid on their backs, both are stupified, and male more gravely affected than female.

10th. Can now turn round from their backs.

10th. Both walk very well, but do not yet both will lie on their backs when on being molested readily turn round.

14th. Apparently almost quite recovered.

15th. Male has slightly affected.

15th. Female very weak and symptoms.

18th. Neuritic normal but still come apparently dying.

20th. Only come drawing up of the legs most noticeable.

Feb. 1st. Pretty normal now though still a little of the nickel attitude.

12th. Normal. Used for other experiments.

Ranae Temporariae.

Each with 125 CuO per kilo. foot subcutaneously.

Ex. 7 Male Wt. = 46.0  8 Male Wt. = 30.0
Jan 10th. Injection under dorsal integument. A little of the solution escaped from the smaller foot.

11th. Dark in colour, lies on its belly. 11th. Same symptoms as other paralysed, with difficulty turns round though less marked from its back

15th. Larger still a little affected. 15th. Smaller apparently normal

19th. Both greatly affected but still can turn round from dorsal position

20th. Both somewhat recovered but movements incoordinated especially in the smaller, fore limbs paralysed

21st. Both now show a certain slowness of movements.

23rd. Reflex excitability begins to be increased

25th. Both lie in the cage with their legs spread out as if they were dead, and yet on stimulation pull themselves together, walk, hop and can turn round from their backs. Fore limbs paralysed so that the breast lies on the floor of the cage, movements inco-ordinate.

29th. The larger in the same condition. 29th. Reflex excitability distinctly increased

30th. Larger found dead. P.M. thoracic pathological, ventricle strongly contracted

31st. Smaller found dead. P.M. Ventricle moderately contracted, doubtful congestion of intestinal mucosa.
Ranae Temporariae

1. Each with 100 ml of peptone free substrate

Male w. 40.0
Female w. 60.0

9th. Injection under dorsal integument.

5th. Both of a dark colour, lie on their bellies, move and flutter. On being molested they draw up their legs and perform incoordinated movements. Can still turn round from dorsal position.

6th. Both greatly affected, movements incoordinated, sounds produced by percussion over the medulla oblongata. Both easily exhausted and can no longer turn round from the dorsal posture.

16th. Somewhat recovered.

7th. Both can now turn round from dorsal posture.
8th. Neither can now turn round.

Male apparently dying. Pulse greatly slowed, reflexes still present, but incoordination well marked.

9th. Both in the same condition.

10th. Both found dead this morning.

P. M. Nothing noteworthy.
December 18th. Injection. All became of a deeper colour where the dose is large; the respiratory movements of the pharyngeal floor have ceased and they are motionless with the eyes retracted, sometimes showing spasmodic movements as if they would vomit. Looking into the pharynx, one sees a mass of bloody froth—this sometimes being expectorated. Where the dose is smaller voluntary movements are sluggish, imperfect and incoordinated, but the reflex excitability remains normal.


20th. Those that remain pretty much in the same condition as before, but the colour is markedly darker, the pupils more perceptible. On pinching also, a scarp of the tail is produced.

21st. The female R. Escul. found dead. P.M. Still some bloody froth in the pharynx, and throughout the whole intestinal canal. There seemed doubtful extravasations were seen in the mesentery. The nerve endings were merely touched during the dissection muscular contraction.
Nickel

followed. Ventral of heart pale and contracted.

12 Dec. A leaf is taken from male. S. Temp. and the muscle
work of its gastrocnemius found to be only 0.660 gram
millimetre - a very small figure, probably accounted for
by the frog being in a dying condition. For special exper-
iments show that nickel has not such a diminishing
effect on muscle work.

The female S. Temp. gradually recovers or at least
lives some time longer without showing anything fur-
ther noteworthy, and so is killed to prevent confusion.

**Experiments**

To ascertain the effect of nickel oxide on the
"work of muscle"

Considering the interesting results obtained
by Hornack (Op. Cit. 3) as to the action of lead,
of copper and of zinc on striped muscle it became
important to test nickel in this respect. The
experiments were carried out with the Kroenecker
Geigel apparatus and with Reuss's modified
Dick's Arbeiteranmesser (Op. Cit. 1622). The method
pursued is set forth by Dr. Rudolph Robert (Op. Cit. 4)
but shortly it is as follows: a gastrocnemius
of the normal frog is cut out, and mounted as that
Nigeria

It may be briefly stated, always by the same strength of Faradic shock, at regular intervals of time, contract and part always the same weight, marking an ordinate on the squared paper, on a vertical cylinder. Thus, when the muscle no longer raises the lever, the combined height of the ordinates in millimeters multiplied by the number of frammeces raised would express the work of the muscle in frammeces millimeters.

No loss of blood is sustained by the frog; the temperature of the room is kept as nearly as possible constant, the frog is poisoned, and when the desired stage of intoxication arrives, the second frammecum is prepared in the same manner, stimulated by the same strength of shock at the same intervals of time as in the case of the normal muscle and thus its work is ascertained. If the muscles be both normal they yield the same results, if both be poisoned they still yield practically the same results so that the operation, and the loss of time is found experimentally not to bias seriously the results, and thus to test first the normal, then the poisoned muscle of the same frog is justified.
Nickel.

Kabler (Op. Cit. 5) and von Mehnigh (Op. Cit. 6) stated that in animals about to die of platinum and of mercury poisoning, respectively, muscular excitability was diminished, but by the Kronecker-Kiesel method a diminution may be detected much earlier than they found by the Dubois-Raymond Coel. It may be found thus in animals that eventually do not die of these poisons. Similar results are given for arsenic by Laser (Op. Cit. 7) and for antimony by Solowitsch (Op. Cit. 8). It may be here stated that simple inspection in these cases is absolutely worthless, the absolute worth of the muscle must be measured.

I give the records of some of the experiments as examples. They may be found in the following table.

Table of Muscle work. Experiments on Brown Reptile

<table>
<thead>
<tr>
<th>No.</th>
<th>Condition of muscle</th>
<th>Number of volts</th>
<th>Length in centimeters</th>
<th>400 500 1000</th>
<th>20 40 80</th>
<th>20.5 14 6.6</th>
<th>42.9 8.9 27.4</th>
<th>27.6 7.8 6.7</th>
<th>31.2 18 38</th>
<th>22.5 9.5 18.5</th>
<th>5.2 5.6 3.1</th>
<th>23.5 4.8 4.2</th>
<th>28.1 4 2.8</th>
<th>20.0 3.8 2.8</th>
<th>3.2 2.5 2.0</th>
<th>22.5 1.8 1.6</th>
<th>28.5 1.3 1.0</th>
<th>25.0 1.3 0.8</th>
<th>22.5 1.0 0.7</th>
<th>20.0 0.8 0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>80</td>
<td>30</td>
<td>10</td>
<td>2</td>
<td>20.5</td>
<td>4.6</td>
<td>49.2</td>
<td>25.4</td>
<td>4.6</td>
<td>31.2</td>
<td>4.9</td>
<td>27.2</td>
<td>7.8</td>
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<td>6.7</td>
<td>23.5</td>
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<td>2</td>
<td>after 72 hours</td>
<td>80</td>
<td>30</td>
<td>10</td>
<td>2</td>
<td>12.0</td>
<td>4.8</td>
<td>49.2</td>
<td>25.4</td>
<td>4.6</td>
<td>31.2</td>
<td>4.9</td>
<td>27.2</td>
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<td>3</td>
<td>after 161 hours</td>
<td>80</td>
<td>30</td>
<td>10</td>
<td>2</td>
<td>21.0</td>
<td>5.6</td>
<td>31.2</td>
<td>25.4</td>
<td>4.6</td>
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<td>4</td>
<td>after 161 hours</td>
<td>80</td>
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<td>49.2</td>
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<td>5</td>
<td>after 161 hours</td>
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<td>28.1</td>
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</tbody>
</table>
Nickel

In Nos. 1 and 2 the poisoned muscle actually yields more than the normal, that is because of the increased temperature. Compared with No. 3 there is diminution of work by 22% in No. 4, but then the temperature has fallen 10°C and the frog has been poisoned 24 hours longer. The diminution in No. 5 is 41% but the temperature is down 11°C and the frog has been poisoned 78 hours longer. In No. 6 the diminution again is 22% but while the frog is heavier the temperature is lower and as compared with No. 3 while the frog is only slightly heavier the temperature is 1°C. lower and the diminution of 22% is readily accounted for.

Considering the numerous factors that influence muscle work (Roberts, Op. Cit.) we have in these experiments a wonderful agreement showing that nickel has no influence whatsoever on the muscle substance.

Thus it differs from platinum, arsenic, antimony and mercury from lead and from iron which in small doses increases muscle work, in large doses diminishes it. (Roberts, Op. Cit. 4)
Muscle Work Experiment No. 1 Group I. II.

M. Temporaria

Weight 190

11:30 a.m. 1 cc. of 11% KI solution is injected and
another 5 cc. then

12:20 Another 10 cc. in all 0.050 KI in 10 cc. per tilo frag.

The reflex excitability of the fish is now greatly diminished and the capacity condition of the nitric acid


<table>
<thead>
<tr>
<th>Time</th>
<th>Normal Gastrocnemius</th>
<th>Nickelized Gastrocnemius</th>
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<tbody>
<tr>
<td>11:40</td>
<td>20.10</td>
<td>12.35 7.8 mm.</td>
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<tr>
<td>11:42</td>
<td>19.80</td>
<td>12.45 7.3 mm.</td>
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<td>11:44</td>
<td>19.20</td>
<td>20.50 5.4 mm.</td>
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<tr>
<td>11:46</td>
<td>19.20</td>
<td>12.55 3.8 mm.</td>
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<tr>
<td>11:48</td>
<td>18.90</td>
<td>1.5 1.3 mm.</td>
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<tr>
<td>11:50</td>
<td>18.60</td>
<td>1.10 1.9 mm.</td>
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<tr>
<td>11:52</td>
<td>18.00</td>
<td>1.15 4</td>
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<tr>
<td>11:54</td>
<td>18.00</td>
<td>1.20 0</td>
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<tr>
<td>11:56</td>
<td>17.40</td>
<td>17.675.0 gram. mm.</td>
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<td>11:58</td>
<td>17.50</td>
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<tr>
<td>15:00</td>
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</tbody>
</table>

Results

In nickel case

Distance of the coil = 80 mm.

Load = 30 grammes

Load was raised 10 times per minute.

In the normal case 20.5 C.

Duration of experiment = 149 minutes

Work done = 25.440 gram. mm. (3) Greatest height 7.8

In the normal case

Duration of experiment = 145 minutes

Work done = 17.675 gram. mm. (3) Greatest height 7.8
Nickel

The nickelised muscle being jet-warmed in the sun's rays which metaniac had reached, it and chance on it a little must have had more active chemical changes than the former, and this would not only account for the lesser duration of its work, but also for the greater amount of work the former is quite evident, the latter is not, but becomes so as we consider that the muscle warmed from the beginning in a case parallel with one that is warmed, then it is almost exhausted. Such energy is evolved.

The distance of the coils of course controlled the strength of the current passed and so was kept constant. The battery was a dynamo.

The leverage of the pen was due to the necessity for having the muscle come distance from the cylinder so that the lever was now one of the 3rd order and the power was applied midway between fulcrum and weight.

No. 2. Muscular Work Experiment. Face 5.

Rana Temporaria. Male. Weight 36.0 (7.2 hours after injection of 0.05 cc. 139 Rie. per kilo. fog.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Height (mm)</th>
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<tbody>
<tr>
<td>0.00</td>
<td>5.0</td>
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<tr>
<td>0.10</td>
<td>5.5</td>
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<tr>
<td>0.20</td>
<td>5.9</td>
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<tr>
<td>0.30</td>
<td>6.5</td>
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<tr>
<td>0.40</td>
<td>6.1</td>
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<tr>
<td>0.50</td>
<td>6.4</td>
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<tr>
<td>0.60</td>
<td>6.0</td>
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<tr>
<td>0.70</td>
<td>5.9</td>
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<tr>
<td>0.80</td>
<td>5.7</td>
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<tr>
<td>0.90</td>
<td>5.5</td>
</tr>
</tbody>
</table>

45 m = 56.5 x 15 x 5 x 20 + 2 = 27.335 centimeter millimeters.
Nickel

Conditions
1. Distance of coil = 50 mm.
2. Load = 20 kgf.
3. Load was raised 15 times per second.
4. Pen's leverage as before.
5. Temperature = 12.5°C

Results
1. Duration of experiment = 115 minutes.
2. Work done = 37,225.0 gramme millimiches.
3. Greatest height = 6.4 mm.

Muscular Work Experiment. Specimen VII.
Rana Temporaria

Dec 30th

<table>
<thead>
<tr>
<th>Time</th>
<th>Height</th>
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<tr>
<td>11.5</td>
<td>5.2</td>
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<tr>
<td>12</td>
<td>5.9</td>
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<td>15</td>
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<td>20</td>
<td>6.1</td>
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<td>25</td>
<td>5.9</td>
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<td>30</td>
<td>4.0</td>
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<td>35</td>
<td>2.3</td>
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<tr>
<td>50</td>
<td>0.2</td>
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<tr>
<td>53</td>
<td>0.0</td>
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</tbody>
</table>

48 min. $37.4 \times 15 \times 5 \times 20 \div 2 = 28,050$ gramme millimiches.

Conditions
1. Same as before.
2. Temperature now is 28°C (before it was 12.5°C).

Results
1. Duration of experiment = 48 minutes (before was 45).
2. Work done = 28,050 gramme millimiches (before = 27,225.0).
3. Greatest height = 6.1 mm. (before = 6.4).
Nickel

E 18. No. 5 Muscular Work Experiment, Sacrifice III.
Rana Temporaria Male, weight 31.0 - 18 hours after injection subcutaneously of 0.05 % i.o = 161 per kilo. Proof.

Dec 25. Time | Height
--- | ---
10.10 | 4.6
15 | 5.5
20 | 5.6
25 | 5.6
30 | 5.6
35 | 5.6
40 | 4.9
45 | 2.3
50 | 1.5
55 | 0.9
11.00 | 0.5
11 | 0.0

55 min. $\frac{41.7 \times 15 \times 5 \times 20}{2} = 31.75.0$ gramme millimetres

Conditions
1. Distance of coils = 85 mm.
2. Load = 20 grammes
3. Load was raised 15 times per minute
4. Here also pull's leverage doubled the weight
5. Temperature 21°C

Results
1. Duration of experiment 55 minutes
2. Work done 31.75.0 gramme millimetres
3. Greatest height 15.6 mm

E 19.
Rana Temporaria Male, weight 35.5

Dec 25. Time | Height
--- | ---
12.5 | 5.6
10 | 7.0
15 | 7.2
20 | 6.6
23 | 6.2
25 | 6.0
30 | 6.0
35 | 0.0
40 | 0.0
45 | 0.0

40 mm. $\frac{35.8 \times 15 \times 5 \times 20}{2} = 26.850.0$ grammes millimetres

Conditions
1. Distance of coils = 80 mm.
2. Load 20 grammes
3. Load was raised 15 times per minute
4. Pull's leverage here also doubled weight
5. Temperature 20.0°C

Results
1. Duration of experiment 40 minutes
2. Work done 26,850.0 grammes
3. Greatest height 7.2 mm
Nickel

No. 5 Muscle-Work Experiment. Group II
Rana Temporaria Male Height 39.0

Dec. 26
Height
3.30 4.12
3.50 5.0
4.00 5.6
4.50 5.4
5.0 4.8
5.5 3.3
H.O. 2.1
5 1.0
10 0.3
13 0.0

43 min. \(31.8 \times 15 \times 5 \times 20 \div 2 = 23,850\) joules millimeters

Conditions
(1) Distance of coil 85 mm.
(2) Load 20 grams
(3) Load was raised 15 times per minute
(4) Penis leverage as before
(5) Temperature 10°C

Results
(1) Duration of experiment 42 minutes
(2) Work done 23,850 joules millimeters
(3) Greatest height 1.5 mm.

