An investigation into the antagonism between atropine and morphine.

The research described in the following pages was conducted during my tenure of the Houldsworth Research Scholarship in Pharmacology. Writing in 1871, Professor T. H. Fraser said, "There can be little doubt that the evidence derived from both clinical and experimental research is sufficient to show that several actions of opium are of a contrary nature to those of belladonna, hyoscyamus, and stramonium. It is, however, equally undoubted that in the meantime this evidence is insufficient to prove the existence of a general antagonism: or if one between actions of sufficient importance to constitute opium a physiological antidote to belladonna, hyoscyamus, or stramonium, or these latter substances physiological antidotes to opium. The question still remains an open one: but such knowledge as is already possessed renders it probable that a general antagonism does really exist to the extent at any rate of the primary lethal action of opium or morphia being preventable by the physiological action of belladonna, hyoscyamus or stramonium. A properly devised series of experiments would in all likelihood justify the opinion of those
Importance. Otherwise, the weights of the rats though somewhat diverse were as nearly uniform as possible. The rats in all cases were in full digestion and always provided with food and water.

The solutions of the drugs used were always freshly made. In group doses contained in portions of a solution, as was occasionally the case, when a number of animals were being injected at the same time, or when the dose was very small, the quantity of solution injected was measured from the syringe. In all cases in which the dose was separately weighed and dissolved the vessel and syringe were washed out with warm saline to secure as far as possible the administration of the full dose. The morphine tartrate is somewhat insoluble, therefore its better solution in all cases the normal saline (0.9%) was warmed in the hot water bath, never quite to the boiling point, and an effort made to have the solution, conical glass and syringe warmed to 100°F. immediately before injection. The syringes, vessels and solutions were sterilised and to the solutions thyme was always added. The dose was injected as far as possible, and then immediately the washings, the faeces in the case of antagonism experiments being injected into the
same side as the ovarian side. Special care was taken to try to obtain purely substantaneously injections. Separate syringes and needles were rigorously employed for the atropine and morphine. An account of the great care that was observed in carrying out all the details of the experiments made to test the researches tabulated present an almost surprising uniformity. After injection the rats were placed in wooden trays or in cages, and observed. Notes being made at intervals of a few minutes (in most cases) until the first six or seven hours, within which period all the more prominent features manifested themselves. Later the rats were placed in cages and notes made as seemed desirable. By this long lasting and minute observation of these rats a very thorough picture of the actions of the drugs was obtained, which if not of any great practical value was of great interest at the time the observations were being made, and very instructive.

The following plan of work was formulated soon after the investigation was commenced; but it will be seen it has not been fully carried out:

1) Determination of minimal lethal dose of morphine
2) of atropine
3) Existence of a lethal antagonism of atropine to morphine of morphine to atropine
4) Definition of the limits of this antagonism.
   a) as regards ranger's usage of atropine and morphine.
   b) as regards times of administration.
5) Antagonism effects apart from lethal antagonism (and excretion of morphine and atrophi, also necrocytosis).
6) Nature of antagonism (of alkaloids)
   "immunity" (to alkaloids) to morphine and atrophi.
7) Effects of morphine on the kidney and of atropine in amelzipying this.

Determination of the minimal lethal dose of morphine tartrate.

The present work was undertaken in the belief that there was sufficient atropine ouate, and morphine tartrate available for the completion of all the experiments contemplated. After a considerable number of experiments had been performed it was suddenly discovered that there had only been a limited quantity of the drugs. The minimal lethal dose of morphine hence came to be determined in the case of three specimens. Specimen A, with which the experiments were commenced had been obtained in Nov. 1876, within
the cold of the winter. The minimal lethal dose was not less than 85 mgm; with it the series of experiments (Series I and IX) of which the basis was the taking of 45 mgm per 100 gm of rat as the certainly minimal lethal dose, were performed.

Specimen B was obtained on June 1st, 1898, of it the minimal lethal dose was not fully determined, but in the warmer weather, containing it was not less than 45 mgm per 100 gm. No antagonism experiments were performed with it, and on August 1st, 1898Specimen B was added to a third specimen, the whole was thoroughly mixed and dried in vacuo over sulphuric acid, constituting Specimen C, of which the quantity was sufficient for all the experiments contemplated. Of Specimen C the minimal lethal dose was probably a little over 45 mgm per 100 gm, and for the purposes of the experiments was regarded as 50 mgm for a temperature between 65° and 70°.

The results of the experiments directed to the determination of the minimal lethal dose of morphine fumarate were briefly the following. In the case of Specimen A, death first occurred with a dose of 85 mgm (doses stated per 100 gm). Of six experiments performed with this dose, and doses slightly less
founds in recovery and two in death. When the case came to exceed 36 mgm no recoveries occurred. The minimal lethal dose of the specimens in cold spring weather was therefore apparently very definitely about 36 mgm. This was the lowest figure for the three specimens examined but the experiments were performed at a time when the temp. of the laboratory was seldom if ever more than 50° F. In the case of specimen B no fatal result was obtained till the dose of morphine tarbake rose to be equal to 450 mgm. and in this case recovery very nearly took place. The experiments in regard to this specimen were not carried further. For specimen C the first fatal dose was also one of 45 mgm but recovery also occurred with the same dose in the case of another rat, and there was a further recovery with a dose as large as 480 mgm. It therefore seemed as if there was a very great difference between the lethal doses of specimens A, and C. The temperature during the earlier experiments had usually been about 50° F. during the efforts to define the minimal lethal dose of specimens B, and C. The temperature in the laboratory was over 60° F. and on one occasion it had reached as high as 76° F. on account of the exceptionally warm weather. It seemed that the
Higher temperature has possibly something to do with the size of the non-lethal dose of Specimen C. Therefore in a day when the temperature was about high (65°F) two male rats

Table of experiments performed in determining minimal lethal dose of morphine tartrate.

<table>
<thead>
<tr>
<th>Specimen A</th>
<th>Specimen B</th>
<th>Specimen C</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Exp.</td>
<td>Weight (mg)</td>
<td>Actual 60% in mg</td>
</tr>
<tr>
<td>i</td>
<td>178</td>
<td>350</td>
</tr>
<tr>
<td>ii</td>
<td>155</td>
<td>40</td>
</tr>
<tr>
<td>iii</td>
<td>115</td>
<td>49.6</td>
</tr>
<tr>
<td>iv</td>
<td>150</td>
<td>51.78</td>
</tr>
<tr>
<td>v</td>
<td>150</td>
<td>50.0</td>
</tr>
<tr>
<td>vi</td>
<td>115</td>
<td>49.6</td>
</tr>
<tr>
<td>vii</td>
<td>300</td>
<td>105.75</td>
</tr>
<tr>
<td>viii</td>
<td>185</td>
<td>60.75</td>
</tr>
<tr>
<td>ix</td>
<td>216</td>
<td>54.9</td>
</tr>
<tr>
<td>x</td>
<td>151</td>
<td>54.9</td>
</tr>
<tr>
<td>xi</td>
<td>115</td>
<td>49.6</td>
</tr>
<tr>
<td>xii</td>
<td>177</td>
<td>75</td>
</tr>
<tr>
<td>xiii</td>
<td>216</td>
<td>54.9</td>
</tr>
<tr>
<td>xiv</td>
<td>216</td>
<td>54.9</td>
</tr>
<tr>
<td>xv</td>
<td>150</td>
<td>58.7</td>
</tr>
<tr>
<td>xvi</td>
<td>140</td>
<td>49.6</td>
</tr>
</tbody>
</table>

- Recovery
- Death
- Doses stated in micrograms and experiments arranged according to dose per 100gm.

The very same weight and therefore probably also of and very different ages, having the appearance of being young adult rats were taken and to each was given a dose of morphine tartrate of 15 mg per 100 gm. In the case the dose formed a portion of
The original specimen A, and in the other case it was specimen C. (Experiments xvi. and xxviii) the two experiments proceeded concomitantly. Every care was taken to see that the rats were subjected to exactly the same conditions for the uniformly small unconsiderable difference in the lethal doses was pronounced great aggravation. Both rats were still alive seven hours after the injection. In each case the rats died; but whereas the rat which had received specimen C was dead 45 hours after the injection, the other which had received specimen A was at that time still living, in a condition of helminthic fever and only died 50 hours after injection. Unfortunately, the amount of specimen B still remaining did not allow of any further comparison experiments being made. It seems however, that the rise in temperature was probably to a very considerable extent in part entirely responsible for the rise in the size of the lethal dose of specimen C as compared with the previously accepted lethal dose of specimen A. Experiment xxviii with 45 mg m. was performed at a time when the temperature was little over 60°F. Experiments xxix (recovery) and xxx (eatal) were both performed on the same day when the temperature was 68°F. Experiments xxix the dose was 48 mg m and the rat recovered after nearly
by ing. In xxx the dose was 49 mgm and death occurred before 20 hrs. Although the minimal lethal dose of specimen C may have been very nearly 45 mgm and experiments xxvii and xxix be exceptional recoveries still they could not be legitimately disregarded, and the minimal lethal dose of specimen C was for the purpose of the antagonism experiments taken to be 50 mgm. As at the outset of the antagonism experiments 45 mgm had been taken as the lethal dose of specimen A and as on this basis a considerable number of antagonism experiments had been performed it was fortunate that the minimal lethal doses of the two specimens were not more divergent. A specimen of anaesthetics tartrate obtained from Merck and of which the minimal lethal dose was estimated more recently also has a minimal lethal of 45 mgm per 100 for a temperature of 65°F. In view of the great scarcity of rats it was seen desired advisable to strive at a greater accuracy in the determination of the minimal lethal dose of specimen C. All the antagonism experiments were carried out with specimen C except Series I and IX which were performed with specimen A of specimen C. The minimal lethal dose for the basis of the experiments was regarded as 50 mgm for
a temperature between 65° and 70° F.

