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Thesis
for the degree of M. D.
of the University of Edinburgh.
On the Physiological Antagonism
of Remedies.

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W B & C. M



1876

The introduction of certain Substances into the system has so long been known to exert such a baneful influence, that Medical Men were at an early period led to attempt the discovery of some means of counteracting this hurtful tendency; but not until Chemistry attained the dignity of a science was much done to lessen the injurious effects of those poisonous Substances.

As the science of Chemistry advanced, and the nature of chemical actions began to be understood, the list of antidotes was very much enlarged; those antidotes owe their virtue to the chemical change which they produce on the poisonous Substances when in the Stomach and alimentary canal.

As examples of this chemical action may be mentioned the use of Carbonate of Magnesia to neutralize the Mineral Acids; or Sulphate of Magnesia to render inert the soluble salts of Baryta, or a solution of common salt in poisoning

by Nitrate of Silver. But as soon as the poison is absorbed into the blood chemical action seems to have no power, and for a long time was felt the want of some counteracting agent that could act after the introduction of the poisonous substance into the system.

Our increased knowledge of the functions of the organism has led to the discovery that some substances modify them in a constant manner, and that other substances act in exactly a contrary direction; and this again has led to the discovery of the physiological antagonism of medicines, or, in other words, that power by which the dangerous properties of one drug may be utilized to antagonize the poisonous properties of another.

This antagonism is very different from chemical action, and owes its influence to the physiological action of one drug so modifying the functions of certain structures, as to prevent changes produced by another drug as would eventually result in death.

The subject is an interesting one and well worthy of investigation, and although much has been

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done to elucidate it, there is still great scope for further research.

Before giving the results of my own investigations into the subject a short account of what has already been done will not be out of place. -

Between Opium and Belladonna

Long before the physiological antagonism had been discovered, in fact so early as the middle of the seventeenth century, the effects of a large dose of Belladonna juice were apparently relieved by the influence of Opium; and from that time many instances have been given where Opium has been administered to remove the poisonous effects of Belladonna, Hyocyamus and Stramonium and vice versa.

The Edinburgh Committee, appointed by the British Medical Association for the purpose of investigating the subject, in their admirable report, give experiments which clearly show that Sulphate of Atropia is antagonistic to Meconate of Morphia within a limited area.

But Meconate of Morphia does not act beneficially

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after a large dose of Sulphate of Atropia, for in those cases the tendency to death is greater than if a larger dose of either substance had been given alone. Dr. Johnson, in a report (published in 1878) of the Chinese Hospital at Shanghai, speaks in raptures of the value of subcutaneous injection of Atropine in Opium-poisoning. Many of the most desperate cases, nearly all suicidal, recovered under this treatment.

Between Strychnia and Chloral Hydrate.

From the experiments of the Edinburgh Committee it is clear that in Rabbits Chloral Hydrate will save life after a fatal dose of Strychnia, and is more likely to save life than Strychnia is after a fatal dose of Hydrate of Chloral.

But the antagonism is limited, for a very large dose of Strychnia may kill before the Chloral has had time to act, or in such a case the dose of Chloral Hydrate may be so large in order to antagonize the effects of the Strychnia as to be fatal of itself.

Chloral Hydrate acts by depressing the excess of

reflex activity excited by the Strychnia, while Strychnia acts after a fatal dose of Hydrate of Chloral by rousing the spinal cord to activity, but seems incapable of removing the coma produced by the action of Chloral Hydrate on the brain.

Between Calabar Bean & Chloral Hydrate

Chloral Hydrate in some cases saves life after a fatal dose of Calabar bean, but the antagonism is limited, as more than a minimum-fatal dose of C. Beans destroys life, notwithstanding the administration of Chloral Hydrate.

There is great likelihood of saving life if the Chloral Hydrate is given first, less when the two are given simultaneously, still less if the Chloral is not given for five or eight minutes after the C. Beans, and no chance at all if the Chloral is not given for eight minutes afterwards.

(From the Report of the Edinburgh Committee)

Between Bromal Hydrate & Atropia

The antagonism is distinct. The Atropia arrests

the excessive secretion of the Salivary glands, and mucous surfaces of the lungs; and this obviates the tendency to death by asphyxia caused by the accumulation of fluids in the air passages, and also contracts the blood vessels, thus counteracting the action of Bromal Hydrate, which causes dilatation by paralysis of the sympathetic.

Bromal Hydrate does not save life after a fatal dose of Atropia. (From Report of Edinburgh Committee)

The Committee also investigated the supposed antagonism between Morphia & C. Bean, and between C. Bean and Strychnia, and between Meconate of Morphia and Theine, Caffeine &c.

Between the two former there was no antagonism whatever. In the experiments with C. Bean and Strychnia symptoms were modified, but there was no instance of recovery after a fatal dose.

Theine sometimes saves life after a fatal dose of Meconate of Morphia and vice versa, but the antagonism is limited.

Between Atropia and Calabar Bean

Dr. Thomas M. Fraser of Edinburgh has made this subject an especial study, and in a paper read before the Royal Society of that City on May 29th 1871, has clearly demonstrated the antagonism that exists between Atropia and Physostigma.

His experiments were conducted generally on rabbits, occasionally on dogs.