No. 6 Muscle-Work Experiment. Group II
Rana Temporaria Male No. 32.0

Dec. 27
Height
10.2 5.0
10.45 5.3
10.5 5.3
10.55 5.1
11.0 5.0
15 4.6
15 2.6
15 0.9
20 0.0

40 min. \(33.8 \times 15 \times 5 \times 20 \div 2 = 25,350\) joules millimeters

Conditions
(1) Distance of coil 85 mm.
(2) Load 20 grams
(3) Load was raised 15 times per minute
(4) Penis leverage doubled weight
(5) Temperature 17°C

Results
(1) Duration of experiment 40 minutes
(2) Work done 25,350 joules millimeters
(3) Greatest height 1.5 mm.
Nickel

Let me now analyze the chief symptoms, and first those connected with the Muscular System.

Muscular System—

A. The twitchings are distinctly "fibrillating" in character and might be due:
   (1) to the action of the nickel directly on the muscle or
   (2) indirectly on the muscle through the nervous system.

They are not the former, because:
   (a) they do not appear first where the poison has been injected.

   (b) they do not occur in a localized muscle even when it is bathed by the poison.

   (c) they always appear in the above-mentioned definite order.

   (d) they do not occur when the muscle is anaesthetized.

   (e) experiments with Kroemer's and Liebel's apparatus show that the excitability of the muscle is not increased.
Nickel

When their connection with the central nervous system is cut off, they no longer twitch spontaneously. They are due to the action of the nervous system because
(a) they appear in the definite order
(b) they do not appear if the nervous system be destroyed or paralysed.

These facts apply also to the explanation of the greater contractions—cramps and convulsions.

B. The paralysis is not muscular since
(a) the muscles are excitable long after death directly and indirectly through the nervous system
(b) the working power of the muscle is not diminished.
Nervous System

These symptoms might be due to affection of (1) the nerve endings in muscle (2) nerve fibres or (3) the motor centres in the spinal cord or brain.

They, or at least the contractions, are not due to affection of nerve endings in muscle because they cease on curarisation or when the nerve is cut, and if the frog be previously curarised or the nerve be cut before the poison is they never appear at all.

This proves also that they are not due to affection of the central nervous system. If, when the brain is laid bare and the spinae are present, we divide fore brain from mid brain then mid brain from hind brain then hind brain from spinal cord they still persist; if the spinal cord be severed from the medulla oblongata, the frog allowed to recover from the shock and then poisoned they still appear. If while they are present the spinal cord be destroyed the convulsion of the entire body during the process is extremely marked but when the cord is completely destroyed they have completely disappeared. Clearly then they are mainly, if not entirely, due to affection of the spinal cord. The excited condition of the spinal motor centres is probably followed by their
Nickel

paralysis certainly the nerve and muscle remain excitable by various stimuli for some time after death.

Whether or not there is any affection of the brain centres is doubtful. The peculiar attitude and the cramps in the early stage give one quite the impression of the action of picro-toxin or of centoxin, strychnin, digitalis or other poison of this group. Wurtemberg (Op. Cit. 9) has an excitation of the cramp centre (Cranumpcentrum) in the medulla oblongata. In this group, Bachm and Schleich (Op. Cit. 10) refer the salt of Barium that Wurtemberg takes exception to this.

Barium occurs very similar to nickel in its action on frog. It does not affect muscle but has seems to act chiefly on spinal cord and brain. It causes a peculiar attitude fibrillary twitches, crotchet tonic spasms followed by paralysis. Bachm and Schleich particularly in strong male specimens frog noticed a very reflex. They noticed in only one case with nickel though it has since been observed experiment only with weaker frog. These authors describe it to a simultaneous spasm of the muscles of the abdominal walls and glottis.
Nickel

the resulting sound being a shrill piercing cry
utterly unlike the usual sounds emitted by legs.

The peculiar attitude of Platinum is quite
different from the Nickel attitude for in the
former the thigh is brought away from the back,
the leg is bent at the knee, and hence the poles
are applied to each other, while in the latter
the thigh is actually nearer the back than normally.

Platinum (Kellers, Op. Cit. 5) causes a
similar train of symptoms but no attitude
is given here by Kellers, the muscle end-
nerve is affected although voluntary motion is suspen-
sed before this has become very marked.

The jerking and convulsions are said by
him to be similar to those caused by Digi-
talirrin and Cocaine.

Dr. Blake, (Op. Cit. 11) causes a state of
nervous and excitement followed by voluntary
motor paralysis and paralysias from central
nervous causes.

Dr. Geyer and Williams, (Op. Cit. 15)
cause slight excitement followed by paralysias.
Cobalt has (as I shall show in a work
to follow this one) a similar action though
Nickel.

Weaker than nickel.

These there are the in this connection most recent and most trustworthy accounts of the action of the metals examined under strict physiological condition, and so far nickel and estall may be taken along with barium, but all three may be separated from iron.

There is probably also a paroxysm of cerebral centres as is shown by the retention of the normal decubitis and the after-sensory step-faction and insensibility to tactile and other impressions.

Ranae Temporariae Male Wt. 46.0

Feb. 14th. 666 Dr. 0 per kilo first subcutaneously.

4.5 Injection of the solution was followed by rhabdomyolysis at the apex.

4.16 Pulse 60. Heart distinctly diminished in size and paler than normal.

4.20 In diastole only a part of the ventricle becomes dark, abdominal compression distends the heart again to the normal and it is now uniformly dark.

4.35 Well marked pulsations of the fore limbs. Heart-wrapping much reduced.

4.35 Heart: minimal exceptible.

4.35 Heart: minimal exceptible.

4.40 The pulse now no longer becomes dark in diastole, is pale and scarcely.

4.50 Pulse 54: small pulse with but little motion of atrium.

5.0 Pulse 44: spasm still well marked.

5.8 Superficial muscle action unvested from underneath the skin.

5.10 Heart a little larger. The respiratory movements have but been suspended.

7.0 Heart was found at a steady still medium size, pale do longer reaching the touch.

Post mortem. Nothing noteworthy.
Nickelet

Experiment

To localise the Nerve Action
Ranae Temporaliae.

(a) The sciatic nerve is prepared and divided, some few twitchings follow distally, but soon complete paralysis is established in left leg.

(b) A stout thread is carried round the upper part of the right thigh, beneath the skin but under the sciatic nerve so that when tied and pulled tight, all communication was cut off between the part distal to the ligature and the pass proximal to it.

(c) About 4 H. O. per kilo. of I. is injected subcutaneously when the spasms and traction supervene nothing of the kind is to be seen in distal part of left leg so that clearly the muscular contraction cannot arise from any direct action on either muscle, nerve ending in muscle, or on nerve trunk for to these of course the nickel had free access. Therefore it must be of central origin. During this stage the nerves axis is divided between the skull and the first vertebra, still the twitching continue. Therefore the spasms emanate from the spinal cord. The spinal cord is divided at the level of the 9th vertebra, and the upper part of the thigh is paralysed but the ankle joint still plays and ceases only when the lower
part of the spinal cord is destroyed.

This experiment was witnessed and my
results confirmed by Dr. Meyer and von Behrstedt.

This is clearly a sympathetic-like action.


Mar. 2d.

(a) The spinal cord of a male and of a female frog
are completely severed. The male loses a good deal
of blood, the female only a few drops.

(b) Today they are found quite recovered from the shock
but with the hind part of the body absolutely paralyzed.

(c) 0.1 cc. of frog's blood injected subcutaneously.

Swore than usual. The twitching appear in the hind legs
for they appear simultaneously with those of the ab-
dominal muscles and fore legs. In the hind legs they
are more violent than usual, and as usual, a
hernia does not fail to appear and conies
again and again till the spinal cord was destroyed,
when it ceases. While the cord was being de-
stroyed the tonus of the hind legs was very vio-

lent.

The action is clearly then one that
is directly on the spinal cord.
Experiment

To localize the Nerve Action

Ranae Temporariae

Pulse 61. The frog is first curarized, small doses being
given at intervals till the desired condition is
obtained. With the motor-nerve ending just paralyzed
3.53 1.800 cc 0 per kilo, frog injected under the arm of
the thigh. The whole of the muscles of the hind
leg are bathed in the solution but never a
 twitch is seen although the muscles remain perfectly
excitable.

Pulse 56.

It is clear that it cannot be a direct action
on muscles nor probably of the motor end of same
either, for they are just curarized and yet this
weak curarisation is not antagonized. For can it
well be on the sciatic nerve directly for this
doubtless also was bathed in the nickel solution.

Ranae Temporariae

This same experiment repeated with 1.000 cc 0 per
kilo, frog with same result.

Blood and Blood Vascular System

Unfortunately the reports of Ayrton (op.cit. 22)
metal.

Experiments do not distinguish between the effects of nickel and of cobalt, but this is of the least importance since I have never found any change in the corpuscles in acute cases, and as cobalt shows in my cobalt work, at any rate probably fallen in a previous article, when he says, they swell up, lose their pigmentation and become transparent, and in short, they even fall to pieces.

Then I mix a blood with any solution of nickel and cobalt; they cause no other change in the corpuscles than any indifferent salt would, and now we see that no coagulation is produced.

Then the heart is exposed, the pericardium being left unopened, it is seen to beat more and more slowly, to become dusky and smaller and pales and not to contract evenly throughout the extent of the ventricle, but the rhythm of auricular and ventricular contraction is never lost. When the abdomen is now compressed or when the foot is simply inverted, the heart swells up, filled with blood, and beats quite well, for a time at least.

Stroma does not disturbed this condition and digitalis excites its usual action on the heart. The various authors before mentioned say iron has not any effect on the first heart action.
Nickel makes it weak and bloodless from a nervous paralysis; mercury olivine it and makes it irregular and may cause that condition where two ventricular contractions precede one ventricular; barium has quite a digitalis like action; platinum affects the cardiac muscle less than it does the voluntary muscles.

I think it very probable that the heart muscle substance like the voluntary muscle substance is little if at all affected, and the effects of abdominal compression and inversion support that view for here we see that the heart can powerfully contract on the blood within it.

Probably there are two main factors at work viz. (1) a base motor paralysis especially of the abdominal blood vessels so that the blood pressure falling very low the heart is not nourished at all the more since the phrenic reflexes is diminished or suspended, and (2) a paralysis of the motor ganglia of the heart this being but a part of the general nervous paralysis.

Thus it is that the heart beats well for a time only on abdominal compression; the nerve energy of the ganglia is soon exhausted.

These are not the results of any
Heart Experiments.

Ranae Temporatiae

Male Wt. 42.0 | Female Wt. 70.0

Feb. 19th.
4.30 Heart laid bare Pulse 70 but ovip. Heart laid bare Pulse 70

to trigger up is excited but ovip. trigger up is excited

350 mli0 per kilo strf injected 357 mli0 per kilo strf injected

under skin of thigh, under skin of thigh.

Soon the heart begins to become smaller and pale, and to beat irregularly and languidly. But on crossing the leg centripetally or compressing the abdomen the heart is again distended, becomes dark in colour and beats powerfully and completely. Even this is not necessary for the same effect may be produced by simply inverting the frog, for the greater mass of blood in its body being below the position of the heart in so simple a manner the blood is made to agitate in the heart.
Heart Experiments - ed.

Feb. 18
7.16 Pulse 51 Heart still mischievous. 7.15 Pulse 67 Heart has now but not as much as a little recovered and apparently beats quite normally.

Feb. 19
11.0 Pulse 40 Still in this condition. 10.0 Found dead.
and behaves similarly under different conditions.

Pulse A2

3.0 Static. Iden.

7.0 Pulse 22. Drug apparently definite.]

28. Rana Temporaria. Male night 30.0

Feb. 19
With 1.0% 0.1% per kilo for injected subcutaneously.

4.35 Heart laid bare perconditum been tested. Pulse A1
4.36 Direction of the middle solution under the skin of the thighs now followed by fibrillar twitching at the feet.
4.38 Pulse 60. Viscerica small and pulse in asystole i.e. more intensely contracted.
4.39 Pulse 54
4.0 Pulse 52
4.05 Indications of twitching of the sole legs.
4.30 There fore leg twitchings are now well begin.
4.35 Pulse 42. Fore twitchings are now general.

4.45 Complete spasms now present. Heart begins to be sluggish in its movements after a few it gets large dark and stands still for a little then resumes to action as before.
4.46 Heart sluggish while there is an absolute torus of the legs.
4.48 Pulse 43 good regular and full, the tonic spasms are now less marked.
5.0 Rigidly of hind legs and complete opisthotonos.
5.10 All spastic contractions the respiratory movements slow and weak.
5.35 Heart is small, pale and sluggish and soon after almost stands still in a condition between asystole and diastole. Now no other movements to be seen throughout the body excepting a few feeble indications at rare intervals of the respiratory movements.

1.0 Heart beats only very seldom is dark in diastole. Proof evidently dying is killed before laboratory is closed.
Nickel

Feb. 26th
Rana Temporaria

5.0 Heart is laid bare and a short time afterwards namely pulse 58. Now the heart is bathed in nickel solution.
5.15 Sinus appear already in the abdominal muscles pulse much slower.
5.20 Twitchings are evident after a spasm of the body the heart in the diaphragm, and when it has commenced again the pulse is 38, the ventricle small and imperfectly filled.
5.45 General action still marked several fibrillary attacks have come before the last the pulse was 26 and the ventricle small. During and after the last the heart became great and well filled and the pulse rose to 32. The legs extended and stiff. (Note here the muscular contractions seem to raise the pressure and quicken the pulse rate at least there is no muscular toning of the heart.)
6.20 Pulse 42. Abdominal compression or total inversion causes the heart to swell up and beat well through an elastic as before.
6.30 Pulse 18! Heart well filled in the diaphragm somewhat irregular now it is killed.

Feb. 30th
Rana Temporaria

5.27 Pulse 48. Heart had been laid bare now some time is bathed in nickel solution.
5.40 Pulse 24. Heart still large, twitchings in abdominal walls and forelimbs the heart the thorax overfilled with blood.
6.0 General action still marked after an effort to free itself from the band the heart stops overfilled with blood.
7.30 Ventricle still smaller but acting well enough.
27th 11. Pulse 10, condition as before. After exposure to air externally increased so that it raises a slight tap on the table eather forth a scratch after several fibrillary regular tetanus supervenes. An exquisite stigmata-like action to hasten absorption from cellular tissues understanding at first why it is due to strychnine but I will them other wise digitalis than the usual action on the heart.

Mar. 12th
Absorption from Surface of Skin: A frog
11.0 Is painted over with the nickel solution and remain more or less worked with the whole day.
6.15 Paralyzed movements are not stimulated suffices the dorsal position for sometime. Is pulled up out of the back in the usual way
7.30 Paralysis more method.
9.0 Found dead.

C.M. nothing characteristic
Ex. 32. Equivalent of "Salt" Experiment

Rana Temporaria. Male 32.0 Female 30.0. Females 15

5.00 A solution of neutral citrate of soda replaced our acid solution of saltpetre and was then slowly injected into the animal. As soon as the injection was made, the animal immediately fell into a state of convulsive twitching of the muscles surrounding the cerebellum and spinal cord.

6.10 No symptoms yet. Dose repeated.

6.30 Now a much solution has been injected and the animal again falls into a state of convulsive twitching of the muscles surrounding the cerebellum and spinal cord.

6.45 Now a much solution has been injected and the animal falls into a state of convulsive twitching of the muscles surrounding the cerebellum and spinal cord.

Female found dead. P.M. Nothing characteristic.

Male still alive and beating its head of salt solution and without any symptoms whatever. It is killed.

Ex. 33. Experiments on Fish

They were taken from the Rhine. The natural dark blue color of the fish became remarkably lighter. Loss of power of equilibrating itself in the water followed, and then gave place to a paroxysm of voluntary motion, then paralysis and finally even the reflex respiratory movements of the gills ceased. The three experiments showed a well-marked gradation in severity of symptoms, according with the dose.

There was doubtless an affection of the central nervous system, together with gastric ulcerative affection, but the experiments are too few to permit much deduction from them. There is however no
Nickel

we shall see an entire agreement which what we
found in other animals.

None of the authors before referred to seem
to have experimented on fish.
Experiments on Pigeons

There are only four in number, but they nevertheless are enough to show that the action of nickel here is pretty much as in the mammal: there is first a dulness and stupor, then feebleness of the voluntary muscles, jerks of different sets of muscles, and unsteadiness of movement, then death supervenes quietly, as far as was noticed, a paralysin of the voluntary motor apparatus preceding it.

