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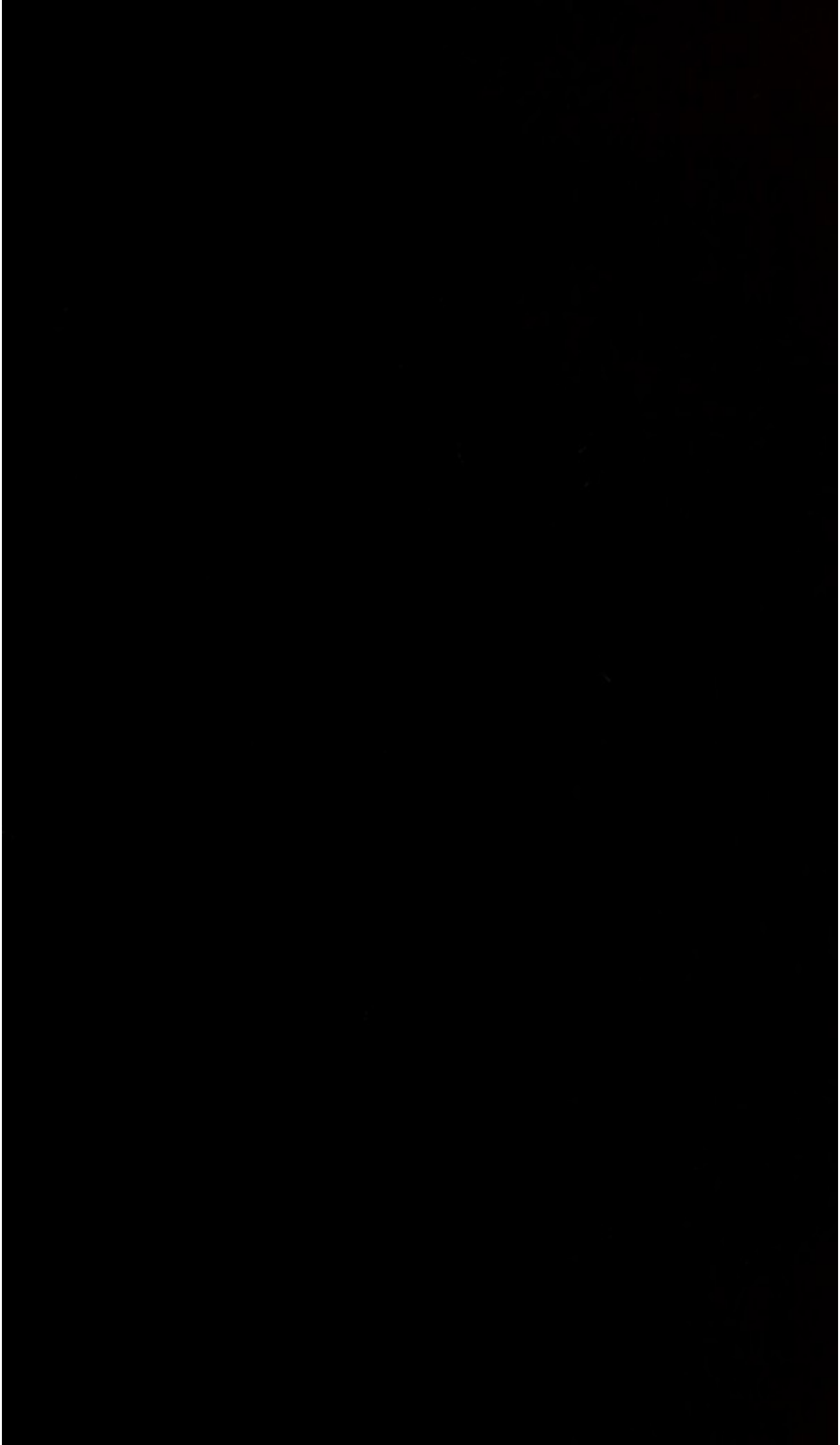
REPORT

ON THE

ANTAGONISM OF MEDICINES

J. HUGHES BENNETT.



RESEARCHES

INTO

THE ANTAGONISM OF MEDICINES;

BEING

THE REPORT OF THE EDINBURGH COMMITTEE OF THE BRITISH MEDICAL ASSOCIATION.

BY

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CHAIRMAN AND REPORTER.

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EDINBURGH:

EDMONSTON AND DOUGLAS.

1875.

THE researches now published must be regarded only as a contribution to the large subject of the Antagonism of Medicines. Had health permitted me to retain my chair in the University of Edinburgh, they would have been continued from year to year, until the inquiry was exhausted. I venture to hope, however, that the method of investigation will commend itself to those who are earnest in the advancement of Therapeutics, and if not prosecuted by the British Medical Association, through means of a Committee, which I should greatly regret, at least individual effort may confirm, modify, and extend, an inquiry on which the future progress of Medicine so much depends. It is with no small satisfaction, therefore, that I have read the valuable memoir recently contributed by my friend and former pupil, Dr. Crichton Browne of Wakefield, on the Antagonism between Picrotoxine and Chloral.

J. HUGHES BENNETT.

Nice, April 1875.

REPORT

OF

THE EDINBURGH COMMITTEE ON THE ANTAGONISM OF MEDICINES.

THE series of researches which I am about to describe owes its origin to the Address on Medicine I had the honour to read to the Association in Chester, at the annual meeting of 1866. I then urged the propriety of endeavouring to solve some of the scientific or practical difficulties with which our profession had to contend. This appeal was responded to, a grant of money was made, and a subscription raised to defray the expenses of a Committee that was to determine the question whether mercury had or had not any power to stimulate the liver to an increased secretion of bile. The report on this subject I had the pleasure of reading to the annual meeting at Oxford in 1868, and I may venture to say that the two years' labour of the Committee finally settled this long disputed subject, and demonstrated beyond the possibility of reasonable objection that in this respect mercury had none of the properties that had so long been attributed to it.* At the following annual meeting, in Leeds, another grant of money was made by the Association to investigate the antagonism of medicines, and again I was entrusted to form a Committee, and, as its Convener, to report the results. The Committee that was formed for this purpose consisted of Dr. McKendrick, my assistant, Dr. James Rogers, formerly of St. Petersburg, Dr. Macadam, lecturer on chemistry, Mr. T. Smith, head of the eminent firm of Messrs. T. and H. Smith, chemists and druggists, Edinburgh (the preparation of whose alkaloids is so thoroughly appreciated, and who at once promised to furnish us with the purest

* *Researches into the Action of Mercury, Podophyllin, and Taraxacum, on the Biliary Secretion*, etc. Second edition, with appendix, 8vo. Edinburgh: 1874.

drugs that could be obtained, gratuitously), and Dr. Edmund Cook, chief chemist in the employment of the Messrs. Smith. This Committee appeared to me to embrace all the essential qualities and to possess all the necessary means and appliances for prosecuting the inquiry. On the resignation of Dr. Cook, who was obliged to leave Edinburgh, Dr. Alexander Bennett was added to the Committee.

At the preliminary meetings of the Committee, it was determined to introduce the substance under examination in solution below the skin of animals, and ascertain, by careful observation—

1. The physiological actions produced.
2. The minimum fatal dose.
3. The influence of one supposed antagonistic substance, on the physiological action of the other when both were simultaneously injected.
4. The influence of the supposed antagonistic substance when introduced some time *before* the fatal one.
5. The influence of the supposed antagonistic substance when introduced some time *after* the fatal one.
6. The limits of the antagonism when such existed.
7. The performance in all cases of a crucial test consisting, when any supposed antagonistic action had saved the animal, in injecting the same dose of the active substance into the same animal a week or ten days afterwards. If death then took place, it was held that the two substances were antagonistic.

By such a method, we hoped to ascertain, beyond the possibility of doubt, whether one drug could really antagonise the fatal or injurious properties of another, choosing in the first instance, for experiment, such as exhibited the most powerful and unequivocal action. In this manner there have been investigated, during the four years over which the Committee's labours have extended, the antagonistic properties existing between—

1. Hydrate of chloral and strychnia.
2. Sulphate of atropia and Calabar bean.
3. Hydrate of chloral and Calabar bean.
4. Hydrochlorate and meconate of morphia and Calabar bean.
5. Sulphate of atropia and meconate of morphia.
6. Meconate of morphia and theine.
7. Meconate of morphia and caffeine.
8. Meconate of morphia and guaranine.
9. Meconate of morphia and infusion of tea.
10. Meconate of morphia and infusion of coffee.
11. Extract of Calabar bean and strychnia.
12. Hydrate of bromal and atropia.

Doubtless these researches would have been much more extended, had not my illness, at the commencement of 1872, and consequent absence from Edinburgh, prevented my taking any very active part in them after the first four subjects named. This also threw such an amount of teaching, systematic and practical, upon my assistant, Dr. McKendrick, as equally to prevent his paying more than occasional attention to the work of the Committee. The absence of Dr. Rogers and Dr. Cook also caused it to stand still for several months. Nevertheless, a large number of experiments have been made and carefully described ; indeed, they amount to 619 in number, the labour of performing, recording, tabulating, and reporting upon which can only be appreciated by those whose time has been occupied in similar investigations.

The experiments have been numbered in the order of their performance, and the results tabulated in columns, so that all the facts are condensed in the smallest possible space, and are easily studied. I shall be satisfied if it appear that the Committee has performed the task entrusted to it, and usefully expended the funds placed at its disposal by the Association.

I.—Antagonism between Strychnia and Chloral Hydrate.

The minimum fatal dose of each of these substances was first ascertained.

A. *On Rabbits.*

Table I.—*Showing the Effects of a Minimum Fatal Dose of Hydrate of Chloral on Rabbits.*

No.	Weight of Rabbit.	Dose in Grains.	Result.	No.	Weight of Rabbit.	Dose in Grains.	Result.
1	4 lbs. 3 oz.	18	Recovery	11	3 lbs.	22	Death
2	4 lbs. 6 oz.	19	,,	12	3 lbs.	21	Recovery
3	4 lbs. 10 oz.	22	,,	13	3 lbs.	19	,,
4	3 lbs. 8 oz.	21	,,	14	4 lbs.	24	,,
5	3 lbs. 9 oz.	20	Death	15	4 lbs. 2 oz.	25	Death
6	4 lbs. 2 oz.	24	Recovery	16	4 lbs. 3 oz.	24	Recovery
7	4 lbs.	26	Death	17	4 lbs.	24	,,
8	3 lbs.	23	,,	18	3 lbs.	22	Death
9	4 lbs. 1 oz.	20	Recovery	19	3 lbs.	23	,,
10	3 lbs. 10 oz.	18	,,	20	3 lbs.	21	Recovery

This table shows that twenty-one grains of hydrate of chloral may be regarded approximately as the minimum fatal dose for a rabbit of three pounds weight. At the same time, it has been observed, both in this research and in others in which chloral hydrate was employed as a hypnotic, that not unfrequently a dose, which in the great majority of instances is not ordinarily fatal, may destroy life. This is a fact of considerable practical importance, and might be explained by the supposition that, in certain conditions of the blood or tissues, chloro-

form may be produced more rapidly than usual by the action, according to the theory of Liebreich, of alkaline salts in the blood on chloral hydrate. The effects produced by chloral hydrate are now so well known as not to require special description. The period of hyperæsthesia is well marked in the rabbit. Frequently a slight pinch will cause the animal to utter prolonged screams, which would not be so occasioned in the normal condition.

TABLE II.– *Showing the Effects of a Minimum Fatal Dose of Strychnia on Rabbits.*

No.	Weight of Rabbit.	Dose in Parts of a Grain.	Result.	No.	Weight of Rabbit.	Dose in Parts of a Grain.	Result.
21	3 lbs. 1 oz.	1-100th	Death in 20 minutes	28	2 lbs. 8 oz.	1-98th	Death in 16 minutes
22	4 lbs.	1-50th	Death in 14 minutes	29	3 lbs.	1-96th	Death in 20 minutes
23	3 lbs. 6 oz.	1-80th	Death in 12 minutes	30	3 lbs.	1-95th	Recovery
				31	3 lbs. 4 oz.	1-98th	,,
24	4 lbs. 2 oz.	1-90th	Recovery	32	3 lbs. 5 oz.	1-98th	,,
25	3 lbs.	1-90th	Death in 28 minutes	33	3 lbs.	1-98th	Death in 45 minutes
26	3 lbs. 1 oz.	1-95th	Recovery	34	3 lbs.	1-96th	Death in 1 hour
27	2 lbs. 10 oz.	1-95th	Death in 18 minutes				

The result of these fourteen experiments indicate that the minimum fatal dose for rabbits of strychnia is 1-96th of a grain for every 3 lbs. weight of animal, or 1-288th of a grain for every pound. Here also it must be understood that the fatal dose is to a certain extent approximative; for in several instances animals died from a smaller dose, apparently from asphyxia produced by strong tetanic convulsions of the muscles of respiration.

Having thus determined the minimum fatal dose of the two substances, the action of both together was investigated.

Influence of Hydrate of Chloral on a Fatal Dose of Strychnia, when both Substances are given simultaneously.—The phenomena produced are described in the following detailed experiment.

Experiment 35.—Female rabbit, weighing 3¼ lbs. The average number of cardiac impulses was 85 in 20 seconds, and the respirations 26 in 20 seconds. One-ninetieth of a grain of strychnia dissolved in 20 minims of distilled water was injected under the skin of the left shoulder. Immediately afterwards, 15 grains of hydrate of chloral in 30 minims of distilled water were injected under the skin of the loins. The animal remained quiet for twenty minutes, apparently becoming drowsy. At the end of that time, slight twitchings of the muscles were observed. Five minutes later, the animal was prone and had a very feeble convulsion, with a tendency

to slight opisthotonos, which state lasted ten seconds. The animal then lay upon its side, apparently in deep hypnotism. During the next two hours, it remained in this condition, the only phenomena observed being—first, twitching of the internal rectus muscles of the eyeballs, and, second, a convulsive start on touching one of the extremities, or on tapping smartly on the table. At the end of three hours from the time of receiving the active substances, the animal began to move about, and it apparently soon became quite well.

Experiment 36.—On the tenth day after the former experiment, one-ninetieth of a grain of strychnia was again injected into the same animal, under the skin over the left loin. The animal remained quiet for five minutes, when it became restless, and moved about with a staggering gait. In two minutes more, it leaped from the table, fell on its side, and had severe convulsions, with an extreme degree of opisthotonos. These convulsive attacks occurred three times, when death ensued, twenty-six minutes after the administration of the poison.

The dose was thus proved to be fatal ; but, as it was comparatively a small one, a series of experiments was made with the view of testing the influence of hydrate of chloral on still larger doses of strychnia, when the two substances were given almost simultaneously. These experiments are registered in the following table.

TABLE III.—*Showing the Results of Varying Doses of Hydrate of Chloral when injected with Fatal Doses of Strychnia.*

No.	Weight of Rabbit.	Dose of Chlor. Hyd. in grains.	Dose of Strychnia in parts of a grain.	Result.	Result of crucial experiment of giving same dose of Strychnia to same animal seven days afterwards.
37	3 lbs. 1 oz.	18	1-80th	Recovery	Recovery
38	3 lbs. 3 oz.	19	1-86th	,,	Recovery after severe spasms
39	3 lbs.	16	1-60th	,,	Death in 20 min.
40	3 lbs.	16	1-50th	,,	Death in 10 min.
41	3 lbs. 2 oz.	16	1-25th	Death	
42	2 lbs. 13 oz.	14	1-70th	Recovery	Death in 18 min.
43	2 lbs. 15 oz.	15	1-60th	,,	Death in 14 min.
44	2 lbs. 10 oz.	15	1-60th	,,	Death in 18 min.
45	3 lbs.	17	1-40th	,,	Death in 10 min.
46	3 lbs.	16	1-40th	,,	Death in 12 min.
47	3 lbs.	12	1-29th	Death in 30 min.	
48	3 lbs. 2 oz.	10	1-60th	Death in 3 hours	
49	3 lbs. 3 oz.	8	1-80th	Recovery aft. severe spasms	Death in 20 min.
50	3 lbs.	14	1-30th	Recovery aft. severe spasms	Death in 14 min.
51	3 lbs.	12	1-24th	Death in 40 min.	
52	2 lbs. 11 oz.	12	1-32nd	Death in 36 min.	
53	2 lbs. 12 oz.	18	1-40th	Recovery aft. severe spasms	Death in 12 min.
54	2 lbs. 13 oz.	17	1-42nd	Recovery	Death in 16 min.
55	3 lbs.	16	1-50th	,,	Death in 12 min.
56	3 lbs.	18	1-54th	Recovery aft. severe spasms	Death in 18 min.

It will be seen from this table that in twenty cases a fatal dose of strychnia was administered simultaneously with varying doses of chloral hydrate. In five instances, death ensued, notwithstanding the action of the latter drug. But in these, with the exception of No. 48, the dose of strychnia was very large, being about four times that of the minimum fatal dose. Even in these cases, however, chloral hydrate prolonged life, and, in No. 48, in which 1-60th of a grain of strychnia was given, with a dose of only ten grains of chloral hydrate, life was much prolonged. This will be more readily seen by comparing No. 48 with the result of the crucial experiments in Nos. 39 and 44, in which the animals died after the injection of 1-60th of a grain of strychnia in twenty and eighteen minutes respectively. These experiments, therefore, show, in a very conclusive manner, that chloral hydrate antagonises fatal doses of strychnia, and modifies the symptoms to a very remarkable extent.

It was found by experience that recovery from a fatal dose of strychnia, even after the administration of an antagonistic dose of chloral hydrate, was rendered more certain if means were taken to prevent, as far as possible, the body of the animal from being irritated. It was frequently observed, after the administration of both substances, that, although the rabbit lay tranquilly on its side, and apparently deeply under the influence of the chloral hydrate, still peripheral irritation caused muscular twitchings and even severe spasm. These phenomena indicated that the reflex excitability of the spinal cord was still increased by the action of the strychnia. The best results, therefore, were obtained, so far as the recovery of the animals was concerned, by placing the rabbit under a large bell-jar, so arranged as to insure perfect ventilation.

Influence of Hydrate of Chloral when injected some time after a Fatal Dose of Strychnia.—A minimum fatal dose of strychnia produces its first visible physiological effects from fifteen to twenty minutes after its introduction into the system. It became a matter of great practical importance to determine how far chloral hydrate could influence the physiological effects of strychnia after these had made their appearance. Twelve experiments were made, with the view of determining this point. The rabbits were as nearly as possible of equal weight and in equally good condition ; the same amount of strychnia was introduced into each. The counteracting dose of chloral hydrate was introduced in the first case almost simultaneously, and in the other cases at successive intervals of two minutes. The following table shows at a glance the result.

TABLE IV.—*Showing the Influence of Hydrate of Chloral given at different intervals of time after a fatal dose of Strychnia.*

No.	Weight of Rabbit.	Dose of Strychnia in parts of a grain.	Dose of Chloral Hydrate in grs.	Interval between the administration of Chloral Hydrate.	Time of the first appearance of effects of Strychnia.	Results.	Remarks.
57	2 lbs. 15 oz.	1-96th	16	Simultaneously	Slight spasms 20 min. after	Recovery	
58	3 lbs.	,,	,,	2 minutes after	No spasms	,,	
59	3 lbs.	,,	,,	4 minutes after	Slight spasms 18 min. after	,,	Slight twitchings of muscles for 3 hrs.
60	3 lbs. 1 oz.	,,	,,	6 minutes after	Slight tetanic spasm 22 m. after	,,	Ditto for nearly 2 hours
61	3 lbs.	,,	,,	8 minutes after	Tetanic convulsion 20 m. after	,,	This animal had numerous tetanic spasms
62	2 lbs. 14½ oz.	,,	,,	10 minutes after	Tetanic convulsion 24 m. after	Death	Died 35 min. aft. strychnia
63	3 lbs.	,,	,,	12 minutes after	Severe tetanic convulsions 20 min. after	,,	Died 32 min. aft. strychnia
64	3 lbs.	,,	,,	14 minutes after	Ditto	,,	Died 29 min. aft. strychnia
65	3 lbs. ½ oz.	,,	,,	16 minutes after	Very severe convulsions	,,	Died 24 min. aft. strychnia
66	3 lbs. 1½ oz.	,,	,,	18 minutes after	Ditto	,,	Died 22 min. aft. strychnia
67	3 lbs.	,,	,,	20 minutes after	Ditto	,,	Died 20 min. aft. strychnia
68	3 lbs.	,,	,,	22 minutes after	Ditto	,,	Died 20 min. aft. strychnia

From these experiments, it will be seen that chloral hydrate becomes less efficient in counteracting the fatal effects of strychnia in proportion as it is administered at more distant intervals of time from that of the administration of the strychnia. If the physiological effects of strychnia showed themselves in a marked way before the animal came under the influence of the chloral hydrate, death was liable to ensue from asphyxia due to tetanic spasm of the muscles of respiration. The sooner the chloral hydrate was given after the administration of strychnia, the more certain was the animal to survive. From this, the practical conclusion follows that, in cases of accidental poisoning by strychnia, the patient should be brought as rapidly as possible under the influence of chloral hydrate, either by subcutaneous injection or even by the direct introduction of the substance into a vein.

Influence of Strychnia when simultaneously injected with a Fatal Dose of Hydrate of Chloral. — It was pointed out by Oscar Lieb-

reich*, who first investigated and brought under the notice of the profession the hypnotic effects of hydrate of chloral, that the injection of minute doses of strychnia had the effect of rousing rabbits from under the influence of deep coma produced by chloral hydrate, and even of saving life after a lethal dose of the latter. As chloral hydrate is now much used in practical medicine, and as not a few cases are now on record of deaths from too large doses, it became of importance to reinvestigate this point. In fifteen experiments, therefore, in which fatal doses of chloral hydrate were first given, and after the animals had come deeply under the influence of the drug, minute non-fatal doses of strychnia were injected. The results are seen in the following table.

TABLE V.—*Showing the Influence of Injecting Strychnia when Fatal Doses of Chloral Hydrate had been previously Administered.*

No.	Weight of Rabbit.	Dose of Chloral Hydrate in grains.	Dose of Strychnia in parts of a grain.	Time between Injection of Dose of Chloral and Dose of Strychnia.	Results.	Remarks.
69	3 lbs. 2 oz.	21½	1-100	15 minutes	Recovery	Killed 4 days afterwards with same dose of chloral hydrate
70	3 lbs. 1 oz.	22	1-93	15 minutes	,,	Recovered 4 days afterwards with same dose of chloral hydrate
71	2 lbs. 15 oz.	22	1-94	14 minutes	,,	Killed 5 days afterwards, ditto
72	3 lbs.	23	1-110	13 minutes	Death	Died in profound coma, with but slight muscular twitchings
73	3 lbs.	24	1-150	10 minutes	,,	Ditto, ditto
74	3 lbs. ½ oz.	21	1-100	12 minutes	Recovery	Recovered 4 days afterwards with same dose of chloral hydrate
75	3 lbs. 1½ oz.	22	1-80	Simultaneously	,,	Killed 6 days do., do.
76	3 lbs. 1¾ oz.	22	1-60	,,	Death	Died in profound coma, with but slight muscular twitchings
77	3 lbs.	25	1-50	,,	,,	Coma, one smart tetanic spasm
78	3 lbs.	24	1-40	15 minutes	,,	Coma, three spasms, opisthotonos
79	3 lbs. 2 oz.	23	1-90	12 minutes	Recovery	Killed 3 days afterwards with same dose of chloral hydrate
80	3 lbs. ¼ oz.	22	1-98	10 minutes	,,	Recovered after same dose 5 days afterwards
81	2 lbs. 14 oz.	23	1-96	20 minutes	Death	Profound coma, slight twitchings
82	2 lbs. 15 oz.	21½	1-92	20 minutes	,,	Ditto, ditto
83	3 lbs.	22	1-100	18 minutes	Recovery	Recovered from same dose, given 4 days afterwards

* Oscar Liebreich, *Comptes Rendus des Séances de l'Académie des Sciences*, 1870, vol. lxx, p. 403.

It will be apparent from a consideration of this table that the evidence in favour of the view that strychnia antagonises fatal doses of chloral hydrate is not so satisfactory as might be expected. In the fifteen experiments, eight recovered from what were supposed to be fatal doses of chloral hydrate (Nos. 69, 70, 71, 74, 75, 79, 80, and 83); but, when the same dose of chloral hydrate was given to the same animals a few days later, four died (Nos. 69, 71, 75, and 79) and four recovered (Nos. 70, 74, 80, and 83). It was also observed that, in those cases in which the animals died notwithstanding the injection of strychnia, they died in profound coma, although, from the muscular twitchings and from the ease with which reflex spasms could be excited, it was evident that the strychnia was physiologically influencing the spinal cord. It would appear, therefore, that there is little hope of saving life after fatal doses of chloral hydrate by the subsequent injection of strychnia. Chloral hydrate acts, not only on the centres of the spinal cord, but also on the brain, as is evidenced by the profound coma following a large dose, and the injected condition of the membranes of the brain found after death. Strychnia, on the other hand, exercises no known influence on the brain; and, although it may stimulate the reflex centres of the cord, depressed in vital activity by the action of chloral hydrate, it cannot relieve the condition of the encephalon, and consequently, even though there may be muscular twitchings and even tetanic convulsions, the animal dies comatose.

B. *On Rats.*

In this inquiry, numerous experiments were made on rats. The animals employed were common brown rats (*Mus decumanus Lin.*) caught in stables. They were from twelve to sixteen ounces in weight. The inquiry was conducted in the same manner as in the case of rabbits, and the general results were found to be the same.

1. *Minimum Fatal Dose of Hydrate of Chloral on Rats.*—This was found to be, after twelve experiments (detailed in Table VI), 1⅞ grains for an animal weighing nearly twelve ounces. In two cases, Nos. 90 and 91, the animals recovered from a dose of two grains; but they appeared to be more powerful and better fed specimens.

TABLE VI.—*Showing the Effects of a Minimum Fatal Dose of Hydrate of Chloral on Rats.*

No.	Weight of Rat in ounces.	Dose of Hydrate of Chloral in grains.	Result.
84	10	¼	Recovered
85	11	½	,,
86	12	1	,,
87	11	1½	,,
88	13	1¾	,,
89	11	1¼	,,
90	11½	2	,,
91	10¾	2	,,
92	11	1⅞	Died
93	11¼	1⅞	,,
94	11½	1 8-9ths	Recovered
95	11½	2	Died

II. *Minimum Fatal Dose of Strychnia on Rats.*— After twelve experiments (detailed in Table VII), this was ascertained to be 1-60th of a grain. It is remarkable that rats required a larger dose of strychnia to destroy life than rabbits, the fatal dose for the latter being about (see Table II) 1-96th of a grain. This is still more striking, if we compare the fatal dose according to pound weight: rat, 1-60th of a grain; rabbit, 1-288th—more than four times less in the rabbit than in the rat. On the other hand, it was noted that, when the physiological effects of strychnia did manifest themselves in the rat, they were much more violent than in the case of the rabbit, and the animal usually died in the very first tetanic spasm. In many other experiments, it was observed that it was more difficult to kill rats than rabbits.

TABLE VII.—*Showing the Effects of a Minimum Fatal Dose of Strychnia on Rats.*

No.	Weight of Rat in ounces.	Dose of Strychnia in grains.	Result.
96	11	1-150th	Recovered
97	11¼	1-140th	,,
98	11½	1-130th	,,
99	12	1-120th	Recovered; slight convulsion
100	11¾	1-100th	,, ,,
101	11¼	1-90th	Recovered; more severe convulsion
102	10	1-80th	Recovered; severe convulsion
103	9¾	1-70th	Severe convulsions, frequently repeated; recovery
104	12¼	1-60th	Convulsions; death
105	12	1-70th	Severe convulsions; recovery
106	12	1-60th	Convulsions; death
107	11	1-60th	,, ,,

III. *Influence of Hydrate of Chloral injected simultaneously with a Fatal Dose of Strychnia.*—This was determined in the following six experiments, which were deemed sufficient to determine the point, so far as rats were concerned.

TABLE VIII.—*Showing the Antagonism between Hydrate of Chloral and Strychnia in Rats.*

No.	Weight of Rat.	Dose of Chloral Hydrate in grains.	Dose of Strychnia in parts of a grain.	Result.	Result of crucial experiment of giving same dose to same animal 5 days afterwards.
108	10 oz.	1¾	1-34th	Died in 16 minutes in severe convulsions	Chloral hydrate apparently had not time to act
109	11 oz.	3	1-44th	Recovered after considerable twitchings in 3 hours	Killed in 20 minutes with same dose
110	11 oz.	3	1-44th	Ditto, ditto	This animal had repeated tetanic spasms; killed with same dose in 18 minutes
111	10½ oz.	2½	1-44th	Died 10 hours after	Slight convulsions; died apparently from effects of chloral
112	11 oz.	2½	1-60th	Died 15 hours after	Ditto, ditto
113	11¾ oz.	2½	1-60th	Died 14 hours after	Ditto, ditto
114	11¼ oz.	3	1-50th	Died 8 hours after	Became suddenly asphyxiated; much mucus in air-passages

This table shows (1) two instances (Nos. 109 and 110) in which the animals recovered from fatal doses of strychnia; (2) that larger than fatal doses of chloral hydrate were required to antagonise fatal doses of strychnia, and that in three instances (Nos. 111, 112, and 113) the animals died apparently from the effects of the former. The convulsions, except in No. 108, were much reduced, both in force and frequency, by the action of the chloral hydrate.