The preparations of Physostigma used in the research were the Sulphate and Extract of the active principle. The Atropia was administered in the form of Sulphate. Having first ascertained the minimum-fatal dose of the Sulphate of Atropia to be 21 grains per three pounds weight of animal (Rabbit). — of Extract of Physostigma to be 1-2 grain per three pounds weight — and of Sulphate of Physostigma to be 0.12 grain per three pounds weight, he proceeded to determine the influence of Atropia on the fatal action of Physostigma.

Out of a number of experiments performed by him I shall extract two.

a. A Rabbit weighing 3^{lbs} 2^{oz} received 2.5 grains of Extract of Physostigma, and five minutes afterwards

0.5 grain Sulphate of Atropia - Recovery took place, but the same animal died, eleven days afterwards, in eleven minutes and a half, after receiving 2.5 grains of Extract of Physostigma.

6. A rabbit, weighing 3^{lb} 8^{oz} received 0.17 grain of Sulphate of Physostigma, and twenty nine minutes afterwards, 0.5 grain of Sulphate of Atropia.

Recovery took place, but in eight days afterwards, the same rabbit, now weighing 3^{lb} 5^{3/4} oz, died in twenty four minutes, after receiving 0.13 grain of Sulphate of Physostigma.

Similar experiments were performed on dogs with a like result, thus clearly demonstrating that Atropia is able to counteract the fatal action of Physostigma.

But Dr. Fraser, judging from the fact that both these substances each possess numerous actions, anticipated that several of these are not mutually antagonistic, and, "that above certain doses, a region may, therefore, be reached where the non-antagonized actions are present in sufficient degree to be themselves able to produce fatal results."

And he argued that "as certain of the actions of the two substances are of a similar nature, when a dose not much above the minimum fatal of the one is counteracted by a small dose of the other, the similar actions are not produced in sufficient intensity, to become, even when combined, important poisonous actions". When, however, a dose considerably above the minimum fatal of the one is given with a large dose of the other, the similar actions may be produced in such intensity as to assume the importance of fatal actions. To determine the exact limits of the counteracting influence of Atropia upon the fatal action of Physostigma Dr. Fraser instituted three series of experiments - the first two to determine the largest dose of Physostigma that can be counteracted by Atropia, and the range of doses of Atropia that can counteract the fatal dose of Physostigma; in the first the Atropia being given five minutes before the Physostigma, in the second the Physostigma five minutes before the Atropia. The third series to determine what limit of time could elapse between the administration of the two poisons to have the proper counteracting effect.

I. Atropia administered five minutes before the Physostigma.

With Minimum fatal dose of Physostigma — while two one hundredths of a grain ~~was~~^{were} insufficient to prevent death, nine one thousandths of a grain, or any dose between that and five grains and one fifth was quite large enough to do so, but if the dose of Sulphate of Atropia be five grains and three tenths, successful antagonism does not occur and death ensues.

Similar experiments were made with one and a half, two, three, and three and a half times the minimum fatal dose of Physostigma with a range of successful antagonism as before, but the range of the last being limited to $\frac{1}{10}$ to $\frac{1}{5}$ of a grain.

But a larger dose of Physostigma than three and a half times the minimum fatal was not able to be counteracted by any dose of Atropia.

II. Atropia administered five minutes after the Physostigma.

With minimum fatal dose of Physostigma - three $\frac{2}{100}$ th of a grain ~~was~~^{was} insufficient, and successful antagonism ranged between $\frac{1}{50}$ of a grain and $2\frac{1}{2}$ grains. Death occurred with a larger dose.

Similar experiments were made with one & a half, two, two and a half, and three times the minimum fatal dose of Physostigma, there being a range of successful antagonism as before, with a range of doses of Atropia able to prevent death diminishing as the dose of Physostigma was increased. Any dose of Atropia was not able to counteract the Physostigma when the dose of the latter was more than three times the minimum fatal.

III Determination of the influence of time between the administration of the two substances, the dose of Physostigma being constant, is $1\frac{1}{2}$ times the minimum fatal. -

a Sulphate of Atropia and Physostigma given Simultaneously	($\frac{1}{50}$ of a grain - insufficient $\frac{1}{20}$ to $2\frac{3}{10}$ - Successful antagonism $3\frac{1}{2}$ or more - Death
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C Sulphate of Atropia Fine { $\frac{3}{100}$ th of a grain - insufficient
 Minutes after Physostigma { $\frac{1}{20}$ to $\frac{2}{3}$ - Successful antagonism
 $\frac{2}{3}$ - death. -

Similar experiments were made up to fifteen minutes, when any dose between $\frac{3}{100}$ th and one grain prevented death. Beyond this Successful antagonism cannot be effected. -

C Atropia before Physostigma - Various experiments were performed, but I shall only give the result when fine grains of Sulphate of Atropia were ~~were~~ administered before $\frac{1}{2}$ times the minimum fatal dose of Physostigma Sulphate.

Death occurred if the interval of time was 15 to 20 minutes; recovery generally took place if given between 25 to 175 minutes. Death again occurred if the interval of time was so great as 180 minutes.

Between Picrotoxicine and Chloral Hydrate
 Dr. J. Crichton Browne has published in the British Medical Journal of March & April 1875 some very interesting experiments with

the above named substances.