But more: After morphia, well-marked, blood normal, cardiac ventricles semi-contracted and pale; some congestion of the intestinal muscera.

Krausen experimented with lead on pigeons, and found the effects quite comparable to those in cases of rabbits and dogs.
Nickel

Pigeon Male 17 400.0 gr. with 0.40 Ni 0 per kilo. Pigeon subcutaneously.

10:00 First injection beneath the skin of the breast.
14:00 The animal stood still while the injection: had not shown anything positive or noteworthy.
16:00 Seem normal.

Ex 37.

Pigeon injection this time of 0.40 Ni 0 per kilo.
Pigeon subcutaneously.
16:10 Chick does not appear greatly affected, perhaps somewhat out of sorts.
17:00 Chick is dull and sleepy.
12:40 Was found this morning lying on its back with respiration heavy. All the organs of different parts of the body come from there to time cannot arise though he would like to. Eyes shut and sleepy.
12:00 Found dead lying on his back as if he had died quietly.

Post mortem examination:
Nothing pathological.

Ex 38.

Pigeon Young 17 2967 gr. with 0.70 Ni 0 per kilo. Pigeon subcutaneously.

1:00 Injection beneath skin of breast.
1:05 Contused and going to fall asleep, dull and stupid.
2:00 Home condition, quiet and spiritless.
4:00 Somewhat recovered.
9:00 Laboratory servant saw it now and found it as if intoxicated, could not walk steadily, swayed backward and forward alternately on its back and its tail. When pushed from the side it stood pretty firmly. Turned on its back it regained.

Aug
Nickel

de feet and was again unsteady.

Post-mortem examination.

After mort's well-marked, some con- 

An example of the intestinal mucosa. 

Piglet showed no pathological changes. 

Ex 39

Pigeon: old. Wt. 3.96 lbs. With 100 hi. 0 per kilo. 

Injection beneath pectoral muscle. 

Addore as if fight to sleep dull and stupid. 

Same condition.

Somewhat recovered.

Normal seemingly.

Free remained evidently normal. It now 

again received 100 per kilo. pigeon in same 

glass. It gradually becomes stupified 

and weak, and dies soon.

Post-mortem examination.

Nothing notably pathological.
Experiments on Guinea Pigs

From a difficulty in obtaining these animals only two could be performed. The only symptoms noted were either apathy or inability to move briskly. Nothing pathological was found.

Guinea Pig I. (Height 436.0) With 0.15% NiO per kilo, Guinea Pig subcutaneously

2:45...somewhat out of sorts. Pierced with one needle but it does not move itself off

11:40...now gradually recovers and appears quite normal.

Guinea Pig II. (Height 460.0) With 0.25% NiO per kilo, Guinea Pig subcutaneously

11:10...injection

12:0...appears somewhat improved but still not much.

3:0...same condition.

5:0...almost completely recovered.

6:0...now normal, apparently completely well again.

7:00...Found dead this morning.

C.M. Examination. Nothing pathological.

Ammonium sulphide applied to the kidneys. Section with Valentine's knife. Showed many convoluted tubules choked with nickel sulphide.

Experiments on Rats

The symptoms manifested after subcutaneous injection of the nickel salts are almost entirely nervous. They became less noisy, more easily excited, became drowsy and dull, though there is a
Nickel

certain restlessness withal. With the latter dose a paralysis of the hind leg now appears and gradually spreads over the body, and the breathing becomes slower and more difficult.

The general paralysis now becomes complete, the breathing shallow and irregular, and death ensues quietly. With smaller doses, this drowsiness and apathy may not be developed or it may pass off. So complete is the apathy sometimes that the rats may be handled freely with perfect impunity. During this stage the ears and feet are decidedly redder from vascular congestion. Eventually with the smaller doses a stage of motory excitement supervenes and this may be expressed by irregular movements especially of the fore legs by meek adduction while walking or by a constant chorea-like tremor of the whole body. In one case the fore legs, while the animal lay on its side affected with voluntary paralysis were moved as if in swimming or revolving. In another case were peculiar opsdemotic eddyings from side to side. Following this excitement there is a paralysis, the congested
Nickel

The body falls, and death supervenes as above described.

Post-mortem examination discloses nothing pathological. Animals are always disturbed by dark fluid blood, the intestines are pale and semi-contracted, the blood corporules are normal. Urine may contain a little albumen.

Rats on the whole are somewhat unsatisfactory animals to experiment on, and since the results of these experiments are in accordance with the results in the case of the higher mammals I shall defer further remarks till I speak of my experiments on dogs.

Aug. 17

11:55

Injection

12:10

Died and go to work. Respiration heavy - 96

12:20

Died to lie down. Heart and the bell jars can be removed without it being turned away.

12:45

Shuts the eyes, and we may be sure it would like to sleep.

2:45

Sleepy, faint but yet restless, still heavy respiration.

20th.

Gradually recovers and today appears normal.

21st.

Second injection this time of .040 gr. per kilo. Rat, subcutaneous.

7:20

Sleepy, and weak movements slow and apparently with difficulty. Respiration more rapid not so much injected as before.

22nd.

Found dead. Post-mortem examination disclosed nothing pathological.
Nickel

Rat

No. 150.0 with 0.50 gi. of 0.1 per kilo, rat subject:

Aug. 21st

9:30 First injection.

10:15 Eye waked, restless, week, Respiration deep 80 breaths.

12:0 Heart in normal condition, breathing and all else normal.

14:0 Somewhat better but still slow of movement.

14:15 Respiration very deep 60 breaths per minute.

2:15 Completely recovered.

10:10 Second injection. This time of 40 gi. 0 per kilo, rat subcutaneous.

11:45 Head, drowsy and restless, respiration 72.

12:0 Still sleepy, pupils of eye considerably dilated.

3:0 Lies on his side, slips beneath his back when as laid, apparently absolutely unconscious, hand limp completely paralyzed. From time to time restless movements.

Respiration not so deep but is 90 to 100 breaths, no sleep, no longer dilated.

3:45 Considerably worse, lies on side, makes no more movements spontaneous. Respiration only 34 irregular in depth and time. Hand appears somewhat swollen. Then touched lips scarcely any signs of consciousness.

7:0 Found dead in the same position in which he was left as to appear to have died quietly.

Post mortem examination. Nothing pathological.

Rat

Aug. 22nd

10:15 Injection in 2% solution.

11:45 Has been getting gradually more and more apathetic.

1:30 Dry, drooping, and compelled to walk in unsteadily.

4:0 Found dead stiff.

Post mortem examination. Carries dilated by dark fluid blood. Ventricle semi-contracted, pale. Vessels contain a pale clear urine, with a few red blood cells and some alliums. Blood above the diaphragm, light, contains some what less blood, coagulated, has a depth of 2 cm., evidently normal.

Rat

Aug. 25th

10:15 Injection in 2% solution.

11:30 Drops of strong movements from side to side.
Nickel

11:45 Several signs of these animals became duller and duller, seemingly relaxed, breathing fairly slow and shallow. Suddenly doubled up, died.


Ex. 46

Rat No. 140 gram with 40 mg. NaO per kilo, subcutaneously

10:56 Injection by 2% solution

11:45 Appears quieter, less easily excited.

1:30 Lying on its side, seems breathing, moves a little when notlaked apparently dying.

3:0 Found dead


Ex. 47

Rat No. 254 gram with 30 mg. NaO per kilo, subcutaneously

10:56 Injection by 2% solution

11:45 Not gradually been becoming more and more apathetic

1:30 Drools and apathetic

4:0 Found dead stiff

Post mortem examination. Nothing pathological. Bladder contracted, as usual.

Ex. 48

Rat No. 337 gram with 20 mg. NaO per kilo, subcutaneously

11:30 Injection

3:0 Lies on its side seems conscious, eyes wide open and staring, breathes with difficulty, fork feet moved and paddling, or swimming, cannot rise, won't bite.

9:0 Found dead on its side

Post mortem examination. Nothing noteworthy
Ex. 49. Rat No. 225 pm, with 15 mg HCl per kilo, rat subcutaneously.

16th. 11:20 Injection

3:0 Lying on side, eyes wide open, seems conscious, could not stand up, breathing difficult

17th. 9:0 Found dead

Post-mortem examination. Nothing noteworthy.

Ex. 50.

Aug. Rat No. 346 pm, with 10 mg HCl per kilo, rat subcutaneously

16th. 11:20 Injection

3:0 Seems pretty well.

17th. 9:0 Seems a little drowsier than yesterday

18th. 3:0 Bell, strong pinching hardly makes it react by biting, move, unsteady, and with great difficulty and has a tremulous like trembling. Breathing is difficult and slow

19th. 9:0 Found dead

Post-mortem examination. Nothing noteworthy.
Experiments on Rabbits

The acute poison may be induced by injecting the solution subcutaneously, into the blood or into the stomach. There is first an acceleration of the heart's action, but no irregularity, at the same time respiration is quicker, often irregular and not unfrequently the movements are very extenuated and as if voluntarily deep and laboured. When the injection is directly into the blood spasm of whole body almost always appear and urine and feces are discharged. Sometimes, though by no means always the pupils became smaller.

If the animal be now freed from the holder, it appears stupified and is paralysed. The paralysis may affect only the hind legs, or only the fore ones, or all four. The hind legs lying together, the fore legs thrown outwards to different sides so that the animal's breast rests on the ground. The cervical muscles may be so weak that the head is not held up - the paralysis is then almost complete, and persists more or less till death.

If the dose be very large the animal may not recover but simply die without other noteworthy symptom. Short of that however, recovery from this paralytic state occurs.
and now the reflexes are decidedly increased, so that the slightest excitation may cause the animal to cover together and tremble all over. Now appear twitchings and contraction of individual groups of muscles, and this excitement becomes general. Respiration becomes slower and more difficult, and sometimes there is well-marked dilatation of the vessels of the carotid and fundi oculi. One of two violent convulsions come on; the breathing is the longer the slower and the more difficult, and after a convolution death follows. If the thorax be now opened the heart is found beating well and regularly and continues to do so for some minutes.

The blood examined microscopically is normal.

Then the course of the case is sub-acute or chronic; the symptoms are much the same, only then the paralytic symptoms are less marked while the excitement symptoms are more or more varied in their character and more persistent, and there are also less of appetite, emaciation and anaemia.

Post mortem examination may show for most it's well marked, the blood of a dark cherry red colour, and fluid or coagulated.
Almost constantly are numerous little extravasa-
vations of blood in the gastric mucosa, and
also though less constantly, in the intestinal
mucosa. In the stomach, they may become con-
cfluent and thus form a great nearly black area
that may be covered by a slimy, dark-coloured
blood-stained layer of matter separating the
mucosa from the gastric contents; or the spots
may have become almost covered by a distinct necrotic
in the intestines, the destruction of tissue never
went as far; the continuity of the mucosal
surface was never broken. No other signs elsewhere.
The diarrhoea is first the passage of the
solid balls of faeces already present in the intes-
tine, but even the faeces become thinner
and eventually are quite fluid; they are never
serous, nor have I ever seen blood in them.

This diarrhoea is certainly quite independent
of the food, for other animals similarly fed
showed none of it. It is not necessarily
accompanied by any change in the appetite.

In one case after a single dose of nickel it came at intervals during thirty days
and might have persisted longer had not
the animal been killed. I think that the
Nickel

First expulsion of ballist faces is due to increased peristalsis just as in the case of Barium. (Op. Cit. 10) where the laid bare intestines is seen to become like a white cord as firmly contracted is it immediately after the injection of the salt. When we consider the comparatively trivial local post-mortem signs on the intestinal mucosa, we are forced to conclude that as with arsenic (Unterberger Op. Cit. 15) and with Barium as with nickel the visceral symptoms are not of local origin.

Also in the lead, platinum, and acute iron poisoning, diarrhoea is noted. Keeler speaking of platinum diarrhoea thinks the vascular dilatation sufficient to account for it. In nickel cases it may be profuse with or without delatation as I have often observed.

The nervous symptoms are altogether very scanty. The toxic volvulus convulsions that are constantly observed after injection of the poison directly into the blood are certainly of purely nervous origin. It might be suggested that they were due merely to disturbance of the heart's action or of the respiration and a consequent apyrase state. This st
Nickel

Jesion is however entirely unsupported by the blood pressure experiments. Probably they are due to direct excitation of the medulla or cord and this is supported by the fact that similar conditions are seen later in subacute cases and that a paralytic or paralysie is the condition that succeeds the excitation. Exactly a similar train of symptoms follows the injection of barium which is referred by Boeck to the picro-toxic group; in this however,细菌 takes exception and suggests that the cramps are merely due to the pain, not to the excitation of brain centres, that is, presume the medulla; by this however, the spinal centres are not excluded, and it seems to me that the subsequent paralysis, which is certainly nervous, is some form of assuming a foregone nervous excitation of the spinal centres.

Consciousness and volition seem to be retained during the paralysis, so that it is not cerebral probably; this is stated also for the similar condition in acute lead poisoning (Har- macht & Lii.) There seems sometimes to be a psychic excitement as noted in experiments by von Brock is mercury poisoning and by White in tin poisoning.
The affection of the spinal cord is the outstanding feature in the cases. The reflex excitability is enormously increased so that a pinch may call forth a violent convolution or a general tremor, even a stamp with the foot on the floor may suffice. Spontaneously there may be a tremor all over, or the tremor may be increased so that the movements of head and trunk are comparable to paralysis agitans in man. Then particularly towards the end of the case the convulsions become more violent and from being clonic become complete tetanic attacks. This may be while the animal is the subject of complete voluntary paralysis. These convulsions are absolutely certain not due to asphyxiating conditions for previous to them the circulation and respiration are quite unaffected. Sometimes the fore limbs are the more paralysed, sometimes the hind limbs. Often cries are uttered sometimes due to spasm of larynx in the convulsions but sometimes probably due to pain.

In one case where the animal was seized, abortion was produced by daily subcutaneous doses of 15 m.p. There was little other symptom. All the young were dead born.
Nickel

In another case the animal showed the peculiarity of having 'transverse' movements.

Rabbit Male 175. 1800. With 0.08 M. P. Per kilo. Rabbit into the blood injection practiced. Slight cramp-like contractions accompanied by the pulse. 15.

Tense, has been further diarrhoea but no other symptoms.

Pulse regular, good - 156.

11th, mor. day.

Has been more diarrhoea in the night, heart was not easily palpable. Pulse good. 11th. Further diarrhoea and no opium.

12th.

Has eaten nothing. Heart not bad, pulse pretty regular, only 88, no opium. Sleeping pretty well.

13th.

Has not eaten during past 24 hours. Pulse regular, 108. Difficult to say whether pulse is 240 or 120.

Feeds well and appears perfectly normal.

Same condition.

Pulse 136. Diarrhoea but in tolerably well condition.

20th.

More diarrhoea but in an enormous excitable jumps about when one禾触 it, and has a sort of chitter when taken hold of.


Pulse 134. Opened and good. Again painful diarrhoea. Socks thin, fired on a great-like, though thick so blood in them. Again in the diarrhoea condition before noticed.

Pulse about 148. Violent diarrhoea in the night. Eats tolerably well, slept somewhat irregular.

Pulse 124 regular and good. Feeds well. Violent diarrhoea which has nothing to do with the feeding, which is quite dry and has no such effect on other animals. Weight = 1330.


Status.I. Pulse 124 good diarrhoea in the night

Pulse 120, good feeding well

Pulse 120, diarrhoea not so marked.

Very severe diarrhoea during the night, had leaps out of the cage when the man came in the morning, sprang round the room in an 'extremely excited' condition, so that he could scarcely catch it. In the evening resumption of 78. Pulse 240, good and it was still as excited as before.
Rabbit. Male 1st. 1685-9. With 010 per kilo. rabbit into the blood.

Pulse 140. Respiration 140. injection into the cerebral venous.

After injection the hecel and respiration are greatly quickened. The ears flared and passage of urine and orini-like movements, though not very marked.

11.16 Let loose from the board. It is now paralyzed but seems stimulated, so that it lies on its side. The pupils a little contracted.

11.20 lying on its side, pile on being molested, its hind legs are most affected. They are both to one side, while the fore legs are thrown outward one on each side. Pulse still quick breathes quietly and so it remains until

11.30 Pulse 132. Respiration 132. 140. Appears quite well no more lameness nor pupillary constriction.

12.00 Pulse 132. Respiration 140. apparently normal.

92. Status semen.

4th. 9.0. 132. 92. Jerkings all over the body. has a dark of rigor and covers when one touches it. Pupils normal.