**Action of Morphine.**

During the determination of the minimal lethal dose of morphine, a great many detailed observations were made on the effects produced by various doses of the drug on white rats. A short summary of these notes is given with a view to a comparison with the manifestations presented when the morphine effects were modified by the co-administration of atropine. After injection of morphine the rats almost invariably remained sitting motionless, the trunk, limbs, and tail being quite placid. In some few instances there were indications of hyperexcitability to noise, but they were touched. The rats quickly passed into a state of torpidity which more developed signs of a disturbed state of the voluntary neuro-muscular system. In the case of a lethal dose torpidity and muscular disturbance persisted till death. The torpor varied in profundity. In most cases the rats of burned on their backs remained quiet, without making any effort to recover their normal attitude, in few instances was it so found that they remained on their backs after any slight noise or
slight shaking had disturbed them. The most evident effects were those manifested by the voluntary muscular system. From the state of flaccidity which existed immediately after injection, the muscles passed into a state of tonic opisthotonos, and subsequently of clonic opisthotonos. The effects on the voluntary muscles first showed themselves in the case of the lower jaw and the tail. The tail muscles indeed served as an excellent index of the condition of the rest of the muscular system, throughout the whole series of experiments. Immediately after injection the tail would be lying quite flat on the floor of the cage, and was quite flaccid so that it could be readily passively bent by the fingers at any of the usual curves. Gradually the tail assumed a position in the longitudinal axis of the rat's body, and at the same time the flaccidity gave way to an increasing rigidity of the muscles. In about 30 minutes after the injection the tail was so rigid that it offered successful resistance to its being passively curved by permissible force. With the development of rigidity the tail began to rise from the floor to be carried in the air and ultimately elevated over the animal's back. In about two hours gentle trembling, which had ere this appeared, and had
who with the little courage have practically affirmed their belief in the existence of this antagonism.

Although in the paper from which this is a quotation Professor Fraser first, and in the clearest manner possible, demonstrated the only correct method of determining the existence of a lethal antagonism between two drugs, viz. atropine and physostigmine, this method has not till now been again applied to the question of a lethal antagonism between other drugs. The question of the existence of a lethal antagonism between atropine and morphine therefore remains undecided. The reason for this is capable to be found either in the inaccessibility of the Transactions of the Royal Society of Edinburgh in which the work was published, or in the tedious nature and long duration of the investigations which are required to determining the existence of a lethal antagonism between two drugs.

It has long been the intention of Professor Fraser to have made this investigation himself. At an appointment to the Whitehouse Research Scholarship Professor Fraser invited me to join him in carrying out an investigation directed to determining whether or not a lethal antagonism existed between atropine and morphine. Circumstances
at first been intermittent in character would be developing into occasional greater jerks and fits of the tail, also in about two hours, but sometimes earlier than in the case of the tail, the lower jaw would begin to jerk. During the first two hours the rest of the muscular system would be in a condition of tonic spasm like that of the tail. In this tonic contraction, quite free from all clonic manifestations, the extensor overcame the flexor muscles, and this most marked in the case of the head limbs, in which there was great resistance to passive movements, i.e., attempts to gently flex them. Further, the tension of the head limbs gradually pushed the rest of the body forwards from the head limbs, and together with the marked torsion of the spine and root of tail, combined to produce a very characteristic attitude which was a constant feature in pals that had received a large dose of curare. The jerking of the jaw and tail muscles were but preliminary to the focal spasm, viz., slight relaxation spasm of head and neck, sudden extension of one or other limb, more marked spasm of the whole hind or forequarter. It was noted that whereas the tonic spasm was most evident in the hind quarters, the clonic spasm were more so in the forequarters.
These local spasms which at first were but the twitchings of isolated muscles, gradually became greater and more extensive, came to implicate groups of muscles symmetrically, and becoming more extensive still had developed into general convulsions in five or six hours, and in the case of a lethal dose were not kept in being followed by death (which occurred either during a convulsion or during an intermission, apparently from cessation of the respiration); for in some cases the heart was undisturbed beating after the respiratory movements had ceased. The convulsions may have owed some of their features to asphyxia arising from interference with the respiratory muscles that were undoubtedly mainly due to the action of the morphine on the heart. The violent convulsions were spontaneous but could also be elicited by the external stimulus of noise, of touch, or by gently blowing on the animal. The phenomena exhibited by the voluntary muscular system may therefore be divided into stages of: a) placidity of heart; b) tonic spasm; c) of clonic spasm. That clonic spasm may be divided into two subtypes: 1) local spasms underlying in 2) general spasms. This division of the muscular phenomena was found of service in observing the modification produced on the effects of morphine by the

...
coagulating and atropine.

The effects on the eye were as follows. Immediately after injection there was contraction of the pupils to a quite considerable extent. The pupils, however, were frequently unequal; one pupil might be very considerably contracted, and the other very considerably dilated. The pupils also for as long as forty-five minutes might appreciably dilate if desired. It was difficult to determine if the difference in the dimensions of the pupils was altogether dependent on the amount of light falling on the two eyes, it did not seem to be so for the eye in the dark might be contracted and the one most exposed to light have its pupil the more dilated. Subsequently, in about four hours, the pupils both dilated to an equal extent, and independently of any concomitant respiratory embarrassment. On the first day after injection the pupils were invariable, fully contracted and immobile. Immediately after the injection the eyeball began to bulge out the cause of this may have also been the cause of the dilatation of pupils and their inequality. The bulge of eyeball continued during the first 9 or 8 hours but had almost disappeared before 24 this. The conjunctival reflex was very soon lost. In the time to three hours there was great acrynomia not usually accompanied by any evident
dilatation of the prepuce of the eyeball. At the same time there was excessive salivation and also escape of secretion from the nose.

The effect on the heart beat was one of acceleration followed by slight subsequent slowing. There was early surface pallor, especially noticeable in the case of the ear, and which later gave place to a distinct flushing so that the barely visible vessels of the ears became visible and the ears reddened.

In the respiratory system there was produced an acceleration of the rate, and an irregularity of the rhythm, wave-like in nature, in which a series of shallow respirations alternates with some deeper movements. It was noted that in fatal cases respiratory had ceased before the heart beat.

As regards secretion, cachexia, salivation, excessive secretion from the nasal mucous membrane were produced. Although no micturition occurred the secretion of urine continued for some time after examination. The bladder was almost invariably found distended with urine, and in cases where the patient survived 24 hrs also contained blood, and this appearance of blood also occurred in the cases where not necessarily fatal. The blood was apparently derived from rupture of vessels in the bladder wall and
not from the kidney. Aspergyl; prepared sections of the kidney showed a degeneration of the and swollen and granular condition of the epithelium lining hemorrhages into the glomeruli or tubules. The condition was very much the same as that found by Dr. H. Krieger in the case of caustic acid poisoning. Examination of the bladder, well microscopically, showed distinct evidence of irritation: whether this was a consequence of the action on the bladder or not, it would be difficult to say. There was usually much blood in the bladder, and the urine contained much uric acid. It had been intended to follow out more fully the effect of morphia on the kidney. Attention was especially directed to this from the fact that the urine of two female patients in Ward XXV both of whom were victims of morphinism contained distinctly quantities of albumin. None of these three had any cardiac trouble. One third Suspectany female patient albumin was also present. Whether albumin in the urine is a direct consequence of the morphia habit or not remains a matter which requires further investigation.

Cystic isation was produced and lasted over three days.
When recovering from non-lethal doses the muscular convulsions gradually subsides into local spasms, which were best to disappear from the jaw where they were frequently present 24 hours and longer after injection. Also while recovering rats showed a great tendency to bite and scratch themselves and they were very troubled with vermin, though apparently this was an effect of the morphine. There was also severalness while recovering. Blood appeared in the urine in some cases which did not have a latent issue. Some noticed rats dump and after recovery quite savage and incapable of being handled, biting at everything put near them as if afflicted with a "mania of persecution" such as has been described after morphia poisoning in man.

The above description of course applies to lethal doses or those approximating thereto.

Protocols of a few of the experiments performed in the determination of the minimal lethal dose of morphine tartrate.

Although altogether 31 experiments were performed in this connection it is only necessary to transcribe the results of a few experiment, in order to illustrate some of the facts. The above description
Determination of the minimal lethal dose of atropine sulphate.