Those experiments clearly demonstrate that in rabbits Hydrate of Chloral is physiologically antagonistic to, and will, in a suitable dose, prevent the effects of, a fatal dose of Picrotoxine.

But the dose of Picrotoxine may be so large as to prove fatal before the Chloral has time to act, or so large that nothing but a poisonous dose of Chloral would be of any avail.

When the minimum fatal dose of Picrotoxine - $\frac{1}{20}$ of a grain - with 10-12 grains of Chloral Hydrate, the Rabbit perfectly recovered after a disturbed sleep of two or three hours duration, instead of dying in about an hour and a half after violent convulsions, but died from the same dose of Picrotoxine a week afterwards.

When $\frac{1}{15}$ of a grain of Picrotoxine was administered with 12-15 grains of Chloral Hydrate, recovery took place after a prolonged sleep, there being only slight restlessness and trifling twitchings.

When $\frac{1}{8}$ of a grain of Picrotoxine was administered with 12 grains of Hydrate of Chloral, satisfactory

recovery took place, but after symptoms which revealed the struggle by the two opposing agents for the possession of the nervous system. This experiment was so interesting that I shall give the particulars of it. Drugs administered at 3.30 P.M. - in ten minutes the rabbit was drowsy, head nodding and breathing very rapid, in eighteen minutes it was lively and able to move about, but in twenty four minutes it was very feeble and swayed visibly when attempting to walk.

In twenty five minutes there were shakings of the head and twitchings of the ears which lasted just ten seconds.

Immediately the movements stopped the animal became very drowsy, nodding frequently, and then let its head fall flaccid on one side.

In twenty eight minutes, sleep having lasted for three minutes, there were a sharp and sudden awakening, and then drawing back of the head and rapid twitchings of the ears & mouth, continuing eight seconds, and again merging into sleep.

There were alternate sleeps and seizures up to forty four minutes when there was a slight attack of clonic spasms, limited to the head, and accompanied by a free flow of saliva from the mouth.

After this no twitchings occurred, but the rabbit fell into a deep sleep which lasted an hour and a half, and then it awoke and began to scramble about.

It was feeble and stupid for three hours more and was not altogether well until next morning.

From this experiment it will be seen that the Hydrate of Chloral, by diminishing the activity of the brain, mitigates the actions of the Picrotoxine which stimulates that organ to excessive discharges of energy.

In fact the Chloral acts by keeping the animal in a drowsy condition until the force of the Picrotoxine has expended itself.

Picrotoxine is only to a very limited extent antagonistic to chloral, however, it does

Secure recovery in some instances, and, when powerless to save life, visibly controls symptoms, rousing the nervous centres from time to time from the torpor caused by Chloral Hydrate, causing intervals of semi-wakefulness in which there are various spontaneous movements.

Picrotoxyne also diminishes the hyperaesthesia which Chloral Hydrate sets up, and somewhat prevents the gradual production of slowness of respiration and fall of temperature always caused by Chloral.

Practically Picrotoxyne and Chloral Hydrate have no antagonistic action in the cat, as they cause death by stopping the action of the heart.

Between Strychnia & Monobromide of Camphor
Dr. Valenti has made researches on the antagonism of the two substances above named, the result of which will be found in the London Medical Record of June 16th 1875.

He found that twelve dogs, after taking a

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Total dose of Strychnia were saved by the use of Bromide of Camphor, the tetanic convulsions being quickly reduced.

The Antagonism is limited and a large dose of the Bromide is required.

Between Belladonna & Jaborandi.

A record of two cases of Belladonna poisoning treated with Jaborandi will be found in the Lancet of March 4th 1876, which clearly shows that an antagonism exists between these two substances.

Such an antagonism was suspected to exist from the fact that in a healthy person Jaborandi causes contraction of the pupil, and profuse perspiration and salivation; whereas after a poisonous dose of Belladonna the skin is dry and hot, pupil dilated, throat and mouth parched.

When under the influence of Belladonna, even poisonous doses of pilocarpine, the active principle of Jaborandi, could not produce

its ordinary physiological effect.
 But in the same patient, after the elimination
 of the Belladonna, Iaborandi was found to
 act in its usual way.

I cannot close this historical part of the subject
 without noticing the experiments of Dr. J. Milner
 Fothergill, which will be found in ~~the~~ his
 practical little work "Digitalis - its mode of
 action, and its use".

Dr. Fothergill, having firmly secured a frog
 to a piece of lath by a bandage, leaving
 the chest exposed, opened the chest with a
 pair of scissors.

The heart was easily seen and readily cleared
 of its pericardium.

Digitalis, having been administered by the mouth
 or hypodermically, the contractions became quicker
 and more complete; soon the distension became
 less complete, especially at the apex which
 remained white and firmly contracted.

The action of the Ventricle then became very

Slow, the diastole being most imperfect, and by and bye the ventricle came to a ~~firm~~ stand-still in firm contraction, the heart being much diminished in size.

To another frog was given Aconite which produced paralysis and arrest of the heart in diastole. The experiment was then varied, and after the action of each drug was well established, the other was administered, the result of which I cannot do better than give in Dr. Ferguson's own words.

He says - "On the action of Digitalis, Aconite certainly had an influence, but it could scarcely be called a marked one, and did not ultimately arrest the contraction produced, even when pushed.