General Conclusions regarding the Antagonism between Chloral Hydrate and Strychnia.

It appears to be established from these experiments:

1. That, after a fatal dose of strychnia, life may be saved by bringing the animal under the influence of chloral hydrate.

2. That chloral hydrate is more likely to save life after a fatal dose of strychnia than strychnia is to save life after a fatal dose of chloral hydrate.

3. That, after a dose of strychnia producing severe tetanic convulsions, these convulsions may be much reduced, both in force and frequency, by the use of chloral hydrate, and consequently much suffering saved.

4. That the extent of physiological antagonism between the two substances is so far limited, that (1) a very large fatal dose of strychnia may kill before the chloral hydrate has had time to act; or (2) so large

must the dose of chloral hydrate be to antagonise an excessive dose of strychnia, that there is danger of death from the effects of the chloral hydrate.

5. Chloral hydrate mitigates the effects of a fatal dose of strychnia by depressing the excess of reflex activity excited by that substance, while strychnia may mitigate the effects of a fatal dose of chloral hydrate by rousing the activity of the spinal cord ; but it does not appear capable of removing the coma produced by the action of chloral hydrate on the brain.

It is scarcely necessary to point out the vast importance of these results to practical medicine and the indications they afford, not only in cases of poisoning by strychnia, but in cases of tetanus and other spasmodic diseases, reflex and central.

At a meeting of the Medico-Chirurgical Society of Edinburgh, on April 6th, 1870, and at the annual meeting of the Association at Newcastle in 1870, I demonstrated experimentally with what certainty rabbits might be saved after receiving a fatal dose of strychnia, by the injection of a solution of chloral hydrate. Take two rabbits of about 3 lbs. weight ; inject under the skin of both 1-96th of a grain of strychnia, and then in one a solution of fifteen grains of chloral : in ten minutes the first one will leap into the air and fall down tetanic and dead ; the other will go to sleep, and in about two hours will wake up as if nothing were the matter. A more certain antidote does not exist.

II.—Antagonism between Sulphate of Atropia and Calabar Bean.

When the Committee commenced their investigations into this subject, the antagonism had already been indicated by Dr. Fraser. It was resolved, however, to determine the question with exactitude. Subsequently, a very lengthened inquiry was published by Dr. Fraser,* with whose general results those of the Committee coincide.

The preparation of Calabar bean employed was in the form of an alcoholic extract made by Dr. Cook, formerly of the firm of Messrs. T. and H. Smith of Edinburgh, now residing in Liverpool. It was prepared as follows. The powdered beans were acted upon with spirit of specific gravity .830, at 60 deg. Fahr., until the powder was ex-

* *Proceedings of the Royal Society of Edinburgh*, 1868-69, pp. 587-590. See also the *Practitioner* for February 1870 ; and an elaborate paper in the *Transactions of the Royal Society of Edinburgh*, vol. xxvi, part iii, for the session 1870-71.

hausted. The clear solution thus obtained was evaporated in a vacuum of twenty-six inches until the spirit was entirely removed. To the residue thus prepared, three ounces of water were added, and the whole was heated gently. The residue was partly dissolved, leaving some oily matter floating on the surface. This mixture was filtered, and a fluid obtained, one ounce of which represented four ounces and a half of Calabar bean; or, in other words, twenty eight grains of the extract free from oil were present in each ounce.

Numerous experiments were made on rabbits and on rats.

A. *Experiments on Rabbits.*

TABLE IX.—*Showing Effects of a Minimum Fatal Dose of the Extract of Calabar Bean on Rabbits.*

No.	Weight of Rabbit.	Dose of grains.	Result.
116	3 lbs. 8 oz.	¾	Died in 1 hour 40 minutes
117	3 lbs. 8 oz.	½	Died in 12 minutes
118	3 lbs. 12 oz.	½	Recovered; ill nearly 24 hours
119	3 lbs. 12 oz.	1½	Died in 7 minutes
120	4 lbs.	¾	Died in 19 minutes
121	4 lbs. 1 oz.	1½	Died in 8 minutes
122	4 lbs. 2 oz.	¾	Recovered; very ill 6 hours
123	4 lbs. 4 oz.	¾	Died in 6 minutes
124	3 lbs. 6 oz.	¾	Died in 29 minutes
125	4 lbs.	¾	Recovered after severe illness
126	3 lbs. 8 oz.	¾	Died in 31 minutes
127	3 lbs. 7½ oz.	¾	Recovered after severe illness

Taking into account the relative weights of these rabbits, it was concluded that three-quarters of a grain of extract of Calabar bean for every three pounds weight of rabbit was the minimum fatal dose of the extract employed; and it is so understood in all the investigations on the supposed antagonistic properties of other substances to Calabar bean. The minimum fatal dose of the extract prepared by Dr. Fraser was 1.2 grains for every three pounds weight of animal; but he states (p. 575) "that the lethal activity of this extract" [the extract given him by Dr. Cook] "is considerably greater than that of the extract prepared by myself".

The symptoms following the subcutaneous injection of three-quarters of a grain of this extract into a rabbit were as follows.

Experiment 126.—Male rabbit, weighing 3 lbs. 8 ounces. Three-fourths of a grain of extract of Calabar bean, dissolved in ten minims of water, were injected under the skin of the back. In a minute and a half, there were slight twitchings of the skin. In three minutes, the breathing became very hurried, and the animal seemed to be dis-

tressed. Saliva now accumulated profusely in the mouth. In two minutes more, the animal rested on its abdomen and chest, and spread out its legs, which were stiff. It attempted to regain its natural position, but in vain. The pupils were now contracted from 7-25ths (their diameter before the experiment) to 3-25ths of an inch. Soft diffluent fæces were passed. At the end of eighteen minutes from the time of the introduction of the poison, the animal was lying on its side. The respirations were much laboured. It remained in this condition for thirteen minutes more, with severe occasional muscular tremors, when it died—that is, thirty-one minutes after receiving the three-fourths of a grain of the extract. In one case (Experiment 123), the animal died from three-fourths of a grain in six minutes; but it was found that this dose usually destroyed life in from twenty-five to thirty-four minutes.

Minimum Fatal Dose of Sulphate of Atropia for Rabbits.

This was investigated before the appearance of Dr. Fraser's elaborate paper in the *Transactions of the Royal Society*, but subsequently to the preliminary note. The results are seen in the following table.

TABLE X.—*Showing Effects of a Minimum Fatal Dose of Sulphate of Atropia on Rabbits.*

No.	Weight of Rabbit.	Dose in grains.	Result.	No.	Weight of Rabbit.	Dose in grains.	Result.
128	4 lbs. 12 oz.	1	No apparent effect	138	3 lbs. 6 oz.	10	Recovered
129	3 lbs.	4¼	Recovered	139	3 lbs. 4 oz.	11	,,
130	2 lbs. 12 oz.	3	,,	140	3 lbs. 4 oz.	12	,,
131	3 lbs.	4	,,	141	3 lbs. 4½ oz.	14	,,
132	4 lbs.	5	,,	142	3 lbs. 9 oz.	16	,,
133	3 lbs. 8 oz.	6	Died in 17 min.	143	3 lbs. 8 oz.	18	,,
134	3 lbs. 6 oz.	6	Recovered	144	3 lbs. 8 oz.	20	Died in 50 min.
135	3 lbs. 9 oz.	6	,,	145	3 lbs. ½ oz.	21	Died in 36 min.
136	3 lbs. 6½ oz.	8	,,	146	3 lbs.	21	Died in 34 min.
137	4 lbs.	9	,,	147	3 lbs.	21	Died in 33 min.

This table indicates that the minimum fatal dose of sulphate of atropia for a rabbit is about twenty or twenty-one grains. In one instance (No. 133), the animal died in seventeen minutes from a dose of six grains. This must have been in some way exceptional, although it cannot be stated in what way it was so, because many rabbits recovered from larger doses.

The effects of sulphate of atropia on rabbits were as follows. Up to four or four-and-a-half grains, no symptoms whatever could be observed.

From four to six grains, there occurred dilatation of the pupil; uneasiness, as manifested by the rabbit moving restlessly about; respirations reduced; and the cardiac impulses were accelerated in number. From six to fourteen grains, in addition to the symptoms noted above, there were, paralysis, more marked in larger than in smaller doses; slight quivering of special groups of muscles; violent starts of the whole body; and a drowsy condition. From fourteen grains to twenty-one grains—the minimum fatal dose—in addition to the foregoing symptoms, there were increasing paralysis, and the respirations were reduced both in number and in depth. The animals died, in those cases in which fatal doses had been given, with severe spasmodic convulsive starts and twitchings. The action of the heart, and the depth and frequency of the respiratory movements, decreased until life was extinct.

After having ascertained the fatal doses of extract of Calabar bean and of sulphate of atropia, the action of the one on the other was next investigated.

TABLE XI.—*Showing First Series of Experiments on the Effects of Calabar Bean Extract and Sulphate of Atropia.*

No.	Weight of Rabbit.	Dose of Sulphate of Atropia in grains.	Dose of Extract of Calabar Bean in grains.	Result.	Remarks.
148	3 lbs. 8 oz.	½	1	Survived for 5 days	Ill for 24 hours; died on 5th day
149	3 lbs. 12 oz.	½	2	Died in 14 minutes	Severe convulsions
150	3 lbs. 4 oz.	2	2	Died in 45 minutes	Convulsions; not so severe as in No. 149
151	4 lbs.	1½	1½	Died in 62 minutes	Ditto, ditto
152	6 lbs.	4½	1½	Died in 25 minutes	Severe convulsions
153	3 lbs. 4 oz.	1½	1½	Died in 30 minutes	Convulsions; not severe
154	5 lbs.	3	1½	Died in 17 minutes	Slight convulsions; died very suddenly

It will be observed from this table that, in one case (No. 148), the rabbit survived for five days. It was very ill for twenty-four hours; it then apparently became well; but on the fourth day it showed no inclination to take food, and on the morning of the fifth day it was found dead in its box. All the other cases died in periods varying from fourteen to sixty-two minutes after receiving the injection of Calabar bean extract. In every case, life was prolonged by the use of the atropia, and the symptoms were modified. This will be seen by comparing the following additional experiments.

TABLE XII.—*Shewing that after Fatal Doses of Calabar Bean Extract the Subcutaneous Injection of Sulphate of Atropia prolongs Life.*

EXTRACT OF CALABAR BEAN ALONE.				EXTRACT FOLLOWED BY SULPH. OF ATROPIA.				
No.	Weight of Rabbit.	Dose in grains.	Result.	No.	Weight of Rabbit.	Dose in grains. C. B.	S. A.	Result.
155	3 lbs. 6 oz.	1½	Death in 8 min.	156	3 lbs. 5½ oz.	1½	½	Death in 34 m.
157	3 lbs. 8 oz.	1½	Death in 7 min.	157*a*	3 lbs. 7 oz.	1½	½	,, 40 m.
158	3 lbs. 7 oz.	1½	Death in 8 min.	159	3 lbs. 7 oz.	1½	½	,, 36 m.
160	3 lbs. 5 oz.	1½	Death in 9 min.	161	3 lbs. 4½ oz.	1½	¾	,, 100 m.
162	4 lbs.	1½	Death in 16 min.	163	3 lbs. 14 oz.	1½	¾	,, 110 m.
164	3 lbs. 10 oz.	1½	Death in 9 min.	165	3 lbs. 9 oz.	1½	1	,, 29 m.
166	3 lbs. 9 oz.	1½	Death in 9 min.	167	3 lbs. 10 oz.	1½	1¼	,, 31 m.

In none of these cases was life preserved, although it was evidently much prolonged by the action of the sulphate of atropia. As the dose of extract of Calabar bean was double the amount of the minimum fatal dose, it was determined to make another set of experiments, in which a smaller dose of extract of Calabar bean was employed. The results are as follows.

TABLE XIII.—*Showing the Influence of Sulphate of Atropia on Minimum Fatal Doses of Extract of Calabar Bean.*

No.	Weight of Rabbit.	Dose in Extract of Calabar Bean.	Grains Sulphate of Atropia.	Result.	Remarks.
168	3 lbs. 10 oz.			Died in 40 hours	During all this time very ill
169	3 lbs. 9 oz.			Recovered	Killed on sixth day with same dose of C. B. extract in 10 minutes
170	3 lbs. 12 oz.			,,	Ditto, ditto, in 7 minutes
171	3 lbs. 11 oz.	1		Died in 90 min.	Symptoms of C. B. poisoning modified, but animal very ill
172	3 lbs. 12 oz.			Died in 3 hours	
173	3 lbs. 14 oz.			Recovered	Recovered from same dose of C. B. extract given 8 days afterwards
174	3 lbs. 9 oz.			,,	Recovered, ditto, ditto
175	3 lbs. 10 oz.			,,	Died with same dose of C. B. extract 9 days afterwards in 12 minutes
176	3 lbs. 12 oz.			,,	Recovered after very severe illness
177	3 lbs. 12 oz.	1		Died in 40 min.	

An analysis of these cases shows that sulphate of atropia prolongs life, and may even save it, after a fatal dose of extract of Calabar bean. In those cases of recovery from a fatal dose of Calabar bean, the animals were for many hours very ill. They were prostrate, and had frequently severe tremors. To favour the chance of recovery, it was found necessary to keep them warm, and to save them from being

annoyed by other rabbits. The doses given to Nos. 173 and 174 were evidently not fatal ones, as the animals recovered from the same doses of Calabar bean extract, without the use of sulphate of atropia, given eight days after the first experiment. It will be observed, also, that No. 176 recovered in the second experiment from a minimum fatal dose of Calabar bean extract nine days after the first experiment. As it appears to be impossible to account for this fact, it is better to reject this experiment. Still we have three cases—Experiments 169, 170, and 175—in which the animals recovered in the first instances from the effects of doses of extract of Calabar bean, as modified by the action of sulphate of atropia, which, given alone some days afterwards, killed in from seven to twelve minutes. In the case of No. 177, too large a dose of extract of Calabar bean was evidently given; but, even in this case, life was much prolonged, seeing that the animal survived forty minutes, when it probably would have died from the same dose of extract of Calabar bean, without the counteracting influence of sulphate of atropia, in from eight to twelve minutes.

It is evident that the antagonistic influence of sulphate of atropia on the effects of extract of Calabar bean is not nearly so well marked as that of chloral hydrate as an antagonist to the effects of strychnia. Even after the introduction of sulphate of atropia, the symptoms produced by the previously injected extract of Calabar bean continue to be well marked. The animal seems to be extremely ill. There are salivation, twitchings of the muscles, and perhaps slight convulsions. This state of things may continue for several hours, and the animal slowly recovers. In the case of strychnia and hydrate of chloral, if the animal be kept undisturbed, it may not exhibit a single indication of the presence of the strychnia, and it becomes roused from the effects of the hydrate of chloral as if it had received it alone.*

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* It is to be noticed that Dr. Fraser quotes the following experiments made with the extract supplied to him by Dr. Cook.

Dr. Fraser's paper, p. 579, *Edinburgh Royal Society Trans.*, vol. xxvi.—"Experiment 57 (*a*). A rabbit, weighing 3 lbs. 8 oz., received two grains of extract of physostigma, prepared by Dr. Cook, and, one minute and thirty seconds afterwards, 0.5 grain of sulphate of atropia. Recovery took place.—Experiment 57 (*b*). Nine days afterwards, the same rabbit, now weighing 3 lbs. 8½ oz., received one grain of extract of physostigma, prepared by Dr. Cook. Death occurred in thirteen minutes and thirty seconds."

Dr. Fraser also observes (p. 575), referring to Experiment 57 (*b*): "The second portion of the experiment shows that the lethal activity of this extract is considerably greater than that of the extract prepared by myself; nevertheless, atropia so completely and successfully antagonised the lethal action as to prevent the occurrence of any symptom of serious import after the administration of a dose twice as large as that by which death was afterwards produced in about thirteen minutes."

It is evident, therefore, that Dr. Fraser must have obtained from Dr. Cook an extract weaker than the one furnished to the committee, because they have never been able to save an animal from a dose of extract above three-fourths of a grain. This point is of considerable practical importance, because it shows that extracts, prepared even by the same individual, may have different strengths.

The experiments made on rabbits clearly show that sulphate of atropia does antagonise fatal doses of extract of Calabar bean, but within a very limited area.

B. *Experiments on Rats.*

Fifty experiments were made on rats with reference to the question of the antagonism between extract of Calabar bean and sulphate of atropia. They were pursued in the same order as in the case of rabbits. In the first instance, the minimum fatal dose of each substance was determined, and then several crucial experiments were made. The results are to be seen in the following tables.

TABLE XIV.—*Showing Minimum Fatal Dose of Extract of Calabar Bean for a Rat of average size* (10 *oz.*)

No.	Weight of Rat in oz.	Dose in grains.	Result.	No.	Weight of Rat in oz.	Dose in grains.	Result.
179	9	1-64th	Recovered	189	10½	1-10th	Died in 14 min.
180	8	1-32nd	,,	190	10	1-12th	Died in 15 min.
181	8	1-20th	,,	191	10	1-16th	Died in 24 min.
182	8½	1-18th	,,	192	9¾	1-16th	Died in 21 min.
183	8	1-16th	Died in 20 min.	193	9¾	1-18th	Recovered
184	9	1-12th	Died in 17 min.	194	8¾	1-20th	,,
185	10	1-8th	Died in 15 min.	195	8½	1-21st	,,
186	10½	1-4th	Died in 12 min.	196	10½	1-24th	,,
187	10½	1-3rd	Died in 5 min.	197	10	1-16th	Died in 23 min.
188	10½	2-3rds	Died in 4 min.	198	10	1-18th	Recovered

From these experiments, it was determined that the minimum fatal dose for a rat of extract of Calabar bean was nearly one sixteenth of a grain. The minimum fatal dose for a rat of sulphate of atropia was then ascertained. The results are as follows.

TABLE XV.—*Showing the Minimum Fatal Dose of Sulphate of Atropia for a Rat of average size* (10 *oz.*)

No.	Weight of Rat in oz.	Dose in grains.	Result.	No.	Weight of Rat in oz.	Dose in grains.	Result.
199	9½	½	No apparent effect	211	9	3⅔	Ditto
				212	10	3¾	Ditto
200	10	⅔	Ditto	213	10½	3 5-6ths	Ditto
201	9¾	4-5ths	Ditto	214	10	4	Ditto
202	11	5-6ths	Ditto	215	10	4½	Ditto; spasms
203	10	1	Ditto	216	10½	5	Ditto; spasms; excitement
204	11¼	1¼	Ditto				
205	10	1⅓	Ditto	217	10	5½	Ditto, ditto, ditto; strong convulsions; died in 6 minutes
206	10	1⅔	Drowsiness				
207	10½	2	Ditto				
208	8¾	2½	Ditto				
209	9½	3	Ditto; slight tremors	218	10½	5⅓	Died in 12 min. with same symptoms
210	9	3½	Ditto, ditto; dilatation of pupil				

It was evident from these experiments that the minimum fatal dose of sulphate of atropia for rats was about from five to five-and-a-half grains.

Having ascertained the minimum fatal dose of each substance, ten crucial experiments were now made, in which the question of antagonism was tried. The results of these are detailed in the following table.

TABLE XVI.—*Showing the Influence of Sulphate of Atropia on the Minimum Fatal Dose of Extract of Calabar Bean in Rats.*

No.	Weight of Rat in oz.	Dose in grains.		Result.	Remarks.
		Cal. B. extract.	Sulph. of Atropia.		
219	10	1-16th	1	Survived for 30 hrs.	The same dose un-antagonised would probably have killed it in 15 to 20 min.
220	10½	1-20th	1¼	Recovered	Not evidently a fatal dose, as it recovered 5 days thereafter from same dose
221	10½	1-14th	1	,,	Killed 5 days afterwards in 36 minutes by same dose
222	10¾	1-12th	1½	Died in 37m.	Life prolonged by sulphate of atropia
223	9¾	1-10th	¾	Died in 20m.	Ditto
224	8	1-8th	1	Died in 18m.	Ditto
225	9½	1-16th	⅔	Survived for 17 h.	This animal was very Ill; died from congestion of lungs
226	9¼	,,	1	Recovered	Killed by same dose 7 days afterwards in 22 minutes
227	10	1-18th	1 1-6th	,,	Recovered again after same dose in 10 days; evidently non-fatal.
228	10	1-17th	1 1-10th	Recovered; very ill 6h.	Died 5 days afterwards in 3 hours from same dose; a weakly rat

The above table shows that, as is the case in rabbits, sulphate of atropia antagonises the action of extract of Calabar bean, but that the area of antagonism is very limited. In all of the above experiments, the extract of Calabar bean was first injected in solution, and was followed immediately afterwards by sulphate of atropia. It is to be observed that, in Nos. 221 and 226, the animal recovered from a fatal dose of extract of Calabar bean by the action of sulphate of atropia; and that the same dose of extract of Calabar bean destroyed life in from twenty-two to thirty-six minutes when given to the same animals several days after the first experiment.

General Conclusions regarding the Antagonism between Sulphate of Atropia and Extract of Calabar Bean.

1. Sulphate of atropia antagonises to a certain extent the fatal action of Calabar bean.

2. The area of antagonism is even more limited than Dr. Fraser has indicated in his paper already referred to.

In all the experiments made in connection with this branch of the inquiry, it was found that so-called antagonism existed within very narrow limits. The danger was, not death by too great a dose of sulphate of atropia, the supposed antagonist, but death from the effects of the extract of Calabar bean. In this respect, there was also a marked contrast to the action of hydrate of chloral on the physiological effects of strychnia. In the latter instance, the danger evidently would be, in a case of poisoning by strychnia, to give too large a dose of hydrate of chloral; whereas, in the case of poisoning by extract of Calabar bean, it would apparently be very difficult to arrest its effects by sulphate of atropia, because a small dose of the latter produces little effect (at all events in rabbits), and the effects of the extract of Calabar bean are so violent as soon to destroy life. It results that, for all practical purposes, atropia, as an antidote to Calabar bean, is useless, and not to be compared with the effects of chloral hydrate, as shown by the Committee under the next head.

III.—Antagonism between Hydrate of Chloral and Calabar Bean.

The minimum fatal doses of these two substances having been already determined in previous researches (see Tables I and IX), it was resolved to investigate the question of antagonism between hydrate of chloral and extract of Calabar bean. The first set of experiments are shown in the following table.

Table XVII.—*Showing the Effects of Extract of Calabar Bean as modified by Hydrate of Chloral—Extract of Calabar Bean given after Hydrate of Chloral—in Rabbits.*

No.	Weight of Rabbit.	Time when Ext. of Calabar Bean was given after Hyd. of Chloral.	Dose of Hydrate in grains.	Dose of Ext. of Calabar B. in grs.	Result.	Remarks.
229	3 lbs. 12 oz.	14 min.	15	¼	Recovery	No convulsions; profuse salivation
230	4 lbs.	6 min.	20	¼	,,	No convulsions
231	4 lbs.	12 min.	15	¼	Died in 2 h. 53 m.	,,
232	3 lbs. 4 oz.	10 min.	15	¼	Recovery	Severe tremors
233	3 lbs. 4 oz.	17 min.	15	¼	Died in 14 min.	Very violent convulsions
234	6 lbs.	20 min.	20	¼	Recovery	No convulsions
235	6 lbs.	,,	20	¼	Died in 1 h. 45 m.	Apparently asphyxiated from mucus

In all of these cases, the hydrate of chloral was given before the Calabar bean, at varying intervals from six to twenty minutes. Now, as hydrate of chloral, in doses of fifteen grains, produces hypnotism in about from fourteen to twenty minutes, it is evident that, in several of the above experiments, the animal was not completely under the influence of the hydrate of chloral when the extract of Calabar bean was given. In all the above experiments, with the exception of No. 233, which was a weakly rabbit, there could be no doubt of the fact that hydrate of chloral modified the symptoms produced by extract of Calabar bean, and postponed the fatal issue of the latter; but in no case was life saved from a fatal dose of the extract. Experiments 231 and 235 are worthy of note, because in these the animals survived for one hundred and thirteen and one hundred and five minutes respectively, after a dose of extract of Calabar bean which would have destroyed life, under ordinary circumstances, in from ten to fifteen minutes. The animal in Experiment 234 survived from a fatal dose of extract of Calabar bean; but, unfortunately, in this case the crucial test of the administration of extract of Calabar bean to the same amount several days afterwards was not applied.

It was accordingly resolved to make a second set of experiments to ascertain, if possible, more precisely, by the application of the crucial test, whether or not life could be saved from a fatal dose of extract of Calabar bean. For this purpose, twelve middle-sized rabbits, weighing from three to three-and-a-half pounds, were collected, and experiments were made as shown in the following table.

TABLE XVIII.—*Showing the Effects of Extract of Calabar Bean as modified by Hydrate of Chloral—Extract of Calabar Bean given after Hydrate of Chloral—in Rabbits.*

No.	Weight of Rabbit.	Time when Hyd. of Chloral was given before Ext. of Calabar Bean.	Dose of Hydr. of Chloral in grains.	Dose of Ext. of Calabar B. in grs.	Result.	Remarks.	Result of crucial experiment performed eight days afterwards.
236	3lbs.	12 min.	15		Death	In 44 minutes	
237	3lbs. 1oz.	10 min.	15		,,	In 80 minutes	
238	3lbs. 2oz.	15 min.	15		,,	In 88 minutes	
239	3lbs.	,,	15		Recovered	No convulsions	Died in 7 m.
240	2lbs. 15½oz.	12 min.	15		,,	Slightly convulsed	Died in 10 m.
241	2lbs. 15oz.	11 min.	15		Death	In 100 minutes	
242	3lbs.	12 min.	15		,,	In 105 minutes	
243	3lbs.	,,	15		Recovered	Convulsed	Died in 6 m.
244	3lbs.	11½ m.	15		,,	,,	Died in 8 m.
245	3lbs. ½oz.	11 min.	15		Death	In 120 minutes	
246	3lbs. 2oz.	12 min.	15		,,	In 56 minutes	
247	3lbs. 3oz.	,,	15		Recovered	No convulsions	Died in 15 m.

It will be seen from Table XVIII that, out of twelve instances, in which a dose of fifteen grains of hydrate of chloral was given ten or twelve minutes before a dose of two-thirds of a grain of extract of Calabar bean, seven died in periods varying from 44 to 120 minutes, while five survived. Those animals which survived were killed eight days afterwards by the same dose of extract of Calabar bean, without the previous administration of hydrate of chloral, in from six to fifteen minutes. The cases of death, Nos. 236, 237, 238, 241, 242, 245, and 246, might not have been fatal if pulmonary congestion and asphyxia from accumulation of fluid in the air-passages could have been avoided. It is warrantable to draw the following conclusions from these experiments.

1. That hydrate of chloral modifies to a great extent the action of a fatal dose of extract of Calabar bean, mitigating symptoms and prolonging life.

2. That hydrate of chloral, in some cases, saves life from a fatal dose of extract of Calabar bean.

In the above experiments, the hydrate of chloral was given first, and in most instances the extract of Calabar bean was not administered until the animal was well under the influence of the hydrate of chloral. The reason for this proceeding was, that little hope was entertained that chloral hydrate could antagonise the effects of extract of Calabar bean, if symptoms produced by a fatal dose of the latter were permitted first to make their appearance. It was resolved, however, to investigate the matter more fully. This was accordingly done in twelve experiments, in all of which the extract of Calabar bean was first administered, and hydrate of chloral was given, in the first experiment, simultaneously, and in the others at intervals of from two to twelve minutes afterwards. At this stage of the inquiry, it was found that the solution of the extract of Calabar bean supplied by Dr. Cook had evidently altered in strength, as two-thirds of a grain constituted a fatal dose for a rabbit weighing three pounds, instead of three-quarters of a grain as had been determined to be the fatal dose in the chloral-strychnia experiments. (See Table IX.) The difference between two-thirds and three-quarters of a grain is one-twelfth of a grain—that is, the fatal dose of the solution of extract of Calabar bean supplied by Dr. Cook had become one-twelfth of a grain less for a rabbit of three pounds weight.

