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THE PHYSIOLOGICAL ACTION OF CARBON MONOXIDE OF NICKEL.

[FROM THE *PROCEEDINGS* OF THE PHILOSOPHICAL SOCIETY OF GLASGOW.]

On the Physiological Action of Carbon Monoxide of Nickel.

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[Read before the Society, 29th April, 1891.]

By the kindness of Mr. Ludwig Mond, we have had the opportunity of examining the physiological action of carbon monoxide of nickel, a substance of unique chemical composition represented by the formula $Ni(CO)_4$. This substance was discovered by Mr. Mond, co-operating with Dr. Carl Langer and Dr. Friedrich Quincke, and its chemical properties have been described by them.† It is a clear liquid of high refractive power, boiling at 43° C. at 751 mm., and having a specific gravity of 1·3185 at 17° C. The fluid is soluble in alcohol, benzine, chloroform, and pure olive oil. It readily evaporates on exposure to the air, the remainder, even in a well-stoppered bottle, undergoing decomposition. For this reason, it must be kept in sealed glass tubes, and we found it difficult to preserve it when the point of the tube was broken off, and a small quantity removed for purposes of experiment, however quickly we sealed up the point in a blow-pipe flame.‡

The method of administration adopted was by subcutaneous injection. The following experiments were, in the first instance, made upon frogs :—

Experiment 1.—At 11.3 a.m., 1·14c.c. injected under skin of the back. The substance evidently acted as an irritant, as the animal contorted its body and rubbed the skin over the seat of the injection with its hind limbs; at 11.30, there was paralysis of fore and hind limbs; at 11.50, respiration was very slow; at

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‡ A notice of a communication on $Ni(CO)_4$, by M. Hanriot, appears in *Nature* of 9th April, 1891, as having been communicated by him to the Société Chemique on 27th February. In this notice it is stated that M. Hanriot found the substance to be more poisonous than carbonic oxide, and that the blood give the characteristic spectrum of co-hæmoglobin. Our work was carried on independently at intervals during last winter.

12.20, the animal was dead. The blood was of a bright red colour, and, when examined with the spectroscope, showed two absorption bands in the position characteristic of carbonic oxide-hæmoglobin. These bands persisted after the addition of sulphide of ammonium.

Experiment 2.—At 2.48 p.m., ·54c.c. injected under skin of back; at 2.51, the frog croaked repeatedly and rubbed irritated spot with its hind legs; at 2.53, we observed that the eyes were remarkably prominent; at 2.56, it rubbed its head with its fore limbs; at 3.12, the eyes were much retracted—the web of the foot examined under the microscope showed a very slow blood stream in the vessels; at 4.20, there was slow respiration; and at 4.22 the animal was dead. A spectroscopic examination showed two absorption bands irreducible by sulphide of ammonium.

Experiment 3.—At 3.25 p.m., ·3c.c. injected under skin of the back; at 3.31, the frog rubbed its back with its hind limbs and its head with its fore limbs; at 3.32, the eyes were retracted; at 3.46, the circulation in the web was very slow; at 3.58, there was gasping respiration; at 4.2, there was almost complete stoppage of circulation in the web; at 4.8, the animal was killed. The heart was beating feebly, and a drop of bright red blood taken from it showed the double absorption band irreducible by sulphide of ammonium.

These experiments all pointed to the poisonous action being similar to that of carbonic oxide.

Experiment 4.—At 10.33 a.m., ·3c.c. injected under the skin of the back of a white mouse; at 10.36, there was slow prolonged breathing; 10.38, convulsive twitchings of limbs, especially of hind legs; 10.39, a general spasm; 10.39½, fibrillar twitchings of muscles; 10.40, gasping breathing, lying on back, paralysed; and at 10.48, the animal was dead. On opening the body the tissues were seen to be of a bright red colour, and the vessels were full of bright red blood. The blood from the heart showed a double absorption band in the spectrum, not changed by addition of sulphide of ammonium. The animal died in 15 minutes.