7.0 Pulse 96. Respiration 120. Movements are still present but they are only slightly marked and are jerky.

6th. 10.0 Pulse 133. Respiration 79. Jerkings always here get.

6.0 Pulse 133. Respiration 52. Jerkings always here get.

11th. 5.45. Rabbit has just been in motion. But now it has a violent convulsion. Circumscribed Flees on its side as of dead.

9th. Jerkings chill. Then it recovers and acts chill quiet.

5.30 Pulse 120. Respiration 75. Pulse jet in media in strength, and skinner off to his feet which he is left at first. As it seems onwards as usual. In a little while it has a perfectly complete general contraction returns lasting a minute.

The one peculiar sensation as seen by the ophthalmoscope. Several little contractions follow.
Rabbit. 11/16th 2170 g, Sprt. 0.1 g per kilo rabbit into blood of

0.1% HgO was injected into the external jugular vein of the rabbit. The rabbit was placed on a table and urine was collected by the rabbit.

Rabbit. Male. 11/4th 1960 g, Sprt. 0.1 g per kilo rabbit injected into external jugular vein.

10:29 Pulse 57, Respiration 72. Urine passed. Rabbit died. The animal was removed to the floor and the heart was found dead this morning.
Nicker

11.30 Pulse 120. Respiration 100. Heart very weak but enormously quickened. How it is let loose from the head, and is ready to be almost completely paralysed, but can still move head and back, pupils very rarified. After this it simply lay and unconscious of everything, the breathing always becoming more and more difficult.

3.20 Heart no longer excitable by the induced current but the other muscles remain perfectly excitable.

Post mortem examination. The muscles of the cardiac and body of the stomach is quite leathery with blood extrusions between which there is a clotting mass of blood and coagulum. Some small opening at lower part of the small intestine. Heart not contracted, somewhat flabby. Blood appears normal. Heart not too full of blood. Pupils still small.

Rabbit. Female 1815.0 hr. with 128.0 per cent. Rabbit.

Experiments begin. Rabbit now quite normal. Rate 132. Pulse 110.

11h.
11h.
12h.
13h.
15h.
16h.

Experiment begins. Rabbit now quite normal. Heart 132, Rate 110. A few more that easily excited. Today 4 11h., 6 12h.
Nickel

Apparatus

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Apparatus appears normal.
Little appetite.
Applies somewhat out of sorts.
This morning 10 young were found by her.
Still no appetite.
Same condition.
Somewhat excited, perhaps by the death of a neighbor in the barn.
Appetite better.

Daily improving its condition.

It appears to have completely recovered from its previous illness and now feels well.
Appears normal and weighs 19.10 lbs.
The daily dose is now therefore about 0.25 ml. or 0.04 miles of body weight.

Gradually getting thinner. Appears bear somewhat weaker.

The pathologic evidence shows the tendency to be very pale. The vessels are not transparent, that there is no color due to the darkness of the color is very remarkable. Pulmonary edema is not increased, but is the diameter of the vessels remarkably conical, it appears to arise from a thrombus of the blood, i.e., a coagula.

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Weight 165.5 lbs.
Nicker

Nov. 21st
22nd
23rd
24th
25th
26th

140 86

 Appeared tolerably well generally heart io regular and strong.

Feb. 1st
2nd
3rd

144 89

160 42

In the morning it seemed unwell unwilling to eat.
In the evening it had diarrhea, was weak, staggered when it was touched and was apt to stumble down at that the forelegs were stretched out sideways and the throat pulled up on the food. Heart strong but irregular. It was difficult to say whether it was only one of the beats out counted. With the more rounded pulse the arterial vessels were extremely small as were those of the ears. Soon after this the arterial vessels became enormously dilated and this did not seem to be due to handling the calf for they were only once grasped and the vessels remained dilated. Then there followed a general tonic contraction of the muscles and this soon passed into a calm state. The animal uttered cries meanwhile which however might be merely due to the contractions. Then followed a state of real mild exhaustion and now the blood pressure was attempted to be taken just before the animal seemed about to die, but it died during the operation. The blood was in very small quantity very pale and watery looking more like blood serum. Yielded much fibrin but had only 2.09% of haemoglobin. It was analysed by Dr. Molyneux's hemometric method. 18 minutes after death taken, slightly and complete and next morning it was fine.

Post mortem examination.

Weight 1300.0. Extremely little fat in any part of the body. Congestive anaemia and well-marked atrophy of every part of the body. (Of course the animal had blood taken from it in great quantity. Still the anaemia was greater than was warranted under such circumstances.)

Note

The excess could not be due to asphyxia for the respiration before it was quite regular, and not was the circulation.
Nickel

Rabbit 9th 1872 health 90 per kilo rabbit subject.

Rabbit 9th, 1872, Resq 180.

Due to day in the '025 90 per kilo rabbit subhumanos.

Appears normal

Rabbit 9th, 180, Resq 37 dusty dull and from milked

Due to day on the belly

Found dead this month

Post mortem examination.

Pulse 140 Resq 82 toto dull and respiration

Due to day on the belly

Found dead this month

Post mortem examination.

Pulse 140 Resq 57 dusty dull and respiration

Due to day on the belly

Found dead this month

Post mortem examination.

Rabbit Male 14th 1872 health 170 per kilo rabbit subject.

Pulse 148 regular, may before injection.

10.0 injection algot the injection it shined little

except that it is quickly and less bright, than it

was: it was extremely active beside the females

now no longer.

6.0 at 6 o'clock, when the pulse — 155.

10.0 pulse very much accelerated fast to the count.

6.0 at 6 o'clock, when the pulse — 155.

Rabbit Male 10th 1872 health 170 per kilo rabbit subject.

Pulse 120 Resq 59 mostly paralyzed. This sometimes

to nerve spontaneously, heaving dizziness and

evidently with an effort. On pinched the left

these reflexes are called vigorously violent but mean-

while it simply lies paralyzed had lost all power

of voluntary movement. The Bay's pressure was

now sought to be abstained from the very first.

The pressure was at a very low pitch and all suffi-

cy still lower for some 14 hours. The animal died with

ticulcns sufficiently due merely to stoppage of
Nickel.

Respiration. Short before death the vessels of the fundus oculi were not dilated.

Note. In this case there appears not to be any laxity of the spinal cord, orbital, orifice nor of the medulla, but of the parts that produce power voluntary motion.

Post mortem examination. Nothing pathological except a fatty liver evidently well advanced and therefore of old standing.

& 59.

Rabbit. Male No. 1835.0 with 0.8 % KO per kilo rabbit subcut.

4th 5th 12th 9th 14th
11th 12th 13th 14th 15th 16th 17th 18th 19th 20th 21st 22nd 23rd
Feb. 10th 11th 12th 13th 14th 15th 16th 17th 18th 19th 20th 21st 22nd 23rd
Feb. 10th 11th 12th 13th 14th 15th 16th 17th 18th 19th 20th 21st 22nd 23rd
20th 21st 22nd 23rd

14.30 Pulse 124 Bpm. — So somewhat excited. Injection.
6.30 Under extreme extaneous paralyzed.
6.15 Somewhat recovered.
7.15 Only a certain amount of movement noticed, which is at some point in the hands.

Rabbit not eaten today.

March 26th. Race 14th.
11th 12th 13th 14th 15th 16th 17th 18th 19th 20th 21st 22nd 23rd

14.30 Pulse 126 Bpm. — Irregular.
15.00 Pulse 120 Bpm. — Pulse extremely quick.
60. Pulse returned quick.

15.30 Pulse 120 Bpm. — Pulse returned quick.

Rabbit male No. 1850.0 with 0.8 % KO per kilo rabbit subcut.

11.10 Injection.
12.10 Pulse 240 Bpm. Race 154.
19.30 — Blood vessels of the little vessels perhaps somewhat dilated.
4.00 Ed. injection this time of 0.2 KO per kilo rabbit subcut.
Nickel

Normal

108.2
23h 11.5
2nd

Third injection this time of 0.30 ml. 0 per kilo rabbit. Then doctor came from timer he found it lying on its side with the head hung back appeared to have convulsions and convulsive and was cold and stiff. Warm and no signs got at 3.30 when observed.

Post mortem examination only a few spots of extravasation of small size on falciio membrane.

Experiments on Dogs

When the nickel solution is injected into the blood there occur here as were seen in the experiment on rabbit, a motor excitement manifested as tremor or spasms and with these or even afterwards occurs without retching or vomiting of foamy, frothy matter and very frequently discolored of faeces turning. Then the dog in freed from the operation board it either lies down as if exhausted or it stands still a while as if it didn't know what to do. Then it lies down, the heart beats rapidly and strongly, breathing is rapid and deep the pupils normal or somewhat contracted.

When the dose is large the respiration becomes more and more the heart remains strong, convulsions occur on and are separated by intervals of sometimes complete motor paralysis and death and supervene, the heart beating for some time after the stoppage of the respiration.
Nickel

When the dose is not so large and particularly when the poison is administered subcutaneously this first sensation which is strictly due to the struggles of the animal at the operation is recovered from and now follow such a train of symptoms as the following. Violent retching and absolute inability to retain any food in the stomach — not even water. Diarrhoea which may be severe but never bloody; tenesmus. Loss of appétite with great thirst. A stomatitis accompanied by difficulty of chewing and swallowing. Blackening of the teeth and gums and the joint forth of a frightful odour. Almost constant eructation of terribly ill-smelling foetid gases which at such acute and at some cases are found to contain retegal, become nearly black in colour, and have a peculiar odour that is quite characteristic. The urine remains at all times of normal colour and may contain considerable quantity
Nickel

of albumen. Emaciation. Sometimes begins as if from pain in the abdomen. May be headache, and slowing of the heart's action. Frequent attacks for convulsions, embarrassment of respiration, exhaustion and death. Necropsy shows no destruction of the haemocytes.

Post-mortem examination may disclose in different cases: Speculate odors about the body which I could recognize as a 'muskel smell' - a characteristic odor. Body exuviated in subacute and in chronic cases and muscles dry. Blood of a very dark purple, coagulated or not, corporaidea in acute cases unaffected; in chronic, fever in mummery and power in pigment. Heart with auricles dilated and dark in color, ventricles contracted or semi contracted and pale. Small extravasations in epicardium and endocardium not in myocardium specially. They were never large, mostly numerous. Most in epicardium of auricles, least in right ventricle.
Nickel

and in mitral valve; might extend thru whole thickness of colliculinae carneae or papillary muscles but never down into the wall. Often large decolourized clots in the auricles, sometimes though rarely punctiform extravasations in the plecturae. The before-mentioned blackening and softening of the palate, gums and teeth. The muscosa of the stomach and intestine—especially the small intestine—may be conflated or show extravasations into the substance: these are most frequent and most marked in the facricia muscosa where they may be conflated and are particularly to be found about the peritoneum here they may be replaced by actual ulcer, or covered by a whitish plough. In the stomach may be undigested putrid food which has remained there for days; in the intestines a fluid matter in small amounts may be foul-stained—never blood stained. In one case infarct of the spleen and in another infected
Nicker.

conjunctivitis. Resorption system usually quite normal though sometimes trivial congestion splotch were noticed over the cerebral convolutions.

The alimentary symptoms thus became much more prominent than in rabbits, and are fresher as in cats.

The mouth and throat symptoms are probably simply a part of the affection of the alimentary canal generally, an inflammation causuing swelling and softening of the mucus, leading to difficulty of chewing and swallowing: alteration and dilatation of the buccal seascions in the mouth leading to marked putrefaction in that cavity and consequent foul odour.

This along with the faeces, of section doubtless accounts for the loss of appetite observed. It also accounts for the invariable thirst so manifestly manifested and this in its turn accounts for the frequent passage of the faeces.
Nickel.

I have some friends who entertain the strong suspicion that in nickel there will really be found Blacker's "coagulation necrosis" of the cortical urinary tubules. The vomiting is an extremely pronounced symptom; it may appear in a few minutes after the administration of the nickel; or it may not come on for days; it may be extremely violent, and sometimes repeated till nothing but a little clear urine is brought up and the animal lies or falls down evidently perfectly exhausted.

As to the aetiology of these alimentary symptoms one can only speculate: they are certainly not of local origin, for though nickel is secreted by the mucosa it is only in small quantity and the introduction of or of large quantities of the nickel salt has little effect in this direction, and indeed the symptoms may have...
Nickel

have very well-marked with but trans- 

real local anatomical changes in the 

tract. Then again we see well-marked 
extravasations in the epi- and endo- 
cardium and pleurae, where a local 
action is entirely out of the ques-
tion. As Schmiedeberg remarks 
we have here as in arsenic acid 
cases conditions wonderfully like those 
found in diarrhoea cholera and in poi-
soning by opium. These effects cor-
respond somewhat also with those of 
barium and corrosive sublimate infe-
icted subcutaneously (Ogilby 62, 
317) They correspond greatly to 
the symptom after platinum and 
these Keilser says may be due to the 
vascular dilatation — with which so 
before stated I cannot agree.

The nervous symptoms are 
much as in rabbits so that little 
need here be said. In one case the 
convulsive were of a decidedly 
epileptiform character since a tonic 
state preceded the clonic convulsions.
Nickel

which were exceedingly violent. Another case showed well-marked opisthotonic spasm due to constriction of the recti occuli. In short-haired dogs the precursor was extremely evident: all the muscles spasmodically into view rapidly and continually as if the dog were cold and having a rigor. The difficulty of respiration is doubtless due to this motor excitement and we shall see that other centres in the medulla are affected and that it is therefore not improbable that the respiratory centre too is affected, first excited, then paralyzed. In their iron experiments Iferes and Willems do not record any motor excitement symptom throughout the whole course of the case, but the lassitude, apathy, and paralysis are well-marked and are ascribed to central nervous causes. Willems says the effects of the iron on dogs are chiefly paralysis of the cord. In human cases they are present, but not
Nickel

very marked, while in platinum cases there do not seem to have been any such excepting the merely asphyxial cramps immediately preceding death. In Hamao's lead experiments on the contrary they are as well marked as in nickel cases and are evidently of a similar character and nature, from their peculiar constant jerky character and from the non-affectation of other centres in the medulla oblongata, and lastly from the fact that section of the spinal cord stops them, he concludes that they are due to excitation of brain centres higher than the medulla oblongata. I think that this is very probable also in the case of nickel.
Experiments on Dogs

Feb. 16th

Dog. Young Male No. 6,500.0 Infl. 205.0 Pre. Hilo. Dog into Blood

July 11th. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

July 11th. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

Wife. Infl. 205.0 Pre. 120.0 Pre. into Dog into Blood

July 11th. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

11th. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

12th. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

13th. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

14th. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

15th. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

16th. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

17th. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

18th. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

19th. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

20th. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

21st. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

22nd. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

23rd. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

24th. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

25th. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

26th. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

27th. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

28th. Operation. 5,000.0 Pre. 120.0 Pre. into Dog into Blood

Evidently normal.

Great thirst, has eaten all his food, lost on fluid and of varying dark colour, as if all such mixed up.

Has done diathesis, is cheerful and well looking.

Taking note, how he may be considered normal.

The estimation and quite well. He has the peculiar smell and there is some conjunctivittion, which is used for a blood pressure experiment after which post mortem above numbers, extravasation in the past.

Nothing.
Nickel

Dog: Young female. 15 lb, 3700, 8½ x 11½ ft. 2nd to 1st.

12:00 Administration of the nickel in 5% solution was the only thing.
4:00 Symptoms were mastication. LAE 10, previously.
2:30. No treatment has been noted.
12:15 The dog was observed, not to be admitted by the slightest objective.
2:00. He was masticating apparently. Nickel only in the hands.
15:45 He seemed to have no change in the slightest appearance.

F. O. The ears are regular, moderately clean and moist. No discharge appears consistent with anything.
7:00. No normal appearance. Raw flesh, however, with headlessness, Pulse 175.
24:00. No change. She had eaten all her regular and 2nd to 1st. 2nd to 1st, on the table.