The result of the twelve experiments are shown as follows:

TABLE XIX.—*Showing Effects of Extract of Calabar Bean as modified by Hydrate of Chloral—Extract of Calabar Bean given before Hydrate of Chloral—in Rabbits.*

No.	Weight of Rabbit.	Time when Extract of Calabar Bean was given before Hydrate of Chloral.	Dose of Extract of Cal. Bean in grs.	Dose of Hydr. of Chloral in grains.	Result.	Remarks.	Result of crucial experiment performed eight days afterwards.
248	3lbs.	Simultaneous	⅛	15	Recovery	Very ill; severe convulsions	Died in 8 min.
249	3lbs. 1oz.	2 min.	⅛	15	,,	Ditto	Died in 7 min.
250	3lbs. ½oz.	4 min.	⅛	15	Died in 49m.	Ditto	
251	3lbs.	6 min.	⅛	15	Died in 30m.	Ditto	
252	3lbs. 2oz.	,,	⅛	15	Died in 27m.	Ditto	
253	2lbs. 15½oz.	10 min.	⅛	15	Diedin 13 m.	Was much affected by Cal. bean extract when chlor. hyd. was given	
254	2lbs. 14oz.	12 min.	⅛	15	Died in 30m.	Nearly dead when chloral given	
255	3lbs.	3 min.	⅛	15	Recovery	Very ill for eight hours	Died in 12 m.
256	3lbs.	5 min.	⅛	15	Survived for 4h.	Died from pulmonary congestion	
257	3lbs. 1½oz.	6½ min.	⅛	15	Died in 24m.		
258	3lbs.	7 min.	⅛	15	Died in 15m.	Ill before chloral hydrate given	
259	3lbs.	8 min.	⅛	15	Died in 12m.	Ditto	

The above tables clearly show that, if hydrate of chloral be given before extract of Calabar bean, so that the animal is deeply under the influence of hydrate of chloral before it receives the extract of Calabar bean, the symptoms of the latter are much modified, and life saved from the effects of what would otherwise be a fatal dose. See Tables XVII and XVIII. On the other hand, chloral hydrate is of comparatively little service as an antagonist to extract of Calabar bean if given some time after the latter. The reason of this is quite evident. Extract of Calabar bean produces its more severe physiological effects ten or twelve minutes after the administration of the fatal dose. In some cases the effects occur even sooner. On the other hand, a rabbit is not deeply under the influence of hydrate of chloral until fifteen or twenty minutes after it has been given. If the effects of extract of Calabar bean appear before those of hydrate of chloral, they usually run quickly to a fatal issue, because the antagonist, hydrate of chloral, is not acting with sufficient vigour to restrain them.

It comes to be considered what is the nature of the physiological antagonism between extract of Calabar bean and hydrate of chloral. Is it a true antagonism, a neutralisation of the physiological effect of the one by that of the other? The effects of the one do not appear to

be completely neutralised by those of the other. Even in those animals deeply under the influence of hydrate of chloral into which a fatal dose of extract of Calabar bean has been subsequently introduced, we do not find a complete absence of the symptoms referable to the presence of extract of Calabar bean. There are still twitchings and startings, tremors, salivation, contracted pupil, etc. But, on the other hand, the tendency to death by convulsions is obviated. If the animal be kept quiet, with a free circulation of air around it, it may recover. Cases of death after the introduction of both substances are to be referred to pulmonary congestion and the accumulation of fluid in the air-passages.

From these experiments, it is evident that, in the action of chloral hydrate and extract of Calabar bean, we have a good example of physiological antagonism. This antagonism is, however, limited, as in all such cases, by two conditions: 1. *By the doses administered.* More than a minimum fatal dose of extract of Calabar bean destroys life, notwithstanding the administration of chloral hydrate. 2. *By the interval of time between the administration of the two substances.* There is a great probability of saving life in those instances in which both substances are given almost simultaneously. This probability is diminished if the chloral hydrate be given five or eight minutes after the extract of Calabar bean; while there is no chance at all if the chloral hydrate be given more than eight minutes after a fatal dose of extract of Calabar bean. But even in those cases in which death occurs after the introduction of both substances, the effects of the Calabar bean are much less marked.

These results must be regarded as very important. Several cases are now on record where ships coming from Africa have discharged Calabar beans on the shore, and which have been eaten by children with more or less poisonous effects. In such cases, the administration of chloral hydrate should at once be resorted to. In Africa, fatal doses are designedly given by the ignorant natives as a test of guilt or innocence; and it will be well to remember that there it may not unfrequently occur that, as civilisation opens up the country to our missionaries and medical men, life may, in this way, not unfrequently be saved.

IV.—Antagonism between Hydrochlorate and Meconate of Morphia and Calabar Bean.

In this inquiry, the minimum fatal dose of hydrochlorate of morphia was first ascertained. As this salt is soluble to the extent of only 1 in 20 of water, it was supposed that the introduction into the system of a rabbit of a large amount of water (three or four drachms) might vitiate the result, and accordingly experiments were made with meconate of morphia, a much more soluble salt. The fatal dose of the latter having been first determined (see Table XXI), experiments were made with the view of ascertaining whether or not there was any antagonism between the two. The results are detailed in the following tables.

Table XX.—*Showing the Effects of a Minimum Fatal Dose of Hydrochlorate of Morphia on Rabbits.*

No.	Weight of Rabbit.	Dose of Hydrochl. of Morphia in grains.	Result.	Remarks.
260	3 lbs. 8 oz.	1	Recovered	Somewhat lethargic for 2 hours
261	4 lbs.	2	,,	Much in same condition for 2 hrs.; pupils contracted
262	3 lbs. 12 oz.	2½	Survived for 48 hours	Ditto, ditto; found dead 48 hours afterwards
263	4 lbs.	3	Recovered	Drowsy and lethargic for 3 hours
264	4 lbs. 8 oz.	2½	,,	Ditto
265	4 lbs. 3 oz.	2½	,,	Ditto
266	,,	4	,,	Ditto; pupils contracted
267	4 lbs.	4½	,,	Ditto
268	5 lbs.	5	,,	Ditto
269	4 lbs.	6	,,	Severe convulsions, with well marked emprosthotonos
270	,,	7	,,	Ditto, ditto
271	,,	8	,,	Ditto, ditto
272	5 lbs.	9	,,	Ditto, ditto
273	4 lbs.	10	,,	Ditto, ditto; convulsions not so severe
274	,,	11	,,	Ditto, ditto
275	,,	13	,,	Ditto, ditto; very severe convulsions
276	,,	13	Died in 70 m.	Convulsions; tendency to move forwards
277	3 lbs. 12 oz.	14	Died in 57 m.	Ditto, ditto
278	,,	15	Died in 53 m.	Ditto, ditto

These experiments show that approximatively a dose of about 13 grains will kill a rabbit of about 4 lbs. in weight, that is, 12 grains for a rabbit 3 lbs. in weight. The predominant symptoms preceding death

by a fatal dose were as follows : restlessness, contraction of the pupil, muscular twitchings, forward movements, convulsions, at first clonic, afterwards tonic—frequently at first there was a tendency to bending of the body forwards (emprosthotonos), but always before death there was opisthotonos, that is, bending backwards.

As already mentioned, experiments were also made with the more soluble salt—the meconate of morphia. The strength of the solution employed was one in four of water. The following experiments were made to determine the fatal dose.

TABLE XXI.—*Showing the Effects of a Minimum Fatal Dose of Meconate of Morphia on Rabbits.*

No.	Weight of Rabbit.	Dose of Meconate of Morphia in grains.	Result.	Remarks.
279	4 lbs.	2	Recovered	No appreciable effect except drowsiness and contraction of pupil
280	,,	3	,,	Ditto, ditto
281	4 lbs. 4 oz.	4	,,	Ditto, ditto
282	4 lbs. 6 oz.	5	,,	Ditto, ditto
283	4 lbs.	6	,,	Ditto ; slight muscular twitching
284	,,	7	,,	Ditto, ditto ; spasms
285	4 lbs. 2 oz.	8	,,	Forward movements ; twitchings ; spasms ; convulsions
286	3 lbs. 14 oz.	10	Died in 132 m.	Ditto ; severe convulsions
287	3 lbs. 15 oz.	12.5	Died in 75 m.	Ditto, ditto
288	,,	15	Died in 65 m.	Ditto, ditto

The above Table, when compared with Table XX, shows that the fatal dose of meconate of morphia is less than that of hydrochlorate of morphia—seeing that about 13 grains of the former will destroy life in rabbits, while only about 10 of the latter are required. The variation may be owing to the superior solubility of meconate of morphia.

Having ascertained approximately the fatal dose of each of these substances, it was resolved to test the question of antagonism to Calabar bean. This was done in ten experiments, in five of which hydrochlorate of morphia, and in the remaining five meconate of morphia was employed. The results will be seen in the following table, in which "H" stands for hydrochlorate, and "M" for meconate.

TABLE XXII.—*Showing the Influence of Hydrochlorate or Meconate of Morphia on a Fatal Dose of Extract of Calabar Bean, Morphia Salt given first ("H." stands for Hydrochlorate, and "M." for Meconate), in Rabbits.*

No.	Weight of Rabbit.	Time betw. administration of Salt of Morphia & C. B. extract, the former given first.	Dose of Morphia Salt in grains.	Dose of Calabar Bean ext. in grains.	Result.	Remarks.
289	3 lbs. 12 oz.	15 m.	5 H.		Death.	8 minutes after receiving extract
290	,,	,,	6 H.		,,	9½ ,, ,,
291	3 lbs. 8 oz.	18 m.	7 H.		,,	10 ,, ,,
292	3 lbs. 12 oz.	8 m.	4 H.		,,	12 ,, ,,
293	4 lbs.	6 m.	3 H.		,,	17 ,, ,,
294	,,	15 m.	4 M.		,,	24 ,, ,,
295	4 lbs. 1 oz.	12 m.	5 M.		,,	18 ,, ,,
296	4 lbs. 2 oz.	14m.	6 M.		,,	6 ,, ,,
297	3 lbs. 9 oz.	10m.	8 M.		,,	4½ ,, ,,
298	3 lbs. 10 oz.	16m.	7 M.		,,	9 ,, ,,

The conclusion to be drawn from these experiments is undoubtedly that meconate and hydrochlorate of morphia are in no way antagonistic to extract of Calabar bean.

V.—ANTAGONISM BETWEEN SULPHATE OF ATROPIA AND MECONATE OF MORPHIA.

NOTWITHSTANDING the numerous experiments and observations which have been made on this subject, a careful investigation into the evidence which existed previously to the committee's inquiry, could not but demonstrate that nothing positive or certain had been arrived at. Extraordinary pains, therefore, were taken to determine the question whether or not atropia and morphia were antagonistic of one another; and the researches now to be described will be found to add largely to our precise and exact knowledge, as compared with the unfounded and contradictory opinions which have hitherto prevailed.*

The inquiry was divided into three parts: 1. To ascertain as precisely as possible the physiological action of meconate of morphia on

* For a record of these, given by Dr. Fraser, see *Transactions of the Royal Society of Edinburgh*, vol. for 1868-69, p. 551.

the rabbit and on the dog; 2. To ascertain in the same way the physiological action of sulphate of atropia on the rabbit and on the dog; and 3. To ascertain the combined action of the two substances, introduced either simultaneously, or the one before the other, in these animals.

1. *The Physiological Action of Meconate of Morphia on the Rabbit and Dog.*

A. *The Rabbit.*

Experiment 299. Rabbit, weighing 3½ lbs. Cardiac impulses, forty-five in ten seconds. Respirations, twelve in ten seconds. Pupils measured in their transverse diameter, 12-50ths of an inch. Six grains of meconate of morphia in thirty minims of water were injected subcutaneously under the skin of the back. In three minutes, the animal lay on its abdomen and chest, with the hind legs extended and stiffened. The transverse diameter of the pupil was now about 11-50ths of an inch. Respirations, ten in ten seconds. Cardiac impulses, forty-two in ten seconds. In two minutes more, the animal attempted to walk, and it progressed forwards with evident difficulty, owing to the weakness of the posterior extremities. When moving, a slight push was sufficient to turn the animal over on its side. In eight minutes more, there were slight convulsive twitches of the muscles of the back, and the animal was now quite narcotised. If allowed to remain undisturbed, it lay flat, with hind limbs spread outwards, and with fore limbs placed close together so as to support the head. It could still be aroused when pushed about. The respirations now numbered seven in ten seconds, that is, a fall of five since the beginning of the experiment. The cardiac impulses were very feeble, but were regular, and were thirty in ten seconds, that is, a fall of fifteen. The animal remained in this condition for nearly three hours. It then slowly recovered. On the following day, it was apparently quite well.

Experiment 300. Rabbit, weighing nearly 3½ lbs. Cardiac impulses, forty-six in ten seconds. Respirations, fourteen in ten seconds. Pupils 12-50ths of an inch. Nine grains of meconate of morphia in forty-five minims of water were injected under the skin over the left flank. The symptoms described in the preceding experiment took place. Thirty minutes after receiving the dose, the respirations were reduced to six in ten seconds. The cardiac impulses fell to thirty-eight in ten seconds; and the pupil now measured 6-50ths of an inch. The muscular twitchings had increased. After a little time, there were severe spasms, coming on with great suddenness, accompanied by

bending backwards of the spine and pawing movements of the fore limbs. These spasms continued for nearly thirty minutes. The animal became weaker. The heart-pulsations were now so feeble that they could not be felt through the parietes of the chest. It died one hour and five minutes after receiving the dose of nine grains of meconate of morphia. When the body was opened immediately after death, the ventricles and the right auricle were still contracting. The right side of the heart was distended and full of dark venous blood. The left side was firmly contracted.

Experiment 301. Rabbit, weighing nearly 3¾ lbs. Received ten grains of meconate of morphia in sixty minims of water. The usual phenomena supervened. While the animal was in the narcotised condition, the sciatic nerve in the right hind leg was quickly exposed, and it was stimulated by a weak induction current obtained from Du-Bois Reymond's electromotor. The nerve responded to the stimulus. The muscles contracted powerfully, either when stimulated directly or when the nerve was touched. A current so weak as to be scarcely perceptible when the electrodes were applied to the tip of the tongue was sufficient to cause contractions. It was also observed that when the electrodes were applied to the nerve, not only the muscles of the limb supplied by the nerve contracted, but frequently those of the other limb, were thrown into movements also. At this stage of the experiment, the animal died in severe convulsions with opisthotonos.

Experiment 302. Rabbit, weighing nearly 3 lbs. 8 oz. Cardiac impulses, forty in ten seconds. Respirations, fourteen in ten seconds. Received nine grains of meconate of morphia. The rabbit having been secured in Czermak's holder, after it was apparently under the action of the meconate, both vagi were exposed in the neck, and each was stimulated by a current of definite strength from Du-Bois Reymond's electromotor. It was found that total stoppage of the heart's contractions followed stimulation for ten seconds. The stimulation was repeated at intervals six times with the same result.

Experiment 303. Rabbit, weighing nearly 3 lbs. 6 oz. Cardiac impulses, thirty-nine in ten seconds. Respirations, fifteen in ten seconds. Pupil, 14-50ths of an inch. It received nine grains of meconate of morphia. When it was in a state of narcotism with slight muscular twitchings, the pupil was measured, and was found to be 12-50ths. The sympathetic nerve on the right side was then exposed. When cut, the pupil at once contracted to 6-50ths of an inch. When the upper end of the sympathetic nerve was stimulated by a weak induction-current, the pupil dilated to 8-50ths.

B. *The Dog.*

Experiment 304. Male black and tan terrier dog, weighing 20½ lbs. Ten minims of a solution of meconate of morphia, containing two grains the meconate, were injected under the skin on the back. In four minutes, it vomited three times. In another minute, it attempted to stand up, and trembled violently. It laid its head down on the floor. In another minute, it lay flat on its abdomen, with the head extended on the fore paws, and the tongue protruded. The pupil was now much contracted. It remained in this condition for half-an-hour. It defæcated a quantity of soft green pultaceous matter. In another half hour, it walked with a staggering gait to the other end of the laboratory, when it lay down and apparently fell asleep. It was roused three hours after the time of receiving the dose of meconate of morphia, and it then took food. It recovered slowly, as for several days it was observed that the hind legs were weak. There seemed to be also, to a slight extent, a loss of co-ordinating power.

Experiment 305. Male Scotch terrier, weighing 14¾ lbs. Three grains and a half of meconate of morphia dissolved in eighteen minims of distilled water were injected under the skin of the back. The phenomena seen in this case were similar to those just described in experiment 304. Thirty-five minutes after having received the dose, the animal was deeply narcotised. The pupils were contracted to a mere point. It could not be aroused in any way. The respirations were slow. The cardiac pulsations were so feeble that they could scarcely be perceived through the walls of the chest. While the animal was in this state, the three following experiments were made as quickly as possible. 1. The sciatic nerve was exposed and stimulated by a weak induction current. It responded to an extremely feeble current. The muscles of the leg also contracted when stimulated directly. 2. The pneumogastric nerve on the right side was exposed in the neck, and stimulated by a weak induction-current. Stimulation was found to arrest the action of the heart. 3. The sympathetic nerve on the right side was exposed and also stimulated by a weak induction current. The heart was then noticed to pulsate more quickly. On cutting the sympathetic and stimulating the cephalic end, the pupil slowly dilated but not to its full size. The animal was then killed. During the operation, there appeared to be complete anæsthesia. On opening the thorax and stimulating the phrenic nerves, the diaphragm contracted powerfully.

From these experiments, the following conclusions regarding the phy-

siological action of meconate of morphia on rabbits and dogs may be drawn.

1. In both animals, meconate of morphia acts on the encephalon and on the spinal cord, but in the case of dogs the action is more cerebral, while in rabbits it is more spinal.

2. As Dr. John Harley states,* either delirium or hypnotic effects may be produced. In the experiments recorded, hypnotism was the predominant effect.

3. In the case of rabbits, death is often produced by convulsions.

4. In both cases, while deeply under the influence of the drug, as stimulation of the motor nerves caused muscular contractions, we must hold that the sensibility and conducting power of the nerves are not destroyed.

5. In both cases, stimulation of the vagus in the neck causes stoppage of the action of the heart. Consequently, the vaso-inhibitory fibres in the vagus are not paralysed by meconate of morphia. It is possible, as Harley appears to think,† that these fibres may be irritated.

6. Stimulation of the sympathetic in both cases causes dilatation of the pupil. Consequently the sympathetic trunk is not paralysed, and the contraction of the pupil must be owing to the cranial origins of the third nerve being irritated, thus causing contraction of the circular fibres of the iris, governed by that nerve, and consequent contraction of the pupil.‡

7. Morphia may affect the action of certain nerves by paralysing the nerve centres from which they issue, but the nerves themselves apparently still retain sensibility and conductivity.

The experiments on the physiological action of meconate of morphia are shortly summarised in the following table.

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* Harley, *Old Vegetable Neurotics.*

† See Harley, "Action on the Pupils", pp. 136-137.

‡ Harley lays great stress on the action of morphia on the vagus, but his facts do not appear to warrant his conclusions. He says (p. 134): "Derangement of the vagus nerve is the main source of the distress which follows; its sentient branches are blunted, and the lungs no longer invite a flow of blood; its motor branches convey only cramp to the muscular parts; the mechanical suction-power of the chest is depressed, and the lungs themselves tend to collapse. The right heart soon becomes distended; cardiac distress is complained of; the pulse loses force and volume, intermits, and syncope results.'

TABLE XXIII.—*Showing the Effects of Meconate of Morphia on Rabbits and Dogs.*

No.	Animal.	Weight of Animal.	Dose in grains.	Result.	Remarks.
299	Rabbit.	3 lbs. 8 oz.	6	Recovered	General description of effect of a non-fatal dose
300	,,	,,	9	Died in 65 minutes	General description of effect of a fatal dose
301	,,	3 lbs. 12 oz.	10	Death	Effects of stimulating sciatic nerve
302	,,	3 lbs. 8 oz.	9	,,	Effects of stimulating the vagi
303	,,	,,	9	,,	Effects of stimulating the sympathetic
304	Dog	20 lbs. 8 oz.	2	Recovered	General description of effect of a non-fatal dose
305	,,	14 lbs. 12 oz.	3½	Killed	Effects of stimulating motor nerves, pneumogastric and sympathetic, while animal was narcotised

2. *The Physiological Action of Sulphate of Atropia on the Rabbit and Dog.*

A. *Rabbits.*

The physiological action of sulphate of atropia has already been so fully studied in rabbits, in previous parts of this research (see Table X), that it need not again be entered upon. In small doses of from two to four grains, the only observable symptoms are dilatation of the pupils, quickening of the cardiac contractions, and of the number of respiratory movements. When four to eight grains are given, in addition to these symptoms, there are slight paralysis, more especially of the hind extremities, and a greater increase in the number of cardiac impulses. Above this dose, the action of the heart and lungs becomes embarrassed—the heart's action being much weakened, and there is also a reduction in the rate of respirations. After doses above sixteen grains, death ensues with paralysis, tremors, spasms, and perhaps convulsions.

B. *Dogs.*

Experiment 306. A Scotch terrier, weighing 16 lbs., received the one-eightieth of a grain of sulphate of atropia in ten minims of water under the skin of the back. Before the substance was introduced, the transverse diameter of the pupil was 10-50ths of an inch. Pulse 118, respirations 18 per minute. In four minutes, the pulse had risen to 280, and was very firm to the touch. The pupils were dilated to their full extent five minutes after the dose. The lips, inner surface of the cheeks, surface of the tongue, and the lining membrane of the nose were all dry. In three-

quarters of an hour, the pulse fell to 250. The animal appeared to be excited. It ran backwards and forwards, came against the legs of the laboratory table, and sometimes sat down and whined. At the end of four hours after receiving the dose, no effects could be observed.

Experiment 307. Four days after the experiment just related, the same dog weighed 16½ lbs. The pupils measured in their transverse diameter nearly 12-50ths of an inch. Pulse 120, respirations 18 per minute. One-fortieth of a grain of sulphate of atropia in ten minims of water was injected under the skin of the back. The same effects followed as in the last experiment. The most marked were acceleration of the pulse and dilatation of the pupil. The following observations were made.

TABLE XXIV.—*Showing the Effect of Sulphate of Atropia on the Cardiac Pulsations, Respiratory Movements, and Diameter of the Pupil of a Dog.*

Time aft. dose of Sulph. of Atropia.	Cardiac pulsations per m.	Respirations per m.	Transverse diameter of pupil in parts of an inch.	Time aft. dose of Sulph. of Atropia.	Cardiac pulsations per m.	Respirations per m.	Transverse diameter of pupil in parts of an inch.
1 min.	130	19	.24	12 min.	232	30	.46
3 ,,	140	20	.26	13 ,,	228	30	.48
4 ,,	146	21	.26	14 ,,	226	32	.48
5 ,,	149	21	.30	15 ,,	232	32	.48
6 ,,	152	23	.36	16 ,,	230	31	.48
7 ,,	164	24	.42	17 ,,	231	31	.48
8 ,,	176	28	.48	18 ,,	232	31	.48
9 ,,	190	28	.48	19 ,,	232	30	.48
10 ,,	210	29	.46	20 ,,	233	30	.48
11 ,,	220	30	.46	21 ,,	233	30	.48

Twenty minutes after the dose, the animal was much excited. It sat on its haunches and swayed its head from side to side. Occasionally, it tried to walk, but there was evident weakness of all the limbs, more especially of the hind extremities. On placing the hand over the wall of the chest, the pulsations of the heart could be distinctly seen and felt. The animal continued in this state for nearly four hours, when it began slowly to recover. It appeared to be out of health, and frequently refused food for four days after this experiment.

Experiment 308. A week after the preceding experiment, the same dog weighed 15 lbs. Pupil 12-50ths. Cardiac pulsations 124 per minute. Respiratory movements 17 per minute. One-twentieth of a grain of sulphate of atropia in ten minims of water was injected under the skin of the left loin. The effects observed were similar to those described in experiments 307 and 308; but the weakness and tottering gait in locomotion were more marked. It recovered.

Experiment 309. Five days afterwards, one-tenth of a grain of sulphate of atropia was given. Weight, 15 lbs. The effects were the same, but more marked. The animal recovered.

Experiment 310. Six days afterwards, the same dog received one-fifth of a grain of sulphate of atropia. Weight 15 lbs. In this instance the animal was evidently only partially conscious three quarters of an hour after the experiment. It did not respond readily to its name, and when roused it could scarcely walk. It was unable to sit up. Although the mouth was parched, it would not drink water. It urinated freely. It remained in this condition, with the heart beating so rapidly as to be almost uncountable, and the pupil dilated to its fullest extent. It then slowly recovered.

Experiment 311. Ten days afterwards, the same dog was 13½ lbs. in weight, but it appeared to be out of condition so far as its skin was concerned. The hair was scanty, more especially near the mouth. In this experiment, half a grain of sulphate of atropia was injected under the skin near the nape of the neck. The effects were the same, although much intensified. The animal lay prostrate, with the head resting on the fore paws, the mouth partially open, and the tongue lolling out. It was insensible. It could not be roused by pushing. There were a few convulsive jerks of the muscles of the back and neck which tended to cause the head to move suddenly backwards. It remained in this condition for nine hours, when it slowly recovered. No further experiments were made on this animal, as it remained out of condition for a long time. It completely recovered.

Experiment 312. The fatal dose of sulphate of atropia for a dog being now evidently approached, it was determined to ascertain it, if possible, with more precision. An experiment was accordingly made on a mongrel English terrier, weighing 15 lbs. Three-fourths of a grain of sulphate of atropia in thirty minims of water were injected under the skin over the left flank. The phenomena observed after this large dose were the same as those just described. One hour after the administration of the dose, the animal was prostrate, with pupils widely dilated. The cardiac pulsations were too rapid to be counted, and they were also so feeble as scarcely to be felt. The respirations were irregular and shallow. There were convulsive twitchings of the muscles, more especially those of the back and neck. The sphincters were paralysed, and the fæces and urine came away frequently. Three hours after the dose, a smart convulsion occurred, the body was bent backwards, the mouth opened widely, the heart suddenly ceased, and the animal was dead.

Experiment 313. In order to establish the point that three-fourths of a grain of sulphate of atropia was a fatal dose for a dog of 14 lbs. or 15 lbs. weight, it was necessary to repeat the experiment in another animal of nearly the same size, and, as far as possible, in the same condition. Three-fourths of a grain of sulphate of atropia dissolved in thirty minims of water were, therefore, injected under the skin over the left shoulder of a young mongrel dog, weighing 16 lbs. After the usual phenomena, the animal died three hours and a quarter after the administration of the fatal dose.

Experiment 314. The following experiment was made to determine the action of sulphate of atropia on the nerves and on the heart. A small terrier of a mongrel breed, weighing 11 lbs., had three-fourths of a grain of sulphate of atropia in twenty minims of water injected under the skin of the back. After the usual phenomena, it was apparently unconscious thirty-eight minutes after the exhibition of the dose. It was then properly secured, and the following experiments were made.

a. As to Effect on the Motor Nerves.—The sciatic nerve in the right hind leg was exposed, and was stimulated by currents from Du-Bois Reymond's electromotor, worked by a Daniell's cell, the zinc surface of which was as nearly as possible twelve square inches. The strength of the current employed was so weak as scarcely to be perceived by the tip of the tongue. The effect was, that, on the application of the electrodes to the exposed nerve, the muscles of the hind limb at once contracted, indicating that the motor nerve-tubes were not paralysed. It was also observed that, on the application of the electrodes to the exposed nerve, the animal moved its whole body. It was impossible to determine whether these movements were purely reflex, associated with no consciousness of pain, or whether the animal really felt pain.

b. As to the Effect on the Pneumogastric Nerve.—The vagi on both sides were exposed as quickly as possible. A pair of electrodes was placed beneath each, and, by means of Pohl's commutator, the electrical arrangements were so made, that either the right or the left vagus could be stimulated alternately, or both at once. The result was, that stimulation of the vagus or vagi produced no appreciable effect on the number of the cardiac pulsations. This will be seen from the following figures, and indicates that atropia, as is now recognised by all physiologists, paralyses either the trunk of the cardiac branches of the pneumogastric nerves, or the intrinsic nerve-centres in the heart with which the cardiac branches are connected. The stimulation was derived from the secondary coil of Du-Bois Reymond's electromotor placed at a distance of fifty *millimètres* from the primary coil, which latter was

in connection with a Daniell's cell, the zinc surface of which measured twelve square inches.

TABLE XXV.—*Showing the Effects of the Electrical Stimulation of the Vagi of a Dog under the Influence of Sulphate of Atropia.*

Time P.M.	No. of Cardiac Pulsations per min. on stimulating.				Time P.M.	No. of Cardiac Pulsations per min. on stimulating			
	Right vagus.	Left vagus.	Both vagi.	Neither.		Right vagus.	Left vagus.	Both vagi.	Neither.
1.20	...	...	...	220	2.2	229	229	...	...
1.22	220	220	...	...	2.4	228	229	...	...
1.24	...	...	220	...	2.6	...	228	...	...
1.26	221	221	...	...	2.8	...	...	...	228
1.28	...	...	220	...	2.10	228	229	...	...
1.30	...	...	...	222	2.12	229	229	...	...
1.32	222	221	...	...	2.14	229	229	...	...
1.34	222	223	...	...	2.16	229	230	...	...
1.36	224	224	...	...	2.18	...	...	230	...
1.38	224	224	...	...	2.20	...	...	...	230
1.40	...	...	225	...	2.22	229	229	...	...
1.42	...	...	...	227	2.24	230	230	...	...
1.44	...	...	...	...	2.26	229	229	...	...
1.46	226	227	...	...	2.28	228	227	...	...
1.48	226	226	...	...	2.30	...	...	226	...
1.50	227	226	...	...	2.32	...	...	...	227
1.52	228	227	...	...	2.34	228	229	...	...
1.54	...	...	227	...	2.36	228	228	...	...
1.56	...	...	...	228	2.38	229	229	...	...
1.58	228	228	...	...	2.40	229	228	...	...
2	228	228	...	...	2.42	...	...	...	228

These experiments on dogs are briefly recapitulated in the following table.