Experiment 5.—At 10.43, a small rabbit, weighing 330 grms., had 1c.c. injected under skin of back. It died in 20 minutes. There was marked paralysis of the limbs, appearing first in the hind limbs. The respirations became extremely rapid and gasping towards the close of life. This was the first case in which the temperature of the rectum was taken at intervals. The first

reading, immediately before receiving the injection, was 35·5° C.; the temperature steadily fell, and at the moment of death it was 32° C. This observation directed us to the remarkable reduction of temperature caused by $Ni(CO)_4$. The next experiments illustrate this point.

Experiment 6.—A larger rabbit than the subject of Experiment 5 was taken, but the weighing was unfortunately overlooked. The animal was wrapped in a towel, and a thermometer was kept in the rectum during the greater part of the experiment. Great care was taken to keep the thermometer always at the same distance in the bowel, as it was found that pushing it a little farther in, or drawing it a little farther out, caused considerable variations. The following are the readings :—

	Temperature of rectum.	Remarks.
12 noon ...	37·3 ...	
12.5 ...	39·1 ...	
12.10 ...	38·9 ...	
12.12 ...	38·8 ...	·13c.c. of $Ni(CO)_4$ injected under skin of back.
12.13 ...	38·5 ...	
12.14 ...	38·5 ...	
12.16 ...	38·4 ...	
12.17 ...	38·4 ...	
12.18 ...	38·35 ...	
12.20 ...	38·2 ...	
12.21 ...	38·2 ...	
12.22 ...	38·1 ...	
12.23 ...	38·0 ...	No convulsions. Respiration slower.
12.24 ...	37·85 ...	
12.25 ...	37·7 ...	
12.26 ...	37·68 ...	
12.27 ...	37·6 ...	
12.28 ...	37·5 ...	
12.28.5 ...	— ...	Twitching of right hind leg.
12.29.5 ...	37·4 ...	
12.30 ...	37·35 ...	
12.31 ...	37·28 ...	
12.32 ...	37·19 ...	Twitching of right hind leg.
12.33 ...	37·1 ...	
12.34 ...	37·0 ...	
12.35 ...	36·91 ...	
12.36 ...	36·81 ...	
12.37 ...	36·8 ...	Slight twitching.
12.38 ...	36·8 ...	
12.39 ...	36·7 ...	

	Temperature of rectum.	Remarks.
12.40	36·6	
12.41	36 5	
12.42	36·47	
12.43	36·39	
12.44	36·31	
12.45	36·25	
12.46	36·18	
12.47	36·1	
12.48	36·01	
12.49	35·94	
12.50	35·95	Thermometer pushed slightly farther in.
12.51	35·95	
12 52	35·9	
12.53	35·89	Micturates on instrument.
12.54	—	
12.55	—	
12.55.5	35·72	
12.56	35·7	
12.57	35·51	
12.58	35·49	Twitching of right hind leg resumed.
12.59	35·4	
1.0 p.m.	35 38	
1.1	35·3	
1.2	35·27	
1.3	35·26	
1.4	35·2	
1.5	35·11	Marked twitching.
1.6	35·09	
1.7	35·06	
1.8	35·02	
1.9	35·99	
1.10	34·91	
1.11	34·9	
1.12	34·88	
1.13	34 9	Micturates on thermometer.
1.14	34·9	
1.15	34·82	
1.16	34·72	Animal allowed to run about a little. Shows weakness of hind limbs. Vessels in ear full of bright red blood.
1.29	33·3	Animal lies quiet on table without being held. Slight tremor in right hind leg. Twitching of right upper eyelid.
1.34	32·5	
1.47	31·93	

	Temperature of rectum.	Remarks.
1.51 ...	31·6 ...	
1.55 ...	31·4 ..	
2.0 ...	31·0 ...	
2.5 ...	30·47 ...	
2.12 ...	30 0 ...	
2.15 ...	29·5 ...	
2.17 ...	— ...	Severe convulsive seizure. Gasping.
2.20 ...	29·3 ...	
2.25 ...	28 6 ...	
2.34 ...	28·1 ...	Rabbit placed in a large jar of pure oxygen.
2.47 ...	26·3 ...	
3.0 ...	26 ...	
3.5 ...	— ...	Respirations 52 per minute.
3.13 ...	— ...	Respirations 40 per minute. Taken out of jar of oxygen, and placed in a box before the fire, to warm the body, which had become perceptibly cold. The temperature rose up to 28·5.
4.30 ...	— ...	Animal died after a severe convulsive spasm.