22:00. No change. She had eaten all her regular and 2nd to 1st. 2nd to 1st, on the table.
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Nocciol

over colonic cannae and at the after sheu exquisito extravasations penetraing the whole thickness of the cannae. These have already been taken out of the body. They date from the first days of the penetration. ThereInside, almost completely filled with a white, thickish, semi-liquid mucus, some extravasations extruded from the cannae. Similar extravasations are also in the bladder and uterus, but they are by no means numerous. Intestinal contents pretty fluid and extremely yellow from masses in the peritoneal spaces. Kidney normal, urinary bladder normal. No fluid. Nocciol was found in the urine taken from the bladder in the post-mortem examination.

Ex 63.

Dec. 11, 1914, 4:20

Dog, young. No. 7,050.01 was subjected to a post-mortem examination. Almost immediately after the application followed without vacuities of any kind. There was a slight mucus.

14:40. Slightness has been observed for some time, and now it comes off. This is the result of the urine, which is not turbid and shows no signs of fermentations. The following are vacuities of movements secreted from time to time.

17:00. Wax left upon the laboratory was placed upon the examination. In the morning, wax found ahead with much fluid about the mouth, possibly saliva, and there had also been waxness to a considerable extent.

Post-mortem examination.

The pain is much engorged on the surface. There is a collection of fluid which is moderately congealed. There are many extravasations in both surfaces, especially the liver, fixed in the subserous surface of the right auricle.

The stomach, while length of small intestine and the large intestine contain a bluish fluid. The interior of the stomach is much congested and shows the pyloric exudate massing and large extravasations as also the large intestine and the upper part of the small intestine. Gall bladder full, homony bladder filled with dark turbid urine but itself normal.

Subject is somewhat excited, and this may account for the high pulse rate. In the whole, however, he is not quite as lively as before.

Kid not eat his supper last night, but has vomited something. Eats when flesh is offered to him. His eyes are somewhat duller.

Note 166. Slept on a look this morning. Completes spitting together with blood pus. Conjunctivitis.

Will not eat. Pulse 84. Feces thin and not well rice.

The regular somewhat weak will not eat, and though he has not eaten for so long yet he has required a good place of strength this morning. Appears to have gained in the abdomen for he looks more sleepy looking and run up with it will not move not steerless himself.

Washes well marked and when unshirred he does not at all as he lies at that he is in a frightfully frightful state. Did not the amount look to be in.

The Mon. Pulse 84. Respiration 24. Pulse perhaps a little weak but regular. Eye will you bad well not get

Urinalysis of urine no trace of blood nor albumin in urine.

Pulse 84 regular but no end other then in the morning.

Otherwise condition of the same.

Found dead, cold, and stiff.

Post mortem examination

Throat, lungs, diaphragm, heart, liver, spleen, and abdominal cavity, covered with a coat of whitish slough. The diaphragm and upper part of peritoneum was completely covered with white whey that appeared to be made of little white lines. The was as first several to his head was want of showing from the lower portion of his body.

Said they were that well with the child symptoms failed: considering how long it was since the dog had eaten anything, this was very remarkable. I did not notice it in any other case.

The intestinal contents are much fluid but in the colon are some masses. The bladder was extremely distended with urine; he did not move to urinate for the last few days and he was always wet and slippery. It may very well be that this was a paralysis of bladder but the whole condition of it so that there was probably continual spitting away of urine.
Dog Old Mule No. 45,000. B. & W. but not of substance.

July 12, 1920, Respiration 15. Breathe rapidly.

5:10 Respiration 15. Breathe rapidly.

4:40 Mucus in the nose and mouth.

4:10 The pulse is weak and rapid.

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Pulse 120  Respiration 22
20 Cyanja quite quietly. A

Pulse 124  Respiration 20.
30 Better today. Have eaten
three pieces of flesh and
 retained them.

Pulse 126  Respiration 14.
40 Drinks a great deal of
water. Heart beat regular
and steady.

Pulse 128  Respiration 14.
50 Heart is beating. Breathe
quite quietly. Appears
steady. Heart as well as
slow in very

Pulse 129  Respiration 14.
7.0 He is before pulse time. He
does not go much or
only a little flesh.

Pulse 125  Respiration 14.
11.0 Heart irregular though
not so

Pulse 127  Respiration 13.
1.0 Heart quite regular in
force

Pulse 129  Respiration 13.
5.0 Heart and bowels regular.

12th.
6.0 102

13th.
7.0 120

14th.
8.0 120

15th.
9.0 120

16th.
10.0 140

17th.
11.0 156

18th.
12.0 156
16

He had eaten nothing. Committed
some of yesterday's food still.

He was now much better,
but somewhat restful.

He had eaten nothing. Committed
some of yesterday's food still.

He was now much better,
but somewhat restful.

He had eaten a good deal of

He has retained

He has retained

He has retained

He has retained

He has retained

He has retained

He has retained

He has retained

He has retained
Nicked

Lake 156.  Respiration: 20.  Heart regular.  Slightly has eaten all the food.  Lips are now clean and will be seen quite recovered.  Noth Separat and food luscious and to day the food looks to want to get rid of the cage.  The horse has turned all that he ate yesterday.  Excreted this morning and upon food new food flesh was offered but he rejected it so that there was still that disposition to eat.  There was still a had area of undigested food which looked like a manner of hump-like in the form.

20th.  5:12

120  6

20th.  10:00

12

18

Abnormal.  Diarrhea able diarhea thin

from face.

20th.  Prepared cement in

bake.  Then the woman's

in front and short shape.  When

the character is another, there

and joined is over the body

so that the neck and trunk

are held inwards and the

hips squelched against but

from the body.  Then she rises

amongst a slight frame, so

as it were to study

partake and where the move

ment in a violent that

he is dashed about the cage

from side to side.  They

come once very quickly and dis

appear moved slowly but still

not just to pay slowly.  They

seem each other with frequency.

Heart we got uncertain

in a place.  I am afraid that to open

the cage with handle was

decidedly unsafe

sound dead.

Post mortem examination, enucleated somewhat
Nickel

... much subcutaneous fat, some of the small intestine was reddish in color, showing only a few small extravasation spots towards the ileum, the mucosa in all instances showed the same, the intestine was dark brown, and tinged in the rectum became blackish. Throughout the whole intestinal mucosa were numerous reddish extravasation spots, especially in the cecum and colon and in the rectum. The mucosa appeared quite fresh, red extravasation to be normal. The bladder had urine normal, pancreas small, soft and congested, kidneys normal, urinary bladder strongly obstructed. The pleurae were reddened free from spots. Heart not congested nor yet flushed moderately full of fluid, dark erythematous-colored blood. Beautiful leukorrhea under the cover of the microscope. Especially the articles were large, white, cellular, completely colorless—old, nothing in nervous system.

Dog: Young female, M. 111.0 with 10.0% of 0.0% petrol. Dog, embalmed.

Place 64. Respiration 16. Before the injection.

Place 70. Respiration 16. Heart irregular in some.

Place 70. Respiration 16. Heart somewhat weak.

Place 70. Respiration 16. Heart well enough.

Place 70. Respiration 16. Heart well enough.

Place 70. Respiration 16. Heart well enough.

Place 144. Respiration 16. Heart well enough.

Place 144. Respiration 16. Heart well enough.

Place 144. Respiration 16. Heart well enough.

Place 144. Respiration 16. Heart well enough.

Place 144. Respiration 16. Heart well enough.

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Place 144. Respiration 16. Heart well enough.

Place 144. Respiration 16. Heart well enough.

Place 144. Respiration 16. Heart well enough.

Place 144. Respiration 16. Heart well enough.

Place 144. Respiration 16. Heart well enough.
**Nickel**

Feeling clinically eso that the chest was to be in -markedly with difficulty or not at all, the major symptoms were the rapidity and the irregularity of the respiration, respiration in -clustering, the deep breathing evidently very nice to diffi -cult breathing. Noteworthy to observe who were in the laboratory the whole external pres -sure was that of a very exaggerated paralysis of the -feet. The patient was seen little of his rapid breathing -clearly and barely and shortly after was found dead but the muscles continued to contract for some time. It is not diffluent that he suffered and pain that they gave him a little chloroform but not sufficient to stop the muscular actions.

Post mortem examination.

Preparation spleen normal. Heart quick with trivial ex -tensions. Heart the epicardium but the rest was -normal. Aspersion distended with gas in the portion -namely fibrous extravasations in the right and gas from the pylorus. In the lower parts of the stomach, many -vesicular extravasations in the urine. In many num -bers the spleen normal. At the end of the aspersion nic -tion that had prolonged, three bodies were dark -weakly evacuated. In the heart, once and again -as an in the body is poor in blood.

**Dog. Weight 5100.6 with 1750 gr. per kilo. of into stomach.**

10th

12.00 A.M. Nothing noteworthy happened.

6.00 P.M. Spleen 140. Nothing noteworthy happened.

11th

8.00 somewhat weak and restless has been -fresh since last evening reducing the night -late his posture last evening and it was said this morn -ing. How this flesh had been offered -but meaten his food but will have nothing from had to this last and will -say 240, regular, and good. He's very much excited -very. We called the office. It's today we are -closed normal.

12th

13th

14th

15th

16th

17th

11.30 750 gr. per kilo. into stomach.

3.0 Lea seems quite unaffected.
Nickel

17th. 5-18 0.250 of the fluid. def into stomach again. After food eagerly but deeply after swallow immediately afterwards vomited a little mucous. Ate only half his supper the other half during the night. Complete normal. Pulse not to be considered. 18th. 6:35 was sent to hospital. When one gets up to have 0.250 of the fluid do not allowing the eaten all his food. Eats easily from the hand. Feces frequently passed fluid (fairy-like) throughout the day. Pulse 122. Quite normal and easier on flesh. After 0.50 have slept. Pulse 85 strong but irregular. Difficult to count exactly he is perceptible. After 0.50 apparently quite normal. He was once vomited this dose. His face was perhaps somewhat fluid. After 0.50 0.100 of the fluid. Happened at an end and not more to be had. Is quite normal.

Experiments on Cats

Here is first the dulness and stupor and very soon a flow of saliva and vomiting. This is not sometimes so prompt and often is quite an reverse as in any case of vomiting after digital sphæra which I have seen. First the food is brought up then some mucous only, finally retching seems to exhaust the animal.
Nickel

enormously, so that it lies on its side completely done out, hardly able to raise its head though evidently quite conscious. The breathing became rapid at first, then slow and deep; finally, normally rapid but shallow.

Motor excitement as jerking or convulsions may now appear, but a paralysis of voluntary motion is gradually developed, and death soon follows. At least with the larger doses.

Post mortem: Rigor mortis: muscles often still contractable directly and through the nerve. Vessels of the heart contracted and pale: auricles distended with dark blood: blood normal: intestinal and sometimes jaundice: mucous membrane congested or inflamed, and the former may have shed its entire epithelium.

Meyer and Williams note.
Nickel.

That iron causes also diarrhoea in addition to the other symptoms, and also in the case of mercury von Mecknig found diarrhoea profuse and watery, though sometimes only vomiting was noted. The author found that in cats the effects were comparable to those in the cases of rabbits and dogs — vomiting and diarrhoea, encephalitis, tremors and paralysis, vaso-motor centre and respiration affected, heart slightly enfeebled.

Ex. 68.

Cat. Strong adult female, 5. 3200 gm. with 0.6 to 0.1 per mille cat subcut. Aug. 11, 1:15. Injection in 10% solution. 23.1.10.20. Never shown any symptoms. No reaction. 0.0.12 to 0.5 subcutaneously. Never any symptoms after an interval of six days. Isolated, in prevent confusion.

Ex. 69.

Cat, W. 2200 gm. with 8 m.p. 0.10 per mille cat subcut. Injection. 9.10.19. The symptoms have subsided after 14 days, but now feel 10 m from 0 per mille cat subcut. Injection. 10:30. 11:30. Breathing and respiration very rapid.
Nickel.

Aug. 23d.
12:10. Well on its side, no longer reacts to stimulus, breathing now normal, exhausted, evidently dying.

2:0. Found dead; evidently has died quietly; persons in next room heard nothing.

Post-mortem. Nothing very noteworthy except some congestion of intestinal Tina.

Ex. 70.

Cat. 17. 2:450 hours. Kilo 10. 15 per kilo, cat subject.

Injection. Cat does not seem very well even after it; before the injection.

4:45. Rejected, and could not vomiting and vomit, still heart normal.

5:00. Barium by laboratory man, was ill, coursed as if in cane, vomit, several convulsions at intervals, hives left shoulder, difficulty and back bent backwards. After a fit it lay on its dead, but when molested could roll out fell immediately.

5:45. 8:0. The man took it apparently dying.

Saw it dead, still warm, side, not colic, no evidence of diarrhea. Body still, veins, veins, normal, normal, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tender, tend
Nickel

Aug 26th 4:10 A.M.

Constant vomiting first of the solid food then of a elite like sugar. Meanwhile the mucus and toxic very noticeable vomit stopped. A very stupidlogg himself down from hardly crawl, except into the dark corner of the safe. Keep 4.10

7:00 Sound dead: stark and stuff

After morn examination absolutely nothing pathological confirmed

Blood Pressure Experiments

Since they were obtained on Germany with Ludwig's large kymograph the curves are to be read from right to left. The curvula is usually in the common carotid artery and the nickel solution is always injected intravenously.

Beginning from ten to fifteen seconds after the injection of the nickel there is in all cases a remarkable fall of the arterial blood pressure (e.g. Barium 0.0001 and
Nickel.

and 4.46.8") and while with the smaller doses there is a gradual recovery (loc. cit.) with the larger and lethal doses, especially if somewhat rapidly injected, the fall in continuous till death supervenes.

The pulse rate is at first in creased, but afterwards it is decreased; really however the pulse is not materially affected.

By referring to the control experiment, Article 7, we ascertain (1) that these effects are not due to the mere injection of a fluid saline water is seen to have no effect. (2) that it is not due to a "lactic action" (Dubosch) i.e. merely saline injection of a solution (a) of the same saline contents, and (b) same amount of alkaline reaction, and (c) differing from the nickel double salt only in the absence of nickel, the place of which is taken by the indifferent sodium, cannot indeed.
**Nickel**

A fall of pressure, but it is quite of a different kind from the nickel fall, not so intense nor by any means so persistent, in fact it is transient. We are thus forced to conclude that the fall in the nickel experiments is specific and due to the nickel solely.

This nickel fall of the arterial blood pressure may be due to:

1. Heart: Here it may be due to:
   - (a) Affection of the muscular substance itself
   - This however is most improbable considering the results of the muscle work experiments, and considering the power of the heart to overcome the effects of increased resistance.
Nickel

I Heart

1) Affection of the nerve supply viz: diminution of the motor nervous energy or increase of the inhibitory activity of the vagus. Now the results of section of the vagus resemble any such affection as the latter and again the effect of increasing the resistance, say by abdominal compression or by mass motor stimulation, completely resembles as well the former as the possibility of these being any affection of the muscular substance. The effects of surgical section may be seen in I. 4.51' in II 11.30' III 12.57' of abdominal compression towards the end of the pacem of increased resistance from cervical spinal stimulation in II.
Nickel

These statements are supported by the facts (1) the observed effects on the first heart;
(2) for some time after death the auricles ventricles may continue to beat regularly and strongly;
(3) the pulse remains for the most part practically unaffected.

Immediately on the pressure falling after the nickel injection the pulse rate shows an increase. This I take to be due simply to the fall of pressure according to the law formulated by March (Op. Cit. 24, Page 178). Hereupon follows a gradual fall that is continuous till death, though when the fatal issue has come the pulse rate is not so greatly lowered. I think this lowering is due solely to the low pressure and consequent mal-nutrition of the organ, though it may well be that the automatic motor ganglia of the heart are affected as we see other parts of the nervous system to be affected by nickel. The primary rise of the pulse is seen wherever these are intact.
Nickel

not where they are all already severed; it is then in complete accordance with Mary's law above referred to. The secondary fall to occur in all cases where there seemed to be a distinct slowing of the heart
the dog was nervously severely affected; evidently there was some real excitement, why I know not but I am not inclined to lay much weight on this case, which stands alone away

II. Walls of the blood-vessels: i.e.
the non-stripped muscle
this by the effects of con-

verse spinal stimulation is completely negatived, for we see the pressure rise enormously consequent
on increased resistance to outflow of blood here we assume that the smooth muscle of the vessel walls is yet unaffected.