TABLE XXVI.—*Showing the Results of Experiments made on Dogs with Sulphate of Atropia.*

No.	Weight of Dog.	Dose of Sulph. of Atropia in grains.	Result.	Remarks.
306 (Same animal used in these experiments at intervals of 5 or 8 days.)	16 lbs.	One-eightieth	Recovered	Dilatation of pupil; acceleration of pulse
307	16 lbs. 8 oz.	One-fortieth	,,	Ditto, ditto
308	15 lbs.	One-twentieth	,,	Ditto, ditto; locomotion affected
309	,,	One-tenth	,,	Ditto, ditto, ditto
310	,,	One-fifth	,,	Ditto, do., do.; partial unconsciousness
311	13 lbs. 8 oz.	One-half	,,	Ditto, do., do.; convulsive twitches of the muscles
312	15 lbs.	Three-quarters	Death in 3 hours	Usual phenomena; death during a spasm
313	16 lbs.	,,	Death in 3½ hours	Usual phenomena
314	11 lbs.	,,	Death	Effects of stimulating motor and pneumogastric nerves

The fatal dose of meconate of morphia and sulphate of atropia, as well as the physiological action of each, both for the rabbit and the dog, having now been determined, the next point was to ascertain whether or not they possessed any antagonistic action. This part of the inquiry is divided into two parts; viz., how far does sulphate of atropia influence the effects of meconate of morphia when given, first, *after*, and, secondly, *before* that drug?

A.—*On Rabbits.*

a.—Sulphate of Atropia given after a Fatal Dose of Meconate of Morphia.

Twenty-one experiments were made on rabbits, in which the sulphate of atropia was administered at various intervals of time after a fatal dose of meconate of morphia. These experiments are contained in the following table (XXVII).

This table shows that, out of twenty-one experiments in which what was held to be a fatal dose of meconate of morphia was followed by a dose of sulphate of atropia, six recovered. When the crucial test was applied to these six rabbits six days later, by injecting ten grains of meconate of morphia without sulphate of atropia, four died, and two recovered. In the case of the latter, the dose of ten grains cannot be considered a fatal dose. In all cases, there could be no doubt that the subsequent injection postponed the fatal issue, if it did not save life. As the sulphate of atropia resembles meconate of morphia in producing convulsions when given in large doses, larger doses of the former than one grain and three-quarters were not given in this set of experiments; but it appeared, from watching the experiments, that the sulphate of atropia favoured the chance of recovery after a fatal dose of meconate of morphia, by causing contraction of the blood-vessels. After sulphate of atropia, the pupil (which was contracted by a dose of meconate of morphia previously given) slowly dilated; and in those cases in which doses of sulphate of atropia, amounting to one and a half or one and three-quarters of a grain, were given within six minutes after the meconate of morphia, the pupil remained nearly of its normal size before the experiment. It was observed also that the vessels of the ear, turgid with blood after the large dose of meconate of morphia, contracted considerably about eight or ten minutes after the introduction of the sulphate of atropia.

TABLE XXVII.—*Showing the Influence of Sulphate of Atropia, when given after a Fatal Dose of Meconate of Morphia, in Rabbits.*

No.	Weight of Rabbit.	Interval of time aft. Meconate of Morphia when Sulphate of Atropia given.	Dose of Meconate of Morphia in grains.	Dose of Sulphate of Atropia in grains.	Result.	Remarks.	State of the Pupil.
315	3 lbs. 10 oz.	Simultaneously	10	$\frac{1}{4}$	Died in 110 minutes	Convulsions; no symptoms of atropia	Pupil became contracted; did not afterwards dilate.
316	3 lbs. 8 oz.	$\frac{1}{2}$ min.	10	$\frac{1}{3}$	Died in 115 minutes	Ditto, ditto	
317	3 lbs. 11 oz.	1 min.	10	$\frac{3}{4}$	Died in 138 minutes	Very slight convulsions; pupil not contracted	
318	3 lbs. 9½ oz.	1½ min.	10	1	Died in 136 minutes	Ditto, ditto	
319	3 lbs. 10 oz.	2 min.	10	1¼	Died in 140 minutes	Ditto, ditto	
320	3 lbs. 9½ oz.	2½ min.	10	1½	Recovered after illness of 3h.	Killed by same dose of meconate of morphia 6 days afterwards in 110 minutes	Pupil never became to any great extent contracted, but retained normal size.
321	3 lbs. 9 oz.	2¾ min.	10	,,	Recovered after illness of 3½ hours	Recovered from same dose 6 days afterwards	
322	3 lbs. 7 oz.	3 min.	10	,,	Recovered	Killed by same dose 6 days afterwards in 90 minutes	
323	3 lbs. 9 oz.	3½ min.	10	1¾	Died in 6 h.	Died of congestion of lungs	
324	3 lbs. 8 oz.	4 min.	10	,,	Died in 2 h.	Slight convulsions	
325	3 lbs. 7½ oz.	5 min.	10	,,	Died in 2½ h.	Ditto	
326	3 lbs. 9 oz.	5¼ min.	10	,,	Recovered	Recovered from same dose 6 days afterwards	
327	,,	5¾ min.	10	,,	Died in 3 h.	Slightly convulsed	
328	3 lbs. 12 oz.	6 min.	10	1⅔	Died in 3½ h.	Slightly convulsed	Pupil was contracted before sulphate of atropia was given; it became dilated in about two hours.
329	3 lbs. 11½ oz.	7 min.	10	1¾	Recovered after illness of 8 hours	Died from same dose 6 days afterwards in 115 minutes	
330	3 lbs. 10½ oz.	8 min.	10	1¾	Died in 6 h.	...	
331	3 lbs. 9½ oz.	9 min.	10	,,	Died in 2½ h.	Died suddenly, apparently by syncope	
332	,,	9½ min.	10	,,	Died in 5 h.	Congestion of lungs	
333	3 lbs. 8 oz.	10 min.	10	,,	Recovered	Died from same dose 6 days afterwards in 108 minutes	
334	3 lbs. 9 oz.	12 min.	10	1½	Died in 4 h.	Congestion of lungs	
335	3 lbs. 8½ oz.	15 min.	10	1¾	Died in 3 h.	,,	

b.—Sulphate of Atropia given before a Fatal Dose of Meconate of Morphia.

In the following eleven experiments, the sulphate of atropia was given in one-and-three quarter or two-grain doses before the meconate of morphia. When the latter was introduced in certain of the cases, the pupil was widely dilated. The results are briefly recorded in the following table.

TABLE XXVIII.—*Showing the Influence of Sulphate of Atropia when given before a Fatal Dose of Meconate of Morphia in Rabbits.*

No.	Weight of Rabbit.	Interval of Time between Sulphate of Atropia and the Meconate.	Dose of Sulphate of Atropia in Grains.	Dose of Meconate of Morphia in Grains.	Result.	Remarks.	State of the Pupil.
336	3 lbs. 11 oz.	20 min.	1¾	10	Died in 2½ hours	Slightly convulsed	Dilated
337	3 lbs. 9 oz.	12 min.	1¾	10	Recovered	Recovered from same dose 6 days afterwards	Ditto
338	3 lbs. 10½ oz.	10 min.	1¾	10	Died in 3 h.	...	Ditto
339	3 lbs. 11 oz.	9 min.	1¾	10	Died in 4 h.	...	Ditto
340	3 lbs. 12 oz.	8 min.	2	10	Recovered	Died from same dose in 2 hrs., 6 days afterwards	Ditto
341	3 lbs. 11½ oz.	7 min.	2	10	Recovered	Died from same dose in 2½ hrs., 6 days afterwards	Ditto
342	3 lbs. 3 oz.	6 min.	1¾	10	Recovered	Recovered from same dose 6 days afterwards	Ditto
343	3 lbs. 4½ oz.	4½ min.	1¾	10	Recovered	Ditto, ditto	Slight contraction
344	3 lbs. 9 oz.	3 min.	2	10	Recovered	Died from same dose in 2½ hrs., 6 days afterwards	Not affected
345	3 lbs. 8 oz.	2 min.	1¾	10	Died in 8 h.	Congestion of the lungs	Not affected
346	3 lbs. 8½ oz.	Simultaneously	1¾	10	Recovered	Died from same dose in 3 hrs., 6 days afterwards	Not affected

It appears from this table that, out of eleven instances in which a dose of sulphate of atropia had been given previous to what was held to be a fatal dose of meconate of morphia, seven recovered—a larger proportion than when the meconate of morphia was given first. Of these seven cases, four died by the crucial experiment of giving meconate of morphia with sulphate of atropia, while three recovered. These numbers are so close that, even although it were admitted that sulphate

of atropia modified the symptoms produced by meconate of morphia, and postponed death, it might be objected that, in those cases of recovery, ten grains of meconate of morphia was not a certainly fatal dose. Eighteen rabbits were therefore collected, of as nearly the same weight as possible; and two sets of experiments were made, in which larger doses of meconate of morphia were employed. In nine cases, the meconate of morphia was given first, and in the remaining nine it was given last. The results are set forth in the following table.

TABLE XXIX.—*Showing the Influence of Sulphate of Atropia on Large Doses of Meconate of Morphia in Rabbits.*

No.	Before or After.	Weight of Rabbit.	Time Meconate of Morphia given, before or after Sulphate of Atropia.	Dose of Sulphate of Atropia in Grains.	Dose of Meconate of Morphia in Grains.	Result.	Remarks.
347	Meconate of Morphia given *before* Sulphate of Atropia.	3 lbs. 10 oz.	5 min.	$1\frac{1}{20}$	11	Died in 60 min.	In all of these cases (347-364) death was postponed. The pupil was slightly dilated in Nos. 350 and 354. It retained its usual size in the others. Death was always preceded by deep coma. No. 359 died from same dose in 90 min., 6 days thereafter.
348		3 lbs. 8 oz.	5 min.	$1\frac{1}{16}$	$11\frac{1}{4}$	Died in 80 ,,	
349		3 lbs. 9 oz.	4 min.	$1\frac{1}{20}$	$11\frac{1}{20}$	Died in 79 ,,	
350		3 lbs. $9\frac{1}{2}$ oz.	$4\frac{1}{2}$ min.	$1\frac{1}{20}$	12	Died in 90 ,,	
351		3 lbs. 9 oz.	5 min.	2	$12\frac{1}{4}$	Died in 105 ,,	
352		3 lbs. $8\frac{3}{4}$ oz.	5 min.	2	$12\frac{1}{20}$	Died in 105 ,,	
353		3 lbs. $8\frac{1}{2}$ oz.	5 min.	2	12	Died in 110 ,,	
354		3 lbs. 8 oz.	$4\frac{3}{4}$ min.	2	12	Died in 110 ,,	
355		3 lbs. 9 oz.	5 min.	$1\frac{3}{4}$	12	Died in 110 ,,	
356	Meconate of Morphia given *after* Sulphate of Atropia.	3 lbs. $9\frac{1}{2}$ oz.	5 min.	$1\frac{3}{4}$	11	Died in 150 min.	
357		3 lbs. 9 oz.	4 min.	2	$11\frac{1}{4}$	Died in 110 ,,	
358		3 lbs. $9\frac{1}{4}$ oz.	4 min.	2	$11\frac{1}{2}$	Recovered	
359		3 lbs. 7 oz.	$4\frac{3}{4}$ min.	2	12	Died in 120 min.	
360		3 lbs. 6 oz.	5 min.	2	$12\frac{1}{4}$	Died in 122 ,,	
361		3 lbs. 11 oz.	5 min.	$1\frac{1}{20}$	$12\frac{1}{20}$	Died in 76 ,,	
362		3 lbs. $11\frac{1}{2}$ oz.	4 min.	$1\frac{1}{20}$	12	Died in 90 ,,	
363		3 lbs. $11\frac{3}{4}$ oz.	5 min.	$1\frac{1}{20}$	12	Died in 100 ,,	
364		3 lbs. $11\frac{1}{4}$ oz.	5 min.	$1\frac{1}{20}$	12	Died in 112 ,,	

In this series of experiments, only one, No. 358, recovered; the others all died in periods varying from sixty to one hundred and fifty minutes. This clearly shows that ten grains of meconate of morphia may be regarded as a minimum fatal dose for a rabbit weighing 3 lbs. 6 oz., or thereabouts. A few may recover from this dose without the aid of sulphate of atropia; but none have recovered, with the exception of 358, either with or without sulphate of atropia, after a dose of eleven grains of meconate of morphia and upwards. It therefore appears that sulphate of atropia is antagonistic to meconate of morphia in rabbits in a limited area, so far as the latter is concerned. It now

became a subject of inquiry to ascertain the result of giving larger doses of sulphate of atropia with somewhat smaller doses of meconate of morphia. Ten experiments were made on this point.

TABLE XXX.—*Showing the Influence of Large Doses of Sulphate of Atropia on Meconate of Morphia in Rabbits; or the Influence of Meconate of Morphia on Large Doses of Sulphate of Atropia.*

No.	Before or After.	Weight of Rabbit.	Time between administration of Meconate of Morphia and Sulphate of Atropia.	Dose of Sulphate of Atropia in Grains.	Dose of Meconate of Morphia in Grains.	Result.	Remarks.
365	Meconate of Morphia given *before* Sulphate of Atropia	3 lbs. 10 oz.	5 min.	4	5	Recovered	Recovered from similar doses given 6 and 12 days thereafter
366		3 lbs. 11 oz.	5 ,,	6	6	Died in 2 hrs.	Failure of action of the heart
367		3 lbs. 13 oz.	4 ,,	8	5½	Died in 3 hrs.	Ditto
368		3 lbs. 6 oz.	3 ,,	10	7	Died in 4 hrs.	Ditto
369		3 lbs. 7 oz.	2 ,,	12	4	Died in 2 hrs.	Convulsions
370	Meconate of Morphia given *after* Sulphate of Atropia	3 lbs. 8 oz.	5 min.	14	9	Died in 69 min.	Ditto
371		3 lbs. 9 oz.	5 ,,	15	4	Died in 70 ,,	Ditto
372		3 lbs. 9½ oz.	4 ,,	18	3	Died in 21 ,,	Ditto
373		3 lbs. 10 oz.	3 ,,	19	5	Died in 40 ,,	Ditto
374		3 lbs. 10½ oz.	2 ,,	21	2	Recovered	Recovered 6 days afterwards from same dose

It does not appear from this table that meconate of morphia favours recovery after a large dose of sulphate of atropia. In several cases—Nos. 372 and 373—the time of death seemed to be rather hastened than delayed, and the animals died in severe convulsions, preceded by tremors and pushing backwards of the body. In all of these cases, it was observed that large doses of sulphate of atropia produced great acceleration of the action of the heart, notwithstanding the administration of meconate of morphia. This appeared to indicate either complete or partial paralysis of the vaso-inhibitory branches of the vagus, or stimulation of the sympathetic. It was important, however, to ascertain more precisely whether or not the meconate of morphia relieved in any way, or to any extent, this paralysis of the vaso-inhibitory nerves.

Experiment 375.—An experiment was accordingly made on a large rabbit, weighing 4¾ lbs. It first of all received seven grains of sulphate of atropia under the skin of the back. The pulse soon became

accelerated. It was then fixed in Czermak's rabbit-holder, and the pneumogastric nerves on both sides quickly exposed. By proper electrical arrangements, one or both nerves were stimulated, and the cardiac pulsations counted before, during, and after the application of the stimulus. It was found that there was no perceptible retardation of the heart's action on stimulating the vagi, indicating paralysis of the vaso-inhibitory nerves. Eight grains of meconate of morphia were now introduced by injection into the jugular vein, and the animal was left undisturbed for four minutes. The stimulus was again applied to the pneumogastrics, with the same negative effect of producing no diminution in the number of the cardiac pulsations. The stimulus was repeatedly applied with the same effect. It was, therefore, proved by this experiment that, while sulphate of atropia did paralyse the vaso-inhibitory nerve-tubes in the vagus, or the intrinsic motor ganglia in the heart in connection with these nerves, the subsequent exhibition of meconate of morphia did not remove this effect; and that, in this respect, the two active substances were not physiologically antagonistic.

The inferences to be drawn from the experiments on rabbits are the following.

1. Sulphate of atropia is physiologically antagonistic to meconate of morphia within a limited area;

2. Meconate of morphia does not act beneficially after a large dose of sulphate of atropia, for in these cases the tendency to death is greater than if a large dose of either substance had been given alone;

3. Meconate of morphia is not specifically antagonistic to the action of sulphate of atropia on the vaso-inhibitory nerves of the heart; and

4. The beneficial action of sulphate of atropia after the administration of large doses of meconate of morphia is probably due to the action sulphate of atropia exercises on the blood-vessels. It causes contraction of these, and thus reduces the risk of death from cerebral or spinal congestion, as is known to occur after the introduction of fatal doses of meconate of morphia. It may also assist up to a certain point, not precisely fixed in these experiments, by stimulating the action of the heart through the sympathetic, and obviating the tendency to death from deficient respiration observed after large doses of morphia.

B.—*On Dogs.*

Dr. John Harley* narrates various experiments made on dogs, "on the combined action of morphia and atropia"; but he does not appear to have given fatal doses of acetate of morphia. The conclusions at which he arrives are as follows.

"*Conclusions.*—I. In the dog, belladonna, when administered simultaneously with opium, more or less completely prevents nausea and vomiting; and, when given previously, entirely prevents these effects. II. Whether given previously, simultaneously, or subsequently, atropia completely counteracts the respiratory restraint on the free action of the heart, which is so prominent an effect of the operation of opium. We can wish for no more perfect an illustration of the beneficial influence of a medicine under suitable conditions than that afforded by the simple and direct action of atropia in relieving the impending syncope which often persists for many hours after a dose of opium. At first, the cardiac systoles are doubled, but a regular expiratory pause remains. During the next sixty or ninety seconds, the systoles become stronger and each one distinctly perceptible to the finger; and at the end of this time the inspiratory intermissions cease, and no trace of their presence remains. The effect is even more marked under the influence of the combined action of morphia and thebaia. III. While the special effects of opium on the muscles of organic life are thus counteracted by the stimulant action of atropia on the sympathetic, the cerebral and anæsthetic effects are intensified and prolonged by belladonna, and hypnosis is converted into narcosis. IV. On the other hand, all the effects of atropia, excepting perhaps the influence on the heart, are increased and prolonged by opium, and the cerebral effect in particular; the insomnia which results from excessive doses is converted into narcotism, or a mixture of narcotism and delirium. V. The simultaneous action of opium retards the evacuation of urine, but in no degree interferes with the elimination of atropia by the kidneys."

After an analysis of, and critical remarks on, twenty-one cases of "opium-poisoning treated by belladonna", Dr. Harley† writes as follows.

"*Conclusions.*—1. That the evidence of antagonism in any given case is inconclusive. 2. Taken individually or collectively, the cases

* Dr. John Harley, *Old Vegetable Neurotics*, p. 269, c. vii.
† Dr. John Harley, *ut supra*, p. 309.

show that belladonna has no influence whatever in accelerating the recovery from the poisonous effects of opium. 3. That somnolency, stupor, narcotism, and coma—the essential effects of the action of opium—are both intensified and prolonged by the concurrent action of belladonna. 4. That belladonna is powerless to obviate the chief danger in opium-poisoning; viz., the depression of the respiratory function. 5. That the results of the combined action of opium and belladonna are the same, whether given in medicinal or toxical doses. While, therefore, belladonna cannot in any sense be regarded as an antidote against opium, but in large doses the exact reverse, it may, under certain conditions mentioned below, and always in very small doses, be used in conjunction with other remedies as a means of aiding the recovery." [The "conditions" to which Dr. Harley alludes are, to give "1-96th of a grain of sulphate of atropia at intervals of two hours, to stimulate the failing power of the heart".]

The views of Dr. Harley are not quite in accordance with those of Mitchell, Keen, and Morehouse,* who write as follows.

"The foregoing experiments and observations authorise us, we think, to draw the following conclusions as to the use of hypodermic injections, and as to the antagonism of atropia and morphia.

"1. Conia, atropia, and daturia, have no power to lessen pain when used subdermally.

"2. Morphia thus used is of the utmost value to relieve pain, and is most potent, in certain forms of neuralgia, the nearer it is applied to the seat of the suffering.

"3. Morphia lowers the pulse slightly, or not at all. Atropia usually lowers the pulse a few beats within ten minutes, and then raises it twenty to fifty beats within an hour. The pulse finally falls about the tenth hour below the normal number, and regains its healthy rate within twenty-four hours.

"4. Morphia has no power to prevent atropia from thus influencing the pulse; so that, as regards the circulation, they do not counteract one another.

"5. During the change of the pulse under atropia, the number of respirations is hardly altered at all.

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* Mitchell, Keen, and Morehouse, "On the Antagonism of Atropia and Morphia, founded upon Observations and Experiments made at the U.S.A. Hospital for Injuries and Diseases of the Nervous System". (*The American Journal of the Medical Sciences*, new series, vol. L. Philadelphia, 1865, p. 67, *et seq.*)

"6. As regards the eye, the two agents in question are mutually antagonistic; but atropia continues to act for a much longer time than morphia.

"7. The cerebral symptoms caused by either drug are to a great extent capable of being overcome by the other; but, owing to the different rates at which they move to affect the system, it is not easy to obtain a perfect balance of effects; and this was made the more difficult from the fact already mentioned, that atropia has the greater duration of toxic activity.

"8. The dry mouth of atropia is not made less by the coincident or precedent use of morphia. Atropia does not constipate, and may even relax, the bowels; morphia has a reverse tendency.

"9. The nausea of morphia is not antagonised or prevented by atropia.

"10. Both agents cause dysuria in certain cases, nor is the dysuria occasioned by the one agent relieved by the other.

"11. Atropia has no ability to alter or lessen the energy with which morphia acts to diminish sensibility or relieve the pain of neuralgic disease.

"12. As regards toxic effects on the cerebral organs, the two agents are mutually antidotal; but this antagonism does not prevail throughout the whole range of their influence, so that, in some respects, they do not counteract one another; whilst, as regards one organ—the bladder—both seem to affect it in a similar way."

The conclusions of the American physicians are, in certain points, opposed to those of Harley. Five experiments were therefore made on dogs, in which what was regarded as a fatal dose of meconate of morphia was given, and immediately afterwards varying doses of sulphate of atropia.

Experiment 375. Male Scotch terrier, weighing 12 lbs. Diameter of the pupil transversely, 12-50ths of an inch. While the animal was sitting quietly on the table, the respirations and cardiac pulsations were counted for sixteen minutes—one observer counting the respirations, another the cardiac pulsations, while a third noted down the figures at the end of each minute, with the following results.

TABLE XXXI.—*Showing the number of the Respiratory Movements and Cardiac Pulsations of a Dog, not affected by Sulphate of Atropia.*

Time.	Respirations per minute.	Cardiac Pulsations per minute.	Time.	Respirations per minute.	Cardiac Pulsations per minute.
1 minute	30	120	9 minutes	31	123
2 minutes	30	121	10 ,,	31	121
3 ,,	29	123	11 ,,	30	121
4 ,,	30	124	12 ,,	31	121
5 ,,	29	120	13 ,,	31	122
6 ,,	30	122	14 ,,	30	120
7 ,,	30	122	15 ,,	30	120
8 ,,	30	122	16 ,,	30	120

These figures show tolerable regularity in the respiratory movements and cardiac pulsations. As is frequently the case in dogs, the cardiac action was somewhat intermittent, but the average number of systoles per minute was nearly constant. Two grains of the meconate of morphia dissolved in twenty-eight minims of water were now injected under the skin of the back. The respiratory movements and cardiac pulsations were then counted in the same way for forty minutes with the following result:

TABLE XXXII.—*Showing the Effects of the Action of Meconate of Morphia on the Respiratory movements and Cardiac Pulsations of a Dog.*

Time after the administration of the drug.	Respirations per minute.	Cardiac pulsations per minute.	Remarks.	Time after the administration of the drug.	Respirations per minute.	Cardiac pulsations per minute.	Remarks.
1 min.	30	120		21 min.	18	82	
2 ,,	30	120		22 ,,	17	82	
3 ,,	29	118	Vomited food.	23 ,,	17	83	
4 ,,	28	117		24 ,,	16	83	Pupil 5-50ths of inch.
5 ,,	28	114					
6 ,,	27	112		25 ,,	16	84	
7 ,,	27	111		26 ,,	16	84	
8 ,,	24	110	Pupil 6-50ths of inch.	27 ,,	16	83	Pulsations were now very feeble.
9 ,,	22	108		28 ,,	17	84	
10 ,,	23	102		29 ,,	18	84	
11 ,,	22	100		30 ,,	18	84	
12 ,,	22	95	Pupil 5-50ths of inch.	31 ,,	19	84	Pupil 4-50ths of inch.
13 ,,	20	98		32 ,,	18	83	
14 ,,	26	95		33 ,,	18	83	
15 ,,	20	90		34 ,,	18	79	
16 ,,	20	90		35 ,,	17	76	
17 ,,	18	86		36 ,,	16	75	
18 ,,	18	84		37 ,,	16	74	Pupil 4-60ths of in.
19 ,,	18	83	Now deeply narcotised.	38 ,,	16	72	
				39 ,,	14	72	
20 ,,	18	83		40 ,,	14	72	

The cardiac pulsations now became so feeble that they could not be counted with accuracy. The respiratory movements were deep and prolonged. The animal was deeply narcotised. Reflex movements were made on touching the eyelashes or the conjunctiva, but there were none on pinching the legs or tail. Fæces were passed involuntarily. There was very little moisture about the mouth. There were slight jerks occasionally of the muscles of the back. The dog continued in this state for four hours, when it began slowly to recover. It recovered entirely. For twenty-four hours it appeared to be feeble in its hinder limbs. Three days afterwards it was quite lively. The dose was nearly, but not quite, a fatal one. Noboby seeing the dog three hours after it had received the two grains of meconate of morphia would have believed in its recovery.

Eight days afterwards it was again subjected to experiment. It then weighed 11½ lbs. The pupil measured 7-50ths of an inch. The respirations and cardiac pulsations were taken during a period of ten minutes. They were found to average—respirations, twenty-eight per minute; cardiac pulsations, one hundred and thirty-two per minute. Two grains and a half of meconate of morphia and one-twelfth of a grain of sulphate of atropia were then simultaneously injected under the skin of the back. Two assistants counted the number of the respiratory and circulatory movements separately, while a third noted the figures down at the end of every minute. This was done for sixty minutes, with the following result. (See Table XXXIII.)

This table shows that (1) the respirations became fewer in number, deeper, and more prolonged; (2) the cardiac pulsations were much increased in number, and they were for a time very powerful, but afterwards they became so weak as scarcely to be felt; and (3) the pupil became contracted, but not nearly to the same extent as would have been produced by the meconate of morphia alone. These results indicate a mutual action between the meconate of morphia and the sulphate of atropia. Meconate of morphia, when given alone, depresses both the cardiac pulsations and the respirations, and contracts the pupil. Sulphate of atropia, when given alone, slightly depresses the respirations, greatly accelerates the cardiac pulsations, and dilates the pupil. When both are given together, as in this experiment (Table XXXIII), the respirations were reduced in frequency, indicating a preponderance in the effect of meconate of morphia; the cardiac pulsations were increased, indicating a stimulant action on the heart produced by the sulphate of atropia; and the pupil was slightly contracted, indicating that, with respect to this structure, there was nearly a balance as regards physiological effect

between the two substances, but the influence was in favour of the meconate of morphia. It is also to be observed that the acceleration of the cardiac pulsations was not nearly so great when both substances were exhibited, as when sulphate of atropia, even in smaller doses, was given alone (see remarks on the physiological action of sulphate of atropia on dogs, BRIT. MED. JOURNAL, October 24th, page 519).