This experiment shows that, after a subcutaneous injection of ·13c.c. of $Ni(CO)_4$, the temperature steadily fell from 38·8° C. to 26° C., and that the animal died in 4 hours 18 minutes. There was a fall of temperature of 12·8°.

Experiment 7.—A rabbit weighing 572 grms. was wrapped in a towel, and the temperature of the rectum was taken at intervals.

	Temperature of rectum.	Remarks.
12.10 ...	38·9 ...	Thermometer in rectum.
2.15 ...	37·0 ...	
2.20 ...	37·0 ...	
2.25 ...	— ...	Thermometer accidentally came out.
2.30 ...	36·5 ...	
2.35 ...	35·8 ...	
2.36 ...	35·5 ...	Thermometer removed.
2.38 ...	35·6 ...	
2.45 ...	35·6 ...	
2.50 ...	36 ...	
2.55 ...	35·9 ...	Animal released and allowed to run about.
3.5 to 3.20	36·6 ...	Temperature remained fairly constant.

As already stated, we found that a slight variation in the distance to which the thermometer was pushed into the rectum

caused a considerable variation in the reading, and, to secure accuracy, we had a mark on the thermometer, and the instrument was inserted up to this mark in each observation.

	Temperature of rectum.	Remarks.
3.21	—	·06c.c. injected below skin of back.
3.27	—	Rabbit less lively; slight paralysis of hind limbs.
3.30	35·8	Vessels in ear full of bright red blood.
3.35	—	Fore limbs weak; animal resting on belly.
3.40	34·7	
3.45	—	Marked weakness of right leg.
3.47	—	Both legs extended.
3.50	34·3	
4.4	34 2	Head falling forwards.
4.10	33·2	No attempt to pull itself together when the animal's limbs were moved.
4.20	33·7	As animal's feet cold, it was placed before the fire.
4.30	33·9	After gasping respiration, animal died.

In this case ·06c.c. killed the animal in 1 hour 10 minutes, and the temperature fell from 36·6° to 33·9°, a fall of 2·7°. The seat of the injection was somewhat congested. Chemical tests showed the presence of nickel in the tissue of that region. The blood also gave reactions showing the presence of nickel.

As ·06c.c. of the pure liquid $Ni(CO)_4$ represented 1 minim of the fluid, and as we were desirous of giving smaller doses, we next attempted to use a solution of 1 of $Ni(CO)_4$ in 10 of chloroform. This we termed the $\frac{1}{10}$th solution, and 1 minim represented ·006c.c. of pure $Ni(CO)_4$.

The following experiments were performed with this solution :—

Experiment 8.—Rabbit weighing 720 grms. Respirations 54 per minute. Temperature of rectum taken repeatedly at intervals, and found to be fairly constant at 38·3°.

	Temperature of rectum.	Remarks.
3.47	—	1 minim (·006c.c. of $Ni(CO)_4$) of nico-chloroform solution injected under skin of back.
3.55	37·1	
4.5	36·2	
4.10	—	Respirations 48 per minute.
4.13	—	Animal eating.

	Temperature of rectum.	Remarks.
4.15 ...	35·6 ...	
4.20 ...	— ...	Eating freely.
4.25 ...	35·75 ...	
4.35 ...	35·7 ...	
4.45 ...	36·2 ...	
4.55 ...	36·3 ...	
5.5 ...	36·5 ...	
5.15 ...	36·5 ...	
5.25 ...	36·0 ...	
5.35 ...	35·9 ...	Animal left running about in a warm room.
7.0 ...	36·4 ...	
8.30 ...	37·0 ...	Animal seemed vigorous and uninjured.

Experiment 9.—On the following day, at 10.35 a.m., the same rabbit had a temperature of 37·35°.

	Temperature of rectum.	Remarks.
10.40 ...	— ...	1 minim (·006c.c. of $Ni(CO)_4$) of nico-chloroform injected under skin of back. (The fluid showed a slight turbidity of a greenish colour.)
10.50 ...	36·5 ...	
11. ...	36·35 ...	
11.10 ...	36·2 ...	
11.20 ...	35·9 ...	
11.30 ...	36·0 ...	
11.40 ...	36·0 ...	
11.50 ...	35·9 ...	
12.0 ...	36·0 ...	
12.10 ...	35·6 ...	
12.20 ...	35·8 ...	
12.30 ...	35·7 ...	
12.50 ...	35·7 ...	
4.40 ...	36·7 ...	