On the contrary, the administration of Digitalis was followed by the most marked results, when Aconite had been given, and the ventricle had become gradually more and more distended, and its contraction more and more imperfect, until a condition of advanced dilatation had been artificially produced, and even when

the heart seemed to have given up all action, and remained in diastole, distended with blood and inert.

When all action had apparently ceased, the first effect was to produce an imperfect contraction at long intervals, then the intervals became shorter and the contractions more complete, some irregularity both as to time and amount of contraction being observed.

Slowly and gradually, however, the distended ventricle recovered itself under the action of digitalis, the contractions being more rhythmical and perfect, and the distension less & less pronounced, until a return to normal contraction and distension was brought about.

If the administration of digitalis were then continued, the same appearances were brought out as when no Aconite had been previously given.

These experiments of Dr. Fothergill, though repeated several times, were merely performed on cold-blooded animals, and their only practical value seemed

to be to illustrate more clearly the action of Digitalis.

An illustration of the utility of this antagonism was recently furnished by a case of Acute poisoning which occurred under the administration of Digitalis.

This case occurred in the practice of Mr. Wm. Dolie, Surgeon, Keighly,

Yorkshire, and is to be found in the British Medical Journal for Dec 21/72

A veterinary Surgeon of that town came home one morning early very much

the worse for drink, walked into his surgery & took a bottle of medicine and

went to bed. He shortly afterwards rang the bell & informed his landlady

that he had swallowed a bottle of poison which would soon prove fatal.

She sent for Mr. Dolie, who, on his arrival, found a two ounce bottle with label

defaced, it contained about half a drachm of brownish liquid which caused

tingling of the tongue, and this satisfied him that it was acetic.

Up to this time (a few minutes) there were no symptoms whatever of poisoning.

He was ordered an emetic & in half an hour vomited freely, but soon the circulation began

to fail, pulse rapid & feeble, hands & feet cold, breathing laboured, the pulse at the

wrist soon became irregular, intermittent & then imperceptible, skin dusky with

clammy sweat, or in fact he was dying. Twenty minims of T. of Digitalis were injected,

and galvanism applied to cardiac region for about 20 minutes, by which time he

began to rally, & then took a mixture of ammonia, brandy & one drachm T. of Digitalis.

This was repeated twice within an hour and he rapidly recovered; he had

swallowed an ounce of Fleming's T. of acetic.

The result of this case was such as to make the further investigation of such antagonism desirable, and it appeared to me that the experiments, hitherto performed on cold-blooded animals, might be repeated with advantage on warm blooded animals.

not only with Digitalis and Aconite, but with other drugs which have an antagonistic action on the circulation.

Accordingly, experiments have been performed to test, in warm blooded animals, the antagonism between

- (1) Digitalis and Aconite
- (2) Atropia and Hydrate of Chloral.
- (3) Atropia and Aconite.

The result of these experiments will be given as we proceed.

Rabbits were the animals used in the research. Before proceeding to give the result of the experiments it will be as well to say a few words about the action of the different drugs employed in the research.

Digitalis belongs to that class of medicines which increase the force of the ventricular contractions, and raise the arterial tension or blood pressure. Its action upon the frog has been noticed in the experiments of Dr. Fothergill.

Minnows die when placed in an infusion of Digitalis; after death the ventricle is firmly contracted and

glutens like a piece of gristle; the auricle being dilated from trying to drive the blood into the tightly contracted ventricle.

On opening birds which have died from the effects of Digitalis the left ventricle will be found to be firmly contracted, the lungs so congested as to be almost hepatised, the right ventricle full of blood.

These experiments were performed by Dr. F. Stupp, and Handfield Jones and Fuller have made similar ~~and~~ experiments on Mammals, with the same effects on the heart after death.

The application of infusion of digitalis to a frog's foot produces contractions of the vessels of the web.

Sulphate of Atropia belongs to the same class of remedies as Digitalis, and in a moderate dose increases the force of the ventricular contractions and raises the blood pressure and quickens the pulse; but Dr. Lauder Brunton has found by experiment that a very large dose lowers the blood pressure in both rabbits and dogs, but quickens the pulse except in those cases where a large quantity of the poison is introduced at once into the heart of the rabbit.

Aconite, on the other hand, belongs to the opposite class of remedies, or to the depressants of the circulation. In ordinary catarrhal fevers, we have the cutaneous vessels contracted and consequent hyperemia of the internal parts; and this results in increased heat production in the interior, and imperfect radiation of the heat by the vessels of the dry burning skin.

For such a condition we do not possess a more efficient agent than Aconite; it lowers the heart's action, and lowers the blood pressure, dilating the peripheral vessels, especially of the skin; a freer stream of blood flows through the skin, the heat is radiated off, and a normal temperature is gained.

Hydrate of Chloral is a depressant of the temperature. It also lowers the action of the heart, but its most marked action is upon the cutaneous vessels.

Probably by the dilatation of the vessels at the surface are the blood pressure and temperature lowered. -

Contrasting the action of those different drugs, one was led to expect an antagonism between Digitalis and Atropine on the one hand, and Aconite and Hydrate of Chloral on the other.

The experiments of Dr. Fraser with Atropia & Physostigma, given in a former part of this paper, further impressed me with the idea that an antagonism might exist between Atropia and Aconite, as Calabar Beans has an action so very similar to Aconite.