III. Vaso-motor nervous system that the different vaso-motor nerves and their terminations in smooth muscle - whatever these be - are unaffected is known by the effects of cervico-spinal stimulation, for then we see that they are quite function-less. It is true that this effect lessening as the case advances but it is also true that the tissues are all dynein and less function-less; it is therefore not necessary to assume a curara-like action of nicotine on the nerve ending.
in the smooth muscle
of the vascular walls
as Reblé does in the case
of platinum.

There is conclusive
evidence that the vaso-
motor centre is remark-
ably affected.

If we stimulate
that centre by completely
cutting off the supply of
cair to the animal we see
that the blood pressure
in the arteries rises, but
as the case advances
the rise becomes less and
less intense and finally instead
of a rise there is a fall
of the arterial blood
pressure following suffo-
cation, and this at a
time when direct stimu-
lation of the vaso-motor
nerves passing down the
cord calls forth the
Nickel.

usual rise of blood-pressure. Clearly then the vasa-motor centre is first paralysed and then is paralyzed.

From a study of Traut's I. it would seem that the vasa-motor centre is at first rendered more excitable, since if we measure the pressure at the end of twenty seconds, in several successive suffocations we find that within that period there is 1st. An increase in the amount of rise viz: at 5.9' the rise is 10½ m.m. Hg

\[
\begin{align*}
30' & \quad 36 \\
47' & \quad 40\frac{1}{2} \\
\end{align*}
\]

2nd. A decrease in the amount of rise viz:

at 5.16 the rise is 26 m.m. Hg

\[
\begin{align*}
38' & \quad 14 \\
50' & \quad 6 \\
\end{align*}
\]
Nicke 2.

(3) An actual fall of the pressure from the beginning of the suffocation to 6.57 twenty seconds of suffocation caused a fall of 1.0 mm Hg. In the succeeding twenty seconds these in a further fall of 1.0 mm Hg.

If these results be confirmed by future experiments we would have in the case of the motor centre for the vascular muscle that same succession of conditions which we saw so often in the case of the motor centre for the voluntary muscles i.e. increased excitability, phrenesis and paralysia. The decrease in the rise of pressure runs into the actual fall in the third period and the two periods may be taken as continuous.

It might be argued that this fall is due to no specific action of the nickel but simply a death or cessation of the power of being...
Excited to functional activity of the tissues of the vaso-motor centre and due to malnutrition this however is hardly tenable because there is absolute loss of excitability of this centre at a time when other parts of the body retain their vitality—conce perfectly or more or less imperfectly. At any rate if it were due to malnutrition simply there would be an affection of the vaso-motor centre to an inordinate extent and this would simply amount to something specific.

Unterbberger (op. cit.) in the case of arsenious acid found that when the pressure was very low neither direct nor indirect stimulation of the vaso-motor centre sufficed to raise the pressure and found that stimulation of the peripheral end of the great splanchnic in
N i c k e l

poisoned eats as long as contrac-
ted the vessels of the corres-
ponding area, while stimulation
of the sympathetic always con-
tracted the urinal vessels even
after death: thus he suggests the
possibility of the vast motor
paralysis not being general i.e.
being confined to the abdominal
vessels. In summarizing up he states
that there is some cardiac par-
alysis.

Rothm and Mickwitz
found that non-lethal doses of
barium chloride raised the pressure
very remarkably, after which it
fell to the normal or with smaller
lethal doses to the abscissa and
death; while larger lethal dose caused
it to fall continuously to the
abscissa from cardiac paralysis.
These results were obtained even
after section of the cord so that
it was due either to heart or
desole themselves.
Nickel.

They excite the heart and leave it undecided whether it is a direct action on the vascular muscle or indirectly through the nerve ends.

Helmholz platinum experiments make the metal have a curara-like effect on the vessels of the intestinal vessels since stimulation of the peripheral cut end of the spinal cord raises the pressure less and less as the case progresses.

Larwood found that lead had no particular influence on the vasomotor centre or on the vascular system.

Heych and Williams give a lowering of pressure for iron, and steel in the case of cats, that suffocation does not raise the pressure when it has fallen very low.

Von Mehnert with mercury found some aesthetic paralysis along with vascular paralysis.
Nickel

The latter nerve stimulation of the peripheral end of the cut spinal cord only raised the pressure a little, e.g., from 32 to 47 mm., but finally does not raise it at all.

As any speaking of nickel (or cobalt) itself finds the affection of the heart as a purely local action on the muscles and on the automatic fascia of the heart.

To sum up nickel differs from lead which has no action on the vascular system, and differs from the other metals tested, from some more, from some less: in some cases we find arterial cardiovascular paralysis, in some vascular paralysis in no case are the phenomena analyzed sufficiently, and probably further experiment will show that all the metals (I have shown that cobalt does) para-
Nickel.

Lyse the vasa motor centre just as nickel does.

I. Rabbit.

Aug.
31st.

Blood pressure
in mm. Hg.

Pulse
per min.

Camula in carotid artery. These figures represent the conditions soon after the experiment is begun and may be taken as representative of the normal. Carotid begun to be injected into the peritoneal cavity. Carotization now practically complete.

Injection centripetally into external jugular vein of 5 cc. nickel solution = 0.005 M. 0, slowly injected.

A marked fall of pressure
beginning of a curve, duration of which 1 cc. solution = 0.010 M. 0 is injected. In all now therefore 0.015 M. 0. Again a fall of pressure in spite of
injection is noted. P纪录 before 60 per minute, after 282 per minute, after 276.

Apparatus stationary during this time and 0.10 M. 0 injected. In all therefore 0.25 M. 0.

Suffocation during 40 seconds. No contraction of the voluntary muscles of animal. Rise of pressure in the first 20 seconds = 105 mm. Hg.

Apparatus stationary during interval of 15 cc. = 0.05 M. 0 thereby injected.

In all therefore 0.040 M. 0. You noticed that Iasco furnie had
Nickel

Blood
Pulse

Per min.

mm. Hg

5:30
65
282

Suffocation rise in first 20 seconds

36 mm. Hg.

32'
47'
47'
6:16:0

Suffocation rise in first 20 seconds

40

Interval during which apparatus in standing

6.68
270

Suffocation rise in first 20 seconds

26

17:14
34:0

Suffocation rise in first 20 seconds

13:46

67

Suffocation rise in first 20 seconds

17:26

48

Suffocation rise in first 20 seconds

50:0

56:16

76

Suffocation rise in first 20 seconds

53:35

55:36

57:10

Abdominal compression causes rise of pressure

End of experiment. It was simply stopped
Post-mortem examination.
Abdominal organs greatly dilated.

Rabbit

Experiment begun. Skin may be taken
anormal pressure and pulse.

Carcass complete. Shortly after
the infusion of blood was
Electrodes introduced first very well placed
Nickel

Blood Pressure

11.5 56 22.8
12.4 34 2.10
12.8 42 2.0
12 62 222
20
27 67 198
83 53.5 204
1.9
51 35 168
58
2.1 30 143
9 165 180
9 165
11
1.5 17 144
.17 17
.22 .1
.25 .1
.27
.40 .15 135
.35 13.5
.40 129
.43
.47 .1
.55 8.5 114
3.0 7.5 114
14.4

- In the spinal cord, but sufficient
- well for my purpose.
- First the injection of nickel into the
- internal jugular vein is commenced.
- Injection of nickel commenced.
- Thus we see a gradual recovery from
- the fall caused by the injection of
- the nickel at first.
- Gaeces passed.

- 2 c.c. Abopine sulph. injected and nickel sus-
- pended.

- Cervical spinal stimulation raises pressure
- from 15 1/2 - 19 = 22 mm.
- Suffocation raises pressure from 14 - 15 = 1 mm.

- Abdominal compression
- Suffocation
- Cervical spinal stimulation
- Nickel resumed.

- Suffocation during 30 seconds
- Pressure 15 1/2 mm Hg. Curb 138 at beginning
- 14 1/2 132 and end.
- Cervical spinal stimulation raises pressure
- from 13 1/2 - 32 = 18 2/5 mm. Hg.
- Suffocation during 46 seconds
- Pressure at beginning 17 mm. Hg. Curb 126.
- 24" after 14 1/2 and end 13 2/5.

- Abdominal compression raises pressure from
- 11 - 40 = 29 mm Hg.
- Cervical spinal stimulation at beginning
- Pressure 8. Curb 114, at end pressure 2 4 5/5 Hg 138.
- Suffocation raises pressure from 7.5 - 7
- = 15 mm. Hg.

- Cervical spinal stimulation raises press-
- sure from 7 - 25 1/2 = 18 5/5 mm Hg.
### Rabbit Large Male

**Nov. 7th**

- **Blood**
  - Pressure: 115\(\text{mm Hg}\)
  - Hematocrit: 56\%
- **Pulse**
  - Rate: 100

**Blood ABX Test**
- **PP**
  - 27.7
  - 210.5
- **SY**
  - 118\% 272.5
  - 186\% 318.2

**Other Details**
- Experiment commenced. Canula into the carotid. No exudate is used. Average of both times probably to be extrapolated on giving the normal pressure at least.
- Injection of 0.66 HCl into external jugular vein. (data not clear)
- "just finished"
- "151" "74"
- "18.0" "just finished"
- Injection of 198 HCl in all completed.
- 4th dose of 0.66. commenced
  - Groups: urine and feces discharged.

Respiratory movements have scarcely any expression in the curve. How they are still less, and at they are scarcely well numerable.

At last the pressure sank gradually and fairly to zero. The pulse is early discernible up to the last two practically are the respiratory curves though there are indeed small.

### Dog

**Nov. 6th**

- **Blood**
  - Pressure: 37\(\text{mm Hg}\)
  - Hematocrit: 160\%
- **Pulse**
  - Rate: 40

**Other Details**
- Experiment commenced. Canula inserted into the carotid artery. Normal before any injection is practised. Intravenous and intracardiac injection into external jugular vein.
- Observation not becoming established a cardiac affection until the artificial respiration is properly working.
<table>
<thead>
<tr>
<th>Date</th>
<th>Blood Pressure</th>
<th>Pulse Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.10</td>
<td>23</td>
<td>94</td>
</tr>
<tr>
<td>24</td>
<td>24</td>
<td>47</td>
</tr>
<tr>
<td>28</td>
<td>28</td>
<td>47</td>
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<tr>
<td>29.25</td>
<td>40.5</td>
<td>21</td>
</tr>
<tr>
<td>44.32</td>
<td>44.32</td>
<td>23.5</td>
</tr>
</tbody>
</table>

On the 5th of March, there was some excitation of the veins, irregularity of pulse, and the animal appeared to be recovering. However, respiration was practically complete, and the renal vessels were patent.

Injection of 1.5 c.c. of 0.1% solution of nicotine was attempted, but artificial respiration was temporarily arrested. It seemed that there was still some activity, though very little, voluntary power, as indicated by the small number of respiratory oscillations. The rise of the pressure from the suffocation was quite insufficient and indeed it may be due chiefly to the small amount of voluntary muscular contraction. The respiratory oscillations afterwards were more marked, and the pulse became regular, but the animal was not breathing sufficiently well to sustain life properly.

Artificial respiration was resumed.

Abdominal compression raised pressure from 24 to 48 mm. Hg. Shortly after, the caudal vein was removed from the animal.

Abdominal compression raised it now to 56 mm. Hg. Two doses of 1.5 cc. of 0.1% nicotine were given. While attending to the injection, the pressure suddenly fell, and all means adopted were in vain.

Post-mortem examination showed the ventricles were of a grayish color, but the auricles beat very fast. On cutting out the small aorta, none of the aorta was found to be obstructed. There was no evidence of any pathological condition.
Control Blood Pressure Experiment.

Commenced.

3.35
Continuing injection of 1 c.c. sodic citrate solution: cramps, and rise of pressure.

Guvra injected: sudden and fast fall of pressure from cardiac paralysis, but there is a speedy recovery of the fluid had sunk somewhat into the muscles.

5 c.c. sodic citrate solution injected. Cramps again follow, but not as violent as before, because the curara has now acted more fully. The fall of pressure is not complete, but there is almost immediately slowing of the pulse, along with which the strength of the cardiac contraction is enormously increased.

15 c.c. distilled water rapidly injected: no effect whatsoever. The curarization is now practically complete.

5 c.c. sodic citrate solution again injected. For the cramps are no longer a disturbing factor and we note that the pressure falls, the pulse rate is diminished while the contractions are evidently more powerful. Then the pulse rate returns itself and is more rapid than it was just before the injection, and meanwhile the pressure rises higher than it was before the injection; then it falls again suddenly. These effects are seen in a measure even after the naph are reversed.
Excretion of the nickel is accomplished chiefly through the urine in which it may be detected soon after its administration in any of the modes, and after a single dose it may be detected for many days. For its certain detection, I evaporated the urine to dryness, incinerated the residue and now extracting the nickel as say the chloride followed the ordinary sulphuretted hydrogen method as so to obtain the black precipitate of its sulphide. In the bile it was similarly detected. In the feces it was found in large quantities and probably their characteristic black, or brown colour was due to nickel sulphide. How much of this came from the bile, and how much from the intestinal secretion, I did not ascertain.

I began but did not finish the estimation of the amount of nickel in the different organs.
Nickel

since I found that in Grass
bury such analyses were as-
vented of as value, that
some of the nickel in ex-
crusted in the intestinal
secretion would seem to
follow from the fact that
high-up in the caecum of
rabbits, where no bile could
possibly have penetrated and
where no blood had escaped
from the vessels nor any lacer-
ation of tissue occurred,
nickel could easily be di-
tected by the above method, and other methods.

On treating sections of the
kidney of animals poisoned with
nickel with ammonium sulphide,
the black sulphide of nickel was
seen to be abundant in the con-
voluted tubules and in the straight
tubules, but its presence within the
capsule of Kowman remains doubt-
ful—in only a few cases have phe-
omena been observed that would indicate
this—actual proof there is not yet.
Cobalt
I shall not treat of cobalt at great length as I have done of nickel, partly because their actions turned out to be very similar, though not identical, and partly because the introductory remarks to the acts of experiment apply very closely to those of cobalt.

The literature is extremely sparse and meagre and is collected in the following pages.

The conditions of experiment, the salt of cobalt used, and its production and mode of administration all are the same as in the case of nickel.
Cobalt

From my experiments Cobalt appears to be a poison even generis. The nitrate and chloride which I experimented with tested by March 5 and by Bethends's methods were shown to be absolutely free from arsenic, and yet 0.01 gm of the substance killed a frog in half an hour, and 0.3 gm a small rabbit weighing 1/2 kilogrammes in 3 hours. The poison seems to act directly on the cardiac muscle. If one cup bore the heart of a frog, then poison it with the cobalt, the frequency of the heart's action sinks to one-half or a fourth the normal, in 5 minutes, in diastole, and mechanical stimulation produces no contractive move. If now the vafi be divided still no action appears so that the sensation cannot
Cobalt

be referred to as a vagal action. Of course it is to be here remembered that vagal section may have very little influence even in the normal frog. In the case of rabbits 0.1 gm. caused first depression, the pulse fell from 178 to 128 per min. Then the doses were poisoning death supervened with increasing depression though the reflex excitability remained. For the sake of comparison two equally heavy rabbits received the one 0.1 cobalt (metallic) as chloride and the other the same quantity of arsenic (metallic) as arseniate of soda. The first showed five minutes after the poison a great depression and diminution of the pulse frequency which lasted 25 hours and then completely disappeared. The other rabbit
Cobalt

three minutes after the injection, suddenly showed several paralytic and died within five minutes: the pulse rate remained unchanged, the breathing was slowed. In both cases there was at the beginning of the intoxication heat myosis.

Translation from Buchheim: Lehrbuch der Arzneimittelkunde, Leipzig 1878.

Also the nickel and cobalt salts introduced in small doses into the intestinal canal induce no toxic symptoms.

Concerning their action when introduced into the blood we possess no yet no sufficient knowledge.


The sulfate and the chloride of cobalt agree in their physiological action on dogs.
and rabbits, and have emetic properties.

Translated from Buchner, Toxicology, Berlin, 1867.

With these salts of manganese:

1. Chloride of manganese, and
2. Permanganate of Potass as the salts of nickel and cobalt agree. Of cobalt combinations, the oxide in 2 dm doses causes the death of dogs in a few hours, and of the chloride, 1/4 fn. from endemically causes vomiting.