TABLE XXXIII.—*Showing the Effect of the Simultaneous Action of Meconate of Morphia and Sulphate of Atropia on the Respiratory Movements and Cardiac Pulsations of a Dog.*

Time after the administration of the drugs.	Respirations per minute.	Cardiac pulsations per minute.	Remarks.	Time after the administration of the drugs.	Respirations per minute.	Cardiac pulsations per minute.	Remarks.
1 min.	28	140		31 min.	15	246	
2 ,,	28	142		32 ,,	15	243	Cardiac pulsations not so strong
3 ,,	26	143	Vomited.				
4 ,,	26	145		33 ,,	15	244	
5 ,,	25	150		34 ,,	16	245	
6 ,,	24	160	Pupil 6-50ths of in.	35 ,,	17	249	Pupil 4-50ths of in.
7 ,,	25	170		36 ,,	18	247	
8 ,,	24	176		37 ,,	15	246	
9 ,,	23	180		38 ,,	16	246	
10 ,,	22	186	Respirations somewhat intermittent.	39 ,,	15	246	
				40 ,,	15	245	Pupil 4-50ths of in.
				41 ,,	16	240	
11 ,,	20	192	A long and deep inspiration every 5th or 6th time.	42 ,,	17	240	Defæcation.
				43 ,,	18	238	
				44 ,,	17	240	
12 ,,	18	199		45 ,,	16	236	Pupil 4-50ths of in.
13 ,,	16	205		46 ,,	14	236	
14 ,,	15	204	Cardiac pulsations full and bounding.	47 ,,	14	235	Cardiac pulsations feebler.
				48 ,,	14	235	
15 ,,	15	204		49 ,,	15	234	
16 ,,	14	207		50 ,,	15	234	Pupil 4-50ths of in.
17 ,,	15	209	Pupil 5-50ths of in.	51 ,,	14	234	
18 ,,	16	210		52 ,,	14	237	
19 ,,	14	212		53 ,,	15	236	
20 ,,	15	219	Pupil 5-50ths of in.	54 ,,	14	235	
21 ,,	15	225		55 ,,	15	235	Pupil 4-50ths of in.
22 ,,	15	230		56 ,,	12	240	Respirations deep and prolonged; cardiac pulsations so feeble that they could scarcely be counted.
23 ,,	14	236					
24 ,,	15	243					
25 ,,	15	243	Pupil 4-50ths of in.				
26 ,,	15	250					
27 ,,	15	250	Reflex action much weaker.				
				57 ,,	15	236	
28 ,,	15	250		58 ,,	15	236	
29 ,,	18	250		59 ,,	15	235	
30 ,,	17	246	Pupil 4-50ths of in.	60 ,,	16	231	

The dog in this experiment died at the end of three hours and a half. It gradually became more and more deeply comatose. There was no evidence of any delirium. Reflex action gradually became more and more feeble; the respiratory movements were fewer and more and more shallow; the cardiac pulsations became so weak as scarcely to be felt,

but they were still rapid, and at last the animal died without any convulsive seizure. The lungs were much congested, and there was fluid in the pleura.

Experiment 376. As it appeared that the animal in the last experiment died from the effects chiefly of the meconate of morphia, it was repeated in a dog of nearly the same weight (11¾ lbs.), giving the same dose of meconate of morphia (two grains and a half), together with a dose of a quarter of a grain of sulphate of atropia. After the usual phenomena, the animal died in six hours. It was observed in this case that the effects of the presence of sulphate of atropia were more apparent than in Experiment 375. The pupil was more dilated, and the cardiac pulsations were for a longer time more rapid and more strong. Still, the animal seemed to succumb to the effects of coma. There were no twitchings nor convulsions.

Experiment 377. A third dog, 12 lbs. weight, received with the same dose two grains and a half of meconate of morphia and one third of a grain of sulphate of atropia. This animal also died at the close of eight hours and a half, and in the same condition of profound coma as in the last two experiments. It was observed that during the first hour, after the simultaneous injection of the two substances, the animal was more wide awake than in the preceding experiments. It tried to sit up, and it looked from side to side, rocking its head in the manner previously observed in a dog after a large dose of sulphate of atropia. This state gradually merged into that of deep coma, from which it was never roused.

Experiment 378. A fourth dog, weighing 14 lbs., received two grains and a quarter of meconate of morphia, together with two-thirds of a grain of sulphate of atropia. This animal continued in a deep stupor for six hours and a half, when it slowly began to recover. The usual phenomena were exhibited throughout the case, with the exception that, during the first two hours, it was evidently in a state resembling delirium. It tried to rise, and rocked its head to and fro. It apparently was not conscious of vision, because, when a rod was held near the eye, it knocked its head against it. This condition, as in Experiment 377, merged into coma, from which, however, the animal recovered.

It was important to ascertain whether or not, in this instance, the dose of meconate of morphia given was, without the influence of the sulphate of atropine, a fatal dose. Accordingly, the animal was kept for ten days, and regularly fed. At the end of that time, it was in good condition, and weighed 13 lbs. The same dose of meconate of mor-

phia, namely, two grains and a quarter, was then given. The animal, about the end of the first hour after the injection of the dose, was in a comatose condition, from which it did not recover. It remained comatose for ten hours, the coma gradually becoming more and more marked.

Experiment 379. The last experiment was so important that it became necessary to repeat it in as nearly the same conditions as possible. A mongrel terrier dog, weighing 13¾ lbs., had simultaneously injected under the skin of the back two grains and a quarter of meconate of morphia and two-thirds of a grain of sulphate of atropia. During the first three hours, it was apparently under the influence chiefly of the sulphate of atropia, inasmuch as the pupil was more dilated than at first, the heart beat more quickly, and the animal rocked its head about in the way characteristic of the action of sulphate of atropia. This condition, as in the former instances, merged into a comatose state, from which, however, the animal recovered. The animal was kept for ten days. At the end of that time, it received the same dose of meconate of morphia (two grains and a quarter). It became comatose in an hour and a quarter, and it was found dead ten hours thereafter. It died with all the symptoms of poisoning by morphia.

These experiments are shortly summarised in the following table:

TABLE XXXIV.—*Showing the Influence of Sulphate of Atropia on a Fatal Dose of Meconate of Morphia in Dogs.*

No. of Experiment.	Weight of Dog.	Dose of Meconate of Morphia in grains.	Dose of Sulphate of Atropia in grains.	Result.	Remarks.
375	12 lbs.	2½	1-12th	Died in 3½ hours	Congestion of the lungs
376	11¾ lbs.	2½	1-6th	Died in 6 hours	Atropia symptoms more marked; died in profound coma
377	12 lbs.	2½	1-3rd	Died in 8½ hours	Ditto ditto
378	14 lbs.	2¼	2-3rds	Comatose for 6 hours; Recovered	Got same dose of meconate of morphia 10 days afterwards, and died
379	13¾ lbs.	2¼	2-3rds	Recovered	Got same dose of meconate of morphia 10 days afterwards, and died.

It appears from the above experiments, that in dogs sulphate of atropia modifies the symptoms of poisoning by meconate of morphia, diminishes their intensity, and may even save life after a fatal dose of the latter. It is therefore decidedly antagonistic, but within a limited area. In man, sulphate of atropia would be too dangerous and uncertain a remedy to depend on in cases of poisoning by opium or any of

its salts, but where the heart's action is greatly diminished it is directly indicated.*

VI.—Antagonism between Tea, Coffee, Cocaine, Theine, Caffeine, and Guaranine, on the one Hand, and Morphia on the other.

This investigation is divided into three parts: 1. An inquiry into the physiological properties of cocaine, the active principle of the plant known as *Erythroxylon coca*, of theine, of caffeine, and of guaranine; 2. An inquiry to ascertain whether or not the active principles theine, caffeine, and guaranine, act as antagonists to fatal doses of morphia or opium; and 3. An inquiry to ascertain whether or not strong infusions of tea or decoction of coffee, when introduced into the stomach, act as antagonists to fatal doses of morphia or opium.

The complete ignorance that existed with regard to all these points rendered an extensive preliminary investigation necessary. It was carried out by Dr. Alexander Bennett, but was watched, and the results confirmed, by the Committee.

1. *The Physiological Properties of the Active Principles, Cocaine, Theine, Caffeine, and Guaranine.*

The general results from thirty experiments on frogs, mice, and rabbits, as to the physiological action of cocaine, were as follows.

1. The physiological actions of erythroxylon coca are due to its proximate principle, cocaine.

2. Cocaine is a powerful poison, inducing a series of symptoms affecting the nervous, respiratory, circulatory, and vaso-motor systems, which terminate, if the dose be large enough, in death.

3. Cocaine, in small doses not ending fatally, produces—1, cerebral excitement, not succeeded by coma; and 2, partial loss of sensibility.

4. In large doses, cocaine produces—1, cerebral excitement; 2, complete paralysis of sensibility; 3, tetanic spasms and convulsions; and 4, death.

5. Cocaine paralyses the entire posterior columns of the spinal cord, also the entire system of peripheral sensory nerves; but the anterior columns of the cord and the peripheral motor nerves are not paralysed.

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* In experiments Nos. 376, 377, 378, and 379, the number of cardiac pulsations and respiratory movements were not counted nor the pupil measured, as the object was to see whether or not life could be saved after a fatal dose of meconate of morphia.

6. Cocaine frequently produces convulsions of a clonic character; but occasionally it causes tetanic spasms, which latter are sometimes so severe as to produce opisthotonos. There is, at first sight, a resemblance between these spasms and those following the administration of strychnine; but, in the case of strychnine, the action of the poison is limited to the spinal cord, the reflex function of which is so much excited that the slightest touch from without, causes powerful spasms. A poisonous dose of cocaine, on the other hand, paralyses the sensory nerves, so that external irritations do not affect the cord; but, notwithstanding, there are strong spontaneous spasms, which are probably caused by the reflex action of the drug on the cord itself, and which spasms are not to be considered as reflex in their nature.

7. Cocaine does not produce muscular paralysis.

8. Cocaine at first increases, then impedes, and lastly stops, respiration.

9. Cocaine at first increases, and finally diminishes, both the force and frequency of the heart's contractions.

TABLE XXXV.—*Experiments with Cocaine.*

No. of Experiment.	Animal.	Doses in grains.	General Effects.	Result.	*Post Mortem* Examination.
380	Frog	1-128th	Slight weakness of limbs.	Recovery	
381	Frog	1-64th	Weakness of limbs.	Recovery	
382	Mouse	1-32nd	Weakness of limbs; slight congestion of cutaneous surface.	Recovery	
383	Frog	1-32nd	Considerable weakness of limbs; respiration impeded.	Recovery	
384	Mouse	1-32nd	Gradual weakness of limbs, ending in complete paralysis; cutaneous congestion; loss of reflex action; prostration.	Death	Congestion of membranes of brain, skin, and viscera. When brain, spinal cord, nerves, or muscles, were irritated with electricity, muscular contractions ensued. Posterior columns irritated, no contractions; anterior columns irritated, strong contractions.
385	Frog	1-32nd	Ligature of the heart; right calf of leg injected. After no movement on irritation, on pinching left calf movements of entire body, including right leg.	Death	
386	Mouse	1-32nd	Same as No. 384; in addition, tetanic spasms.	Death	Same as No. 384.
387	Frog	1-16th	Gradual prostration; paralysis of limbs and loss of reflex action.	Recovery	

TABLE XXXV.—*Experiments with Cocaine. (Continued.)*

No. of Experiment.	Animal.	Doses in grains.	General Effects.	Result.	*Post Mortem* Examination.
388	Frog	1-12th	Weakness of limbs at first; paralysis of limbs after. Loss of reflex action; stoppage of respiration; congestion of skin; stasis of blood in capillaries.	Death	Same as No. 384.
389	Frog	1-10th	Ligature of femoral artery; symptoms same as No. 388; No difference in two legs.	Death	Same as No. 384. No difference between two legs.
390	Frog	1-10th	Observation on lower part of spinal cord, which was exposed. Same as No. 388.	Death	Same as No. 384.
391	Frog	1-10th	Observations on upper part of spinal cord, which was exposed. Same as No. 388.	Death	Same as No. 384.
392	Frog	1-10th	Spinal cord exposed during life. Any part of cord touched with needle, strong muscular contractions. Other symptoms same as No. 384.	Death	Same as No. 384. When posterior columns were irritated with point of needle, no muscular contractions; when anterior columns were irritated, contractions ensued.
393	Frog	1-8th	Same as No. 388, but more rapid.	Death	Same as No. 384.
394	Rabbit	3+2+2+2+3	From first dose, congestion of ears; from second dose, slight cerebral excitement; from third dose, great irritability, no loss of sensibility; from fourth dose, congestion of ears increased; from fifth dose, depression, staggering gait. Numbers of respirations and pulsations of the heart—1st increased, and 2nd diminished. Temperature: 1st diminished, & 2nd increased.	Recovery	
395	Frog	1-32nd	Same as No. 384. Number of respirations—1st increased, 2nd diminished, and 3rd stopped.	Death	Same as No. 384.
396	Frog	1-32nd	Same as 384. Pulsations of the heart—1st increased, 2nd dimin., & 3rd stopped.	Death	Same as No. 384.

10. Cocaine produces at first contraction, afterwards dilatation or paralysis, of the capillaries and small blood-vessels, with stasis of the blood, indicating first irritation and subsequent paralysis of the vaso-motor nerves. This action of cocaine upon the capillary blood-vessels, now described for the first time, is of great interest, as it simulates the action of the drug in this respect to that of nitrite of amyl described by Dr. Richardson.

Numerous experiments (about seventy) were made with theine, caffeine, and guaranine, on cats, rabbits, mice, and frogs.

TABLE XXXVI.—*Experiments with Extract of Coca.*

No. of Experiment.	Animal.	Dose in grains.	General Effects.	Result.	*Post Mortem* Examination.
397	Frog	1	No apparent effects.	Recovery	
398	Mouse	1	Slight weakness of posterior extremities.	Recovery	
399	Frog	1+¼ carb. pot.	No apparent effect.	Recovery	
400	Frog	2	Weakness of limbs; impaired respiration.	Recovery	
401	Frog	2+½gr. carb. pot.	Symptoms same as No. 400.	Recovery	
402	Mouse	2	Weakness of limbs; congestion of under cutaneous surface; slight convulsion; prostration; loss of reflex action.	Death	Heart beat feebly; thoracic and abdominal viscera congested; when spinal cord, sciatic nerve, or muscles were irritated with Faradic current, there were muscular contractions.
403	Frog	3	Weakness at first; stoppage of respiration; loss of reflex action; prostration.	Death	Heart still beating; congestion of the thoracic and abdominal viscera; when brain irritated, contraction of muscles of face ensued: current applied to cord, nerves, or muscles, powerful muscular contraction.
404	Frog	4	Prostration, with symptoms as in No. 403.	Death	Appearances & phenomena as in No. 403.
405	Frog	5	Rapid prostration; symptoms the same as No. 403.	Death	Appearances & phenomena as in No. 403.
406	Rabbit	12	No apparent effect.	Recovery	

The following tables show the effects on the respirations, cardiac pulsations, and temperature.

TABLE XXXVII.—*Showing the Effects of Cocaine on the Respiratory Movements of a Rabbit.*

Normal Respirations taken at intervals.

1. Per ¼ minute, 48	5. Per ¼ minute, 34	9. Per ¼ minute, 44
2. ,, 48	6. ,, 40	10. ,, 40
3. ,, 42	7. ,, 44	11. ,, 40
4. ,, 40	8. ,, 36	12. ,, 42

Respirations after Injection of Cocaine per ¼ Minute

13. 38 per ¼ minute, at 12.44 P.M.	31. 64 per ¼ minute, at 1.20 P.M.
14. 54 ,, 12.46 ,,	32. 60 ,, 1.25 ,,
15. 50 ,, 12.48 ,,	33. 50 ,, 1.27 ,,
16. 56 ,, 12.50 ,,	34. 56 ,, 1.29 ,,
17. 52 ,, 12.52 ,,	35. 50 ,, 1.31 ,,
18. 54 ,, 12.54 ,,	36. 60 ,, 1.33 ,,
19. 56 ,, 12.56 ,,	37. 64 ,, 1.35 ,,
20. 48 ,, 12.58 ,,	38. 58 ,, 1.37 ,,
21. 44 ,, 1.0 ,,	39. 56 ,, 1.39 ,,
22. 42 ,, 1.2 ,,	40. 50 ,, 1.41 ,,
23. 45 ,, 1.4 ,,	41. 68 ,, 1.43 ,,
24. 52 ,, 1.6 ,,	42. 70 ,, 1.46 ,,
25. 44 ,, 1.8 ,,	43. 58 ,, 1.48 ,,
26. 50 ,, 1.10 ,,	44. 56 ,, 1.50 ,,
27. 54 ,, 1.12 ,,	45. 56 ,, 2.3 ,,
28. 56 ,, 1.14 ,,	46. 62 ,, 2.5 ,,
29. 58 ,, 1.16 ,,	47. 54 ,, 2.7 ,,
30. 60 ,, 1.18 ,,	48. 56 ,, 2.9 ,,

TABLE XXXVIII.—*Showing the Effects of Cocaine on the Cardiac Pulsations of a Rabbit.*

Normal Cardiac Pulsations taken at intervals.

1. Per ¼ minute, 68	5. Per ¼ minute, 54	9. Per ¼ minute, 60
2. ,, 60	6. ,, 60	10. ,, 66
3. ,, 60	7. ,, 60	11. ,, 66
4. ,, 64	8. ,, 62	12. ,, 66

Pulsations after Injection of Cocaine.

13. 62 per ¼ minute, at 12.45 P.M.	31. 78 per ¼ minute, at 1.26 P.M.
14. 64 ,, 12.47 ,,	32. 84 ,, 1.28 ,,
15. 66 ,, 12.49 ,,	33. 76 ,, 1.30 ,,
16. 64 ,, 12.51 ,,	34. 82 ,, 1.32 ,,
17. 68 ,, 12.53 ,,	35. 80 ,, 1.34 ,,
18. 70 ,, 12.55 ,,	36. 78 ,, 1.36 ,,
19. 64 ,, 12.57 ,,	37. 78 ,, 1.38 ,,
20. 58 ,, 12.59 ,,	38. 56 ,, 1.40 ,,
21. 64 ,, 1.1 ,,	39. 72 ,, 1.42 ,,
22. 64 ,, 1.3 ,,	40. 86 ,, 1.45 ,,
23. 60 ,, 1.5 ,,	41. 80 ,, 1.47 ,,
24. 70 ,, 1.7 ,,	42. 74 ,, 1.49 ,,
25. 84 ,, 1.9 ,,	43. 75 ,, 1.51 ,,
26. 56 ,, 1.16 ,,	44. 80 ,, 2.44 ,,
27. 80 ,, 1.18 ,,	45. 82 ,, 2.6 ,,
28. 86 ,, 1.20 ,,	46. 90 ,, 2.8 ,,
29. 84 ,, 1.22 ,,	47. 80 ,, 2.10 ,,
30. 82 ,, 1.24 ,,	48. 76 ,, 2.12 ,,

TABLE XXXIX.—*Showing the Effects of Cocaine on the Respiratory Movements of a Frog.*

Normal Respirations taken at intervals.

1. Per ¼ minute, 20	5. Per ¼ minute, 18	9. Per ¼ minute, 22
2. ,, 22	6. ,, 24	10. ,, 21
3. ,, 21	7. ,, 22	11. ,, 21
4. ,, 21	8. ,, 18	12. ,, 21

Respirations after Injection of Cocaine.

13. 32 per ¼ minute, at 8.34 P.M.	24. 11 per ¼ minute, at 8.45 P.M.
14. 36 ,, 8.35 ,,	25. 11 ,, 8.46 ,,
15. 35 ,, 8.36 ,,	26. 9 ,, 8.47 ,,
16. 36 ,, 8.37 ,,	27. 9 ,, 8.48 ,,
17. 28 ,, 8.38 ,,	28. 4 ,, 8.49 ,,
18. 32 ,, 8.39 ,,	29. 6 ,, 8.50 ,,
19. 18 ,, 8.40 ,,	30. 6 ,, 8.51 ,,
20. 16 ,, 8.41 ,,	31. 5 ,, 8.52 ,,
21. 8 ,, 8.42 ,,	32. 2 ,, 8.53 ,,
22. 9 ,, 8.43 ,,	33. 1 ,, 8.54 ,,
23. 13 ,, 8.44 ,,	34. 0 ,, 8.55 ,,

TABLE XL.—*Showing the Effect of Cocaine on the Cardiac Pulsations of a Frog.*

Normal Pulsations taken at intervals.

1. Per ¼ minute, 10	5. Per ¼ minute, 11	9. Per ¼ minute, 12
2. ,, 12	6. ,, 10	10. ,, 12
3. ,, 11	7. ,, 11	11. ,, 10
4. ,, 12	8. ,, 11	12. ,, 10

Pulsations after Injections of Cocaine.

13. 16 per ¼ minute, at 8.53 P.M.	26. 12 per ¼ minute, at 9.6 P.M.
14. 15 ,, 8.54 ,,	27. 12 ,, 9.7 ,,
15. 14 ,, 8.55 ,,	28. 10 ,, 9.8 ,,
16. 14 ,, 8.56 ,,	29. 11 ,, 9.9 ,,
17. 12 ,, 8.57 ,,	30. 10 ,, 9.10 ,,
18. 12 ,, 8.58 ,,	31. 9 ,, 9.11 ,,
19. 13 ,, 8.55 ,,	32. 8 ,, 9.12 ,,
20. 12 ,, 9.0 ,,	33. 9 ,, 9.13 ,,
21. 13 ,, 9.1 ,,	34. 8 ,, 9.14 ,,
22. 12 ,, 9.2 ,,	35. 6 ,, 9.15 ,,
23. 13 ,, 9.3 ,,	36. 7 ,, 9.16 ,,
24. 10 ,, 9.4 ,,	37. 6 ,, 9.17 ,,
25. 12 ,, 9.5 ,,	38. 6 ,, 9.18 ,,

TABLE XLI.—*Showing the Effects of Theine on the Respiratory Movements of a Rabbit.*

Natural Respirations taken at intervals.

1. Per ¼ minute, 36	5. Per ¼ minute, 38	9. Per ¼ minute, 30
2. ,, 30	6. ,, 30	10. ,, 27
3. ,, 30	7. ,, 32	11. ,, 28
4. ,, 35	8. ,, 37	12. ,, 21

Respirations after Injection of Theine.

13. 30 per ¼ minute, at 12.33 P.M.	31. 34 per ¼ minute, at 12.51 P.M.
14. 42 ,, 12.34 ,,	32. 36 ,, 12.52 ,,
15. 48 ,, 12.35 ,,	33. 40 ,, 12.53 ,,
16. 50 ,, 12.36 ,,	34. 36 ,, 12.54 ,,
17. 50 ,, 12.37 ,,	35. 36 ,, 12.55 ,,
18. 52 ,, 12.38 ,,	36. 40 ,, 12.56 ,,
19. 50 ,, 12.39 ,,	37. 36 ,, 1.5 ,,
20. 44 ,, 12.40 ,,	38. 30 ,, 1.10 ,,
21. 40 ,, 12.41 ,,	39. 35 ,, 1.11 ,,
22. 42 ,, 12.42 ,,	40. 38 ,, 1.12 ,,
23. 40 ,, 12.43 ,,	41. 37 ,, 1.13 ,,
24. 35 ,, 12.44 ,,	42. 36 ,, 1.14 ,,
25. 35 ,, 12.45 ,,	43. 35 ,, 1.15 ,,
26. 34 ,, 12.46 ,,	44. 36 ,, 1.20 ,,
27. 32 ,, 12.47 ,,	45. 35 ,, 1.22 ,,
28. 33 ,, 12.48 ,,	46. 26 ,, 1.24 ,,
29. 38 ,, 12.49 ,,	47. 17 ,, 1.26 ,,
30. 36 ,, 12.50 ,,	48. 14 ,, 1.27 ,,

TABLE XLII.—*Showing the Effects of Theine on the Cardiac Pulsations of a Rabbit.*

Normal Pulsations of the Heart taken at intervals.

1. Per ¼ minute, 80	3. Per ¼ minute, 90	5. Per ¼ minute, 80
2. ,, 78	4. ,, 78	6. ,, 80

Pulsations of the Heart after Injection of Theine.

7. 84 per ¼ minute, at 1.47 P.M.	15. 86 per ¼ minute, at 2.15 P.M.
8. 80 ,, 1.58 ,,	16. 70 ,, 2.18 ,,
9. 86 ,, 2.0 ,,	17. 74 ,, 2.22 ,,
10. 88 ,, 2.5 ,,	18. 84 ,, 2.28 ,,
11. 80 ,, 2.6 ,,	19. 74 ,, 2.52 ,,
12. 80 ,, 2.7 ,,	20. 86 ,, 2.55 ,,
13. 82 ,, 2.8 ,,	21. 70 ,, 2.58 ,,
14. 86 ,, 2.9 ,,	

TABLE XLIII.—*Showing the Effects of Theine on the Temperature of the Ear of a Rabbit.—Normal Temperature of Rabbit,* 33.8 C.

Temperature after Injection of Theine.

2. 33.2 per ¼ minute, at 2.0 P.M.	10. 33.5 per ¼ minute, at 2.33 P.M.
3. 34.2 ,, 2.5 ,,	11. 33.4 ,, 2.40 ,,
4. 34.1 ,, 2.8 ,,	12. 33.4 ,, 2.45 ,,
5. 34.9 ,, 2.10 ,,	13. 33.5 ,, 2.50 ,,
6. 35.5 ,, 1.15 ,,	14. 32.8 ,, 2.55 ,,
7. 34.6 ,, 2.18 ,,	15. 33.9 ,, 2.58 ,,
8. 34.9 ,, 2.22 ,,	16. 33.5 ,, 3.0 ,,
9. 35.1 ,, 2.25 ,,	17. 33.9 ,, 3.4 ,,

TABLE XLIV.—*Showing the Effects of Caffeine on the Respiratory Movements of a Rabbit.*

Natural Respirations taken at intervals.

1. 34 per ¼ minute, at 1.10 P.M.	4. 33 per ¼ minute, at 1.13 P.M.
2. 32 ,, 1.11 ,,	5. ,, 1.14 ,,
3. 28 ,, 1.12 ,,	6. ,, 1.15 ,,

Respiration after Injection of Caffeine.

7. 42 per ¼ minute, at 1.17 P.M.	13. 40 per ¼ minute, at 1.35 P.M.
8. 44 ,, 1.19 ,,	14. 46 ,, 1.37 ,,
9. 42 ,, 1.21 ,,	15. 30 ,, 1.40 ,,
10. 46 ,, 1.24 ,,	16. 30 ,, 1.42 ,,
11. 46 ,, 1.29 ,,	17. 34 ,, 1.45 ,,
12. 40 ,, 1.33 ,,	18. 36 ,, 1.48 ,,

TABLE XLV.—*Showing the Effects of Caffeine on the Cardiac Pulsations of a Rabbit.*

Normal Pulsations of the Heart taken at intervals.

1. Per ¼ minute, 86	3. Per ¼ minute, 82	5. Per ¼ minute, 78
2. ,, 80	4. ,, 76	6. ,, 82

Pulsations after Injection of Caffeine.

7. 90 per ¼ minute, at 1.16 P.M.	11. 82 per ¼ minute, at 1.30 P.M.
8. 86 ,, 1.18 ,,	12. 74 ,, 1.35 ,,
9. 84 ,, 1.22 ,,	13. 48 ,, 1.45 ,,
10. 80 ,, 1.25 ,,	14. 40 ,, 1.48 ,,

Immediately after death, heart beats 12 per ¼ minute.

TABLE XLVI.—*Showing the Effects of Caffeine on the Temperature of the Ear of a Rabbit.—Normal Temperature of the Ear,* 33.9 c.

Temperature after Injection of Caffeine.

1. 35.6 c. per ¼ minute, at 1.20 P.M.	3. 36.6 c. per ¼ minute, at 1.35 P.M.
2. 35 c. ,, 1.27 ,,	4. 34.9 c. ,, 1.45 ,,

TABLE XLVII.—*Showing the Effects of Guaranine on the Respiratory Movements of a Rabbit.*

Normal Respirations taken at intervals.

1. Per ¼ minute, 41	3. Per ¼ minute, 34	5. Per ¼ minute, 32
2. ,, 36	4. ,, 30	6. ,, 30

Respirations after Injection of Guaranine.

7. 48 per ¼ minute, at 4.20 P.M.	19. 36 per ¼ minute, at 4.50 P.M.
8. 34 ,, 4.22 ,,	20. 36 ,, 4.55 ,,
9. 44 ,, 4.26 ,,	21. 28 ,, 5.0 ,,
10. 50 ,, 4.31 ,,	22. 28 ,, 5.2 ,,
11. 64 ,, 4.32 ,,	23. 30 ,, 5.5 ,,
12. 52 ,, 4.33 ,,	24. 28 ,, 5.8 ,,
13. 38 ,, 4.35 ,,	25. 20 ,, 5.12 ,,
14. 38 ,, 4.38 ,,	26. 34 ,, 5.15 ,,
15. 40 ,, 4.40 ,,	27. 18 ,, 12.20
16. 42 ,, 4.43 ,,	28. 20 ,, 12.22 } Next
17. 42 ,, 4.45 ,,	29. 22 ,, 12.34 } morning
18. 31 ,, 4.48 ,,	30. 22 ,, 12.26

TABLE XLVIII.—*Showing the Effects of Guaranine on the Cardiac Pulsations of a Rabbit.*

Normal Pulsations of Heart taken at intervals.

1. Per ¼ minute, 66	3. Per ¼ minute, 78	5. Per ¼ minute, 72
2. ,, 72	4. ,, 72	6. ,, 68

Pulsations of Heart after Injection of Guaranine.

7. 78 per ¼ minute, at 4.21 P.M.	19. 78 per ¼ minute, at 4.50 P.M.
8. 80 ,, 4.23 ,,	20. 60 ,, 4.55 ,,
9. 70 ,, 4.25 ,,	21. 74 ,, 5.1 ,,
10. 74 ,, 4.30 ,,	22. 76 ,, 5.3 ,,
11. 74 ,, 4.33 ,,	23. 86 ,, 5.7 ,,
12. 74 ,, 4.34 ,,	24. 80 ,, 5.8 ,,
13. 86 ,, 4.35 ,,	25. 80 ,, 5.12 ,,
14. 86 ,, 4.37 ,,	26. 80 ,, 5.18 ,,
15. 90 ,, 4.38 ,,	27. 88 ,, 1.21 } Next
16. 90 ,, 4.43 ,,	28. 86 ,, 12.23 } morn-
17. 90 ,, 4.46 ,,	29. 78 ,, 12.25 } ing.
18. 78 ,, 4.49 ,,	30. 86 ,, 12.27

TABLE XLIX.—*Showing the Effects of Guaranine on the Temperature of the Ear of a Rabbit.—Normal Temperature of Ear,* 32.3 C.