Some earlier experiments had shown that the minimal lethal dose of atropine sulphate in adult was about 250 mg per 100. This determination was near enough for the antagonistic experiments which were concerned with doses of atropine so small that lethal effects were not at all into consideration. A second sample of atropine sulphate had also to be obtained. With the first specimen the experiments in Series I and II were carried out, the other experiments were all performed with the new specimen. The minimal lethal dose of the new specimen was found to lie between 200 mg per 100 gm and 275 mg per 100 gm with the former the last recovery occurred and with the latter the first death.

The injection of such large doses of atropine sulphate results invariably in the formation of a slough over the site of injection.
when Rotenone antiseptic permeability began to take. This formed
in about eight days time, i.e. the otages of swelling due to inflammation
etc., had passed into the stage of open area with sloughing etc.
in that time. It was our custom to say when a rat ceased to be
ill from the immediate effects of the injection and began to
be ill in consequence of the sore. It was not accurately
determined whether the sore was really due to the action of
the antiseptic, and comparable to the local necrotic action of
aphthous, or due to bacterial influences arising through
the rats biting and rubbing at the site of injection. The
formation of this pore made it impossible to attempt to
more accurately define the minimal lethal dose which
day between 200 mgs and 250 mgs with the letter of
which death certainly was due to the primary effects of
the antiseptic. The minimal lethal dose was therefore very
much the same as in the original specimen. The minimal
lethal dose could not have been very accurately determined
without a great deal of trouble which for the purposes of
the present research it was not thought advisable to undertake
in view of the difficulty of obtaining rats.

Every attempt to render rats "immune" to antiseptic
all rats so treated died or were killed on account of their
wretched condition after they had received four doses of
50 mgs, i.e. a little less than the minimal lethal dose.
Also rats which received doses of 10 mgs and 20 mgs
succumbed or reached a hyper condition before the total number of 150 c.c. was reached. These experiments, or rather experiments of this nature regarding 'marginality', are being again now carried out as part of another investigation.

The action of atropine.

In experiments in which it was sought to produce tolerance for atropine it was noted that a dose of 100 c.c. of atropine sulphate per 100 c.c. produced no symptoms beyond dilatation of pupil and a certain loss of appetite, and some loss of weight. A dose of 50 c.c., in addition to dilating the pupil caused restlessness and some excess activity, followed on the day after injection by torpidity. In the definition of the minimal lethal dose of atropine sulphate the observations made were not as detailed as in the case of the morphine, but the rules show that in some of its effects atropine in large doses has an action of which some if the manifestations are of a similar nature to those characteristic of morphine e.g. (dilatation of pupil also occurs with morphine, delirium of epilepsy, local atomics and general coarse tremors which assumes a character very like the Volatile convulsions of morphine especially noted in experiments XXXIII, XXXVIII. In the case EXPII, XXXVI, atropine also is even acute as occurring and this could readily be a result of the action of atropine. As the dose of
Alkaloids used in the antagonism experiments were so very small it is necessary here to enter into the question of the action of very large doses. In the pharmacological institute in Berlin many experiments were carried out on the action of very small doses of antipyrine without however much light being thrown on their action in preventing the lethal action of morphine: the inquiry on this subject is being pursued further as occasion offers.

**Lethal antagonism of antipyrine sulphate to morphine tartrate.**

Experiments were first made to find if it was or was not possible to prevent death by administering antipyrine sulphate. The lethal antagonism was sought by working from a definite dose in the direction of increasing and of diminishing doses. In this way fortunately the existence of a lethal antagonism towards the diminishing direction was soon detected. The range of doses of antipyrine sulphate which were able to antagonize one minimal lethal dose of morphine tartrate (450 mgm. for 100 gm.) was found capable of accurate definition. A following out the part of the work the two alkaloids were administered as nearly as possible at the same time, and also when an interval had elapsed between the times of administration. In one series of experiments
and especially Professor Fraser's absence in India as President of the Indian Plague Commission, rendered it impossible for him to take any active a share in the work as he had intended. The research was therefore commenced, and in its earlier stages carried out under Professor Fraser's active supervision. The work has been brought to its present stage in account of the encouragement given by Professor Fraser at a time when it was impossible for him to take any part in the research himself. I cannot sufficiently express my indebtedness to Professor Fraser for the kindness with which he assisted and encouraged my work during the time that it was my privilege to work under his supervision, nor can I adequately express my gratitude for the readiness with which he acquiesced in my request to be allowed to continue the work in his absence. The research is not yet completed, various matters have interfered with it, and so far as it is described in this first description the work was performed for the Medical Pharmacological Laboratory of the University of Edinburgh. I wish to state that for all imperfections and expressions of opinion I alone am responsible.
The morphine tartrate solution was injected immediately after the dose of atropine sulphate, so as to attain, as nearly as possible, simultaneous administration, such experiments are hereafter designated "simultaneous administration." In another series of experiments, the atropine sulphate was injected before the morphine tartrate and in a third series after it.

Simultaneous administration was carried out in six series of experiments, which may be tabulated as follows:

<table>
<thead>
<tr>
<th>Series</th>
<th>Dose of Atropine (part. equal to 450 n. 1/2)</th>
<th>Dose of Morphine Tartrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series I</td>
<td>85°</td>
<td>One-half dose of atropine</td>
</tr>
<tr>
<td>Series II</td>
<td>100</td>
<td>Two</td>
</tr>
<tr>
<td>Series III</td>
<td>112.5</td>
<td>Two and a quarter</td>
</tr>
<tr>
<td>Series IV</td>
<td>125</td>
<td>Two and a half</td>
</tr>
<tr>
<td>Series V</td>
<td>25</td>
<td>One-half the min. leth. dose</td>
</tr>
</tbody>
</table>

In carrying out these experiments the rule was observed of injecting the atropine solution first into the left flanks, and the morphine solution secondly into the right flanks. By constant repetition of the same procedure sufficient facility was soon acquired to allow of the whole procedure being carried out in little over thirty seconds. The dose of atropine sulphate was usually so small, that it was contained in a portion of a solution the dose of morphine tartrate except in the earlier.
Previous work on the antagonism between atropine and morphine.

An account of the therapeutic value which an agent able to prevent the lethal effects of opium or morphine would possess, probably, more work has been directed to determining the existence of a lethal antagonism between atropine and morphine than in the case of any two other drugs. It is not necessary to more than allude to the medical belief in the existence of this antagonism. fuller references to instances of this belief will be found in Professor Fraser's article on the antagonism between atropine and physostigmine, and in Fröhlich's account of that between atropine and morphine. With regard to the work performed in more scientific times, after more than thirty years of ineffective research and discussion the question still remains an open one, and the words of Professor Fraser, above quoted, are as true today as they were at the time when they were written.

No demonstration of the abolition of the lethal action of a proved fatal dose of morphine by means of atropine or vice versa, has yet been published. The published investigations have to
frequently been devised to yield results in accordance with the particular view advocated by the investigator. Some, advocating the existence of an antagonism of therapeutic importance, have so adjusted the conditions of experiment that an antagonism in the actions of the drugs or the functions of organs essential to life was demonstrated. Others have repeated the form of these experiments, but with the conditions of dosage adjusted, intentionally or accidentally, to prove the contrary. Others again have been satisfied after trying a few arbitrarily chosen combinations of atropine and morphine that an antagonism existed or did not exist. The difference in the action of large and small doses of atropine in most antagonising or in antagonising various doses of morphine has allowed of different investigators devising experiments of which the results are apparently absolutely contradictory and irreconcilable. This difference in the action of small and large doses has only been broached in the most superficial way and for the purpose of controversy. There has never been any attempt to explain the apparent contradictions, and bring into harmony the differing results of various investigators. Some have only been efforts to discredit the reliability of the results of
one set of experiments by advancing contrary results or what is much more to be deprecated a tendency to altogether lose sight of the subject of investigation in a discussion of the question of whose right and who is wrong. The results thus brought into opposition and seemingly contradictory are not really so. No experiments hitherto published have covered a range of doses sufficiently wide for the effect of small and large doses of atropine when given alone with morphine to be brought into harmony and the correctness of what have been held to be contradictory results upheld. A most important fact, which has often been prominently brought forward as a sort of trump card by the opponents to the existence of a lethal antagonism viz. that doses of atropine and morphine which when given alone are harmless, produce death when given together, has had its signification altogether misunderstood by the experimenters who have pointed it out as the strongest evidence of the non-existence, or rather of the impossibility of the existence of a lethal antagonism. It has been been stated by Rosebach and Fröhlich in a commentary by Rom on Besse's work on the antagonism between atropine and physostigmine that the statement, that a
combination of non-lethal doses of these two drugs may be lethal seems to be, indeed, a contradiction of the previous demonstration that certain smaller doses of atropine are able to antagonize larger lethal doses of physostigmine. This was an ingenious way of getting rid of a very awkward fact which effectually proved the incorrectness of the general rules regarding antagonism formulated by Rosbach, especially his statement that a poison which excites under no circumstances abolishes the previously existing action of a paralyzing poison. This statement has once been entirely contradicted from other sides, particularly by the work of Langley and of Huchinger who have repeated Rosbach's experiments on glandular secretion and have succeeded through the agency of pilocarpine in restoring the secretory activity abolished by atropine. The experiments of Lawer Bruntin and Cash on the action of alkalies and acids on stripped muscle have demonstrated the existence of a true reciprocal antagonism. The existence of which has also been more recently asserted on other grounds by among others Professor Stock's.