It is to be noted that cobalt is always met with rendered impure by the presence of arsenic, and that these phenomena as well as poisoning from smalt are to be referred to the arsenic.

Translated from Buchner, Toxicology, Nürnberg, 1867.

According to C. F. Gmelin's experiments the cobalt salts act in general like the nickel salts, and few of cobalt...
Cobalt.

chloride injected into the stomach of a dog, induced only repeated vomiting.

2) Six grains of cobalt sulphate injected into the stomach of a rabbit killed it in a few hours. On dissection the gastric mucosa at the cardia and was found stuffed with dark red spots and of the greater curvature were broad brownish-red spots. In the lungs were two or three dark red spots of the size of a lentil and which could not be displaced.

3) Three grains of the sulphate dissolved in two drachms of water and injected into the jugular vein of a small dog, caused a minute vomiting several times repeated. Vomitus also appeared. Next day the vomiting recurred, the animal was very dull-looking, and from time to time gave signs of pain.
Cobalt.

The pulse was accelerated. On the fourth day death supervened. In dissection reddened spots were seen in the stomach and duodenum. The ileum projecting into the colon formed a valve-like process perhaps by continual retching and vomiting, during three days.

4) Twenty grains of cobalt chloride were injected into the external jugular vein of a small dog; there followed some deep respirations. The heart beats became inappreciable and death supervened within half an minute. The result appeared to depend on a paralysis of the heart.

5) Twenty-four grains of dry chloride of cobalt laid in a wound in a dog neck appeared to cause much pain. Wounding followed in five minutes. The dog gradually got better.
Cobalt.

well next day.

Translated from "Die Gerichtlich-Chemische Ermittelung von Giften, W. Degenoff, U. Schirmer, 1876.

Cobalt is chiefly used in the preparations of pigments, e.g., Persian green, Yurte, and Smalt. Also certain cobalt salts are used to make sympathetic ink.

Ayensu's work is quoted in the introduction to Part I where nickel and cobalt are taken together and no distinction of their different actions is made.

Heppert (see Part I) almost leads one to infer that the cobaltous salts are not poisonous, for he writes: "Nickel and cobalt salts may be as, "coated and the former are poisonous." Bergerefft and Parygenor diluted cobalt as they had done nickel, by their electrolytic method (see Part I)."
Cobalt.

In the Dispensatory of the United States of America, Philadelphia 1879, it is stated that an oxide of cobalt prepared by precipitating the chloride with potassium ferricyanide has been employed in rheumatism. It is emetic in doses of 10 to 20 grs. The salts of the metal are irritant poisons.

We thus see that emesis and cardiac paralysis are in the main the symptoms found in these few notices, and post-mortem inflammatory changes in the fasciae, pericardia. We notice also that "cobalt" is an ambiguous term which may mean either the metal or "cobaltium," a compound, of it used in the making of pigments and always associated with more or less of arsenic, hence the necessity for always testing the salts employed in so as to be sure of their purity. Then all combined however we see that definite knowledge of the action of cobalt on the animal organism really does not...
Cobalt.

Experiments on frogs were very numerous, but I select only four for transcription and these include the type symptoms. The follow resemble those of nickel. Work experiments performed under the same conditions as in the case of nickel.

The symptoms of cobalt poisoning agree very closely with those of nickel, and include the nico-ordnack movement and peculiar drawing up of the hind legs, uniformly dark colour of the skin, involuntary motor weakness, spastic action, fibrillar, clonic and tetanic contractions, the chilly cry, precocious paroxysms ending in paralysis, ultimate diminution of the heart action and death.

By exactly the same experimental methods as those employed in the case of nickel, I have localized the action of cobalt in the nervous centres of spinal cord certainly, of brain probably, and
probably also in the ganglia of the body generally. In all of these cases of excitement precedes one of paroxysm and then gradually progressing the animal dies from the insufficiency or cessation of one of the vital organic functions, respiration or circulation.

The special muscle work experiments show the absence of any affection of the striated muscular substance and thus indicate the impossibility of any direct affection of the heart's muscular substance. There is always a marked difference of the work of the normal and adrenalinised muscles, but it remains more than the control experiments seem to be consistent with the assumption of no particular action of adrenalin on the muscle substance.

**Rana Temporaria**

tr. 50.0 grammes

with 0.400 CC of per cent. of adrenalin

Rube pepper, 57, before injection.

5:30 Distillation: The legs are drawn up on to the back in the same peculiar jerking way as unnoticed in case of metal poisoning.
Jan. 27th.

The muscles of the entire body twitch just as in the guinea pig. The above-mentioned contraction of the left in still present. Same condition.

28th.

Same weaker in its movements but this is the only change.

29th.

Still weaker. Heart not strongly contracted.

30th.

Found dead. Heart not strongly contracted.

31st.

Rana Temporalia. 40.0 grammes with 4400 parts of 1 per cent eau de Javel.

Rana Temporalia. 40.0 grammes with 1 per cent eau de Javel.

Pulse regular. No before injection.

Injection.

The specimen drawn up by well seen. Laid on its back at first partially and will not turn round when prodded. It can still help the muscles of the entire body twitch constantly and violently and from time to time make strange-like contractions of the legs appear. The fore limbs are stretched out laterally, as if parted, so that the breasts lay on the ground. The heart motion as seen that the body walls appear to be quicker.

The twitching of the arms disappears, and the twitching of the arms.

The heart condition only not as marked.

The parietes is more pronounced.


Found dead. Heart not contracted, nothing pathological.

Rana Temporalia. Female. 65 grammes with 0.666 fr. 60 parts of 1 per cent eau de Javel.

Injection.

4:35 Movements inco-ordinate, peculiar drawing up of leg as in guinea pig cases, better yet evidently weakened. Heart not still can turn round from the dorsal position.

5:00 Movements are slow and inco-ordinated, twitching very
marked no longer supports herself well and as has
fallen to death.

She fibrillary contractions are beautifully seen in
all the limbs. The right sciatic in ventral
immediately the contractions cease in that limb.
 Pretty much deceased now.

Curare is administered and the twitching cease. So
extremely feeble twitchings are sometime noticeable in
the foot toe of the side the nerve of which is cut.
When aimed the central and are probably purely
accidental, from various causes.

Found dead.

Sektic - ventricle contracted and pale, anemic full
of blood. Nothing else noteworthy.

**Rana Temporaria** Male, Weight 26.5 grammes
With 0.666 60 per cent. of curare subcutaneously.

4.5

A few little twitchings of the fore toes, so decided,
palpated seems to retain the dorsal position when it moves.
the motions are very incoordinated. Seems struggle.
no longer.

5.0

These are some twitchings of the arms, it lies quite at
rest as is paralysed. Though it can still move a little.
Then laid on his back it seems to turn itself, but fails.
It makes clumsy incoordinated movements in 106
attempts.

5.5

**Status Discess.**

Supposed paralysed twitchings still, breathing yet,
and digits slightly on being touched, on being subjected
it suffers a violent general tetanic contraction
which is not abolished or diminished by complete
section of the spinal cord behind the sacrum.

Experiment ended.

**Muscle Work Experiments.**

First performed with 0.300 C.S. subcutaneously 6.38 p.m.

<table>
<thead>
<tr>
<th>Temperature</th>
<th>18°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse taken</td>
<td>130 per minute</td>
</tr>
<tr>
<td>Second leg amputated after 6 days</td>
<td></td>
</tr>
<tr>
<td>Gait</td>
<td>Normal</td>
</tr>
<tr>
<td>Distance from cord</td>
<td>52 m.m.</td>
</tr>
<tr>
<td>Time taken</td>
<td>26 minutes</td>
</tr>
<tr>
<td>Work done</td>
<td>48,750 joules</td>
</tr>
</tbody>
</table>

Second performed with 0.300 C.S. subcutaneously 6.38 p.m.

<table>
<thead>
<tr>
<th>Temperature</th>
<th>20°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse taken</td>
<td>130 per minute</td>
</tr>
<tr>
<td>First leg amputated after 15 days</td>
<td></td>
</tr>
<tr>
<td>Gait</td>
<td>Normal</td>
</tr>
<tr>
<td>Distance from cord</td>
<td>52 m.m.</td>
</tr>
<tr>
<td>Time taken</td>
<td>26 minutes</td>
</tr>
<tr>
<td>Work done</td>
<td>97,750 joules</td>
</tr>
</tbody>
</table>
Muscle Work Experiments

Ex. 81
Prof. David R. Esculenta No. 82 of 170 for amputation of first toe.

12:13 1 cc. of 25% CO solution = 0.025 CO
injected into the abdominal vein, throughout the whole soft
muscle tissue until

12:16 Similar dose

12:18 250 mg. 0.025 CO
injected into the abdominal vein, throughout the whole soft
muscle tissue until

12:20 Similar dose

12:25 No reaction has followed

12:28 First of amputated and its work determined. 2.5 kgf. of amputated and its work
determined.

Distance of film = 67 mm.

Temperature = 18° C

Matter 120 grams

Time taken 26 minutes

Work done 48,675.0 gram mm

The blood serum was as impreated with the 
back solution that it of a beautiful white color
and dropped away from the feebles.

Ex. 82
Male Rana Esculenta No. 114.0 Sammals
Feb. 10th: Normal

Distance of film = 88 mm.

Temperature = 18° C

Matter 120 grams

Time taken 22 minutes

Work done 82,675.0 gram mm

The first, after the amputation of the
second of the first toe, was
injected with 0.025 CO per kilo.

Feb. 12th: Distance of film = 88 mm.

Temperature = 18.5° C

Matter 120 grams

Time taken 18 minutes

Work done 41,875.0 gram mm

The first, after the amputation of the
second of the first toe, was
injected with 0.025 CO per kilo.

Feb. 14th: Distance of film = 88 mm.

Temperature = 18° C

Matter 120 grams

Time taken 22 minutes

Work done 82,675.0 gram mm

The first, after the amputation of the
second of the first toe, was
injected with 0.025 CO per kilo.

Feb. 16th: Distance of film = 88 mm.

Temperature = 18° C

Matter 120 grams

Time taken 18 minutes

Work done 41,875.0 gram mm

The first, after the amputation of the
second of the first toe, was
injected with 0.025 CO per kilo.

Feb. 18th: Distance of film = 88 mm.

Temperature = 18° C

Matter 120 grams

Time taken 22 minutes

Work done 82,675.0 gram mm

The first, after the amputation of the
second of the first toe, was
injected with 0.025 CO per kilo.
Cobalt

mine returns. After the lesion the reflex excitability was greatly lowered. There were no twitching but the moves remained quite possible. The heart beat regularly with intact pericardium 26 times per minute. The second of voice was not amplified and experiments with an abode. The trunk was killed.

Experiments on Rats

Chewing in nickel incordination and weakness of muscular movement, the drowning, and the trembling movements. In one case a diarrhoea. The dissections showed either nothing pathological or some vascular injection of the alimentary mucous membrane. In the case of white rats the injection and reducet of the feet and ears were well marked early in the case, afterwards it disappeared, and the paws became pale, cold and bloodless. Post-mortal. Some injection of the al-

3/45 Rat

With 0.020 C.O. per kilo. Not subcutaneously

Aug. 23 Injection practised.
12:15 Respiration got deep.
2:45 Appears somewhat drowsy. only.
19th. Apparently normal.

With 0.040 C.O. per kilo. Not subcutaneously.
Experiments on Rats cd.

Aug. 19th

4.0 Last on its side, breathing difficult, mottled, it rises but cannot move quickly, is laziest and weak, lies down at once or at other, falls over down.

6.40 Still weak and sleepy. Respiration seems all right when laid on its back, it cannot turn round again. Eats sugar, it chokes very much.

10.0 In the same condition.

28th. Found dead. Static showed nothing pathological.

Expt. 84. Rat

Aug. 12th

With 0.020 CO petals, pet subcutaneously

9.30 Injection practised.

10.0 Respiration 50, drowsy, unconscious, restless.

10.35 Eats and feels well. Is it from injected blood vessels?

12.0 Eats and feet no longer injected. Drowsy still as before.

4.0 Respiration 100. Condition same as before.

23rd. 6th

It has gradually become drowsier, sleepier and weaker. Has lost no appetite, some metallic diarrhoea and to-day (26th) it died. Section showed the stomach greatly injected. Nothing else noteworthy.
Experiments on Guinea Pigs are only two in number and show only a dulness or stupification and weakness of the extremities, the hind limbs especially. Post-mortem only gastric hyperaemia, haemorrhages or erosions.

Guinea Pig 1. 270.0f. with 0.020 CO per kilo. Guinea Pig subcutaneously

Aug. 18th
12:30 Injection practised.
2:15 No symptoms.
19th
20th 3.0
21st
22nd 3.0
23rd
24th 3.0
25th
26th
27th
14:0 With 0.080 CO per kilo. Guinea pig subcutaneously. After this dose it lies dull and weak looking almost as if it had been dead this morning.
Post-mortem examination. Nothing remarkable except the duodenum, which was empty of food.

Guinea Pig with 0.060 CO per kilo. Guinea pig subcutaneously

Aug. 19th
10:55 Injection practised.
11:05 Being on its back apparently stupified. Keep 64. Appears not to thin off rapidly where its left leg.
12:15 Somewhat recovered.
3:0 Very ill. Hind legs completely paralysed. Still stupified. Found dead this morning.

Post-mortem examination. Nothing pathological except at the posterior curvature of the stomach where there were very large haemorrhages and erosions. The wall was almost eviscerated.
Experiments on Rabbits

The animal let loose from the operating table after direct injection of the cobalt into the blood lies on its side, weak and exhausted, looking, with its pulse slow and regular, and the pupils normal. There may be passage of faeces and urine. The urine is of a very dark rich brown colour and contains the cobalt abundantly. In fatal cases the respiration becomes slower and more and more difficult until asphyxia convulsions occur and the animal dies.

In non-fatal cases the voluntary motor paralysis soon in all the more serious cases and particularly marked in the hind limbs, is gradually recovered from in the fatal cases it extends and becomes complete paralysia. The heart continues to beat and the blood columns of the retina remain unperturbed, when observed by the ophthalmocope for a long time after the cessation of respiration.

Post mortem.
Inflammatory changes in the fascia
and intestinal mucous membranes, mostly of small size, in the pleurae pulmonalis, in the epicardium, and in the endocardium.

Rabbit Male Wt. 1600.0 gr. With 0.010 Co O per
kilo, rabbit into the blood

Pulse 120 before injection.
12:40 injection practised. On being let loose from the board it lies down on its side as if weary, exhausted, looking, pulse 122, good. Pupils normal, breathing some-
since very quick, something not. Can ride lip when it is undisturbed. Some diarrhoea. Urination.

1.0Betty much in eerie condition. When it has been set
up it at once falls down again.

3.0Pulse 112 regular and good. Pupil and breathing normal.

May 10, 12:00 Pulse 104, go to bed well no more diarrhoea. Urine
very dark brown, coat practically normal.

Pulse normal, though the urine is still dark brown.

2nd
3rd
4th
5th
6th
7th
8th
9th
10th

3rd
4th
5th
6th
7th
8th
9th
10th

The continuing normal and urine gradually of

0.020 Co O per kilo, rabbit into the blood.

Pulse 162 before injection.

11:0 Injection after this operation pulse 128, it lies down
as if released, pupils not perceptibly contracted,
respiration normal.
Experiments on Rabbits.

Feb. 26th.

12.00 P.M. Food preparation normal, ate close to the floor and lay very, but moved quickly when disturbed.

12.15 Suddenly it falls down and lies on its side, pulse 160. Somewhat restless, pupils constricted, breathing difficult, eyes open and with difficulty.

12.20 Pupil dilated. On trying to move it against the reposition is becoming slower and with greater difficulty and the pulse becomes slower. Umbilicus with opisthotonos appear. This new pulse with and then the breathing is with great difficulty, urine in nervous and it dies apparently from respiratory paralysis for the respiration has ceased the heart is still to feel for some time after that it cannot be felt, if they teen to beat on opening the chest and the blood gushes if the heart does not beat for long after the cessation of respiration.

Autopsy examination.