Dr. Fraser found that the bean dilated the peripheral vessels, and depressed the action of the heart in a very marked degree.

Preparations used in the research - Digitalis and Aconite were given in the form of solutions of the active principles - Atropia was administered in the form of Sulphate. The Hydrate of Chloral was dissolved in water.

All were administered by subcutaneous injection.

The first object obviously to be attained was to ascertain the minimum - fatal dose of the drugs to be employed, and then to see the action of the antidote proposed.

Great care was taken in administering the different doses, and the notes of each ~~case~~ experiment were taken at the time. Crucial experiments were in all cases performed in seven days.

I. Digitalis & Aconite

Table showing the Minimum - fatal dose
of Aconitin.

no of Experiment.	Weight of Rabbit.	Dose of Aconitin.	Result.
1	4 ^{lb} 7 ^{oz}	1/400 grain	Recovery
2	3 5	"	"
3	2 14	"	"
4	1 11	"	Death 1 hour
5	1 10 1/2	1/300	" 2 1/2 hours
6	1 2 1/2	"	" 1 1/2 "
7	1 9	1/350	Recovery
8	1 8	1/400	Death 1 hour
9	1 8	"	" 5 hours
10	1 8	1/500	" "
11	3 1	1/255	" "
12	3 1	1/200	" 1 hour
13	1 8	1/600	Recovery
14	1 8	"	"
15	1 8	1/500	Death 1 1/4 hr
16	3 2	1/200	Recovery
17	3 0	"	Death 1 hour

From the table above it will be seen that the minimum fatal dose of Aconitin for a rabbit weighing three pounds is the three hundredth part of a grain, while the five hundredth part of a grain is required to kill one weighing one pound and a half. In two cases where the rabbits weighed each one pound and a half the six hundredth of a grain was insufficient to prove fatal. This is rather interesting and proves that as the animal gets smaller the dose of Aconitin must be slightly increased in proportion. It is rather strange that in Experiment seven a rabbit weighing one pound, eight ounces recovered after receiving $\frac{1}{500}$ of a grain of Aconitin; in this case, however, the poison had a very powerful effect, the animal lying on its side as if dead, but ultimately recovering.

It is worth contrasting these results with the experiments of Buckle, who states that $\frac{1}{60}$ of a grain of German Aconitin is required to kill a rabbit of 3^{lbs} weight.

Table showing the Minimum fatal dose of Digitaline

No. of Experiment.	Weight of Rabbit.	Dose	Result.
18	3 ^{lbs} 4 ^{oz} .	$\frac{1}{15}$ grain	Recovery
19	2 . 14	$\frac{1}{15}$	"
20	2 . 14	$\frac{2}{15}$	"
21	2 . 12	1 grain	"
22	2 . 7	$\frac{1}{2}$ grain	"
23	2 . 6	2 grains	"

In all the above experiments the only action brought about by the Digitaline was slight lowering of the frequency of the pulse, and increase, in a small degree, of the impulse of the heart against the walls of the chest. There were no marked symptoms of any kind.

The preparation, although obtained from Moctore and Son - London was ^{evidently} not good.

Another preparation was obtained from Messrs T and H. Smith, and in all future experiments the Digitaline used was from that well known firm.

Table showing the Minimum - fatal dose of
 Digitaline prepared by Messrs T. & H. Smith.

No. of Experiment.	Weight of Animal.	Dose.	Result.
24	1 ^{lb} 11 ^{oz}	1/10 gr.	Recovery
25	1 . 11	2/10	"
26	1 . 9	3/10	"
27	2 .	4/10	"
28	2 . 7	5/10	"
29	2 . 2	6/10	"
30	2 . 6	8/10	"
31	3 . 4	1 grain	"
32	3 .	"	"
33	1 . 7	6/10	"
34	2 . 14	1 1/10	"
35	1 . 8	7/10	"
36	1 . 12	1 grain	"
37	2	"	"
38	2	1 2/10	"
39	3 . 1	1 8/10	"
40	2 . 2	2 gr.	Death 2 hours
41	2	1 4/10	" 47 "

No. of Experiment	Weight of Animal	Dose	Result
43	1 ¹ / ₄ 8 ³ / ₄	1 ³ / ₁₀ grs	Death 3 hours.
44	2. 15.	2 grains	" 72 "
45	2. 1	1 ⁴ / ₁₀	" 52 "
46	1. 13	1 ³ / ₁₀	" 57 "

By a reference to the above table it will be seen that the Minimum fatal dose of Digitaline prepared by Messrs T. and H. Smith was one grain and four tenths of a grain for a rabbit weighing about two pounds. -

From the doses above it appeared as if this preparation was not much better than that obtained from Morson and Son, but such were the results obtained. It will be seen that when the dose is no more than the minimum-fatal, a very long time elapses before the death of the animal; and is quite a contrast to the time a rabbit takes to die after receiving a fatal dose of Aconitine.

Table showing the effect of Digitaline on fatal doses of Aconitin - drugs given simultaneously

No. of Experiments	Weight of Rabbit	Dose of Digitaline	Dose of Aconitin	Result
47	2 ^{lbs} 3 ^{oz}	4/10	1/200 gr.	Death in 30 Minutes
48	2. 4.	7/10	1/200 gr.	" " 60 "
49	2. 12	1 grain	1/200 gr.	" " 11 hours.