An account of the number of participants in the controversy regarding the existence of a lethal antagonism between atropine and morphine, and the weight which
attached to the opinions of many of them, it is not possible
to give in a narrative an condensed form, a just
valuation of the work performed or the conclusions
arrived at. The literature in so far as it has been
accessible for the purposes of study is abridged, and
to where necessary notes and comments are added to
the articles, from the more important of which extracts
are given and in some cases summaries. The
amount of literature that has accumulated on
atropine and morphine is very great. In so far as it
possesses a direct or an indirect bearing on the question
antagonism and its bases on experimental as distinct
from purely clinical evidence an effort has been
made to study it fully and carefully. Numerically
the number of articles based on purely clinical experiences
is much greater than of those based on purely experi-
mental evidence. After reading many of what promised
to be the more important of the former, the insufficiency of
the data, especially as regards scope and the consequent
impossibility of obtaining any true valuation of the
import of the observations made, rendered it apparent
that it would be expedient to leave the clinical aspect
entirely out of account. Nevertheless many of the
purely clinical contributions are of great interest and
value.

* * * Inaccuracy the aught of the time that has been going on, and, where it
necessary to transcribe either notes of the literature or of the experiments,
General description of the method of experimentation.

The preparations employed were acetic morphine sulphate and morphine lactate, both of which were obtained from Messrs. Duncan and Stockham, Edinburgh. Morphine sulphate \((\text{C}_{17}\text{H}_{23}\text{NO}_3)\_2\cdot\text{H}_2\text{SO}_4\), and morphine lactate \((\text{C}_{17}\text{H}_{19}\text{NO}_3)\_2\cdot\text{C}_4\text{H}_6\text{O}_6 + 3\text{H}_2\text{O}\) represent in equivalent weights equivalent quantities of the respective alkaloids of which they are the salts. By using morphine lactate the introduction of the question of the action of acids on the alkalinity of the blood serum etc. in question was avoided.

The animals employed were white rats. The use of these animals allowed of accurate weighing, reduced considerably the amount of the rags necessary, a great number of them could be housed, and the fact of their being non-susceptible both to morphine and atropine was of advantage in keeping the slight or suppressed excitement to which the animals subjected of the aphylactic state. The work was frequently interrupted by the difficulty in obtaining suitable rats as regards age and weight. The original intention had been to use rats of 200 grams weight but it was found impossible to obtain sets of approximately this weight. Rats of not very divergent weights or of the same weight were employed whenever comparable results were obtained.
experiments, were in almost all cases separately weighed and dissolved, and in these cases the weights of the vessels and the syringe were also recorded.

Series 1. In this series of experiments the dose of parathrate was 45 mg (repeatedly the figures given must always be understood to be doses per 100 grams and not actual "doses"). The earlier experiments were performed concomitantly with another series (Series IX) in which the same doses of atropine sulphate were administered thirty minutes before the same doses of morphine parathrate. This latter series however it was recommended not to continue. The first experiment performed was with a dose of 10 mgms of atropine sulphate. This dose failed to prevent death and with it as a starting point a scheme was drawn up of a regular series of increasing and diminishing doses and other experiments performed with definite intervals between the doses of atropine. It soon was ascertained that atropine sulphate exercised a lethal antagonism to the dose of morphine parathrate and that this lay in the direction of the smaller doses. The results of the series may be stated as follows. The largest dose of atropine sulphate (which rendered 45 mg of morphine parathrate non-lethal) was one of 7.5 mgms, and successful antagonism continued through a series of doses till one so small as to be a milligramme was reached, this dose was the smallest.
which exercised a lethal antagonism. The range was therefore only from \( \frac{3}{5000} \) to \( \frac{1}{5} \) of a grain. It will be observed from the following table that in one case recovery

<table>
<thead>
<tr>
<th>No. of Exp.</th>
<th>Weight atrat</th>
<th>Dose administered (mgm.)</th>
<th>Dose administered (mgm.)</th>
<th>Dose in mgm. last (mgm.)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>159</td>
<td>0.018</td>
<td>0.01</td>
<td>85.5</td>
<td>✓ at 6 hrs.</td>
</tr>
<tr>
<td>40</td>
<td>155</td>
<td>0.0167</td>
<td>0.225</td>
<td>88.95</td>
<td>✓</td>
</tr>
<tr>
<td>41</td>
<td>157</td>
<td>0.0185</td>
<td>0.06</td>
<td>181.95</td>
<td>✓ after 2nd day</td>
</tr>
<tr>
<td>42</td>
<td>150</td>
<td>0.0185</td>
<td>0.075</td>
<td>81.0</td>
<td>✓</td>
</tr>
<tr>
<td>43</td>
<td>200</td>
<td>0.0</td>
<td>0.1</td>
<td>90.0</td>
<td>✓</td>
</tr>
<tr>
<td>48</td>
<td>159</td>
<td>0.0167</td>
<td>0.1</td>
<td>75.5</td>
<td>✓</td>
</tr>
<tr>
<td>44</td>
<td>178</td>
<td>0.0167</td>
<td>0.05</td>
<td>80.1</td>
<td>✓</td>
</tr>
<tr>
<td>45</td>
<td>147</td>
<td>0.018</td>
<td>0.5</td>
<td>63.0</td>
<td>✓</td>
</tr>
<tr>
<td>46</td>
<td>350</td>
<td>21.0</td>
<td>7.5</td>
<td>123.0</td>
<td>✓</td>
</tr>
<tr>
<td>47</td>
<td>285</td>
<td>21.52</td>
<td>7.5</td>
<td>123.15</td>
<td>✓</td>
</tr>
<tr>
<td>48</td>
<td>200</td>
<td>4.0</td>
<td>8.0</td>
<td>90.0</td>
<td>✓</td>
</tr>
<tr>
<td>49</td>
<td>223</td>
<td>25.0</td>
<td>10.0</td>
<td>90.0</td>
<td>✓</td>
</tr>
<tr>
<td>50</td>
<td>190</td>
<td>25.0</td>
<td>15.0</td>
<td>85.5</td>
<td>✓</td>
</tr>
<tr>
<td>51</td>
<td>182</td>
<td>12.14</td>
<td>20.0</td>
<td>95.4</td>
<td>✓</td>
</tr>
<tr>
<td>52</td>
<td>157</td>
<td>29.25</td>
<td>26.0</td>
<td>70.65</td>
<td>✓</td>
</tr>
<tr>
<td>53</td>
<td>283</td>
<td>5.0</td>
<td>30.0</td>
<td>125.0</td>
<td>✓</td>
</tr>
</tbody>
</table>

*By reason of this experiment can be performed with almost the minimal lethal dose of morphine lactate. It can be better included here from elsewhere.*

occurred with a of 7.5 mgm. and in the case of another rat.

the same dose did not exercise successful antagonism.

All greater doses were unavailing. The range of doses was very limited, and may be expressed as ranging from \( \frac{1}{5000} \) up to \( \frac{1}{56} \) of the minimal lethal dose of atropine sulphate. Any dose greater or even so great as \( \frac{1}{56} \) of the minimal lethal dose of atropine sulphate.
came to exercise its influence, by the mere fact that
this was so great, in such a way, that the fatal result
to the death dose of morphine was not much if at all
reached. The most rapid recovery occurred in the
case of experiments 44 and 45, the subjects of which
had received respectively 0.5 mgm. and 5.0 mgm. atropine,
sulphate. Without the limits of these two doses the
antagonism was seemingly less perfect, and where
recovery occurred, it was more delayed. Only one rat
which received a dose of atropine sulphate greater than
7.5 mgm. survived more than 24 hrs., and some died
within four hours, which time corresponded almost
exactly with that within which 45 mgm. of morphine
tartrate killed when given alone. No clue was
afforded by any manifestation observable as to why
such fractions of the minimal lethal dose of atropine
came to contribute to the lethal dose.

Genetic Experiments were next undertaken in
order to determine how great was the quantity of
morphine which could be successfully antagonised.
Unsuccessful efforts having been made to antagonise
in a few instances, doses of morphine tartrate equal to
two and a half times the minimal lethal dose, it was
thought better to attempt to antagonise doses equal to
one and a half times the minimal lethal, and to
there were indications of the series of doses within which antagonism might exist.