1. 29.8 per ¼ minute, at 4.14 P.M.	7. 33.5 per ¼ minute, at 4.48 P.M.
2. 33.5 ,, 4.25 ,,	8. 35.0 ,, 4.50 ,,
3. 34.6 ,, 4.30 ,,	9. 33.4 ,, 5.5 ,,
4. 35.1 ,, 4.32 ,,	10. 33.3 ,, 5.12 ,,
5. 34.6 ,, 4.35 ,,	11. 34.3 ,, 12.30 ,, next
6. 34.0 ,, 4.43 ,,	morning.

The physiological effects of theine, caffeine, and guaranine seem identical with those of cocaine. The actions of all will be understood from the following selected experiments with theine.

Experiment 410. *One-Sixteenth of a Grain of Theine: Frog: Recovery.* —The one-sixteenth of a grain of theine, dissolved in twenty minims of water, was injected under the skin over the back of a healthy middle-sized frog. Almost immediately afterwards, the respirations, which normally had been about 80, were increased to 120 per minute. Seven minutes afterwards, the respirations had diminished to 80 per minute. The frog was now distinctly sluggish in its movements; it made attempts to leap, but did so feebly. When placed on its back, it recovered its normal position with difficulty. When its toe was pinched with a pair of forceps, it drew up its leg. If its limbs were pulled out, they were drawn up slowly. Two minutes afterwards, these symptoms were increased; and in three minutes more the limbs were very weak, and the animal lay on its belly without their support. When placed on its back, the frog was unable to recover its position, but lay there with its limbs drawn up; and, when the skin or toes were pinched, the limbs were moved, but sluggishly. The respirations had diminished to 40 per minute. Five minutes later, the frog still lay motionless on its back, with its limbs extended. All four legs were completely paralysed, and they remained in whatever position they were placed. When any portion of the skin was pinched, the animal made no movements. On touching the eyeballs, the eyelids did not close. The respirations had diminished to 26 per minute; and they were very irregular, some being deep, and others superficial. There was marked congestion of the under cutaneous surface, which was of a reddish purple colour. The mucous membrane of the mouth and tongue was also deeply congested. When the web of the foot was examined under the microscope (twenty-five diameters), the capillaries and small blood-vessels were found enlarged and engorged with blood, and there was in them complete stasis of the circulation. The heart was beating, but respiration had stopped. The frog remained in this prostrate condition for eleven minutes, when slight spasmodic movements were observed in the limbs. Four minutes later, it made feeble attempts to move its legs; and, when its toe was pinched, it drew them up. Four minutes afterwards, the animal gave a very feeble leap, and tried to crawl along the table. It sat on all-fours; and, when any portion of its skin was pinched, it made attempts to move. The respirations, although still irregular, had risen to 20 per minute. Eighteen minutes afterwards, the frog jumped readily, especially if it were irritated. It croaked

vigorously when touched; and in half an hour it was apparently in its natural state, with the exception of looking feeble. Next morning, it was found in its normal condition.

In this experiment, we find that, shortly after the administration of the theine, the frog gradually lost motor power and all evidences of reflex action, the animal being reduced to a state of complete prostration. The number of the respirations was first increased, and subsequently diminished; congestion of the cutaneous and mucous surfaces was produced, with enlargement of the small vessels, and engorgement of blood in the capillaries, with stasis of blood in their interior. From all these effects the frog recovered gradually, after remaining under the influence of the drug for more than an hour.

It was now to be determined what portion of the nervous system is affected by theine, to account for the loss of motor power and reflex action.

Experiment 413. *One-twelfth of a Grain of Theine: Frog: Death: Post Mortem Examination.*—One-twelfth of a grain of theine, dissolved in thirty minims of water, was injected under the skin over the back of a healthy middle-sized frog. A series of symptoms ensued almost exactly similar to those in the preceding experiment, only somewhat more rapidly, and ultimately causing the death of the animal. On *post mortem* examination, the limbs and body generally were flaccid. The skin, especially on its under surface, was congested, of a reddish purple colour. On pinching with a pair of forceps any portion of the integument, no contraction of the muscles followed; but, on the application of the electrodes of a faradic current, there were strong muscular contractions. A flap of the skin about an inch square was reflected from the back; and, when the electrodes were applied to the extremity of it, there were no movements; but when they were applied to the skin near the muscles, these contracted feebly. When one of the limbs was removed from the rest of the body, and a reflected portion of the skin was treated in a similar manner, the same phenomena ensued. The head was amputated; and, on thrusting the point of a needle into the brain, the muscles of the face and eye contracted. The exposed part of the spinal cord was also irritated with the electrodes of a weak faradic current, and strong muscular contractions of the body and limbs ensued. The cervical portion of the spinal cord, about a quarter of an inch in length, was then isolated by carefully removing with a pair of scissors the bodies of the vertebræ. On applying the electrodes of the weak current to the anterior columns of the cord, there were powerful contractions of the lower limbs. On irritating the posterior columns in a similar

manner, these contractions were very feeble. On dissecting out the sciatic nerves, and pinching them with a pair of forceps, or applying the electrodes to the lower portions of them, strong contractions of the posterior limbs ensued; when to the upper portion, there were powerful contractions of the upper part of the body. On applying the electrodes to the gastrocnemii and other muscles, they contracted strongly. On opening the cavities of the thorax and abdomen, the heart was found beating feebly, at the rate of 64 per minute. All the internal viscera, especially the liver and bowels, with the mesentery, were deeply congested, and their vessels engorged with blood.

We find in this experiment not only enlargement of the small blood-vessels and capillaries, with engorgement and stasis of blood, during life, as proved by inspection of the web of the foot under the microscope, but that, after death from a fatal dose of theine, there was a similar condition of the skin and internal viscera, showing that the drug paralyses the capillary system, probably by its action on the vaso-motor nerves. This effect was subsequently proved by experiments on mammals. It is also shown that the motor filaments of the brain and upper part of the spinal cord, the anterior columns of the cord, the motor nerves, and the muscles, were apparently in a normal condition; but that the posterior columns of the cord were partially paralysed. To ascertain if the peripheral sensory nerves of the skin were also affected, a large flap of the integument was reflected. On applying the electrodes of a faradic current to its extremity, no muscular contractions ensued, proving that the sensory nerves of that portion had been paralysed. If the electrodes were placed on the reflected skin close to the muscles, these contracted feebly; probably owing to direct action of the electricity on the motor nerves of the muscles, as they were proved not to be reflex by the same phenomena occurring when a limb was removed from the body. Whether the sensory nerves of the muscles also are affected or not, will be shown in the succeeding experiment.

Experiment 415. *One-tenth of a Grain of Theine: Mouse: Death: Post Mortem Examination.* — One-tenth of a grain of theine, dissolved in ten minims of water, was injected under the skin over the back of a white mouse weighing three drachms. For fifteen minutes, no effects were observed. When its tail was pinched, it uttered a cry, which it did before the drug was administered. At the end of this time, it became sluggish in its movements, being weakened in all four limbs, but especially in the posterior ones. It could only crawl along the table, but could not run. Five minutes later, when placed on its back, the animal lay there with its limbs occasionally kicking; and it

turned over on its belly with great difficulty. On pinching its tail, it did not cry, but struggled, and attempted to get out of the way. Five minutes afterwards, the mouse lay helpless on its side. The under surface of the body, the feet, legs, and mouth, were much congested and very red; the ears not markedly so. When the foot was pinched, the animal pulled away its leg. Five minutes later, when placed on its back, it lay there with limbs occasionally moving, and scratching itself with its toes. When its tail or skin was pinched, the animal made very slight efforts to move. When its toe was pinched, it drew its leg out of the way; it did not seem to feel a pinch of the ear. When the eyeball was touched, the eye did not close. When its face was touched, the muscles did not move. Congestion of the skin was still considerable. Twenty minutes afterwards, the animal had gradually become prostrate. When any portion of the body was pinched except the toe, there were no signs given of sensation. When the toe was pinched, there were slight muscular contractions of the limb. Congestion of the cutaneous surface had nearly disappeared, and the animal lay helpless and immovable. Respiration had stopped, and ten minutes later the mouse was dead. Immediately after death, an examination of the body was made. The heart was still beating feebly. The integument, the thoracic and abdominal viscera, were all deeply congested, and their blood-vessels engorged with blood. On amputating the head and irritating the upper portion of the spinal cord with the point of a needle, there were feeble contractions of the muscles generally, which were much increased on applying to the same place the electrodes of a weak faradic current. On thrusting the needle into the brain, the muscles of the face contracted powerfully. About a quarter of an inch of the cord was carefully dissected out by removing with a pair of scissors the bodies of the vertebræ. On applying the electrodes very gently to the posterior columns, there were slight contractions of the muscles of the lower limbs. On touching the anterior columns, there were strong contractions. On exposing the sciatic nerves, and pinching or applying the electrodes to them, the limbs were powerfully contracted. On irritating the muscles, they contracted strongly under electrical stimulus. The membranes of the brain were found much congested, but its substance appeared healthy. The spinal cord was not congested, and seemed in its normal condition.

In this experiment, it is seen that the effects of theine on a mammal are similar to those produced on a frog. The mouse lost its motor power. When irritated or pinched, it seemed to have lost its sensibility. Respiration was stopped, and complete prostration and death

ensued. There was great congestion of the skin and internal organs, pointing to the influence the drug has on the vaso-motor system. There was congestion of the membranes of the brain, which explains the cerebral excitement which is occasionally, although not in this instance, met with after the administration of theine. As in the preceding experiment, the motor filaments of the brain, cord, nerves, and muscles, were intact; while the sensory filaments of at least the spinal cord were paralysed. The slight movements produced by irritating the posterior columns were probably due to transmitted electricity, owing to the small size of the cord of a mouse. This was afterwards proved to be the case by experiments on larger animals. All these facts prove that the loss of motor power of the animal during life was not due to paralysis, either of the motor columns of the spinal cord, the motor nerves, or the muscles. They show, however, that there is at least paralysis of the sensory columns of the cord; and whether the peripheral sensory nerves are affected or not, will be shown in a following experiment. Death probably resulted from paralysis of the nerves connected with the respiratory processes. In this experiment, the mouse died quietly, without convulsions; but in many instances the animal has tetanic spasms and opisthotonos immediately preceding death, having symptoms somewhat allied to those produced by strychnia. Theine differs from strychnia in this respect: in the latter, there is increased reflex action of the cord, so that the slightest touch induces a tetanic spasm; in the former, there is no such excitability, as, the posterior columns being paralysed, and the animal not feeling any irritation, no spasm is induced, but convulsions occur without a stimulant.

Experiment 412. *One-twelfth of a Grain of Theine: Frog: Ligature of Femoral Artery: Death: Post Mortem Examination.*—The left femoral artery of a healthy middle-sized frog was tied, and one-twelfth of a grain of theine, dissolved in thirty-five minims of water, was injected under the skin over the back. In ten minutes, the animal was almost prostrate. It lay on its back, but was still able to contract its limbs when they were pinched, which both did with equal strength, the left leg, perhaps, being somewhat more sluggish than the right. Fifteen minutes later, the frog was apparently dead. The head was amputated. On irritating the upper portion of the cord with the electrodes of a weak faradic current, the two limbs contracted powerfully, and apparently with equal strength. When the sciatic nerves were dissected out and irritated or pinched, similar muscular contractions took place in

both legs. The other symptoms and *post mortem* phenomena were similar to those described in Experiment 413.

This experiment supports former observations in proving that the peripheral motor nerves are unaffected by theine. In tying the artery of the limb, the poisoned blood is prevented from circulating through it ; consequently, while the rest of the body is affected, it remains in comparatively a healthy condition. After the introduction of the drug, the animal gradually became prostrate ; but at no stage of the symptoms was there any special or marked difference between the two legs. (It may be mentioned, that cutting off the supply of blood to the limb produced slight weakness of that leg.) On irritating the spinal cord or the sciatic nerves, no difference was observed in the contractile powers of either of the posterior extremities. This proves that the peripheral motor nerves are not paralysed ; otherwise the leg which had been poisoned would, on irritation, have been more sluggish in its movements than the limb from which the theine had been excluded by the ligature of the artery. In reality, the latter leg was the feebler of the two. This experiment shows nothing with regard to the sensory peripheral nerves, as, the posterior columns of the cord being affected, reflex action is destroyed.

Experiment 385. *One-twelfth of a Grain of Cocaine or Theine : Frog : Ligature of the Heart.*—The heart of a healthy middle-sized frog was exposed by carefully dividing the sternum with a pair of scissors, and a ligature passed round its base, and tied so as to interrupt the circulation. The one-twelfth of a grain of theine, dissolved in ten minims of water, was then injected under the skin of the calf of the right leg. In four minutes, both of the posterior extremities were partially paralysed. On pinching the skin over the right calf with a pair of forceps, no muscular contractions of any kind followed. On pinching the skin over the left calf, there were contractions of all the muscles of the body, including the right leg. On pinching any other portion of the skin, except the right leg below the knee, the animal struggled. A one-twelfth of a grain of theine, in ten minims of water, was then injected under the skin of the calf of the left leg. Three minutes afterwards, when the toe of this limb was pinched, the muscles did not contract; but, on pinching either of the anterior extremities, all four legs contracted.

In the former experiments, it has been pointed out that theine paralyses the posterior or sensory columns of the cord, but that it does not affect the motor filaments of the brain or cord, the motor nerves, or the muscles. The object of this experiment was to determine the local

effect of theine upon the peripheral sensory nerves. The heart was tied so as to prevent any circulation of blood in the body. The operation produced partial paralysis of the limbs, probably owing to the want of proper blood-supply. When the drug was injected into the calf of the right leg, subsequent irritation of the foot did not induce muscular contraction of that limb; but, on irritating the toe of the left leg, there were distinct contractions of all the limbs, including the poisoned one, showing that reflex action was unimpaired, and that the motor nerves of the poisoned leg were unaffected.

This supports the preceding experiment in proving that the nerves of the motor system are not paralysed by theine, otherwise a pinch of the left leg (unpoisoned) would not have produced contraction of the right (poisoned). It also proves that the peripheral sensory nerves are paralysed, as, in this instance, the cord not being under the influence of the drug, the loss of motion of the right leg was due to the local effect on the sensory nerves. This was further shown by injecting theine into the left or hitherto unpoisoned limb. A few minutes afterwards, when it was pinched, the previous muscular contractions were found to have disappeared. The sensory peripheral nerves had been paralysed. When either of the anterior extremities were pinched, the muscles of the entire body, including both poisoned legs, contracted, showing that, although the sensory nerves of both limbs were paralysed, the motor nerves were intact. Thus theine paralyses the posterior columns of the cord and the peripheral sensory nerves, but it does not affect the anterior columns or motor nerves.

Experiment 427. *Six Grains of Theine: Rabbit: Death: Post Mortem Examination.*—Six grains of theine, dissolved in two drachms of water, were injected under the skin over the back of a healthy white rabbit weighing 2 lbs. 3 oz. Almost immediately afterwards, the ears were observed to become paler than before; then suddenly they appeared of a bright red colour, all the vessels being enlarged and congested. After remaining in this condition for half a minute, they again became pale and anæmic. These sudden changes from extreme pallor to intense congestion alternated for about five minutes, each stage being about a quarter of a minute in length, after which time the ears became permanently red, hot, and congested. The animal then became restless and somewhat excited, but not hyperæsthetic; and it trembled slightly. When its toe or ear was pinched, it struggled. The force of the heart's pulsation was stronger; and the rapidity of the beats, as well as the respiratory acts, quicker than before. The pupils were unaffected. Three minutes later, the hind legs straggled slightly, and they seemed to

have lost power. Two minutes afterwards, all four extremities were considerably weaker, and the rabbit was unable to stand upright, but lay flat on its belly, with all its limbs stretched out on the table. When its toe was pinched, it did not struggle so much as formerly; still it pulled away its leg, and attempted to crawl along, which it did in a shaky and laboured manner. The breathing was laboured and slow, the heart's pulsations were feeble, and the animal trembled. The ears were still intensely hot to the touch, and congested. Eight minutes later, the animal could not make the slightest effort to stand, or move its body by means of its legs. All excitement had disappeared, and it lay quiet on its side. On pinching its toe very hard, it did not give any evidence of feeling pain, and did not move. The ears were still congested and hot, and the pupils were somewhat contracted. For twenty minutes the animal lay in this prostrate condition, breathing in a laboured manner, when it suddenly took a tetanic spasm, with slight opisthotonos, which lasted for about a quarter of a minute. The congestion of the ears had now almost entirely disappeared. For the

TABLE L.—*Experiments with Theine.*

No. of Experiment.	Animal.	Dose in grains.	General Effects.	Result.	*Post Mortem* Examination.
407	Frog	1-120th	Slight weakness of posterior extremities.	Recovery	
408	Frog	1-64th	Weakness of posterior extremities.	Recovery	
409	Frog	1-32nd	Paralysis of limbs; loss of reflex action; respiration impeded.	Recovery	
410	Frog	1-16th	Complete paralysis of limbs; loss of reflex action; respiration impeded; cutaneous congestion.	Recovery	
411	Frog	1-12th	Gradual prostration; paralysis of all the muscles; loss of reflex action; respiration stopped; congestion of cutaneous surface & mucous membrane of mouth and tongue.	Recovery	
412	Frog	1-12th	Femoral artery tied; same effect as No. 411; no difference between two legs.	Death	
413	Frog	1-12th	Complete prostration; loss of reflex action; stoppage of respiration; cutaneous congestion; stasis of blood in capillaries.	Death	Heart still beat; congestion of viscera; muscles contracted when electricity was applied; when spinal cord, nerves, or brain irritated, muscr. contractions occurred.
414	Frog	1-10th	Complete prostration; loss of reflex action; stoppage of respiration; congestion of cutaneous surface.	Recovery	

TABLE L.—*Experiments with Theine. (Continued.)*

No. of Experiment.	Animal.	Dose in grains.	General Effects.	Result.	*Post Mortem* Examination.
415	Mouse	1-10th	The same as No. 414.	Death	Same as No. 413. Spinal cord exposed; anterior column irritated, contraction of muscles ensued; posterior column irritated; no contractions.
416	Frog	1-8th	Same as No. 414, but more rapid.	Death	Same as No. 413.
417	Frog	1-8th	Femoral artery tied; symptoms same as No. 414, but tetanic spasms in addition; no difference between two legs.	Death	Same as No. 413. No difference between two legs when electricity was applied.
418	Frog	1-4th	Rapid prostration, with tetanic symptoms.	Death	Same as No. 413.
419	Frog	1-3rd	Upper part of spinal cord exposed during life; rapid prostration; after death, on touching anterior columns of cord, contraction of all the muscles; on touching poster. columns, no contractions; before death, muscular contractions followed irritation of the posterior columns.	Death	Same as No. 413.
420	Frog	1-3rd	Lower portion of cord exposed during life; same as No. 419.	Death	Same as No. 413.
421	Frog	½	Very rapid prostration and loss of reflex action, with usual effects.	Death	Same as No. 413.
422	Frog	1	Almost instantaneous prostration.	Death	Same as No. 413.
423	Rabbit	1+1	No effects from first grain; slight weakness of posterior extremities from second grain.	Recovery	
424	Rabbit	1	Femoral artery tied; contraction of pupil very slight; no other effect; leg of animal was paralysed by operation.	Recovery	
425	Rabbit	2+2 +2+2	From first and second dose, no effects. From third dose, ears hot and congested; no other effect. From fourth dose, animal paralysed and prostrate; tetanic spasms; contraction of pupil.	Death	Membranes of brain congested; substance of brain and spinal cord healthy; internal viscera congested; muscles contracted when electrodes of Faradic current were applied; when applied to nerves or spinal cord, muscular contractions ensued.
426	Cat	4+4	From first dose, great irritation and cerebral excitement; depression afterwards. After second dose, excessive salivation; partial paralysis of posterior limbs; tetanic spasms; tongue and mouth congested; mucous discharge from bowel.	Death	Nerves found sensitive to pinching. The same as No. 425.

TABLE L.—*Experiments with Theine.* (*Continued.*)

No. of Experiment.	Animal.	Dose in grains.	General Effects.	Result.	*Post Mortem* Examination.
427	Rabbit	6	Observations on respiration—number, 1st increased, and 2nd diminished. Complete paralysis of all four limbs; laboured breathing; loss of reflex action; congestion and heat of ears; pupils contracted; tetanic convulsions.	Death	Same as No. 425.
428	Rabbit	6	Observations on heart's pulsation—number, 1st increased, and 2nd diminished; otherwise same as No. 427.	Death	Same as No. 425.
429	Cat	6	Irritable at first; staggering gait; excessive salivation; discharge of mucous from bowel; subsequent depression.	Recovery	
430	Cat	6+3	From first dose, irritation and cerebral excitement; embarrassed respiration; subsequent depression; profuse salivation; staggering gait; animal stupid and drowsy. From second dose, mucous discharge from bowel; mouth and tongue congested; vomiting.	Death	Same as No. 425.
431	Rabbit	8	Ears congested; staggering gait; pupils contracted; laboured breathing.	Recovery	
432	Rabbit	8	Ears congested; pupils contracted; paralysis of legs; reflex action lost except in head; tetanic spasms; opisthotonos.	Death	Same as No. 425.
433	Rabbit	12	Spinal cord exposed during life; posterior column touched, animal cried and struggled. After injection of theine, complete prostration & loss of reflex action; on touching posterior column it did not move away or cry; on touching anterior column, muscles were contracted.	Death	Same as No. 425.

next seven minutes, the animal took tetanic spasms at intervals, occurring spontaneously, and not brought on by pinching or other external irritations. Evidence of sensibility had disappeared from all parts of the body except the head, where it seemed to be normal. The eyelids winked when the eyeballs were touched, and even when the hands were clapped before them. When any portion of the face was touched, its muscles contracted. The animal, although completely paralysed in its limbs, looked intelligent, as if sensation was unaffected. Ten

minutes later the pupils were considerably contracted, the breathing slow and irregular, and the heart-beats not palpable. It died after a tetanic spasm.

An examination of the body was made as soon after death as possible. On applying the electrodes of a weak Faradic current to the exposed spinal cord, the muscles of the lower limbs contracted. On removing with a pair of scissors the bodies of the vertebræ, and isolating about half an inch of the cord, in the dorsal region it was observed that, although muscular contractions followed irritation of both the anterior and posterior columns, these were much more marked in the case of the former. On thrusting a needle into the brain, the muscles of the face and eye contracted. The sciatic nerves and muscles were found apparently in normal condition. The membranes of the brain were much congested, but its substance appeared healthy, as was also the spinal cord. All the internal viscera were deeply congested, their vessels being engorged with blood.

In this experiment, the loss of motor power and other symptoms, already described in the mouse, ensued. The early stage was indicated by cerebral exitement, irritation, and restlessness of the animal, which subsequently disappeared, and was followed by depression and insensibility to irritation. It is to be observed, however, that the animal never seemed to lose its intelligence. It was watchful, followed every motion of the experimentor, although it was unable to make any movement. From the effects observed in the blood-vessels of the ear, it is evident that theine affects the vaso-motor nerves, first by irritating and afterwards by paralysing them, as evidenced by the change in the action of the heart and the frequency of its beats, also in the tonicity of the smaller vessels by first contracting and lastly by relaxing them. This same action also explains the increase and subsequent diminution of the respirations which ultimately caused the death of the animal.

Experiment 430. *Six Grains of Theine: Cat: Death: Post Mortem Examination.*—Six grains of theine, dissolved in a drachm and a half of water, were injected under the skin over the back of a healthy cat, weighing 4 lbs. 1 oz. In ten minutes, the animal became very angry and irritable. Fifteen minutes later, this excitement had increased, the animal had a watchful anxious appearance, prowled about, and when touched with a stick, bit at it and growled. If any noise or motion were made, it arched the back and made a hissing noise. The legs appeared weakened, and although it still could walk about, it preferred sitting in a corner of the room. Its mouth and tongue were very red, and there was an abundant secretion of saliva, which constantly trickled

out of its mouth. The cat defæcated and micturated several times. Forty minutes later, it continued in much the same condition. Salivation was profuse. Animal suffered from tenesmus, and it had a constant straining from the bowel of a clear fluid, like mucus. The limbs, especially the posterior ones, were much weakened, but the animal could still run with difficulty. It could not jump; it made attempts to do so over a bench about two feet high, but failed. The breathing

TABLE LI.—*Experiments with Caffeine.*

No. of Experiment.	Animal.	Dose in grains.	General Effects.	Result.	*Post Mortem* Examination.
434	Frog	1-128th	Very slight weakness of posterior extremities.	Recovery	
435	Frog	1-64th	Slight weakness of posterior extremities.	Recovery	
436	Frog	1-32nd	Considerable weakness of limbs; respiration impaired; reflex action diminished.	Recovery	
437	Frog	1-16th	Almost complete paralysis; respiration stopped; almost complete loss of reflex action; prostration; cutaneous surface congested.	Recovery	
438	Frog	1-12th	Complete prostration; respiration stopped; reflex action lost; under surface of skin, tongue, & mouth, congested; stasis of blood in capillaries.	Death	Heart beat feebly; great congestion of viscera. When brain was irritated, muscles of face contracted; on irritating spinal cord, nerves or muscles, there were muscular contractions.
439	Frog	4-12th	Ligature of femoral artery; symptoms same as No. 438; no difference between the two limbs.	Death	Same as No. 438; no difference between the two legs
440	Frog	1-10th	Spinal cord exposed during life; symptoms the same as No. 438. On touching anterior or posterior columns with point of needle, strong muscular contractions followed. After caffeine was injected, no contractions followed on touching the posterior column, while anterior column remained as before.	Death	Same as No. 438.
441	Frog	1-8th	Prostration and loss of reflex action; congestion of skin; stoppage of respiration.	Death	Same as No. 438.
442	Frog	1-3rd	Rapid prostration and loss of reflex action, with usual symptoms.	Death	Same as No. 438.
443	Frog	1	Ligature of femoral artery; very rapid prostration & loss of reflex action; no difference between the two limbs.	Death	Same as No. 438. No difference between the two legs.

TABLE LI.—*Experiments with Caffeine. (Continued.)*

No. of Experiment.	Animal.	Dose in grains.	General Effects.	Result.	*Post Mortem* Examination.
444	Rabbit	1+1 +1+1	From first & second dose, no effects; from third dose, congestion of ears, cerebral excitement, contraction of pupil, staggering gait; from fourth dose, partial paralysis of limbs, reflex action diminished.	Recovery	
445	Rabbit	4	Numbers of the respirations & pulsations of the heart—1st increased, and 2nd diminished. Temperature of the ear—1st diminished, and 2nd increased. Ears at first anæmic, subsequently hyperæmic; breathing laboured; pupils contracted; paralysis of limbs; loss of reflex action; tetanic spasms; opisthotonos.	Death	Membranes of brain & internal viscera congested; substance of brain and spinal cord healthy; electrodes of current applied to cord, nerves, brain, or muscles, produced muscular contractions.
446	Cat	6	Irritation and cerebral excitement; mouth and tongue congested; staggering gait; tenesmus & mucous discharge from bowel; salivation excessive; subsequent depression.	Recovery	
447	Cat	8	Same as No. 446; in addition, prostration, loss of reflex action, and tetanic spasms.	Death	Heart beat feebly; the same as No. 445.
448	Cat	8	No marked effect for about half an hour. Death from sudden tetanic spasm.	Death	Same as No. 445.
449	Rabbit	12	Spinal cord exposed during life; posterior columns touched with point of needle, animal struggled and cried out; anterior columns touched, animal struggled. After injection of caffeine, when posterior columns were touched, animal did not cry out, but struggled slightly; when anterior columns were touched, strong muscular contractions ensued. Symptoms same as No. 445.	Death	Same as No. 445.

was laboured and irregular. The redness of the tongue and mouth, as well as the excessive irritability of the animal had disappeared. It was quiet, lay in a corner, stupid and drowsy. It drank freely of water. Twenty minutes later, it was prostrate and lay on its side, its limbs quite helpless. It paid no attention to a pinch of the toe or a blow on the tail with a stick. It seemed, however, to be intelligent,

as its eyes watched every movement of the observer, and when the hands were clapped before its face it growled. The salivation and discharge from the bowel were excessive. Pupils were contracted, and the breathing was laboured. Five minutes later, the cat took a series of tetanic spasms, and shortly afterwards died.

The *post mortem* examination and phenomena were similar to those in the preceding experiment.

In the cat, the general nervous symptoms are much the same as in the rabbit, with this exception, that the cerebral excitement and subsequent depression are much more marked. There was no evidence of hyperæsthesia, but rather a gradual loss of sensibility. In addition, there was excessive increase of the salivary secretion, and straining from the bowels of a profuse mucous discharge. The cat died after a severe tetanic spasm.