It seemed of little use going on with this series of experiments, as the poisonous effects of the Aconitin were developed too quickly to allow much counteracting influence on the part of the Digitaline.

In the experiments performed to find out the minimum - fatal dose of Digitaline, it was found that some hours elapsed before the influence of the poison was much felt; and in Aconite poisoning the respiration becomes so speedily affected, it appeared as if the Digitaline would have more chance of protecting rabbits from the poisonous effects of Aconitin if given some hours previously. The results will be seen in the following table.

Table showing the effect of Digitaline given at various intervals of time before Aconitine

No. of Experiments	Weight of Rabbit	Dose of Digitaline	Interval of time	Dose of Aconitine	Result	Critical Experiment
50	2 ^{lb} 14 ^{oz}	1 ⁴ / ₁₀ gr	9 hours	1 ³ / ₁₀₀	Recovery	Death in 30 Minutes
51	1. 8	7 ¹ / ₁₀	"	1 ⁵ / ₁₀₀	"	" 1 ¹ / ₂ hours
52	2	1 gr.	7 ¹ / ₂ hrs	1 ³⁵ / ₁₀₀	"	" 4 ¹ / ₂ "
53	1. 12	"	"	1 ⁴ / ₁₀₀	"	" 1 hour
54	2.	1 ² / ₁₀	5 ¹ / ₂ hrs	1 ³ / ₁₀₀	Death 10 hrs	
55	3. 1	1 ⁸ / ₁₀	"	1 ² / ₁₀₀	Recovery	Death 1 hour.
56	2. 7	7 ¹ / ₁₀	"	1 ³ / ₁₀₀	Death 1 hour	
57	2. 7	4 ¹ / ₁₀	"	1 ³ / ₁₀₀	" 1 ¹ / ₂ hrs	

From the table above it will be seen that Digitaline, when given some hours previously, ~~has~~ has the power of protecting rabbits from fatal doses of Aconitine.

Out of eight rabbits experimented on five recovered. In the cases where death occurred, the Digitaline was administered only five hours previously.

From this it appeared that the Digitaline had

a better chance of protecting if given a few more hours beforehand, or between seven and nine hours, as in the first four experiments.

However, in one case where the Digitaline was given only five hours before the Aconitin, the rabbit recovered, notwithstanding the large dose of the latter poison - viz - the two hundredth part of a grain to a rabbit weighing about three pounds.

The crucial experiments were very satisfactory, as the five rabbits in which recovery had formerly taken place, died from exactly the same dose of Aconitin, a week having elapsed, and all the animals being healthy and quite recovered from the effects of the first experiments. These facts, however, are not of much practical value, as the antidote requires to be given first; but Digitalis seems to have a more beneficial effect in Aconite poisoning in the human species, as evidenced by Mr. Dobie's Case at Yorkshire.

Table showing the effects of Aconitin on fatal doses of Digitaline.

No. of Experiment	Weight of Rabbit	Dose of Digitaline	Interval of time	Dose of Aconitin	Result
58	2 ^{lb} . 42	18/10	5 Minutes	1/500	Death 1 1/4 hours
59	"	"	1 hour	1/600	" 2 "
60	"	15/10	1 1/2 h's	1/500	" 2 1/2 "
61	2. 1	"	5 Minutes	1/700	" 1 1/4 "
62	1. 12	14/10	1 hour	"	" 1 1/2 "
63	2.	"	25 1/2 h's	"	" 28 "
64	1. 9	12/10	1 hour	"	" 1 1/2 "

After Digitaline

From the above table it will be seen that Aconitin has not the power of saving rabbits after fatal doses of Digitaline.

Out of seven rabbits experimented on, all died.

However, it must be mentioned, that the preparations of Digitaline used in this series of experiments, although manufactured by Messrs. T. & H. Smith, was proved afterwards to be a much better one than ^{that} used to find out the minimum-fatal dose, one rabbit weighing one pound

and twelve ounces dying in two hours from one grain and four tenths of a grain; another weighing one pound and nine ounces dying in one hour from one grain & one tenth of a grain. So that the rabbits used in these experiments received more than the minimum - fatal dose of digitaline, but how much more, time did not permit me to ascertain.

This shows what an unsatisfactory preparation digitaline is, and how a first rate firm can send out the same drug of such varying strength. All the previous attempts to ascertain the minimum - fatal dose of digitaline were thus upset, and as this paper required to be given in by a certain date, it was out of my power to renew the experiments with the stronger preparation of the drug.

II Atropia and Chloral Hydrate.

Table showing the Minimum fatal dose of Chloral Hydrate.

No. of Experiment	Weight of Rabbit	Actual dose of Chloral	Grains per Pound	Result
65	3 ^{lbs} 29	22 ³ / ₄ grains	7	Recovery
66	2. 3	21 ³ / ₄	10	Death in 5 ¹ / ₂ hours
67	2. 2	25 ¹ / ₂	12	Recovery
68	2	20	10	Death in 14 hours
69	4	40	10	" " 7 "
70	2. 11	18 ² / ₁₆	7	Recovery
71	3. 4	32 ¹ / ₂	10	"
72	4 7.	44 ³ / ₈	10	"

In the experiments of the Edinburgh Committee the Minimum-fatal dose of Hydrate of Chloral was found to be seven grains per pound weight of animal, while Dr. Crichton Browne, as the result of his experiments, could not estimate it at less than twelve grains per pound weight.