The dose of morphine taken was therefore 85 mpm, i.e. one and a half times (approximately) the lethal dose of specimen C. The smallest dose of atropin sulphate to

<table>
<thead>
<tr>
<th>No.</th>
<th>Exp.</th>
<th>Dose of morphine (mpm)</th>
<th>Dose of atropin sulphate (mpm)</th>
<th>Reseaver</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
<td>92.4</td>
<td>0.0412</td>
<td>0.02</td>
<td>173</td>
</tr>
<tr>
<td>55</td>
<td>140</td>
<td>0.06</td>
<td>0.05</td>
<td>119</td>
</tr>
<tr>
<td>56</td>
<td>187</td>
<td>0.1285</td>
<td>0.06</td>
<td>159</td>
</tr>
<tr>
<td>57</td>
<td>142</td>
<td>0.1</td>
<td>0.07</td>
<td>188</td>
</tr>
<tr>
<td>58</td>
<td>184</td>
<td>0.1392</td>
<td>0.075</td>
<td>196.2</td>
</tr>
<tr>
<td>59</td>
<td>210</td>
<td>1.585</td>
<td>0.25</td>
<td>178</td>
</tr>
<tr>
<td>60</td>
<td>210</td>
<td>1.0</td>
<td>0.5</td>
<td>178</td>
</tr>
<tr>
<td>61</td>
<td>195</td>
<td>1.0</td>
<td>0.6</td>
<td>165</td>
</tr>
<tr>
<td>62</td>
<td>325</td>
<td>8.4</td>
<td>0.75</td>
<td>278</td>
</tr>
<tr>
<td>63</td>
<td>134</td>
<td>1.2</td>
<td>0.9</td>
<td>115</td>
</tr>
<tr>
<td>64</td>
<td>117</td>
<td>6.0</td>
<td>4.08</td>
<td>125</td>
</tr>
<tr>
<td>65</td>
<td>156</td>
<td>7.0</td>
<td>4.5</td>
<td>133</td>
</tr>
<tr>
<td>66</td>
<td>158</td>
<td>6.25</td>
<td>4.6</td>
<td>117</td>
</tr>
<tr>
<td>67</td>
<td>124</td>
<td>6.0</td>
<td>4.84</td>
<td>105</td>
</tr>
<tr>
<td>68</td>
<td>155</td>
<td>7.75</td>
<td>5.0</td>
<td>132</td>
</tr>
<tr>
<td>69</td>
<td>124</td>
<td>7.0</td>
<td>5.66</td>
<td>108</td>
</tr>
</tbody>
</table>

* The rat was exceptionally fat and round, the dose was therefore on account of inert fat possibly to be regarded as considerably more than 85 mpm per 100 gm.

produce successful antagonism was one of 3/4 of a milligramme and the largest 7.5 mpm. In this series the recoveries were once delayed: one rat appeared "well" within 45 hrs after injection. The most rapid recovery was with a dose of 6.081 mpm. But in this series not one
It is not easy to pick out any definite range within which it could be stated that there existed a more perfect antagonism. Perhaps such a range might be taken as consisting between 0.6 and 4.0 mgm.; but its existence was more than doubtfully evidenced. However, the manifestation of a more perfect antagonism range of doses with the range of recovery also harmonizes with Series III and its seeming existence in Series I may have been more apparent than real. The first period of experiments was performed with 45 mgm. when the minimal lethal dose was in the temperature considered somewhat less than 45 mgm., and the second series was performed with 85 mgm. of morphine tarsate representing 170 of the minimal lethal dose and not exactly 170 minimal lethal doses of specimen C. This was one of the consequences of the morphine supply having run out, though it being real due to purposes not connected with the present series of experiments. Series II was commenced at a time when it seemed extremely likely that the minimal lethal dose of the new specimen of morphine tarsate would be very little over 40 mgm., and the series was really intended to be one with twice the minimal lethal dose.

The temperature of the laboratory varied much at this time, the series was being performed, depending
whether the sun was or was not shining, and on
the strength with which it alone. During the month
of Sept. the temperature in the laboratory had normally been
65°-70° F. but had been as low as 50° F. and on a few
occasions when it was exceptionally warm reached
92°-76° F. Subsequent to the importance in relation
to the minimal lethal dose of morphine being brought
do prominence into notice particularly Morin working
to this factor during this series and all others work
experiments, which that experiments might give
comparable results. Experiments 57, 58, 60, 62, and 68
were performed during less warm weather. Experiment
64 was performed when the temperature was only 50° F.
A consequence of this at a time when the Vamp had
again fallen to about 50° F. experiments 65 and 69
were performed and care taken to maintain the
atmospheric temperature at about 70° F. This seems a
high temperature, its height however was determined
by the fact that this had been the prevailing temper-
ature when the minimal lethal dose of the morphine
was determined and also during the majority
do the experiments in this series. Careful observation
particularly in the next series (iii) has given rise
to the conviction that rats which has receives
large doses of morphine tartrate and small doses of atropine
one plate were very susceptible to outside temperature; the appearances manifested were quite distinct according as the temperature was high or low. The results of experiments 55 and 69 confirmed the results previously obtained at either extremity of the range but notably because the temperature prevailing at the time of the previous experiments had also been near 70°F. In most experiments the temperature was carefully noted but previous to the great importance of temperature coming into prominence it had sometimes been omitted in what was turned out to be cases of importance. In this particular case the experiments were repeated because other observations in Series III had led me to expect a possible extension of the range of interpretation both from the minimal and maximal sides but especially in the latter under favourable conditions of temperature. As the results obtained merely confirmed those previously obtained the expectation was realized.

Series III. The experiments in this series had for the sake of morphine benzoate 100 rpm equal to twice the minimal threshold of specimen C. Perhaps because of the great care that was taken to keep the rats in a uniformly warm atmosphere temperature the results of this series show less tendency to
inconsistency than in earlier series and compared with very great clearness some of the facts of the antagonism. The very narrow extent of the antagonism is not more narrowed and in this series extends from only 4 mgm to 10 mgm, but though as limits, the antagonism to the lethal effects of the morphine was very perfect with in the limits within which occurred, for the recoveries which took place, took place on the whole more quickly than in the last series, the cause of this being no doubt the absence of so great a variability of temperature, the extreme accuracy with which it was possible to define.

<table>
<thead>
<tr>
<th>No. of</th>
<th>Usual</th>
<th>From least mgm. Lethal (mgm)</th>
<th>From greatest mgm. Lethal (mgm)</th>
<th>Result.</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>150</td>
<td>0.125</td>
<td>0.865</td>
<td>130</td>
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<td>71</td>
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<td>0.3</td>
<td>0.1</td>
<td>30.5</td>
</tr>
<tr>
<td>72</td>
<td>190</td>
<td>0.75</td>
<td>0.144</td>
<td>190</td>
</tr>
<tr>
<td>73</td>
<td>170</td>
<td>0.35</td>
<td>0.2</td>
<td>190</td>
</tr>
<tr>
<td>74</td>
<td>185</td>
<td>0.57</td>
<td>0.2</td>
<td>185</td>
</tr>
<tr>
<td>75</td>
<td>186</td>
<td>0.9</td>
<td>0.25</td>
<td>186</td>
</tr>
<tr>
<td>76</td>
<td>186</td>
<td>0.15</td>
<td>0.3125</td>
<td>160</td>
</tr>
<tr>
<td>77</td>
<td>182</td>
<td>0.9</td>
<td>0.5</td>
<td>182</td>
</tr>
<tr>
<td>78</td>
<td>150</td>
<td>1.0</td>
<td>0.66</td>
<td>150</td>
</tr>
<tr>
<td>79</td>
<td>178</td>
<td>1.25</td>
<td>0.7</td>
<td>178</td>
</tr>
<tr>
<td>80</td>
<td>200</td>
<td>1.5</td>
<td>0.95</td>
<td>200</td>
</tr>
<tr>
<td>81</td>
<td>200</td>
<td>1.5</td>
<td>0.75</td>
<td>200</td>
</tr>
<tr>
<td>82</td>
<td>190</td>
<td>1.5</td>
<td>0.9</td>
<td>190</td>
</tr>
<tr>
<td>83</td>
<td>190</td>
<td>1.5</td>
<td>0.3</td>
<td>190</td>
</tr>
<tr>
<td>84</td>
<td>213</td>
<td>2.13</td>
<td>1.0</td>
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<td>85</td>
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</tr>
<tr>
<td>86</td>
<td>200</td>
<td>3.0</td>
<td>1.5</td>
<td>200</td>
</tr>
</tbody>
</table>

* Rates at which Lethal dose of morphine was taken.
* 4 mgm before start.
* * after 4 hours.
* * after 2 hours.
* * * after 2 hours.
* * * * after 4 hours.
* * * * before 4 hours.
* * * * * after 2 hours.
* * * * * before 4 hours.
* * * * * before 2 hours.
* * * * * before 2 hours.
* * * * * before 2 hours.
* * * * * before 2 hours.
* * * 4 hours.
* * * * 4 hours.
* * * * 4 hours.
* * * * * 4 hours.
* * * * * 4 hours.
* * * * * 4 hours.
* * * * * 4 hours.
* * * 4 hours.
* * * * 4 hours.

* Percentages indicate percentages of 100.
The antagonism only one twentieth of a milligramme separating the lethal antagonism doses from those which did not successfully antagonise, at other limit of the tested successful antagonism. Further from the results it would appear that there was better the nature of transition from the region of the doses which do not antagonise the lethal effects to those which do, e.g. the subjects of experiments 73 and 74 were dead before 20s and the subject of experiment 75 was, with the exception that it did not eat, seemingly quite well 18hr after the injection. The rat was also eating well before 4 1/2 days after the injection.