The animal throughout the experiment appeared to be little affected, but there was a fall of temperature. In both experiments, 8 and 9, the temperature rose after the effect of the injection had passed off.

Experiment 10.—The same rabbit as was subjected to Experiments 8 and 9 was again used. At 1.35 the temperature of the rectum was 38°, and it was found to be fairly constant. The solution of $Ni(CO)_4$ in chloroform showed a dirty greenish precipitate,

which was suggested to be hydrated oxide of nickel, produced by the chloroform not being anhydrous.

	Temperature of rectum.	Remarks.
1.36 ...	— ...	2 minims (·012c.c. of $Ni(CO)_4$) of nico-chloroform were injected under the skin of the back.
1.45 ...	37·9 ...	
2.0 ...	38·0 ...	
2.5 ...	— ...	Animal drowsy, as if affected by chloroform.
2.20 ...	37·2 ...	
2.50 ...	37·0 ...	
3.15 ...	37·0 ...	
4.10 ...	36·8 ...	
4.35 ...	36·5 ...	

In this experiment there was a slight fall of temperature. The rabbit, although carefully looked after, was found dead in its hutch two days later. The bladder was distended with urine, the kidneys were congested, there was serous fluid in the pricardium, the left ventricle was empty and the right was full of clot. No trace of nickel could be discovered in the heart, blood, or urine. Probably the chloroform solution had decomposed, and no $Ni(CO)_4$ was present. The slight fall of temperature may have been due to the chloroform.

We attempted, but without success, to use a solution of $Ni(CO)_4$ in pure olive oil. Thus: the point of a small sealed tube containing ·75c.c. of $Ni(CO)_4$ was broken underneath the surface of 86c.c. of pure olive oil.

Experiment 11.—A rabbit, weighing 1290 grms., at 2.46 had a temperature in the rectum of 38·1° C.; at 2.49, 20 minims of olive-oil-solution of "nico" (1/85c.c. of $Ni(CO)_4$) were injected under the skin of the back. At 3 o'clock, there was no perceptible effect; at 3.1, the temperature was 38°·1 C.; at 3.24, 37°·7 C.; at 3.43, 37°·6 C.; and at 4, 37·6 C.

Experiment 12. — A small house-mouse had 10 minims = 1/172c.c. of $Ni(CO)_4$ of olive-oil-solution of "nico" injected under skin of back. No effect was observed.

We next made a solution of $Ni(CO)_4$ in pure anhydrous chloroform, as follows:—A small sealed tube, containing ·75c.c. of $Ni(CO)_4$, was broken in a dry, well-stoppered bottle containing 16c.c. of anhydrous chloroform, and 1 minim represented 1/300c.c. of $Ni(CO)_4$.

Experiment 13.—A rabbit weighing 1460 grms. was the subject of the next experiment.

	Temperature of rectum.	Remarks.
2.34 ...	— ...	Injected 10 minims of chloroform-solution of "nico." 1/30th c.c. of $Ni(CO)_4$.
2.36 ...	39·0 ...	
2.50 ...	38·6 ...	Weakness of hind limbs.
2.57 ..	38·5 ...	
3.00 ...	38·3 ...	
3.5 ...	38·25 ...	
3.10 ...	38·2 ...	
3.15 ...	38·0 ...	
3.20 ...	37·9 ...	
3.25 ...	37·7 ...	
3.30 ...	37·5 ...	
3.35 ...	37·2 ...	
3 40 ...	37·0 ...	
3.45 ...	36·8 ...	
3.50 ...	36·6 ...	
3.57 ...	36 3 ...	
4.0 ...	36·2 ...	
4.7 ...	36·1 ...	Animal eating turnip.
4.12 ...	35·8 ...	
4.15 ...	35·5 ...	Animal left with complete paralysis of hind limbs, and the temperature still falling.
6.45 ...	33.2 ...	Hind legs still paralysed; not eating; pupils dilated.
7.35 ...	32·8 ...	

Next day the animal was alive, and the hind limbs were paralysed.