Such a difference existed between the results of those two sets of experiments, that it was

thought advisable to experiment a little further, the result of which will be seen in the table above. Seven grains per pound was found insufficient to kill in two cases.

Out of five rabbits experimented on with ten grains per pound, death occurred in three, and recovery took place in two cases, while one rabbit recovered from a dose equal to twelve grains to the pound.

From this it will be seen that an approximate result could only be attained, but in later experiments crucial tests will always be performed to make sure that a dose sufficient to kill had been given in the first instance.

In estimating the fatal dose of Chloral Hydrate, it must be kept in mind, that, owing to the dilatation of the cutaneous vessels, a much smaller dose will kill if the rabbit is in any way exposed to cold.

Dr. Lander Brunton has made some very interesting experiments as to the action of Chloral.

After large doses, he found the temperature fall so low that it could no longer be measured

by ordinary clinical thermometers.

After finding out the dose that would kill an animal when exposed to the air, he gave this quantity to two similar animals, wrapping up one in cotton wool. The one so wrapped up survived, while the other died.

Then he found out the dose that was fatal after wrapping up in cotton wool, and gave that to similar animals, one being wrapped up in wool and the other put into a warm chamber.

The one in wool died; the other recovered.

A still larger dose was fatal to the one in the warm chamber. -

It may be as well to mention that the experiments above were performed in a moderately warm room, the rabbits being laid before a small fire as soon as the Chloral had taken its effect. -

Minimum - fatal dose of Sulphate of Atropia.

Advantage was taken of the experiments of the Edinburgh Committee, and of Dr. Fraser, who found the minimum - fatal dose to be twenty one grains per 3rd weight.

Table showing the effect of Sulphate of Atropia on fatal doses of Chloral Hydrate drugs given simultaneously

No. of Experiment	Weight of Rabbit	Actual dose of Chloral	Dose of Chloral per pound	Dose of Atropia	Result	Crucial Experiment
73	3 ⁴ 121	45 grs	12 grs	6 grs	Survived 3 days	
74	3. 6	40 1/2	"	4	Death in 1 hour	
75	2. 11	32 1/4	"	5	" 1 1/2 hrs	
76	4. 3	50 1/4	"	8	Recovery	Recovery
77	3. 14	47 3/4	"	7	Death 12 hours	
78	3. 12	41 1/4	11	3	" 3 days	
79	1. 8 1/2	18 3/8	12	8	" 7 hours	
80	1. 8	18	"	"	" 4 hours	

By referring to the table above it will be seen that small doses of Sulphate of Atropia have not, as was expected, the power of saving life after fatal doses of Chloral. Out of eight rabbits experimented on two survived for three days, but that was probably owing to the dose of Chloral being scarcely large enough. One recovered, but in the crucial experiment the same dose did not prove fatal.

Table showing the effect of Chloral Hydrate
on fatal doses of Sulphate of Atropia
drugs administered simultaneously.

No. of Experiment	Weight of Rabbit	Dose of Atropia	Dose of Chloral	Result	Critical experiment
73	1 ^{lb} 9 ^{oz}	12 gr	8 gr	Death in 20 minutes	Recovery.
74	2. 7.	18	12	Recovery	
75	1. 9	12	10	Death in 2 hours	
76	1. 9	"	10	" 5 "	
77	1. 11	"	6	" 1 1/2	
78	1. 10 1/2	"	3	" 1 hour	

By a reference to the table above it will be seen that Chloral Hydrate has not the power of saving life when administered with fatal doses of Sulphate of Atropia. Out of six rabbits experimented on only one recovered, and that ~~dead~~ ^{recovered} in the critical experiment, which shows that it had not got a fatal dose in the first instance.

This result was scarcely to be wondered at, as Dr. Lauder Brunton found, as was mentioned

in a former part of this paper, that large doses of Sulphate of Atropia lowered the blood-pressure, the opposite effect of small doses, which raise the blood-pressure.

One curious result was observed in this series of experiments. All the rabbits appeared to die from Chloral poisoning; in a few minutes after the administration of the drugs they were in a perfectly comatose condition; there were no twitchings or startings as is always the case in poisoning by Sulphate of Atropia.

In fact, the Sulphate of Atropia seemed to have the effect of assisting the action of the Chloral, and of making the rabbits die from very small doses of the latter drug. -

III. Atropia and Aconitin

Table showing the actions of various doses of Sulphate of Atropia on fatal doses of Aconitin, the Atropia given always first, but at different intervals of time before the Aconitin.