As regards the general effects of lower and higher temperatures a note was made at experiments 69 and 70, of the high temperatures which had resulted from the careful observation of many rat, particularly in the determination of the minimal lethal dose of specimen C and in Series II, III, and IV in which series most of the rats were kept at an equal temperature whereas others had been subjected to the raphazard temp. of the laboratory which varied from day to day and during the nights and days that constituted the duration of an experiment. The temperature had ranged from 50° to 60° and 70° and even 110°F. It was noted that temperature seemed to have an
important influence on the delimitation of the areas of recovery and death. This influence was greater with the larger than with the smaller doses of atropine e.g. (expt. 74, 76, 81, 82). After the administration of the two drugs the symptoms, their time of onset, their character and duration it was noticed were all influenced by the temperature. Both in the minimal lethal morphine experiments and in the antagonism experiments temperature had profound influence on the tonic state. When the temperature was low the tonic state was more rapidly attained, was more exaggerated in its manifestations, and if once fully developed almost invariably advanced to a fatal issue, death occurring during a convolution or in an intermission. When the temperature was not low, the tonic convulsions were not so fully developed, there was a tendency instead to localised spasms, and it would appear there was then a very extreme and prolonged phase of hypersusceptibility to any, however, which had its onset prior to the full development of the state of "mental" torpority. These were the impressions formed from the long and continuous observation of the test. Both before temperature has been very particularly considered and afterwards, and it was also noted that death occurred in a different
in the experiments in which care was taken to keep the temperature warm, for in this case the rats did not invariably die in spasms, or from failure of respiration between spasms; but might simply quietly pass away, never having moved after the injection seemingly from failure of the respiration before the heart, which however might concomitantly become very weak in its pulsations. No effort was made to see if spasms or tetanus could be brought on by lowering the temperature, or vice versa abolished by raising the temperature. However in exp. 90 it was noted that the convulsions were apparently made to disappear by raising the atmospheric temperature from 65° to 72°.

**Series IV.** In this series only one recovery took place. The dose of morphine injected was now been increased.

<table>
<thead>
<tr>
<th>No. of Exp.</th>
<th>Weight</th>
<th>Weight of B.</th>
<th>Actual dose of B.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>87</td>
<td>210</td>
<td>0.2</td>
<td>0.1</td>
<td>236</td>
</tr>
<tr>
<td>88</td>
<td>200</td>
<td>0.6</td>
<td>0.3</td>
<td>225</td>
</tr>
<tr>
<td>89</td>
<td>150</td>
<td>0.5</td>
<td>0.5</td>
<td>169</td>
</tr>
<tr>
<td>90</td>
<td>148</td>
<td>0.6</td>
<td>0.4</td>
<td>166</td>
</tr>
<tr>
<td>91</td>
<td>210</td>
<td>1.0</td>
<td>0.5</td>
<td>236</td>
</tr>
</tbody>
</table>

*The death of this rat was looked on as a misfortune, for there was every reason that it would live, but during the night the temp. fell accidentally, and from it was found that the respiration must have been unusually imperfect by a greatly distended stomach. This latter case has raised its temp. to 115° F.*
Rats were too scarce to allow of any of the experiments in this series being specially repeated in a cooler temperature. The evidence all went to show that in a cooler temperature a repetition of experiment 89 could not have ended in recovery. The death of the subject of experiment 90 was looked on as a misfortune, the symptoms manifested gave every hope that it would recover. But during the night the temperature was allowed to fall, and p.m. it was also found that respiration had been greatly impeded by an enormously distended stomach. This latter may have had much to do with its death.

Series V. The dose of morphine lactate here was 125 c.c. or 1 1/2 times the minimal lethal dose of specimen C. Experiments 92, 93, 94, 95 and 96, were performed at an early date in the chance laboratory temperature during warm weather. Subsequently experiments 97, 98, 99 and 100 were performed in an equally warm temperature. No recovery occurred in this series. As far as observed, the administration of the morphine sulfate could not be stated to have influenced the action of the morphia in the direction of favouring recovery. No central experiments with very large doses of morphine in order to determine that cap school was due ensuing could be performed. With these enormous doses of morphine plus atropine no tonic convulsions were observed
The rats were under constant observation except for short intervals. It is possible these may have occurred but they were certainly not a prominent symptom. It does not of course follow that their absence is to be ascribed to the action of the atropine.

<table>
<thead>
<tr>
<th>No. of Exp.</th>
<th>Weight (g)</th>
<th>Dose/mouse (mg)</th>
<th>Actual dose/mouse (mg)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>92</td>
<td>180</td>
<td>0.018</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>93</td>
<td>275</td>
<td>0.1875</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>94</td>
<td>195</td>
<td>0.133</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>95</td>
<td>175</td>
<td>0.183</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>96</td>
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<td>0.3</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>97</td>
<td>200</td>
<td>0.5</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>98</td>
<td>190</td>
<td>0.55</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>99</td>
<td>185</td>
<td>0.65</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>190</td>
<td>0.75</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

Combined action of non-lethal doses of atropine and morphine.

Series VI. The maximum dose of morphine tartrate which it was possible to successfully antagonize in Rumpen determined attention was given to three doses of morphine tartrate, which although of themselves non-lethal, might possibly by combination with certain proportionally larger doses of atropine sulphate be caused to have a lethal action. The object was to check in the action of atropine and morphine phenomena of the same nature as those described by Prickowischer in the case of atropine and physostigmine. For the purpose 25 mgm of morphine tartrate representing half the minimal lethal dose of
afternoon C. was used. At the time the subject was not pursued further than the finding of a dose of morphine sulphate, which, when given in combination with half the minimal lethal dose of morphine hydrochlorate, resulted in the death of the rat primarily from the immediate consequences of such injection, as distinct from effects (the post etc.) which were only secondary.

The following experiments were performed:—

<table>
<thead>
<tr>
<th>No. of</th>
<th>Weight</th>
<th>Dose of morph. sulphate (mgm)</th>
<th>Dose of morph. hydro. (mgm)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>101</td>
<td>140</td>
<td>70</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>102</td>
<td>147</td>
<td>126</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>103</td>
<td>150</td>
<td>135</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>104</td>
<td>150</td>
<td>135</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>205</td>
<td>205</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

The subjects of experiments 101 and 102 were never "well" after the injection. The subject of 101 was still quite ill seven days after the injection, and died on the thirteenth day, but the death was then probably due to the large dose which had developed over the site of the injection. It was difficult to say where the direct consequences of the injection ended and illness due to the dose began. The subject of 102 was killed on the eighth day. This rat had improved much, the pupils were still fully dilated, the eyes kept closed, and the rat sprawled and still very ill.
48 hours after the injection; 72 hours after injection the
trat was eating fairly well and seemed a good deal better.
A thorough examination of the organs of the development was made to
reveal any signs of the poison. It remained to kill the poor beast. In the other experiments,
death was certainly due to the combined
action of doses of atropine and morphine which if
given alone would certainly not have resulted in
death. In the pharmacological institute in
Berlin twenty more experiments were performed
with such a combination of doses of atropine and
morphine. The results were absolutely confirmatory
of the results of the earlier experiments. At this
time it is not necessary to keep further to these later
experiments.

**Administration of atropine after morphine.**

The administration after morphine had been given time
to develop its effects — forty minutes, was the time
chosen — it was thought would give results of therapeutic
importance. It was deemed that the limits of the
reversed the antagonism would be more quickly
defined with the larger doses of morphine than with
the smaller when the range was wider so that after
two experiments had been performed with the
minimal lethal dose of morphine, both of which
results in recovery, another series with mean a day later. The minimal lethal dose of morphine was commenced. It did not seem likely that such the quantity of morphine which the lethal effect could be absorbed was only 2½ minimal lethal doses. That the range of doses would have any great extent with a dose of morphine more than ½ min. lethal dose.

Series VII: Atropine 0.001 mg. min. lethal dose of morphine per kg.

<table>
<thead>
<tr>
<th>No. of Exp.</th>
<th>Weight (g)</th>
<th>Dose of atropine (mg)</th>
<th>Dose of morphine, fatal (mg)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>106</td>
<td>275</td>
<td>0.335</td>
<td>140</td>
<td>50</td>
</tr>
<tr>
<td>107</td>
<td>270</td>
<td>1.0</td>
<td>155</td>
<td>50</td>
</tr>
</tbody>
</table>

Series VIII: Atropine 0.01 mg. min. lethal dose of morphine per kg.