Experiment 433. *Twelve Grains of Theine: Rabbit: Spinal Cord exposed during Life.*—A healthy white rabbit, weighing 2 lbs. 2 oz., was carefully fastened down on its belly. An incision was made through the skin along the upper part of the spine, about two inches in length, and the vertebral column exposed. By means of bone-forceps and scissors, portions of the vertebræ were removed so as to expose a piece of the spinal cord about a quarter of an inch in length. On touching the posterior columns with the point of a blunt needle, the animal struggled violently and uttered loud cries. Twelve grains of theine, dissolved in two drachms of water, were then injected under the skin of the belly. In ten minutes, the symptoms already described in preceding experiments commenced—congestion of the ears, etc. On pinching the toe, the animal did not appear to feel it. On touching with the point of a blunt needle the posterior columns of the cord, the animal struggled, but not nearly so violently as before, and it did not cry out. When the anterior columns were touched, there were violent convulsions of the body. Five minutes later, the animal was completely paralysed in all its limbs, and presented all the usual symptoms of prostration. A fresh portion of the cord was exposed by cutting away some of the vertebræ below the original wound. On touching, as before, the posterior columns, the rabbit only quivered slightly. On touching the anterior columns, marked muscular contractions of the limbs followed. The animal was shortly afterwards killed, and similar phenomena were observed after death as have been already described.

The object of this experiment was to confirm, during life, what had already been concluded from *post mortem* examinations, viz., that theine

paralyses the posterior columns of the spinal cord, while the anterior columns remain apparently unaffected.

TABLE LII.—*Experiments with Guaranine.*

No. of Experiment.	Animal.	Dose in grains.	General Effects.	Result.	*Post Mortem* Examination.
450	Frog	1-128th	No apparent effects.	Recovery	
451	Frog	1-64th	Animal sickly; slight weakness of poster. extremities	Recovery	
452	Frog	1-32nd	Weakness of limbs.	Recovery	
453	Frog	1-16th	Partial paralysis of limbs; reflex action impaired; respiration impeded; congestion of cutaneous surface.	Recovery	
454	Frog	1-12th	Prostration; almost entire loss of reflex action; respiration stopped; congestion of cutaneous surf.	Recovery	
455	Frog	1-8th	Complete prostration & loss of reflex action; respiration stopped; cutaneous congestion also of mucous membrane of tongue and mouth; stasis of blood in capillaries.	Death	Heart beat feebly; congestion of skin and internal viscera. On irritating brain, spinal cord, nerves or muscles, there were muscular contractions; anterior columns of cord irritated, strong contractions of limbs; posterior columns irritated, no contractions.
456	Frog	1-4th	Rapid prostration & loss of reflex action; otherwise the same as No. 455.	Death	Same as No. 455.
457	Rabbit	4	Number of the respirations & pulsations of the heart—1st increased, and 2nd diminished. Temperature of the ear—1st dimin. and 2nd increased. Ears—1st anæmic, and 2nd hyperæmic. 1st cerebral excitement, & 2nd depression; paralysis of limbs; subsequently apparent recovery, but afterwards died in sudden tetanic convulsion.	Death	Membranes of brain and internal viscera congested. Substance of brain and spinal cord healthy. Electricity applied to brain, cord, nerves or muscles, produced muscular contractions.
458	Rabbit	4+2	From 1st dose, ears congested, and cerebral excitement. From second dose, complete paralysis of limbs; loss of reflex action; contraction of pupil; tetanic spasms, with opisthotonos.	Death	Same as No. 457.
459	Cat	6	Irritability & cerebral excitement; subsequent depression; partial paralysis of limbs; respiration impeded; tongue and mouth congested; tenesmus & discharge of mucus from bowel.	Recovery	

TABLE LII.—*Experiments with Guaranine.* (*Continued.*)

No. of Experiment.	Animal.	Dose in grains.	General Effects.	Result.	*Post Mortem* Examination.
460	Cat	6	Same as No. 459; in addition, tetanic spasms and opisthotonos.	Death	Same as No. 457.
461	Rabbit	8	Exposure of spinal cord during life. On touching posterior columns with point of needle, animal struggled and cried out; on touching anterior columns, animal struggled. Guaranine produced effects as in No. 457. On touching posterior columns, animal did not struggle or cry out; on touching anterior columns, muscular contractions of limbs ensued.	Death	Same as No. 457.

From these experiments, and those in the Tables L, LI, and LII, the general conclusion may be drawn, that, as cocaine, theine, caffeine, and guaranine chemically resemble one another, so do their physiological actions seem precisely similar.

Numerous observations made on larger animals (cats and rabbits) with the three last substances demonstrated the following facts, in addition to those already determined with cocaine.

1. These three alkaloids—theine, caffeine, and guaranine—produce an increase of the salivary secretion.

2. They produce a peculiar form of tenesmus, accompanied by a copious discharge of clear mucus from the bowels.

3. They usually produce contraction of the pupil.

4. They affect the temperature by (1) slightly lowering and (2) increasing it.

Although we have not been able to demonstrate that these four properties also belong to cocaine, we have every reason to believe, judging from their other analogies, that if similar doses of it were given the same results would ensue.

2. *The Antagonism between Theine, Caffeine, and Guaranine, on the one hand, and Meconate of Morphia on the other.*

A. *Antagonism between Theine and Meconate of Morphia.*

The physiological action of theine having been determined by Dr. Alexander Bennett, the Committee had next to ascertain its minimum fatal dose. The experiments were performed on rabbits and cats, because the symptoms produced by the action of theine on these animals, more especially the latter, were very characteristic.

TABLE LIII.—*Showing the Minimum Fatal Dose of Theine in Rabbits.*

No. of Experiment.	Weight of Rabbit.	Dose in grains.	Result.	Remarks.
461/1	4 lbs.	2	Recovery	No effect, except flushing of the ears.
462	3 lbs. 8 oz.	3	Recovery	Ditto. Slight paralysis.
463	3 lbs. 7 oz.	4	Recovery	Ditto. Paralysis more marked.
464	3 lbs. 4 oz.	5	Recovery	Very marked paralysis; twitches.
465	3 lbs. 2 oz.	6	Death	Convulsions; excitement.
466	3 lbs. 2½ oz.	5½	Death	Ditto ditto.
467	3 lbs. 3 oz.	5¼	Recovery	After severe tetanic spasms.
468	3 lbs. 3¾ oz.	5½	Recovery	Ditto ditto.
469	3 lbs. 4 oz.	5¼	Recovery	Ditto ditto.
470	3 lbs. 4½ oz.	5¾	Death	Severe tetanic spasms.

These experiments show that the fatal dose of theine for a rabbit of from 3 lbs. 4 oz. to 3 lbs. 2½ oz. is between 5¼ and 5½ grains.

TABLE LIV.—*Showing the Minimum Fatal Dose of Theine in Cats.*

No. of Experiment.	Weight of Cat.	Dose in grains.	Result.	Remarks.
471	4 lbs. 14 oz.	4	Recovery	Great excitement.
472	4 lbs. 10 oz.	5	Recovery	Ditto; slight paralysis.
473	4 lbs. 9 oz.	6	Death	Excitement; convulsions in 23 min.
474	4 lbs. 15 oz.	6	Death	Ditto; ditto in 26 min.
475	4 lbs. 14½ oz.	5½	Death	Ditto; ditto in 24 min.
476	4 lbs. 15 oz.	5¼	Recovery	After excitement, partial paralysis & slight convulsions.

The minimum fatal dose for a cat of nearly 5 lbs. weight is therefore about 5½ grains. This is nearly the same fatal dose as in the rabbit. The chief point of difference between the action of theine on the cat and on the rabbit is the intense excitement produced in the former. This is well illustrated by the following experiment, No. 473.

Experiment 473. A male cat, weighing 4 lbs. 9 oz., had six grains of theine injected under the skin of the back. For five minutes, nothing was observed. At the end of this period it began to move backwards and forwards, and the excitement gradually increased until the close of

fifteen minutes after the administration of the drug, when it seemed to be frantic. These fits of intense cerebral excitement afterwards occurred at intervals of two or three minutes. Between them the animal lay quiet. It appeared to be extremely susceptible to irritation. A stick brought near it was immediately bitten. Salivation became very profuse. Twelve minutes after the dose had been given, the cat had difficulty in moving its posterior extremities. This difficulty gradually passed into complete paraplegia. Thirty minutes after, it could not move the hinder part of its body, but its senses were very acute. The animal noticed every movement made near it, and it tried to bite. The paralysis gradually invaded the fore extremities also, and the cat was unable to sit up. It lay with its head slightly raised, but still there was the same acuteness of the senses of hearing and vision, and it was easily irritated. It remained in this condition for an hour and a half, when, after two very severe clonic spasms, it died.

The narrative of the above experiment indicates intense cerebral excitement associated with gradual loss of the functions of the spinal cord.

a. On Cats.

The next point was to determine how far theine could antagonise a fatal dose of morphia in a cat. Before this could be done, it was necessary to ascertain what was the minimum fatal dose of meconate of morphia for a cat. This was approximately fixed by ten experiments at from 1½ to 1¾ grains. These experiments are summarised in the following table.

TABLE LV.—*Showing the Minimum Fatal Dose of Meconate of Morphia in Cats.*

No. of Experiment.	Weight of Cat.	Dose in grains.	Result.	Remarks.
477	4 lbs. 6 oz.	¼	Recovered	No evident effect.
478	4 lbs. 9 oz.	½	Recovered	Drowsiness.
479	4 lbs. 10½ oz.	¾	Recovered	Drowsy; dry mouth; slight feebleness in walking.
480	4 lbs. 5¾ oz.	1	Recovered	Ditto; more marked.
481	4 lbs. 10 oz.	1¼	Recovered	Other symptoms more marked.
482	4 lbs. 9¼ oz.	1½	Recovered	Nearly comatose, but could be roused.
483	4 lbs. 10½ oz.	1¾	Death	In comatose state 2 hours after; found dead 6 hours after.
484	4 lbs. 13 oz.	1¾	Death	Found dead 10 hours after.
485	4 lbs. 13 oz.	1½	Recovered	This animal was ill until the end of 16 hours, when it began to recover.
486	4 lbs. 11 oz.	1½	Recovered	Began to recover 12 hours after.

These experiments show that for an average sized cat a dose of 1½ grains of meconate of morphia is nearly fatal, while a dose of 1¾ grains

is certainly so. The general effects are precisely similar to those already described as occurring in the dog. The only point of interest is that, with small doses, we observed dryness of the mouth; but large doses produce salivation. When salivation did occur, it was so profuse as to endanger the life of the animal, if comatose, from suffocation.

Having determined the fatal dose, for a cat of average size, of theine to be about 5½ grains, and of meconate of morphia to be from 1½ to 1¾ grains, the following experiments were made: in these, the substances were injected simultaneously.

Experiment 487. A female cat, weighing 4¼ lbs., had 1¼ grains of meconate of morphia and 5 grains of theine subcutaneously injected simultaneously. In five minutes, profuse salivation occurred. There was much cerebral excitement, manifested as already described. In five minutes more, the animal fell on its side in a violent tetanic spasm of the whole body, which continued for about thirty seconds. On recovering from this spasm, it lay on its side, quiet, and breathing very rapidly. Three minutes afterwards, another severe tetanic spasm occurred. The mucous membrane of the mouth was now dry and congested. The respirations became irregular. After slight convulsive twitches of the body, death ensued, thirty-four minutes after the introduction of the active substances.

Experiment 488. A male cat, weighing 6½ lbs., had 1½ grains of meconate of morphia and 6 grains of theine injected simultaneously. The usual phenomena occurred, and the animal died, after a severe convulsion, forty minutes after the dose.

Experiment 489. A male cat, weighing 7 lbs., had 1¾ grains of meconate of morphia and 6 grains of theine injected simultaneously. There were no apparent effects produced in this case until fifty-two minutes afterwards, except that the animal lay in a corner of the cage in a drowsy state. It then began to move uneasily about, had slight risus sardonicus, lay down upon its side, extended its limbs, the respirations became more and more irregular, and death ensued sixty-five minutes after the dose. In this case, there was not, from first to last, any convulsive seizure.

Experiment 490. The last described experiment appeared to be so important, as indicating an antagonistic action between the two substances, as to call for repetition under conditions as nearly similar as possible. A male cat, weighing 6¾ lbs., had 1¾ grains of meconate of morphia and 6 grains of theine injected simultaneously. The effects were precisely similar to those described in last experiment, and the

animal died, without any convulsions, at the end of eighty minutes after the dose.

The conclusions to be drawn from these experiments are as follows. 1. There appeared to be an antagonistic action between the two substances, inasmuch as the symptoms produced by either were considerably modified, but life was not saved; and 2. The meconate of morphia delayed the appearance of the convulsions characteristic of the action of theine, while, on the other hand, the theine did not appear to affect in a marked way the action of the meconate of morphia. As the latter conclusion did not appear to be sufficiently obvious at this stage of the inquiry, the question was re-examined in a second set of experiments some time afterwards. In this second set of experiments, smaller doses of theine were given.

Experiment 491. A male cat, weighing 6¾ lbs., had 1¾ grains of meconate of morphia and 4 grains of theine subcutaneously injected simultaneously. Nothing particular was observed for thirty minutes, except that the animal appeared to be in a drowsy condition. At the end of that time, it began to move about uneasily, and manifested, by its efforts to escape from the cage, considerable cerebral excitement. This continued for fifteen minutes, when it subsided into a comatose condition. It remained in the state of coma for eight hours, when it gradually recovered. It was again subjected to experiment eight days afterwards.

Experiment 492. The same cat now weighed 6½ lbs. A grain and three-quarters of meconate of morphia were subcutaneously injected. It quickly passed into a drowsy condition. At the end of an hour after the injection of the morphia, it was deeply comatose. Pinching the foot excited very feeble reflex movements. It remained in this state for nearly twelve hours. When observed at that time, it was in a condition difficult to describe. When roused, it raised its head and looked around with a vacant stare. When pushed, it attempted to walk, but could scarcely do so. After progressing a few feet, it fell down and relapsed into the comatose state. This animal recovered, proving that the dose of 1¾ grains of meconate of morphia was not a fatal dose.

Experiment 493. A cat, weighing 5 lbs. 14 oz., had two grains of meconate of morphia subcutaneously injected. After the usual phenomena, this animal passed into a state of profound stupor or coma, and it was found dead at the end of six hours.

Experiment 494. A cat, weighing 5 lbs. 15 oz., had two grains of meconate of morphia subcutaneously injected. Immediately thereafter four grains of theine were subcutaneously injected. Twenty minutes

thereafter, it passed into a drowsy condition, which gradually developed into coma. So far as could be observed, there were no symptoms indicating the presence of theine. Forty minutes after the first injection, as the coma was becoming more and more profound, a second dose of three grains of theine was introduced subcutaneously. Ten minutes after the second dose, there were slight muscular twitchings, more especially of the muscles of the face and mouth. These increased in severity until fifteen minutes after the second dose, when the animal had a severe tetanic spasm, similar to that produced by theine. It was now observed that the coma was not profound. The animal occasionally raised its head and looked about; it attempted to shift its position; and when a stick was placed between its jaws, these closed quickly upon it. It remained in this condition for three hours; from that time it slowly recovered.

Experiment 495. Eight days afterwards, the cat used in experiment 494 was weighed, and its weight was now found to be 5 lbs. 13 oz. It appeared well and in good condition. Two grains of meconate of morphia were now introduced subcutaneously. The cat passed quickly into a state of stupor, which relapsed into coma. From this comatose condition it did not recover, as it was found dead in its cage twelve hours afterwards.

Ten experiments were now made in as nearly the same conditions as possible. These, along with the experiments just described, are stated, as regards general results, in the following table. (See Table LVI.)

This table shows without doubt that theine influences the physiological action of meconate of morphia, because, after a dose of that drug, which alone would produce coma, if theine be also introduced, it is followed by a period of cerebral excitement. Although the limits of the antagonistic action are narrow, it will be seen—(1) that while a cat may recover from the effects of a dose of 1¾ grains of meconate of morphia given alone, it will rarely recover (Experiment 494) from the effects of a dose of 2 grains, even should the effects of the latter dose be modified by those following the introduction of 4 or 5 grains of theine; (2) that in three cases (Nos. 501, 504, and 505) the animals recovered from the effects of 1⅞ grains of meconate of morphia and 4 to 5 grains of theine, while they died when the same dose of meconate of morphia was administered eight days afterwards; (3) that when the dose of theine was increased beyond 5 grains, the animals invariably died apparently from the effects of the theine (Experiments 488, 489, 490). The important result, however, is shown that fatal doses of

meconate of morphia (1⅞ and even 2 grains) may be completely antagonised by theine.

TABLE LVI.—*Showing the Effects in Cats produced by the simultaneous action of Meconate of Morphia and Theine.*

No of Experiment.	Weight of Cat.	Dose of the Meconate of Morphia in grains.	Dose of Theine in grains.	Result.	Remarks.
487	4 lbs. 4 oz.	1¼	5	Death	Died after convulsions in 34 min.
488	6 lbs. 8 oz.	1⅝	6	Death	Ditto ditto in 40 min.
489	7 lb.	1¾	6	Death	No convulsions; death in 65 min.
490	6 lbs. 12 oz.	1¾	6	Death	Ditto; death in 80 min.
491	6 lbs. 12 oz.	1¾	4	Recovery	Coma for 8 hours; cerebral excitement.
492	6 lbs. 8 oz.	1¾	No theine	Recovery	Coma for 12 hours.
493	5 lbs. 14 oz.	2	No theine	Death	Coma; death in 6 hours.
494	5 lbs. 15 oz.	2	4 3 gr. 40 m. aft. first	Recovery	Coma; muscular twitchings.
495	5 lbs. 13 oz.	2	No theine	Death	Profound coma; found dead 12 hours afterwards.
496	5 lbs. 14 oz.	2	5	Death	Coma; afterwards slight excitement; then deeper coma.
497	6 lbs.	2	5	Death	Ditto ditto.
498	5 lbs 8 oz.	2	5	Death	Coma; then slight convulsions, followed by deep coma.
499	5 lbs. 9 oz.	1⅞	4	Recovery	Coma at first; afterwards slight excitement; then coma; recov.
500	6 lbs.	1⅞	5	Recovery	Coma; considerable excitement.
501	6 lbs. 1 oz.	1⅞	4	Recovery	Ditto ditto; killed 8 days thereafter, in 8 hours by same dose.
502	5 lbs. 15 oz.	2	4	Death	Coma; excitement; coma.
503	5 lbs. 14 oz.	2	5	Death	Ditto ditto ditto.
504	5 lbs. 10½ oz.	1⅞	5	Recovery	Coma; great excitement; killed 8 days afterwards by same dose.
505	5 lbs. 12 oz.	1⅞	4	Death	Coma; excitement; found dead 8 days thereafter, 14 hours after same dose.

b. On Rabbits.

A few experiments were made on rabbits as to the antagonism between meconate of morphia and theine. These are briefly recorded in the following table. (See Table LVII.)

The experiments on rabbits were considered so unsatisfactory, that they were not prosecuted further, because it was evident that in this animal meconate of morphia did not produce effects comparable to those following the action of the substance in carnivorous animals. The specific action of salts of morphia in rabbits is to produce, in addition to a stupor not nearly so profound as in carnivorous animals like the dog or cat, convulsions of an epileptiform character. Theine produces somewhat similar effects in rabbits. At the same time, it was observed that the drowsy appearance following soon after the exhibition of meconate of morphia in rabbits was much less marked in those instances in which theine was also administered.

TABLE LVII.—*Showing the Effects in Rabbits produced by the simultaneous action of Meconate of Morphia and Theine.*

No. of Experiment.	Weight of Rabbit.	Dose of Meconate of Morphia in grains.	Dose of Theine in grains.	Result.	Remarks.
506	4lbs.	5	4	Death	Severe convulsions.
507	3 lbs. 14 oz.	4	5	Death	Ditto
508	3 lbs. 15 oz.	4	5	Death	Ditto
509	4 lbs. 1 oz.	5	5	Death	Ditto
510	4 lbs. 1½ oz.	6	5	Recovery	After severe convulsions, this animal slowly recovered; died from same dose of morphia 8 days afterwards.
511	4 lbs. 10 oz.	7	5½	Death	Convulsions.
512	3 lbs. 12 oz.	8	5¾	Death	Ditto.
513	3 lbs. 10 oz.	4	6	Recovery	Severe convulsions; recovered after same dose of morphia 8 days thereafter.
514	3 lbs. 15 oz	3	5¾	Recovery	Severe convulsions; recovered after same dose of morphia 8 days thereafter.
515	4 lbs.	4	5	Death	Very severe convulsions.
516	4 lbs. 1 oz.	4	5	Death	Ditto ditto.
517	4 lbs. 1 oz.	4	5¼	Death	Ditto ditto.

B. *Antagonism between Caffeine and Meconate of Morphia.*

This question was investigated in exactly the same way as had been done with theine and meconate of morphia, and the results were the same. As has been shown by Dr. Alexander Bennett, the physiological actions of theine and caffeine are so similar as to make it impossible to distinguish the one from the other. The following experiments were made on cats, because, as has been stated above, experiments on rabbits with these drugs were not considered satisfactory. As the experiments were precisely similar to those made as to the action between theine and meconate of morphia, it is not necessary to give them in detail. They are summarised in the following table.

TABLE LVIII.—*Showing the Minimum Fatal Dose of Caffeine on Cats.*

No. of Experiment.	Weight of Cat.	Dose in grains.	Result.	Remarks.
518	4 lbs. 14 oz.	3	Recovery	Slight excitement.
519	4 lbs. 11 oz.	4	Recovery	Great excitement.
520	4 lbs. 13½ oz.	5	Recovery	Ditto, and convulsions.
521	4 lbs. 10 oz.	5	Recovery	Ditto ditto.
522	4 lbs. 15 oz.	5	Recovery	Ditto ditto.
523	4 lbs. 15½ oz.	5	Death	Intense excitement; convulsions; death in 2 hours,
524	5 lbs.	6	Death	Intense excitement; convulsions; death in 2¼ hours.
525	5 lbs. 1 oz.	5	Recovery	Excitement; convulsion.
526	4 lbs. 10½ oz.	5½	Recovery	Ditto ditto.
527	4 lbs. 11 oz.	5¾	Death	Excitement; convulsions; survived for 8 hours.

These experiments appear to show that the minimum fatal dose of caffeine for a cat of about 5 lbs. weight is approximately near six grains. The effects produced were similar to those following the introduction of theine.

The question of antagonism was then investigated as follows.

TABLE LIX.—*Showing the Effects on Cats of the simultaneous injection of Meconate of Morphia and Caffeine.*

No. of Experiment.	Weight of Cat.	Dose of Meconate of Morphia in grains.	Dose of Caffeine in grains.	Result.	Remarks.	Effects of crucial experiment eight days afterwards.
528	4 lbs. 4 oz.	1⅞	3	Death	Coma; this was a weakly animal.	
529	4 lbs. 6 oz.	1⅞	4	Recovery	Excitement, followed by stupor.	Death in 4 hrs.; coma.
530	4 lbs. 8 oz.	1⅞	5	Recovery	Ditto ditto.	Recovery.
531	4 lbs. 9 oz.	1⅞	4	Recovery	Ditto ditto.	Recovery.
532	4 lbs. 15 oz.	2	4	Death	Coma; slight convulsions.	
533	5 lbs.	2	4	Death	Ditto ditto.	
534	5 lbs. 1 oz.	2	4	Death	Ditto ditto.	
535	5 lbs. 3 oz.	1⅞	4	Recovery	Stupor for 10 hours.	Death in 6 hrs.; coma.
536	4 lbs. 12 oz.	1¾	4½	Recovery	Stupor for 12 hours.	Recovery.
537	4 lbs. 13 oz.	1¾	4¾	Death	Convulsions; coma.	
538	4 lbs. 12 oz.	1¾	4	Death	Ditto ditto.	
539	4 lbs. 13 oz.	1¾	4½	Death	Ditto ditto.	
540	5 lbs.	1⅞	4	Recovery	Coma; slight convulsion.	Death in 5 hrs.; coma.
541	5 lbs. 2 oz.	1¾	4	Recovery	Coma; no convulsn.	Recovery.
542	5 lbs. 2 oz.	1½	4	Recovery	Ditto ditto	Recovery.
543	5 lbs. 2½ oz.	1½	4	Recovery	Ditto ditto.	Recovery.
544	5 lbs.	1½	4	Recovery	Ditto ditto.	Recovery.

An analysis of this table shows the very important result that in three cases (Nos. 529, 535, and 540) the animals recovered after a dose of 1⅞ grains of meconate of morphia and 4 grains of caffeine, while they died after the administration, eight days after the first experiment, of 1⅞ grains of meconate of morphia alone. On the other hand, in two instances (Nos. 530 and 531) the animals survived the crucial experiment. When the dose of meconate of morphia was less than 1⅞ grains (as in Nos. 536, 541, 542, 543, and 544), the animals survived both the simultaneous action of the drugs and the crucial experiment. In these cases, it is fair to suppose that a dose of 1⅞ grains was not a fatal dose for these particular animals. From these facts, it seems reasonable to believe that caffeine antagonises the action of meconate of morphia by modifying the symptoms, and even to the extent, in certain instances, of saving life. On the one hand, the animal may die from the effects of too large a dose of caffeine, and, on the other, from the

effects of too large a dose of meconate of morphia; but there is a point between the two actions where the physiological effect is such that life may be saved from doses which would otherwise prove fatal.

C. *Antagonism between Guaranine and Meconate of Morphia.*

Six experiments were performed with the view of ascertaining whether guaranine in any way acted as an antagonist to meconate of morphia. The results were similar to those obtained with theine and caffeine; and the inquiry was not prosecuted any farther. These experiments are shortly noted in the following table.

TABLE LX.—*Showing the Effects in Cats of Guaranine and Meconate of Morphia.*

No. of Experiment.	Weight of Cat.	Dose of Meconate of Morphia in grains.	Dose of Guaranine in grains.	Result.	Remarks.
545	5 lbs. 1 oz.	1	4	Death	Much excitement; died 2 hours afterwards.
546	5 lbs. 3 oz.	1	3	Death	Much excitement; died in 3 hours.
547	6 lbs.	2-3rds	3	Recovery	Excitement; no stupor; partial paralysis.
548	6 lbs.	2-3rds	No guaranine	Recovery	Deep stupor; paraplegic for many hours.
549	6 lbs. 1 oz.	4-5ths	3	Death	Excitement; convulsions.
550	6 lbs. 2 oz.	4-5ths	No guaranine	Death	Coma; no convulsions.

There could be no doubt, from these experiments, that guaranine modified to a considerable degree the physiological action of meconate of morphia. The animal in experiment No. 547 recovered after a simultaneous dose of two-thirds of a grain of meconate of morphia and three grains of guaranine; but, in experiment No. 548, the same animal, seven days afterwards, recovered from a dose of two-thirds of a grain of meconate of morphia administered alone. This showed that two-thirds of a grain of meconate of morphia for this particular animal was not a fatal dose; but the symptoms were considerably different in the two instances. In the first experiment, No. 547, in which both drugs were given, there was excitement with no stupor; while in the second experiment, No. 548, in which the narcotic was given alone, there was no excitement, but deep stupor approaching to coma.

D. *Antagonism between Infusion of Tea and Meconate of Morphia.*

Five experiments were made on dogs with reference to this point,

but they were abandoned on account of the difficulties attending the investigation and the unsatisfactory results obtained. The preparation employed was made from a strong extract, prepared by Dr. Cook from three pounds of the best green tea, by dissolving the extract in warm water. This aqueous solution of the extract, while tolerably warm, was injected into the stomach of the animal by means of a stomach-pump. The difficulties attending this method of inquiry were as follows. 1. The tea was frequently vomited within so short a period after its introduction as not to afford time for the exercise of any antagonistic action to the effects of the meconate of morphia, which it might be supposed to possess. 2. The animal was so much excited by the operation of the introduction of the stomach-pump, that it was very difficult afterwards to say how far the effects were produced by the operation, and how far by the introduction of the tea. As a general example of the kind of action, the following two experiments may be quoted.

Experiment 551. A mongrel terrier dog, weighing 24 lbs., had one grain of meconate of morphia in forty minims of warm water injected subcutaneously under the skin of the back. The usual effects were produced of slight nausea, restlessness, stupor, passing into a semicomatose condition, in which latter state the animal continued for a period of six hours. It then slowly recovered.

Experiment 552. The same dog, five days afterwards, was now found to weigh 23 lbs. All the effects of the meconate of morphia had disappeared. One grain of meconate of morphia in forty minims of warm water was subcutaneously injected under the skin of the back. Immediately thereafter, eight ounces of a strong aqueous solution of the extract of tea were injected into the stomach. Five minutes afterwards, this was rejected by vomiting. At the end of another period of five minutes, another injection of eight ounces of tea was given. Part of this was almost immediately rejected. The animal was now very restless and irritable, and it was by no means easy to make any observations of its condition, as it readily attempted to bite. Ten minutes after the last injection of tea, a third dose of eight ounces was given. This was retained. The dog was now much excited. It ran up and down in the laboratory, with a staggering gait. Occasionally it would lie down for a few moments, and again rise to begin its perambulations. There was no stupor strictly speaking, but it had a dull heavy expression of eye. There was no coma. It urinated freely and frequently. There was also diarrhœa attended apparently by tenesmus. The dog continued in this condition for nearly six hours. At the end of this time it began slowly to recover. The most evident effect in this ex-

periment was the intense restlessness of the animal. There could be little doubt that the tea counteracted the physiological action of the meconate of morphia.