No. of Experiment	Dose of Atropia	Interval	Dose of Aconitin	Weight of Rabbit	Results	Critical Experiment
79	1 gr	1 min	$\frac{1}{500}$	1 $\frac{1}{2}$ 7 $\frac{1}{2}$	Recovery	Recovery
80	4 gr	"	$\frac{1}{450}$	2. 7	Death	
81	4	5'	$\frac{1}{300}$	2. 7	Recovery	Death in 90 minutes
82	4	10	"	1. 8	"	" 30 "
83	3	6	$\frac{1}{200}$	2. 6	"	" 2 $\frac{1}{2}$ hours
84	3	5'	$\frac{1}{300}$	1. 7	Death 5 h's	
85	2	8	$\frac{1}{500}$	1. 8	Recovery	Death in 1 hour
86	2	10	"	1. 3 $\frac{1}{2}$	"	" 40 minutes

By a reference to this table it will be seen that small doses of Sulphate of Atropia have the power of protecting rabbits from the effects of fatal doses of Aconitin.

Out of eight rabbits experimented on six recovered, ~~from~~ and in one of those the dose of Aconitin was twice the Minimum-Jabal.

Two only of the eight died viz. numbers 80 and 84. In number 80 the rabbit survived for two hours, and was then put into an outhouse, as the lateness of the hour rendered the further watching of it undesirable. All the other rabbits were kept in a warm room, and as aconite has the effect of dilating the peripheral vessels, the exposure may have had some hand in its death during the night.

The dose of Atropia (19) in this case was very small. In number 84 the dose of Aconitin was very large, or more than double the Minimum-Jabal, but even in this case the animal survived for five hours. In the crucial tests five out of the six died after receiving the same dose of Aconitin.

In experiment 79 1500" of a grain failed to kill a rabbit weighing 1^{lb} 7^{oz}, which shows that this dose, although generally fatal in a rabbit weighing about one pound and a half, is not invariably so.

Table showing the effect of small doses of Aconitin on fatal doses of Sulphate of Atropia drugs given simultaneously.

No. of experiments	Weight of Rabbit	Dose of Atropia	Dose of Aconitin	Results	Crucial experiments
87	2 ⁴ 102	21 gr	1/900	Death in 3 hours	
88	"	"	1/500	" 3 days	
89	1. 8	11	1/800	Recovery	Death in 3 hours
90	1. 6	"	"	"	Recovery.
91	1. 5	"	"	Death in 30 minutes	
92	1. 9	12	"	" 20 "	
93.	1. 5	11	"	" 20 "	

By looking at this table it will be seen that small doses of Aconitin have very little power of saving life when administered with fatal doses of Sulphate of Atropia.

In experiment 88 life was prolonged for three days, and complete recovery took place in experiments 89 and 90, but in the crucial test only the rabbit used in experiment 89 died.

The rabbit used in experiment 90 recovered, which

Shows that at first it had not received a fatal dose.

This was rather curious and shows that a rabbit weighing 1^{lb} 8^{oz} sometimes recovers from a dose of Sulphate of Atropia which generally kills one weighing two ounces more, as will be seen by comparing experiments 89 and 90.

Another series of experiments was instituted to ascertain how long after a fatal dose of Aconitin could a rabbit be saved by small doses of Sulphate of Atropia, as practically speaking Atropia would be of no use whatever in poisoning by Aconite if the antidote had to be administered some minutes previously.

The results of these experiments will be seen in the following table.

Table showing how long fatal doses of Aconitin may be counteracted by small doses of Sulphate of Atropia.

No. of Experiment	Weight Rabbit	Dose of Aconitin	Interval time	Dose of Atropia	Result	Critical Experiment
94	2 ^{lbs} 4 ^{oz}	$\frac{1}{300}$ gr.	2 Minutes	4 grains	Recovery	Death
95	2 . 6	"	4 "	"	"	"
96	2 . 0	$\frac{1}{350}$	6 "	"	"	"
97	1 . 15	"	8 "	"	"	"
98	1 . 13	$\frac{1}{400}$	10 "	"	"	"
99	2 . 9	$\frac{1}{300}$	13 "	"	"	"
100	2 . 2	$\frac{1}{350}$	16 "	"	"	"
101	2 . 1	"	20 "	"	Death in 12 hours.	
102	1 . 8	$\frac{1}{300}$	25 "	"	" 1 hour	

This series of experiments gave very great satisfaction, as, by a reference to the table, it will be seen that small doses of Sulphate of Atropia saved rabbits from dying from the poisonous effects of Aconitin, even when the administration of the atropia was put off for sixteen minutes.

When the Atropia was not given for 20 minutes,
life was prolonged for twelve hours.

If twenty five minutes elapsed before the administration
of the Atropia, death occurred at the usual time.
The crucial tests in this series of experiments were very
satisfactory, as all the rabbits which had formerly
recovered, died in a week afterwards from exactly
the same dose of Aconitia.

It may be as well to mention that the administration
of Sulphate of Atropia did not prevent the symptoms
of Aconite poisoning developing themselves, it only prevented
the animals from dying without modifying the
symptoms in any manner.

The results of this series of experiments was considered of
great practical importance, as in cases of Aconite
poisoning, or even when nasty symptoms arise from
its administration, it is as well to know of a
medicine that has such a ^{marked} power over its action.

Before concluding this paper I must acknowledge
the assistance ^{I have received} (with the experiments) from
Dr. J. Milnes
F. McGill. My attentions to the subject of the

Physiological antagonism of remedies received a considerable impetus from several conversations which I had casually with him.

It was decided between us to perform a series of experiments, the results of which are given in this paper, and although under my roof, they were performed with the assistance of Dr. Fothergill.

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April 26. 1876

In Order
Christian