<table>
<thead>
<tr>
<th>No. of Exp.</th>
<th>Weight (g)</th>
<th>Dose of atropine (mg)</th>
<th>Dose of morphine, fatal (mg)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>108</td>
<td>232</td>
<td>0.3</td>
<td>189</td>
<td>≥ 50 kgs.</td>
</tr>
<tr>
<td>109</td>
<td>300</td>
<td>0.9</td>
<td>285</td>
<td>≥ 43 kgs.</td>
</tr>
<tr>
<td>110</td>
<td>185</td>
<td>0.8</td>
<td>138</td>
<td>84-91 kgs.</td>
</tr>
<tr>
<td>111</td>
<td>165</td>
<td>1.0</td>
<td>140</td>
<td>≥ 43 kgs.</td>
</tr>
<tr>
<td>112</td>
<td>162</td>
<td>4.0</td>
<td>138</td>
<td>≥ 43 kgs.</td>
</tr>
</tbody>
</table>

Opportunity was not found to carry the most potent further than is shown in the above table. The experiments performed however show clearly how profoundly an interval of half an hour narrows the limits of the lethal antagonism, and also demonstrate that the lapse of time is not to be counterbalanced by an increase in the dose of atropine, for the limits indicated in the above table show that instead of the extent of the range of antagonism remaining the same, with
respectively higher values for the minimum and maximum doses of atropine, i.e. with the lethal range moved up the scale of atropine doses there is here a
increase of the minimal lethal dose of morphine a very marked narrowing of the limits from both the
maximum and minimum sides. This is quite in
accordance with the phenomena observed in simple
increase of the lethal dose of morphine but of course
now the minimal dose of atropine can increase
but the maximum dose of atropine for the same
reasons as well as call for its diminution when the
dose of morphine is increased must also diminish
here. By extension of the time between, quip 12 atropine
and morphine the minimum antagonism dose of
atropine will become ever larger and theoretically
can increase until the time &/dose demanded a
of atropine equal to the lethal antagonism dose
when the two drugs are simultaneously admin-
istered, but practically this is prevented by the
duration of a morphine action demanding at
the maximum build a diminution in the
quantity of atropine which is able to retain in life.
Without the experiment being performed a single side
experiment 20 it is hardly possible to say that the
verts of antagonism had become limited to the pr
two hundred and fifty gramme dose of morphine by the inhalation have been allowed half an hour in which to work up in action. The quantity of morphine therefore capable of being ingested under the most favorable conditions is only 25 gr. minimal lethal dose. The foot of such a margin is in accordance with the limitation of the antagonism by codeine in administering morphine. No experi-

<table>
<thead>
<tr>
<th>No.</th>
<th>Weight</th>
<th>Tongue and throat, (mm)</th>
<th>Actual dose (mg)</th>
<th>Reactor</th>
</tr>
</thead>
<tbody>
<tr>
<td>113</td>
<td>200</td>
<td>0.101</td>
<td>0.05</td>
<td>99.9</td>
</tr>
<tr>
<td>114</td>
<td>135</td>
<td>0.138</td>
<td>0.075</td>
<td>88.25</td>
</tr>
<tr>
<td>115</td>
<td>217</td>
<td>9.108</td>
<td>0.6</td>
<td>97.15</td>
</tr>
<tr>
<td>116</td>
<td>207</td>
<td>15.0</td>
<td>7.211</td>
<td>93.75</td>
</tr>
<tr>
<td>117</td>
<td>293</td>
<td>22.5</td>
<td>7.5</td>
<td>135.0</td>
</tr>
<tr>
<td>118</td>
<td>250</td>
<td>27.0</td>
<td>10.0</td>
<td>113.6</td>
</tr>
<tr>
<td>119</td>
<td>188</td>
<td>29.0</td>
<td>10.82</td>
<td>88.25</td>
</tr>
<tr>
<td>120</td>
<td>238</td>
<td>23.85</td>
<td>15.0</td>
<td>71.15</td>
</tr>
<tr>
<td>121</td>
<td>245</td>
<td>47.0</td>
<td>20.0</td>
<td>110.25</td>
</tr>
<tr>
<td>122</td>
<td>157</td>
<td>39.75</td>
<td>25.0</td>
<td>76.64</td>
</tr>
<tr>
<td>123</td>
<td>234</td>
<td>44.0</td>
<td>30.0</td>
<td>105.95</td>
</tr>
<tr>
<td>124</td>
<td>152</td>
<td>45.6</td>
<td>30.0</td>
<td>66.4</td>
</tr>
</tbody>
</table>

ments were performed with doses of morphine extract greater than one and a half minimal lethal dose.

Series IX. This series in which atropine was administered half an hour before morphine excludes experiments most of the earlier experiments. The experiments have been carried so far as is indicated in the above table and the existence of an antagonism has been demonstrated when it was suggested that a series of experiments in which the atropine was given half an hour after the
Morphine would have a greater practical value. The results in this series show perhaps more incisiveness than in any other series, probably, because of the lesser skill that was exercised in making the earlier subcutaneous injections, which at first on account of the great thinness of the rat's skin was not always with certainty attained. The deaths in experiments 119 and 113 are undoubtedly quite accidental and due to some other incidental cause. Of course in such a series of experiments in which the atropine was injected half an hour before the morphine, smaller doses of morphine would be expected to limit the antagonism at either end of the range. So, notwithstanding the series is of little value and is only included here because this description via description of the research as it was conducted.

The action of morphine as modified e.

The actual notes of the experiments extend to 165 closely written pages of this size. The transcription of such a mass of notes would serve little purpose, because in view of the detailed way in which observations were made on every experiment the order of many experiments are practically repetitions of similar detail, time and time again. The results of some of the antagonism
experiments are here given in tabular form. This method of stating the observations made gives them a definiteness which the notes themselves, done in a more or less casual way, do not possess. On starting a summarising of great masses of necessary facts out of time, a few or two typical experiments will be transcribed in full. The summary was made by first tabulating all the facts then reducing the number of these details by making new tables out of which all useless or confusing quadrals were omitted, so as to obtain a certain uniformity, without presenting a falsely definite picture of the experiments.

It would be difficult to say whether in observing into which the lethal action of morphine was modified by the co-administration of atropine alone, and knowing that the combination was that of atropine and morphine would able to recognise the manifestations as such. All the whole I would be inclined to say that if ignorant of the facts of the combination I should not have been aware of it, and had not perhaps recognised the symptoms (e.g. eye). With the action of the drugs individually,
### Table 1: Summary of Key Findings

<table>
<thead>
<tr>
<th>Category</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Economic Impact</td>
<td>Significant increases in market value and job creation</td>
</tr>
<tr>
<td>Environmental Impact</td>
<td>Reduction in greenhouse gas emissions</td>
</tr>
<tr>
<td>Social Impact</td>
<td>Improved quality of life and community engagement</td>
</tr>
</tbody>
</table>

### Analysis

The results from the study indicate that the implementation of sustainable practices has a positive impact on all three aspects: economic, environmental, and social. The data shows a correlation between the adoption of sustainable practices and the overall improvement in the community's well-being.

#### Key Recommendations

- **Economic:** Increase funding for research and development in sustainable technologies.
- **Environmental:** Implement stricter regulations on waste management and energy consumption.
- **Social:** Enhance public education programs to promote awareness and participation in sustainable activities.

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The effectiveness of the practices described above has been proven through case studies and empirical data analysis. Further research is recommended to explore additional strategies for maximizing the benefits of sustainable practices.
A voluntary movement and the capacity was more
marked the less the dose of morphia administered. The temp-
perature was less prominent, for the rats were heavily and
commonly recumbent, placed in their backs, and as a rule
they also showed during the first five or six hours a much
greater readiness to give response to voice or touch. There
was not infrequently a prolonged period of hyperexcitability
both these or similar. As regards the motor phenomena, the
plagued tonic extension seemed to come on sooner, and
with the larger doses of morphia its onset was marked
by such an extension of the limbs even to the digits that
the rat came to be raised on the fully extended limbs
with its back highly arched and its nose to the floor
and came to present thus a peculiar and character-
istic attitude like a stuffed annabelle or better
like a tortoise. This was transient, and gave
way to a rigidity of the limbs and spine as marked
as in the morphine alone but with little or no change
from it. The attitude of extended hind limbs pushing
rest of body forward, at same time that most of tail
and lower end of spine were dorsiflexed, so character-
istic of morphine alone was still produced. The
local opomas certainly had their onset delayed;
instead of appearing at the first they had not
appeared in 3 hours, in 6 or more, etc., with small
case of atropine, with larger dose of atropine only fine tremors occurred, and if the dose of atropine was large enough then local pains were altogether abolished. Convulsions in the same way were delayed, insensible severe and abolished i.e. atropine abolishes the tetanic action of morphine. It may here be remarked in passing that Langer has working and says with the assistance of Professor Böhme concludes that the lowering of blood pressure in morphine poisoning plays an altogether unimportant role also that the disturbance of respiratory never is sufficient to cause death, that much more constantly there was a stage of tetanus and that death caused not by fall in blood pressure and by respiratory disturbance, but through central nervous weakness consequent on the severe tetanus. It was a priori scarcely to be perceived how atropine could assist in alleviating this. Langer has performed his experiments on dogs and upholds both on the ground of experimental and clinical evidence the non-existence of an antitoxin. His writings on the matter are perhaps the best that have been published in support of the views of Bing but all his three main assertions are proved wrong by the present experiments for circulatory and respiratory are improved, and severe tetanus
...the action of atropine.

In regard to this very slight change was only between morphine alone and with atropine beyond the
constant and immediate fall of tension of the pupil, one
sign seemingly of the presence of atropine to some slight degree
the action of the morphine, as it also seems to have a
much more rapid lesser effect than morphine. Atropine
of the eyeball, lachrymation, loss of conjunctival reflex
etc. occurs in both. The rat is a very favorable
subject for studying the heart and respiratory phenomena,
while with care it was noted that the heart shows
greater acceleration than with morphine alone. The
respiration shows greater acceleration, but also shows
irregularly, the shallowness and tendency to a Cheyne-
Stokes-like type, and subsequent damp of the rate
after the earlier acceleration were constant phenomena
with smaller dose of atropine still occurs from
cessation of respiration before the heart. Constipation
only occurs for 24 hrs, and sometimes for not last as
long. Urine was also passed within 24 hours and the
appearance of blood in the urine was present. The addition
of the atropine had seemingly a marked beneficial effect
on the respiration of rats of e.g. 10/15 experiments (see
summary) e.g. experiments 76, 77, 78, 79, 81, 82, 84 both the
inside atropine was too small and when it was too large the
Respiration ceased before the heart.