	Temperature of rectum.	Remarks.
11.15 ...	29·5 ...	In rectum.
	31·3 ...	In mouth.
12.30 ...	32·2 ...	Mouth.
3.30 ...	32·5 ...	Mouth.
5.30 ...	32·5 ...	The animal was kept in a box near the fire.
6.20 ...	33·5 ...	
8.30 ...	34·7 ...	
9.40 ...	34·4 ..	Still paralysis of hind limbs.

At 10.40 on the following day the temperature of the rectum was 31·3° C. The animal was weak, refused food, and the bowels were loose. Next morning it was found dead.

This experiment shows that the 1/30th c.c. (·033) of $Ni(CO)_4$ in ·4c.c. of anhydrous chloroform was lethal, and caused a fall of temperature of no less than 9·5°.

As it is well known that chloroform causes a fall of temperature a control experiment was performed in which the same quantity of anhydrous chloroform was given as in Experiment 13, but without $Ni(CO)_4$.

Experiment 14.—A rabbit, weighing 1342 grms., had at 4 p.m. 10 minims (·6c.c.) of anhydrous chloroform introduced below the skin of the back.

	Temperature of mouth.	Remarks.
4.0 ...	38·8 ...	
4.25 ...	38·5 ..	
4.30 ...	— ...	Rabbit drowsy.
4.35 ...	37·6 ...	
5.0 ...	37·3 ...	
5.15 ...	36·9 ...	
5.30 ...	36·1 ...	
5.45 ...	35·5 ...	
6.0 ...	34·7 ...	
6.15 ...	34·3 ...	
6.25 ...	34·1 ...	
8.30 ...	35·2 ...	Rabbit running about.
9.17 ...	36·0 ...	
9.35 ...	36·0 ...	

At 10.45 a.m. next day the temperature was 38·2°, and the animal was quite well. This experiment showed a fall of temperature 4·7° in the course of 2 hours 25 minutes, when the temperature began to rise, and the normal temperature was regained next morning. In Experiment 13, the temperature had fallen 5° in about the same period of 2 hours 25 minutes, but it continued to fall for 24 hours longer, when it began slowly to rise. The effect of $Ni(CO)_4$ was therefore much greater and more persistent than the effect of the chloroform in which it was dissolved.

As 1c.c. of the liquid $Ni(CO)_4$ at 17° C. contains ·4470 grm. of nickel, we next studied the action of a corresponding amount of nickel in an aqueous solution of nitrate of nickel of such a strength that 1c.c. contained ·4470 grms. of nickel. Two solutions of this in water of the strength respectively of 1 in 300 and of 1 in 20 (the same strength as in Experiment 13) were used.

Experiment 15.—A rabbit weighing 1836 grms. had. at 4.30, a temperature in the mouth of 38·9. Ten minims (·6c.c.) of

1/300th solution of nitrate of nickel in the water containing the same amount of nickel as 1/450th c.c. of "nico" were injected under skin of back. The temperature was unaffected. At 6.16 it stood at 39·1 and at 8.45 at 38·6. Then 10 minims (·6c.c.) of 1·20 solution containing the same amount of nickel as 1/30c.c. of "nico" (as in Experiment 13) were injected below skin of back. At 9.15 the temperature was 38·9, at 9.40 at 37·6, and at 10.50 on the following day it was 38·8. We may conclude that a reduction of temperature is not caused by a quantity of nickel equal to that in the doses of $Ni(CO)_4$ which produced the remarkably persistent fall of temperature, as in Experiments 6 and 8.

We next endeavoured to examine roughly the gases of the blood after poisoning by $Ni(CO)_4$.

Experiment 16.—A rabbit, weighing 997 grms., at 2·58 had 2 minims (·13c.c.) of pure $Ni(CO)_4$ injected below skin of the back.

		Temperature of mouth.	Remarks.
2.58	...	38·7	
3.13	...	37·6	
3.21	...	37·5	
3.30	...	36·3	
3.40	...	36·1	
3.50	...	35·1	
4.4	...	33·1	
4.47	...	—	Animal died after severe convulsions.

The animal was bled from the neck, and the blood was quickly introduced into a Torricellian vacuum produced by a mercurial gas pump. A small quantity of gas was obtained, and this was found on analysis to contain carbonic oxide.* No trace of nickel was found in the gases, but it was found in the blood from which the gases were drawn.