An attempt was made a week afterwards to repeat this experiment on the same animal, but it failed completely, as the tea was quickly rejected by vomiting. It was noticeable, however, that in this case the excitement was much less. The general results of these experiments are recorded in the following table.

These experiments were considered to be so unsatisfactory, that they were abandoned. The great difficulty was, that the tea was rejected so quickly by the stomach. This irritability of the stomach was not the effect of the introduction of the tea by the stomach-pump, but was due to the action of the meconate of morphia. That this is the true explanation, is supported by the two following considerations: 1. That in the dog the action of meconate of morphia alone is almost invariably to produce nausea and vomiting; and 2. That when six or eight ounces of warm tea are injected into the stomach of a healthy dog, without meconate of morphia, there is no nausea or vomiting.

TABLE LXI.—*Showing the Effects in Dogs of Infusion of Tea and Meconate of Morphia.*

No. of Experiment.	Weight of Dog.	Dose of Meconate of Morphia in grains.	Dose of Infusion of Tea in ounces.	Result.	Remarks.
551	24 lbs.	1	No tea	Recovery	Nausea; restlessness; stupor; slight coma.
552	23 lbs.	1	8 ounces 8 ounces	Recovery	Nausea; excitement; no stupor or coma.
553	26 lbs.	1½	24 ounces in 4 doses	Death	Tea rejected by vomiting; stupor; coma; death in 3 hours.
554	24 lbs.	1	20 ounces in 3 doses	Death	Ditto; death in 2¾ hours.
555	26 lbs.	2-3rds	16 ounces in 3 doses	Death	Ditto; death in 8 hours.

E. *The Antagonism between Meconate of Morphia and strong Decoction of Coffee.*

It was found that a strong decoction of coffee was rejected so quickly by the stomach, while the animal was affected by meconate of morphia, as to take away all hope of exercising any influence on the physiological action of that drug.

The whole series of experiments on the antagonism between tea, theine, etc., and morphia, as now detailed, appears so encouraging, as to merit further inquiry. The importance of the subject cannot be overestimated. Not only should further experiments be made on animals,

but observations instituted on man with limited doses which could easily be carried out. Clinically, also, in hospitals, much might be done to further this investigation.

In the autumn of 1869, I received a letter from Professor Sewell of Quebec, directing my attention to the influence of tea as an antidote to poisoning by opium. He refers to a case of his published in the *Lancet* for July 1865 or 1866, and says: "As I consider the case a most important one, showing the wonderful power of green tea, not only in poisoning by opium, but also in that by alcohol in the coma of fever, and probably in puerperal convulsions, and in other cases of absorption of urea, I give you the case from memory. Mrs. H., aged 34 (or thereabouts), wife of a medical man, had suffered for years with, as I understood, something like angina, for which she had consulted almost all the physicians in Europe, yourself, I think, among the rest. The only relief she ever got was from chloroform inhalations. On one occasion, when suffering from one of her attacks, I assisted her husband in administering three pounds of this fluid, which was continued uninterruptedly till the whole three pounds were expended. On the occasion of the last attack, which she had in this city, she felt the paroxysm coming on about 4.30 P.M.; and, between this hour and 11.30 the same night, she took two drachms of Battley's sedative solution of opium every half-hour, or fourteen drachms of the medicine in seven hours. Between half-past eleven and twelve, she had a convulsion-fit; I saw her a few minutes afterwards, and found her in the following condition: coma perfect; pupil contracted to a pin's point; perfectly cold up to the hips and elbows; face drawn and cadaverous; pulse imperceptible; *respiration two in three minutes.* This state of things is verified by one of my colleagues, who considered the case hopeless, and allowed me to administer what I pleased, saying she had not ten minutes to live. In the meantime, I had prepared the strongest possible infusion of green tea, and shortly after twelve I administered, *per rectum*, half-a-pint, my friend and I watching the result. In twenty-five minutes, the pulse at the wrist became perceptible; the face was less pale; and she *breathed six times in the minute*, instead of twice in three minutes. The same quantity of tea was then given, also by injection; and, to make a long story short, at 4 A.M., four hours after the commencement of the attack, she addressed me by name, saying, 'she could not see me, but that she recognised my voice'; at 8 A.M., she was out of danger. I have since had three cases of poisoning by alcohol in children, aged one year, five years, and six years. In the two latter, the coma was complete, but all were restored to consciousness in an hour or less.

Will you, if you have the opportunity, give this remedy a trial in all cases of coma caused by an empoisoned state of the blood?"

It was in consequence of the above letter, that I directed so much pains to be taken in the investigation of this subject by the Committee; and, although far from complete, it will, I trust, be regarded by the profession as no unimportant contribution to the inquiry. I especially regret that ill health, and the consequent resignation of my chair, should have prevented my prosecuting, as was my intention, this matter thoroughly in the clinical wards.

VII. The Antagonism between Extract of Calabar Bean and Strychnine.

This subject has been investigated by Nunneley,* Vée,† and Eben Watson.‡ The result of these inquiries is that there can be little doubt the paralysing effects produced by the extract of Calabar bean modify, to a considerable extent, the powerful tetanic convulsions caused by strychnia; but there is no proof that recovery may take place after a fatal dose of either the one or the other drug. As, in the progress of this research, the minimum fatal dose of each substance had already been carefully ascertained, the opportunity was taken of testing this question. Twenty-four experiments were made on as many rabbits of nearly the same weight. In the first twelve rabbits, a minimum lethal dose of strychnia was first introduced, and four minutes thereafter a minimum lethal dose of extract of Calabar bean (Table LXII). In the second set of twelve rabbits, the process was reversed: the animal first received the minimum lethal dose of extract of Calabar bean, and four minutes thereafter a minimum dose of strychnia (Table LXIII).

In these experiments, there was no instance of recovery except in Experiment 560; but in this instance the dose of strychnia was not fatal, as the animal survived after the same dose when administered eight days afterwards.

It will be seen from Table LXIII that not only was there no instance of recovery from a fatal dose of strychnia or of extract of Calabar bean, but that death ensued after the introduction of even non-fatal doses of both substances. It appeared, during the progress of these experi-

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* "On the Calabar Bean: its Action, Preparation, and Use." (*Lancet*, 1863.)

† *Recherches Chemique et Physiologique sur la Fève du Calabar.* Par le Dr. Amédée Vée. Paris: 1865.

‡ "On the Physiological Action of the Ordeal Bean of Calabar, and on its Antagonism to Tetanus and Strychnia Poisoning". (*Edinburgh Medical Journal*, May 1867.)

ments, that the animal was more likely to recover if subjected to

TABLE LXII.—*Showing the Effects of Strychnia and Extract of Calabar Bean on Rabbits. The dose of Strychnia was first introduced; four minutes thereafter the dose of Extract of Calabar Bean.*

No. of Experiment.	Weight of Rabbit.	Dose of the Extract of Calabar Bean in grs.	Dose of Strychnia in grains.	Result.	Remarks.
556	3 lbs. 10 oz.		1-60th	Death	Convulsions; death in 9 minutes.
557	3 lbs. 9½ oz.		1-60th	Death	Ditto do. 10 do.
558	3 lbs. 11 oz.		1-60th	Death	Ditto do. 9 do.
559	3 lbs. 9 oz.		1-80th	Death	Ditto do. 8½ do.
560	3 lbs. 11¼ oz.		1-80th	Recovery	8 days thereafter recovered from same dose of strychnia.
561	3 lbs. 7¾ oz.		1-80th	Death	Convulsions; death in 12 minutes.
562	3 lbs. 6 oz.		1-70th	Death	Ditto do. 9 do.
563	3 lbs. 8 oz.		1-70th	Death	Ditto do. 12 do.
564	3 lbs. 9 oz.		1-70th	Death	Ditto do. 15 do.
565	3 lbs. 7 oz.		1-50th	Death	Ditto do. 15 do.
566	3 lbs. 10 oz.		1-40th	Death	Ditto do. 6 do.
567	3 lbs. 9¾ oz.		1-90th	Death	Ditto do. 20 do.

the action of one or other of the substances alone, than when both were introduced. At the same time, the character of the symptoms produced

TABLE LXIII.—*Showing the Effects of Strychnia and Extract of Calabar Bean on Rabbits. The dose of Extract of Calabar Bean was first introduced; four minutes thereafter the dose of Strychnia.*

No. of Experiment.	Weight of Rabbit.	Dose of the Extract of Calabar Bean in grs.	Dose of Strychnia in grains.	Result.	Remarks.
568	3 lbs. 10 oz.	⅛	1-60th	Death	Severe convulsions in 10 minutes; death in 15 minutes.
569	3 lbs. 9½ oz.	⅛	1-60th	Death	Convulsions in 8 minutes; death in 18 minutes.
570	3 lbs. 11 oz.	⅛	1-50th	Death	Convulsions in 12 minutes; death in 21 minutes.
571	3 lbs. 12 oz.	⅛	1-80th	Death	Convulsions in 14 minutes; death in 18 minutes.
572	3 lbs. 13 oz.	⅛	1-70th	Death	Convulsions in 17 minutes; death in 29 minutes.
573	3 lbs. 8½ oz.	⅛	1-56th	Death	Convulsions in 7 minutes; death in 10 minutes.
574	3 lbs. 8¼ oz.	¼	1-80th	Death	Convulsions in 14 minutes; death in 19 minutes.
575	3 lbs. 9¼ oz.	¼	1-90th	Death	Convulsions in 21 minutes; death in 36 minutes.
576	3 lbs. 8 oz.	¼	1-100th	Death	Convulsions in 31 minutes; death in 37 minutes.
577	3 lbs. 10 oz.	⅓	1-110th	Death	Convulsions in 32 minutes; death in two hours.
578	3 lbs. 9½ oz.	⅓	1-112th	Death	Convulsions in 26 minutes; death in 1½ hours.
579	3 lbs. 8¼ oz.	⅓	1-120th	Death	Convulsions in 40 minutes; death in 1 hour.

by the action of either the one or the other substance are considerably

modified by the presence of the presumed antagonist. Thus, the convulsions caused by the action of strychnia on the spinal cord are not so violent, and have not so much of the character of tetanus, when modified by the action of extract of Calabar bean. On the other hand, the prostration and profuse secretion from the air-passages produced by the influence of extract of Calabar bean are not so great, when the animal is at the same time subjected to the action of strychnia. But I have had no example of recovery from a fatal dose of either drug. On the contrary, the advent of death was accelerated. Strychnia and extract of Calabar bean, therefore, are not antagonists in the sense that the administration of the one can save life after the administration of a fatal dose of the other; but they may be considered as antagonists in the sense that the action of the one modifies the symptoms of the other. The extent of the action is not at all comparable to the action of hydrate of chloral and strychnia.

VIII. The Antagonism between Bromal Hydrate and Atropine.

As preliminary to the investigation of this matter, the physiological action of bromal hydrate was examined and compared with that of chloral and iodal. This inquiry was carried out by Dr. McKendrick, for whose account of the investigation into this subject we refer to the *Edinburgh Medical Journal* for July 1874, where it is given at length. The following were the conclusions arrived at.

1. Bromal hydrate is a more active substance physiologically than chloral hydrate. A rabbit weighing 4 lbs. requires about twenty grains of chloral hydrate to cause death, whereas four or five grains of bromal hydrate are quite sufficient to kill.

2. Chloral hydrate produces, in small doses, or soon after a large dose, marked hyperæsthesia, followed by anæsthesia. Bromal hydrate never produces hyperæsthesia, and anæsthesia only when the animal is in such a state of coma that there is no hope of its recovery.

3. Chloral hydrate does not usually produce great contraction of the pupil. Bromal hydrate always does.

4. Chloral hydrate acts chiefly on the cerebral hemispheres; and never, so far as we know, has been known to cause convulsions. Bromal hydrate acts less vigorously on the hemispheres, and more on the ganglia at the base of the brain and on the spinal cord, the animal frequently dying in a state of opisthotonos.

5. After death from chloral hydrate, fluid is rarely found in the shut sacs of the body. In the case of death from bromal hydrate, fluid is almost invariably found.

6. Chloral hydrate does not usually stimulate the salivary glands to the same extent as bromal hydrate does; but in this instance there are exceptional cases in which chloral hydrate causes excessive secretion of saliva in animals.

The Action of Iodoform.

There is a difficulty in the way of obtaining knowledge of the action of iodoform, on account of its want of solubility in any menstruum suitable for subcutaneous injection. It is scarcely soluble in water, acids, or aqueous alkalies, but it is readily soluble in alcohol, ether, and oils, both fixed and volatile. A number of experiments were performed with a solution, consisting of one grain of iodoform in five grains of alcohol and fifteen grains of water. The effects were very similar to those produced by chloral, with these exceptions. (1) There was no period of hyperæsthesia. (2) There appeared to be a feeling of irritation of the nostrils, as the animals rubbed the nose frequently with the fore-paws. (3) Ten grains subcutaneously injected into rabbits of 3½ lbs. weight produced profound sleep for a period of four hours. Twelve grains killed rabbits of the same weight in 2¼ hours. The fatal dose thus appears to be smaller than in the case of chloral, and larger than in the case of bromal. (4) There were no convulsions. (5) The pupils were only slightly contracted. (6) There was no fluid in the cavities of the body after death from iodoform, while it was always found after death caused by bromal hydrate, and frequently in cases of poisoning by chloral hydrate.

The physiological action of bromal hydrate, having been examined, the antagonism between it and atropine was next investigated. With this view, the minimum fatal dose of bromal hydrate was fixed for rabbits of average weight. The following table gives the results of these experiments. (See Table LXIV.)

From this table it appears that, for a rabbit weighing from 3 lbs. 8 oz. to 3 lbs. 11 oz., the minimum fatal dose is four grains.

The following experiments were then performed with the view of ascertaining whether or not life could be saved from an otherwise fatal dose of bromal hydrate by the subsequent action of small doses of atropine. (See Table LXV.)

This is a clear example of physiological antagonism; and it is one of the few in which an explanation can be offered. Death from the effects of a minimum fatal dose of bromal hydrate is due almost invariably to the accumulation of saliva in the mouth and mucus in the air-passages. This accumulation is frequently so excessive as to suffocate the animal and cause death by asphyxia. The convulsions which

usually occur immediately before death in cases of poisoning by bromal hydrate are due to asphyxia, or the action of venous blood on the nerve-centres. Atropine arrests this secretion, partly by diminishing the action of the salivary glands, and also by causing contraction of the blood-vessels in every part of the body. This contraction diminishes

TABLE LXIV.—*Showing the Minimum Fatal Dose of Bromal Hydrate for a Rabbit.*

No. of Experiment.	Weight of Rabbit.	Dose of Bromal Hydrate in grains.	Result.	Remarks.
580	3 lbs. 8 oz.	½	Recovery	No effect, except slight contraction of the pupil.
581	3 lbs. 10 oz.	¾	Recovery	Do. do.
582	3 lbs. 12 oz.	⅞	Recovery	Do. do.; slight lacrymation.
583	3 lbs. 9 oz.	1	Recovery	Do. do. do.
584	3 lbs. 10½ oz.	1¼	Recovery	Do. do. do.
585	3 lbs. 9 oz.	1½	Recovery	Do.; quickened respiration; salivation more profuse.
586	4 lbs.	1¾	Recovery	Distress; injected mucous membranes; profuse salivation; extreme contraction of pupil.
587	4 lbs. 1 oz.	2	Recovery	Do. do.
588	3 lbs. 12 oz.	2¼	Recovery	Do. do.
589	3 lbs. 11 oz.	2½	Recovery	Do. do.
590	3 lbs. 10½ oz.	2¾	Recovery	Do. do.
591	3 lbs. 11 oz.	3	Recovery	Nearly asphyxiated; ditto.
592	3 lbs. 9½ oz.	3¼	Death	Died from asphyxia, from accumulation of mucus in air-passages.
593	3 lbs. 10 oz.	3½	Recovery	After a long illness, recovered.
594	3 lbs. 11 oz.	3¾	Recovery	Do. do. do.
595	3 lbs. 11¼ oz.	4	Death	Died in 20 minutes.
596	3 lbs. 11 oz.	4	Death	Died in 19 minutes.
597	3 lbs. 9¾ oz.	4	Death	Died in 18½ minutes.

TABLE LXV.—*Showing the Results of varying Doses of Atropine when injected simultaneously with Fatal Doses of Bromal Hydrate.*

No. of Experiment.	Weight of Rabbit.	Dose of Atropine in grains.	Dose of Bromal Hydrate in grains.	Result.	Remarks.
598	3 lbs. 9¾ oz.	⅛	4	Death	Died in 20 minutes, with usual symptoms.
599	3 lbs. 10 oz.	1-6th	4	Death	Died in 22 minutes, ditto.
600	3 lbs. 9 oz.	¼	4	Death	Died in 17 minutes, ditto.
601	3 lbs. 8 oz.	⅜	4	Death	Died in 19 minutes; salivation much less; convulsed.
602	3 lbs. 7½ oz.	½	4	Death	Died in 37 minutes, from asphyxia.
603	3 lbs. 6 oz.	⅝	4	Death	Died in 40 minutes, ditto.
604	3 lbs. 9 oz.	5-6ths	4	Death	Died in 38 minutes, ditto.
605	3 lbs. 10 oz.	¾	4	Death	Died in 39 minutes, ditto.
606	3 lbs. 12 oz.	1	4	Recovery	In all of these cases, the excessive secretion was arrested by the atropine. The pupil was contracted in Ex. 606 & 607, but was of medium size in Ex. 608 and 609. Three days afterwards, all were killed in about 20 minutes by the same dose of bromal hydrate alone.
607	3 lbs. 14 oz.	1¼	4	Recovery	
608	3 lbs. 12 oz.	1½	4	Recovery	
609	3 lbs. 9½ oz.	1¾	4	Recovery	

the supply of blood to all the serous and mucous surfaces, and consequently there is less secretion from these surfaces. It is evident, therefore, that small doses of atropine favour recovery in cases of poisoning by bromal hydrate.

As it was manifestly a matter of considerable practical importance to ascertain how far non-fatal doses of bromal hydrate could influence fatal doses of atropine, ten experiments were performed with regard to this point. The chief results of these are detailed in the following table.

TABLE LXVI.—*Showing the Results of varying Doses of Bromal Hydrate when injected simultaneously with Fatal Doses of Atropine.*

No. of Experiment.	Weight of Rabbit.	Dose of Bromal Hydrate in grains.	Dose of Atropine in grains.	Result.	Remarks.
610	3 lbs. 14 oz.	½	3½	Death	Died in 18 minutes; usual phenomena following atropine.
611	3 lbs. 13½ oz.	¾	3½	Death	Died in 19 minutes; ditto.
612	3 lbs. 12 oz.	1	3½	Death	Died in 27 minutes; ditto; pupil not so widely dilated.
613	3 lbs. 11 oz.	1¼	4	Death	Died in 34 minutes; ditto.
614	3 lbs. 11½ oz.	1½	4	Death	Died in 33 minutes.
615	3 lbs. 12 oz.	1¾	4	Death	Died in 40 minutes.
616	3 lbs. 13 oz.	2	3¾	Death	Died in 37 minutes.
617	3 lbs. 9 oz.	2¼	3¾	Death	Died in 34 minutes.
618	3 lbs. 9¾ oz.	2½	3¾	Death	Died in 20 minutes.
619	3 lbs. 9½ oz.	3	3	Death	Died in 10 minutes.

These experiments were not encouraging, as all the animals died. They survived for a longer time when the doses of the drugs were in the proportions of from 1¼ to 2¼ grains of bromal hydrate to 3¾ or 4 grains of atropine. Beyond these limits, death occurred earlier. It would therefore appear that although, as seen from Table XLV, small doses of atropine may save life after fatal doses of bromal hydrate, the converse does not hold good; that is, life is not saved after fatal doses of atropine by the subsequent action of bromal hydrate.

GENERAL CONCLUSIONS.

THE general results obtained from the investigations detailed in the preceding report are the following.

I. *As to the Antagonism between Strychnia and Chloral Hydrate.*

In this investigation, one hundred and fourteen experiments were performed.

1. After a fatal dose of strychnia, life may be saved by bringing the animal under the influence of chloral hydrate.

2. Chloral hydrate is more likely to save life after a fatal dose of

strychnia, than strychnia is to save life after a fatal dose of chloral hydrate.

3. After a dose of strychnia has produced severe tetanic convulsions, these convulsions may be much reduced both in force and in frequency by the use of chloral hydrate, and consequently much suffering saved.

4. The extent of physiological antagonism between the two substances is so far limited, that (1) a very large fatal dose of strychnia may kill before the chloral hydrate has had time to act; or (2) the dose of chloral hydrate must be so large in such a case to antagonise the fatal dose of strychnia, that there is danger of death from the effects of the chloral hydrate.

5. Chloral hydrate mitigates the effects of a fatal dose of strychnia by depressing the excess of reflex activity excited by that substance; while strychnia may mitigate the effects of a fatal dose of chloral hydrate by rousing the activity of the spinal cord, but it does not appear to be capable of removing the coma produced by the action of chloral hydrate on the brain.

II. *As to the Antagonism between Sulphate of Atropia and Calabar Bean.*

In this investigation, one hundred and fourteen experiments were performed.

1. Sulphate of atropia antagonises to a slight extent the fatal action of extract of Calabar bean.

2. The area of antagonism is more limited than even Dr. Fraser has indicated in his paper on the subject.

III. *As to the Antagonism between Hydrate of Chloral and Calabar Bean.*

In this investigation, thirty-one experiments were performed.

1. Hydrate of chloral modifies to a great extent the action of a fatal dose of extract of Calabar bean, mitigating symptoms and prolonging life.

2. Hydrate of chloral in some cases saves life from a fatal dose of extract of Calabar bean.

3. If hydrate of chloral be given before extract of Calabar bean, so that the animal is deeply under the influence of hydrate of chloral before it receives the extract of Calabar bean, the symptoms produced by the latter are much modified, and life is saved from the effects of what would otherwise be a fatal dose.

4. Chloral hydrate is of little service as an antagonist to extract

of Calabar bean, if given some time after the latter. If the symptoms of the action of Calabar bean be in full operation, it will not save life, however it may modify symptoms.

5. The antagonism is limited—

a. By the amount of dose of the extract of Calabar bean—more than a minimum fatal dose of extract of Calabar bean destroying life, notwithstanding the administration of chloral hydrate.

b. By the interval of time between the administration of the two substances. There is a great probability of saving life in those instances in which the animal is under the influence of chloral hydrate before the subcutaneous injection of the extract of Calabar bean; there is less probability when both substances are given simultaneously; there is still less if the chloral hydrate be given from five to eight minutes after the extract of Calabar bean; and no chance at all if the chloral hydrate be given eight minutes after a fatal dose of extract of Calabar bean.

6. Even in cases in which a fatal result follows the action of the two substances, the physiological effects of extract of Calabar bean are considerably modified by those of hydrate of chloral.

IV. *As to the Antagonism between Hydrochlorate and Meconate of Morphia and Calabar Bean.*

In this investigation, forty experiments were performed.

Hydrochlorate and meconate of morphia in no way antagonise extract of Calabar bean.

V. *As to the Antagonism between Sulphate of Atropia and Meconate of Morphia.*

In this investigation, eighty-one experiments were performed on rabbits and dogs.

A. *In Rabbits:*

1. Sulphate of atropia is physiologically antagonistic to meconate of morphia within a limited area.

2. Meconate of morphia does not act beneficially after a large dose of sulphate of atropia, for in these cases the tendency to death is greater than if a larger dose of either substance had been given alone.

3. Meconate of morphia is not specifically antagonistic to the action of sulphate of atropia on the vaso-inhibitory nerves of the heart.

4. The beneficial action of sulphate of atropia in cases of poisoning by meconate of morphia is probably attributable to the action which the former substance possesses of contracting the blood-vessels, and thus diminishing the tendency to cerebral and spinal congestion produced by salts of morphia.

B. *In Dogs:*

Sulphate of atropia modifies the physiological action of meconate of morphia, and may even save life after a fatal dose of the latter. The limit, however, is so narrow as to be of no practical service.

VI. *As to the Antagonism between Tea, Coffee, Theine, Caffeine, and Guaranine, on the one hand, and Meconate of Morphia on the other.*

In this investigation, one hundred and seventeen experiments were performed.

1. Theine is antagonistic to meconate of morphia, inasmuch as the action of the one substance modifies that of the other, and may even save life from a fatal dose of either substance.

2. Meconate of morphia delayed the appearance of the convulsions characteristic of the action of theine; but, on the other hand, theine, if given in large doses, did not affect in a marked degree the action of meconate of morphia, because symptoms of poisoning by theine were soon manifested.

3. Further experiments on cats showed that, (*a*) while a cat may recover from the effects of a dose of 1¾ grains of meconate of morphia given alone, it will not recover from the effects of a dose of 2 grains, even although the effects of the latter dose are modified by those following the introduction of 4 or 5 grains of theine; (*b*) that in three cases the animals recovered from the effects of 1⅞ grains of meconate of morphia and 4 to 5 grains of theine, while they died when the same dose of meconate of morphia was administered eight days afterwards; (*c*) that, when the dose of theine was increased beyond five grains, the animals invariably died, apparently from the effects of theine.

4. Experiments on rabbits, as to the antagonism between meconate of morphia and theine, were found to be unsatisfactory as regards the purposes of this inquiry, because both drugs produce epileptiform convulsions in these animals.

5. The results obtained in investigating the action of caffeine and guaranine as antagonists to meconate of morphia were similar to those observed with reference to theine.

6. Experiments were made on dogs to ascertain the effects of strong infusions of tea and decoctions of coffee as antagonists to meconate of morphia. These were unsatisfactory, chiefly because the tea or coffee was usually vomited so soon as to prevent the possibility of the exercise of any physiological antagonism. At the same time, it was observed in several instances that the administration of tea or coffee so excited the animals as to prevent them from falling into stupor or coma after a dose

of meconate of morphia, which would have produced this effect had the tea or coffee not been given.

VII. *As to the Antagonism between Extract of Calabar Bean and Strychnine.*

In this investigation, thirty experiments were performed.

Although the symptoms produced by either substance were modified considerably by the action of the other, there was no instance of recovery from a fatal dose.

VIII. *As to the Antagonism between Bromal Hydrate and Atropia.*

In this investigation, thirty-six experiments were performed.

1. There is a distinct physiological antagonism between bromal hydrate and atropine.

2. After a fatal dose of bromal hydrate, the introduction of atropia arrests excessive secretion from the salivary glands and mucous surfaces of the lungs, and thus obviates the tendency to death from asphyxia caused by the accumulation of fluids in the air-passages. Atropia also causes contraction of the blood-vessels, and thus antagonises the action of bromal hydrate, which causes dilatation of these vessels by paralysis of the sympathetic nerve.

3. While atropia may save life after a fatal dose of bromal hydrate, the converse apparently does not hold good, as we have never succeeded in saving life after a fatal dose of atropia by the subsequent injection of bromal hydrate.

In concluding this report, I feel it to be necessary to allude especially to the labours of two members of the Committee—viz., first, Dr. Alexander Bennett, who completely worked out the physiological actions of cocaine, theine, caffeine, and their allied compounds; and, secondly, Dr. McKendrick, on whom the bulk of these researches ultimately devolved, and by whom the lengthened investigation on the antagonism between the sulphate of atropia and meconate of morphia was carried out. To him also we are indebted for the remarkable discovery of the antagonism between bromal hydrate and atropia. The long survey into which I have entered can convey no adequate idea of the many hours spent in laborious toil; of the skilful manipulation, sustained power of observation, judgment in inventing and comparing the results of experiments, and, I may add, patience under failures, which have characterised the efforts of these gentlemen. Even the account of the investigations themselves, with the tabulated results of the experiments, can give only a feeble conception of the laboratory

work accomplished. The preparation of the report and its careful revision was in itself a work demanding no small time and labour.

I venture, however, to say that such are the toils and sacrifices required by modern medicine, if it be sincerely desired to solve existing difficulties, and prosecute those new inquiries which are so necessary for maintaining its position as a science and as an art. I sincerely trust that no parsimony nor error in administration will restrain the British Medical Association from continuing the noble efforts it has commenced, and rewarding by liberal grants the arduous labours of men who will dedicate themselves to these pursuits. It is gratifying to know that the present and, it is to be hoped, the future flourishing state of its finances, will enable it to take a lead in this patronage of scientific and practical endeavour for the benefit of humanity. I shall always esteem it a proud distinction for myself that I first indicated at least one method in which this could be accomplished,* and have demonstrated, in the two reports I have had the honour of laying before the Association, on the one hand, how error may be corrected,† and, on the other, how new fields may be acquired for the therapeutist in neutralising poisons and extending our means for the cure of disease.

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* See Address in Medicine for the year 1866, delivered at Chester.

† *Researches into the Action of Mercury, Podophyllin, and Taraxacum on the Biliary Secretion;* being the Report of the Edinburgh Committee of the British Medical Association. Second edition. Edinburgh: Edmonston and Douglas, 8vo, 1874.