Pupil contracted again. A few punctures of the median femoral of both sides gives rise to the gastric and intestinal muscles. His free scattered masses in the intestines. Two endocardial extravasations of small size on papillary muscles also, but most dorsal vein quite normal.

Ex 89.

Rabbit Large Male. 1876. 0.4 oz. with 0.040 Co

25th.

Take before injection 150.

12.45 Injection not much noteworthy noticed immediately. Pulse 200 fast, hard and regular. 124 lay an irregular line were paralyzed, but it can rise when muscles were forced by the servient dead, there had been no discharge and pupils were not contracted. In short, nothing remarkable to relate.

Post mortem examination.

Excising a number of very small extravasations in the jejunal muscles. And one, on the broad at the lower end of the loop, intestines, nothing pathological in any organ and all were carefully examined — not detected.
Note:

Cobalt was found in the contents of upper end of caecum, since there had been no diarrhoea, and no gall had come down so far as the caecum, and since there was no sign of blood effusion, nor of any laceration of tissue being crushed, we may fairly assume that the cobalt was secreted by the caecum and was present in the intestinal secretion.

Rabbit No. 1739.05 with 0.015 CO per kilo.

 Pulse 232. Respiration 228. Temperature 39.95°C.

11.30 Injection practised.

3.0 Has shown no symptoms noteworthy. Temp 40.0°C.

Receives 0.025 CO per kilo. additional.

6.48 Apparently normal.

9.00 Normal.

Thrombosis of vein "sustained" and apparently not well but spells beyond this nothing of remitted and at

3.00 It was found dead.

Post mortem examination:

Lungs filled with blood. Numerous little extravasations in the epicardium and some

at the pylorus. Elsewhere nothing.

Rabbit. Female No. 1685.05. Chemically poisoned.

Pulse: 268. Respiration: 120. 

Commenced with 0.002 CO daily.
Experiments on Rabbits. cd.

Dec. 17th
18th
19th
20th
21st
22nd

Feb. 4th
14th
15th
24th
25th

Mar. 1st
2nd
3rd
8th
15th

Pulse. Respiration.
188
184
120
150
200
120
144

Height 163.0 fr.

Dose increased to 0.006 CO daily.

Dose increased to 0.010 CO daily & 1,700 gm.

Fundus would remain normal.

Injection practised at 7:30 afterwards it did not seem affected. None of ears dilated.

Blood normal 0.010 CO given.
0.080
0.010
0.010
0.010
0.010

Each day has received 0.010 CO 60 & 1370.5 gm.

Mean of several results differing insignificantly from each other = 12.2%
Experiments on Dogs

On injecting the cobalt solution into the blood the respiration becomes greatly accelerated. There is vomiting and passage of feces. The vomiting first brings up contents of stomach, then mucus and persists a long time. The passage of feces may be really a sort of nervous diarrhea where the fluid is spouted forth in an almost continuous stream. Urine may now be passed. Let loose from the operating table it lies on its side exhausted, the breathing now gradually becomes more like the normal and recovery rapidly sets in. In fatal cases the breathing gets gradually deeper and more difficult, and convulsions, probably asphyxia, precede the fatal issue. For several minutes after death the heart still beats. Where the case is less acute, spasmodic jerks of different parts may be noted. The urine passed sufficiently long after the cobalt
has been administered, is of a rich dark brown colour and contains abundant cobalt.

Post mortem.

The pathological changes noted are, cattavacations of small size in the epicardium and endocardium. The gastric and intestinal contents are bloody mucus, and the alimentary mucosa is congested in various degrees and may have haemorrhage co nuneous as to be confluent. The surface of the brain seemed to be hyperaemic.

When the urine is allowed to stand till decomposed a copious deposit of rich purple and crimson-coloured crystals falls consisting mainly of triple phosphates containing some cobalt compound bound up with it. This is a delicate test for cobalt in the urine.

Dog. Old male ft. 5,350 of fr. with 300 per hils def. subcutaneously.

Pulse 120 somewhat irregular before injection.

11. 45 Injection

Nothing was noticed after this excepting that he soon let fall a great many of pieces.

6. 30 Pulse 140. Pretty regular. Slightly thorny.
Experiments on Dogs.

Pulse 122. Good and regular. Seems normal.

\[ \text{Normal.} \]

Dog Young Males. Wt. 20,450 g. 6 hr. with 0.30 C. O

3.0 ml. of injected into blood directly

injection into the metatarsal skin. The respiration is accelerated and immediately begins to become more rapid. Within brought to the cage the quiet breathing continues. As dog the mucous membrane and diaphragm, etc., is a little self-down as if intoxicated. It might be said this is simply from the struggles during the operation; but having had ample time to recover from this and being a fear-stricken animal, I think the results are fairly due to the cobalt.

3.0 hr. Pulse 200. Regular and pretty strong. There has been some vomiting and diarrhea of the same character.

4th. Nothing noteworthy appears lively and well; pulse regular and good.

100. Urine very dark and contains a very large quantity of amebal.

5th. Pulse 150, regular and good. To the right eye is some pus, but it is the left nictiling to be seen.

The urine showed nothing, striking but was made very specially thrown away by the servant. What remained showed questionable evidences of cobalt.

6th. 3rd. 16th. Seems normal.

10th. 12.20 2 cc. of a cobalt solution is 100 C. 0 per kilo. Def injected into the blood. During the operation there was no least movement or struggle but there came a large quantity of fluid feces and this was followed by an enormous quantity of a severe fluid. After dlying operation was done and rapid and no remarkable change in it was observed. Pupils unchanged. Vision only indicated. Afterward the pulse was 97; not very strong and regular as before, possibly merely from a sensation of the excitement of the operation. 12.50 Pulse now good, will not yet eat anything, vomiting some mucus.

3.0 Pulse 128; good and regular, pronounced much muc. mucus.
Feb. 15th.

The patient is exhausted, breathes regularly, but as if with an expiratory dyspnea. No fever, nor any change of the pupil has been noticed.

Wakes feebly, gets general convulsions, and dies. The respiration gradually ceasing, but the heart beats long after the breathing has ceased. No miosis has been remarked.

Post-mortem examination.

Pupils, lungs and pericardium normal. Blood dark and coagulated. Heart filled with blood and only one lentil-sized extravagination in the epicardium. Heart muscle is absolutely normal. Endocardium especially of ventricles and particularly of left ventricle, both on the walls and valves, show large and small extravagations. As described elsewhere. In the heart, some congestion of the lungs.

Contents of stomach somewhat blood-stained mucus. Gastric mucus red all over, especially the pylorus and in its neighborhood. The stomach was extremely dilated and here were many numerous little extravagations. This reduces to a passing condition of the duodenal mucosa, but the gastric redness was very prominent while the duodenal was not and thus a distinct line marked the transition. Only one small solid mass of contents in the intestines. The rest was a dirty-looking reddish-brown fluid. The intestinal mucosa was reddened all over and death congestion spots and extravagations were present all over. It was most on duodenum, the stomach, the jejunum and last in the vermiform appendix. Splenic, liver, and pancreas normal. No peritonitis. Urinary bladder empty, its mucosa normal. Kidneys congested. Feces have been very dark brown in both times. Obst detected in the bile.

Dog

Young Male No. 2, 6 lbs. 6 oz. received 0.030 Gr per kilo, as if into the blood.

Mar. 2.

Pulse good 120.

12.0 Perfusion performed. Immediately some solid feces passed, soon he vomited. Pupils remain normal, then be quite quiet. Heat good 120.

12.40 Pulse 144.0. Heart beat very strong, some diarrhea, feces thin, brown and contain blood.
Experiments on Dogs, ca.

May 3.0
Case 175. Good. Some more diarrhoea, nothing to breath, except that the urine is deep brown, tannish red. Urine and has no albumene.

5.30
Case 176. Poor. Very much vomit. Process: 60 TID m. pilocarpin were given subcutaneously in doses at intervals, in order to obtain saliva for analysis, but the saliva did not flow as was wanted, and we gave things to make breathing point lead, and also saline has flowed, but nothing to report of.

Post-mortem about 18 hours after death.

Feb. 21st. 9.30
Dog St. George, Male Wt. 57.400 lb. with 0.050 C0 per lb. of into blood

12:30 Injection prepared.
3.0 Pulse 80. Before injection.
3.30 Pulse 80, good but not regular as normally. No feces passed, has vomited much frothy liquid, inconso matter, pretty frothy.
5.45 Lie on his side, inspiration difficult, from time to time opson of scam character and of white members. The face was also very violently contracted and so the teeth well shown. The respiration became more and more difficult and accompanied by a sound as if there were opson of the lungs. During the expiration the head is not to be felt and only at 6.10.

Immediate after death the chest wall is opened, but pericardium is left mitral, the heart beats quite well for 6 or 7 minutes longer.

Post-mortem examination. 24 hours after death.
Reflexes perfect. Blood is dark and coagulated. Stools normal. Gastric contents clear fluid.
and brownish-coloured, intestinal contents very little in intestine and of same nature as in stomach. Bowels do not contain the faecal material, and extravasation increase in number; and are most pronounced in rectum. Tumors pleuræ, pericardium, liver, spleen, and pancreas all normal. Some cells cardiac extravasation: none elsewhere in heart. Urinary bladder contains a few g. of dark brown urine. Urinary ducts are freely dilated, bladder is greatly congested, and has numerous smaller and larger opaque spots are doubtful extravasations and of these are on the cerebellum and none on the white substance.

Dog Male Ht. 5'00. of fs. Weight 0.380 C. 0 per

Pulse 120, good, just before injection.
0.50 Injection of 0.50 g. blood pressure during operation.
1.00 Vomited of bile stained mixture.
3.00 Pulse 120, good, regular, stands quietly, but looks miserable. See vomiting, much frothy, tough material, and there has been dehydration, but there is
4.00 good thin and vigorous. The vomiting and dehydration have ceased for some time.
8.00 For some time past he has breathed deeply, and as if with difficulty, and has given expressions as if pain. The breathing became more and more difficult, only once were spasms of the chest beyond
8.20 Death supervened quite quietly, the heart cannot be felt to beat. Gentle, and aperture is immediately made in the chest wall, the periosteum, pleuræ, and lungs, and through the heart is seen to beat quite regularly for 5 minutes after death.

Post mortem examination 24 hours after death.
Supra normal. Adrenals normal. Blood dark and
coagulated, some coagulation of glottis, epiglottis,
and trachea, lining and pleurae normal. Heart
has weakly coagulated blood no decomposed coagula
present. Absolutely no thrill pathologic on ends—
mean epi- or pericardium. Both ventricles con-
tacted, pleurae normal. Much fasting con-
tenent partly bureaus, partly purple or black flour
Experiments on Dogs—ed.

Blood admixture, and closely applied to the mucosa is a layer of black matter evidently death-made-up of blood. Gastro-mucosa at the cardiac esophagus and pylorus is approached, that extravasation spots become more numerous and eventually confluent so gaps to form black masses. Intestinal contents thick and brown no solid masses. Whole length of intestinal mucosa contracted and loose with extravasations in the duodenum jejuni and caecum quite opalescent to form dark masses. Kidney normal, urinary bladder contracted, normal! Liver and pancreas normal, spleen with marginal infarcts. Liver of don a water large, while grey substance is congested and there spots of green congestion may be even small extravasations. White matter with well-marked peritoneum.
Cobalt.

Blood Pressure Experiments

On injecting the Cobalt into the blood directly we do not notice any remarkable change in the rate or character of the Pulse. First however it is usually accelerated but after a time its frequency diminishes. When the pressure is low and suffocation is established we see that the beats become extraordinarily large.

The blood pressure falls usually gradually, sometimes however rather suddenly and reaches a minimum—practically zero.

We do not distinguish any noteworthy difference between the pressure curves of nickel and of cobalt and since I have fully dealt with the former it seems superfluous to treat of the latter at greater length.
Blood Pressure Experiments

Dog

67 kilos.

Experiment commenced. Carotid and femoral artery

Exposure continued

Tie evident that the character of the
Blood Pressure Experiments

10.36 Press. 80 mm. Hg
Abdominal compression raises the pressure only slightly and temporarily.

12.15 140

Notable normal pressure at 140 mm. Hg.

2.30 74 244

CNV denervated.

3.30 188

Aspiration during 20 seconds, no rise either during or after it.

5.30 188

Cervical spinal stimulation not attained to its maximum effect raises the pressure to 216 mm Hg.

Notable compression raises pressure from 58 mm Hg = 15 mm Hg.

One followed a succession of curves.

1) Sphagiae showing that the middle portion of the vagus motor system is paralysed, since there is no rise of pressure, and showing that the head beate regularly and strongly.

2) Cervical spinal stimulation which raises the pressure at once.

The pressure first gradually loses 90, 124, 104, 56, 73, 57 mm Hg in the last. The pressure before stimulation was only 23 mm Hg. Then is pressed that neither the vagus nor the nerve fibre nor the peripheral terminations nor the vascular muscle is neutral of effect.

Therefore it is the vagus motor which these results and suggests these conclusions for we see that the heart can still maintain a higher pressure.
Blood Pressure Experiments

No. Rabbit

10th

11.33 Injection of cobalt solution into blood of external jugular vein

12.30 Normal pressure after the vasa have been cut and compression established.

12.30 Injection of cobalt commenced.

12.30 Oscillation of the injection of 0.2 Cobalt has a high point 445 m. mm. 4th

11.44 Similar oscillation after smaller dose followed by low point 267 m. mm. 9th

11.54 Low point of oscillation 155 m. mm. 17th

12.17 Average high = 3 c.c. solution of atropine injected 12 m. at anesps. 

12.17 Another 1 c.c. of atropine sulph.

12.14 After c.c. solution has been given.

12.14 Low point of oscillation 65 m. mm. 14th

12.13 Abdominal compression.

12.12 S. Water injected to contrast effect of vein water injection.

Large Male Rabbit

May injection into the external jugular vein.

10.35

88 268 52

Before injection commenced.

Injection of 0.5 c.c. solution = 138 C.C.

50 Spasms.

11.1 Pressure passed.

12.33 This dose of 5 c.c. just finished.

21

576 296 32

62 250 28

5 330 16

7 58 350 12

21 576 296 32
Blood Pressure Experiments

Mar 10th.

11.33 582 27 97
.39 575 552 72
.46 63 109 44
.55 22 171 20

12.06

which caused pressure to 66 mm Hg
and depressed the pulse to 72 per min.
and the respiration to 16. Similar rise
are seen to follow similar doses.

Third dose of 138 CO just finished.
Fourth about to be finished.

Suffocation practiced for 30 sec.
Blood pressure during aspiration at beginning = 20

The respiratory pulsations are due to
the effect of the animal's efforts to
breathe and the intra-thoracic abnorm-
ally. It is noticed that while
the pressure falls, this effect is
more or less marked.
Just after repo, the pressure sank gradually to 70.

The respiratory movements ceased,
but pulse waves were seen long
after this has happened.
Excretion of Cobalt

Chiefly this is through the urine which, as long as appreciable quantities of cobalt are present, has a rich and dark brown colour. Many states that the blood corpuscles are broken up and destroyed: it is possible that the brown colour of cobalt urine has led him astray for he might suppose that this dark brown colour was due to decomposition products of the blood pigments. It is not so, as proved by spectrum analysis.

When the urine is allowed to decompose a rich crop of beautifully tinted crimson and violet crystals are formed—these form chemical and microscopic examination turned out to be triple phosphate crystals, which had taken up some cobalt and became coloured differently as is indicated by Rose in Gmelini's "Organische Chemie."

I have not yet been able to col...
Cobalt.

least sufficient of the brown-coloured cobalt compound in order to analyse it: it is completely precipitated by basic acetate of lead and when the precipitate is washed with hot water, the brown colour may be extracted from the washed precipitate by a solution of carbonate of ammonia. The solution may now be placed over sulphuric acid, and so may be obtained a brown solid residue which is presumably the brown coloured compound. Some cobalt remains in the urine unprecipitated by the basic acetate of lead, and some remains unextracted by the ammonia carbonate. This cobalt evidently is excreted in different forms of combination. The colouring of the triple phosphate crystals seems to be a very delicate test for cobalt in the urine.

I have detected it also in the bile and intestinal juice, and therefore
also in the faces which derive probably from its sulphide their black, or very dark brown color.

Nickel & Cobalt.

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Nickel & Cobalt.

Nickel & Cobalt

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