Two experiments were made in which the animal was caused to breathe an atmosphere containing the vapour of $Ni(CO)_4$.

Experiment 17.—A rabbit, weighing 1090 grms. was placed in a belljar containing 24 litres of air; a small tube containing ·6c.c. of $Ni(CO)_4$ was broken inside the jar and the fluid evaporated very quickly. As 1c.c. of the liquid, $Ni(CO)_4$ at 17° C., contains ·87146 grm. of CO, which at 0° and 760 mm. yields 696·5c.c. of gas, 0·6c.c. would yield about 417·9c.c. of CO gas, as 1 molecule of

* The gas analysis was performed by Dr. G. G. Henderson, Chemical Laboratory, University of Glasgow.

$Ni(CO)_4$ contains 4 molecules of CO, the animal breathed an atmosphere containing 0·432 per cent. of $Ni(CO)_4$ gas.

3.0	... ...	Animal placed in jar.
3.7	... ...	Agitated, muscular tremors, urination, defæcation.
3.13	... ...	Animal sitting up on hind legs ; no paresis ; vessels of ear full of bright red blood.
3.25	... ...	Weak in movements, but no marked symptoms ; removed from jar.
3.26	... ...	Temperature of mouth 37·3.
3.40	... ...	Trembling and weak on legs.

The rabbit was found dead next morning, showing a lethal effect after breathing an atmosphere containing ·432 per cent. for 25 minutes.

Experiment 18.—A rabbit, weighing 489 grms., was placed at 3.45 in the 24 litre jar, the air of which contained ·58c.c. of $Ni(CO)_4$ = 0·41 per cent.

3.45	... ...	Animal placed in jar.
3.46	... ...	Vessels in ears full of bright red blood ; animal agitated.
3.56	... ...	No very evident effect, except animal rubbing its nose with fore paws.
3.57	... ...	Another quantity of ·69c.c. of $Ni(CO)_4$ = 0·49 per cent. of $Ni(CO)_4$ gas was added. The air contained now nearly 0·9 per cent. of $Ni(CO)_4$.
4.0	... ...	Violent convulsions ; animal lying on belly with the hind legs stretched out. Great difficulty in breathing. The animal was quickly removed and placed in a large jar of pure oxygen.
4.10	... ...	Died in severe convulsions.

It was rapidly bled, and the blood was passed into vacuum, and a small quantity of gas was obtained. This gas contained carbonic oxide, but no trace of nickel. The metal was found in the blood. Quantitative measurements of the gases were not made, as the object, at this stage of the inquiry, was to ascertain the presence or absence of carbonic oxide in the blood.

The general results of the investigation may be briefly summarised thus :—

1. $Ni(CO)_4$, is a powerful poison when injected subcutaneously.
2. The vapour of $Ni(CO)_4$ in air, even to the extent of less than 0·5 per cent., is dangerous.

3. The symptoms are similar to those caused by carbonic oxide.
4. The spectrum of the blood of an animal poisoned by $Ni(CO)_4$ is that of carbonic-oxide-hæmoglobin, and it is not reduced by sulphide of ammonium.
5. When the substance is injected subcutaneously it is probably in part dissociated in the tissues, as there is evidence of the existence of nickel in those tissues, but the nickel also finds its way into the blood and is found there.
6. The substance produces a remarkably prolonged fall of temperature even when given in small quantities. This may be accounted for by the hæmoglobin being prevented, to a large extent, from supplying the tissues with oxygen. "Nico," as we may for convenience term this remarkable substance, makes it possible to give graduated doses of carbonic oxide and thus to reduce temperature by directly interfering with the respiratory exchanges occurring in the tissues. The objections to its use as an antipyretic are that, owing to its poisonous properties, it is difficult to inject it subcutaneously in sufficiently small doses, while it is not easy to obtain a solution in any menstruum in which decomposition will not take place. If a convenient method of dissolving it could be devised, $Ni(CO)_4$ might become a valuable antipyretic, the *modus operandi* of which is intelligible.

We intend to continue the investigation more especially as to (*a*) the solubility of the substance; (*b*) the quantitative effects on the gases of the blood; and (*c*) the quantitative effects on the gases of the air breathed by an animal under its influence.