Atropine and morphia when taken together do not act with equal effect in any combination, they do not annihilate each other's action. The reaction must be a very complicated one. As has already been remarked the effects produced by a combination of the two drugs presented a picture almost quite new, and which without previous knowledge one could not readily at all recognize as being that of morphia modified by atropine. What is much more surprising is the extreme smallness of the doses of atropine which so fundamentally alter the action of morphia. This extreme smallness of the dose is in keeping with the fact that in isolated organs the most powerfully antagonistic effects are produced e.g. on the heart by doses of atropine, parasympathetic, when given alone would be without action. The antagonism is only a perfect antagonism and will be alluded to later when its nature comes to be more fully discussed.

**General Summary**

The account of the experimental work has been completed. It has been demonstrated that in white rats atropine sulphate administered in almost surprisingly small doses annihilates, before and after, with such doses of morphia tartrate as to retain in life animals that would otherwise have died, and that atropine sulphate is only able to retain in life when it is administered simultaneously with morphia tartrate, provided
Les been constructed after the method of Aronson and Fraser and exhibit the features of the antagonism as they have been demonstrated in the course of experiments in which the two drugs were simultaneously administered. The scale of abscissa is represented as increasing from left to right, every two perpendicular divisions being equal to ½ of a milligramme. This large scale was necessary in order to display the features of the range of antagonism. The red horizontal line represents the minimal lethal dose of morphone; the lines drawn parallel to it represent increase or decrease by one-half of the minimal lethal dose. The area below the level of the minimal lethal dose and extended laterally to the right is of very great extent on this scale and is not represented sufficiently for the experiments performed in this region being increased. Experiments in which recovery occurred are represented by • (60½%); those in which death occurred by + (cross). The line a-b which passes between these two series of approximates the area of recovery (red) from the area of non-recovery (blue). The whole intermediate area indicates that portion of the area of recovery within which the antagonism depends very largely on the maintenance of a suitable capable temperature without which recovery is substantial or does not occur. This
Influence of temperature was only marked with the larger doses of morphine. The very gradual descent of the line a-b, below the level of the minimal lethal dose of morphine is the noted.

Some remarks on the nature of the antagonism.

The relation of the dose of amytal to the dose of morphine in the simultaneous administration experiments is worthy of attention. There would appear to be a very definite relation between the increase in the lethal dose of morphine, and the increase in amytal. Therefore, the necessary in the minimum and maximum doses that limit the antagonism. It is not rational that the increase required in the minimum limit ohes have a very definite relation to the decrease demanded in the maximum limit of the extent of antagonism, and further that the minima and maxima of different series should have a very definite relation to one another. If these relationships can be deduced a step in the direction of obtaining a more, insight into the nature of the processes involved in the antagonism will have been taken. All sorts of methods of treating the figure obtained from the experiments have been
tried with but not different results, the simplest method became in the end the most promising, and at least gives some information of interest. The results may be stated as follows:

<table>
<thead>
<tr>
<th>Table i: Series</th>
<th>One min. leth. dose of At required a minimal of 0.025 mg., and an Atleon of more than a comp. of 0.75 mg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series I</td>
<td>0.075 mg.</td>
</tr>
<tr>
<td>Series II</td>
<td>0.075 mg.</td>
</tr>
<tr>
<td>Series III</td>
<td>0.75 mg.</td>
</tr>
</tbody>
</table>

or if this be stated in equivalents for each half min. leth. dose of morphine:

<table>
<thead>
<tr>
<th>Table ii:</th>
<th>One half min. leth. dose required a minimal of 0.028 mg., and an Atleon of more than 0.75 mg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series I</td>
<td>0.028 mg.</td>
</tr>
<tr>
<td>Series II</td>
<td>1.5 mg.</td>
</tr>
<tr>
<td>Series III</td>
<td>0.062 mg.</td>
</tr>
</tbody>
</table>

The figures in the series of minimal doses have a relation and those of the series of maximal doses have also a relation and these relations may be expressed in terms of Table ii as follows:

<table>
<thead>
<tr>
<th>Table iii:</th>
<th>Minimal may be represented by 1/16, maximal may be represented by 16 according to 1/16.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series I</td>
<td>by 2</td>
</tr>
<tr>
<td>Series II</td>
<td>by 4</td>
</tr>
<tr>
<td>Series III</td>
<td>by 1</td>
</tr>
</tbody>
</table>

Stated in words, this means that a half minimal lethal dose in Series II requires twice as much atropine and a half minimal lethal dose in Series III four times as much atropine as a half minimal lethal dose in Series I. A half minimal lethal dose in Series II can only stand one quarter, and in Series III only one sixteenth as much atropine as a half minimal lethal dose in Series I. It is intelligible that an additional
If a minimal lethal dose might be not only lethal, but to speak more than lethal, i.e. possesses of excessive lethal potency when added to an already lethal dose. The figures above given show that in series ii—i.e. lethal potency may be measured by the atropine equivalent—the lethal potency of each half minimal lethal dose was equal to that of one minimal lethal dose alone, i.e. the lethal potency was doubled, and similarly in series iii it is quadrupled. One would have expected that the lethal potency would be likewise doubled and quadrupled at the maximum limits of the series. But instead of being doubled it is quadrupled and instead of being quadrupled it is sixteen times as great, this however is not a contradiction but really the consequence of the lethal potency of morphine being doubled and quadrupled. Because by this respect the influences acting between the atropine and morphine at the maximum limit and leading to death must be in the same proportion accentuated—i.e. the lethal potency of the morphine creeps up, it calls forth an equally increased reaction from the atropine. Both Stage therefore, as it were, make demands on the area of recovery (i.e. in the chart etc.) and once it is
that there is the so much greater encroachment on the area of recovery from the maximal side of the curve. It also follows that increase in the lethal dose of morphine reaches a stage where theoretically antagonism requirements call for more, and the relation between the quantity of morphine and the (maximal) quantity of atropine demand less atropine — equilibrium is no longer possible, nor is lethal antagonism. There must exist a point at the apex of the area of recovery where the dose that just antagonizes the morphine is very nearly the dose that is just too much. So soon as the quantity of atropine required by the amount of morphine, for the successful antagonism of the latter, is such, that it is also a dose too large to be compatible with life, the quantity of morphine has ceased to be capable of antagonism. For example on the above principles and figures two and a half minimal lethal doses of morphine call for at least 0.2 mgm of atropine (i.e. 16 times 0.0125 mgm value of half minimal lethal dose in Series I) for each half minimal lethal dose present. But on the maximal side such a dose of morphine demands that for each half minimal lethal dose there shall not be more than 0.015 mgm.
Antagonism is impossible therefore, and the maximum quantity of &mash; morphine capable of antagonism must be below this amount. In the experiments it chances that 24th. Leth. dose of morphine was after a great deal of trouble antagonised. The dose of morphine was 0.338 mg. Hallowance be made for unavoidable error it will be recognized that the amount of morphine capable of being antagonised and the amount of atropine with which it is theoretically possible to antagonize it are not very inaccurately located by this arbitrary recovery among the fourteen experiments with a dose of morphine greater than two minimal lethal doses. In view of limited number of experiments performed with doses of morphine less than one lethal dose any attempt to bring the conditions pertaining in this area into similar numerical relationship would at present parasites too much of the nature of pure speculation to justify any attempt to do so.

It is all necessary to enter into any discussion of what is meant by chemical and physiological antagonism. It need be only remarked here that the apart from all other consideration the numerical relations between the doses of atropine which
antagonize the smaller and large doses of morphine at the limits of the range of antagonism sufficiently and conclusively prove that the action is not a chemical one. Here is not the slightest evidence in support of the view of those who advocated that such antagonistic action is chemical. The facts are all dead against the fundamental law of chemical reaction that any share whatsoever in the production of the antagonism. The increase in the size of morphine does not call forth a proportionate increase of all the antagonizing doses of atropine with the same ratio between the minimal and maximal antagonizing atropine doses as that with a pair comparable the range would be measured off as of equal extent for each increment of morphine, only increased by the scale of atropine doses. An such conclusion exists. Reaction is a physiological one whereby the action of morphine is modified or hindered, it cannot be said to be annihilated. By the atropine in their doses of atropine and morphine have not been shown to exist which if given together remain physiologically neutral combination in the body. August 9, 1900.

This investigation into the antagonism between
adrenaline and morphine supports the strongest way the validity of the explanation which Prof. Dr. S. has given of the limitations which are the characteristic of such lethal antagonisms between two drugs. In the combined action of the two drugs that equilibrium, so to speak, which is essential to life is only established within certain limitations of the doses of either, i.e. the multiple of the minimal lethal dose which can be antagonised is limited, and the quantities of the antagonising agent are also limited. The causes which underlie this limitation are indicated by a study of the actions of the two drugs when given alone and when given together. Experiments on the antagonism between adrenaline and morphine demonstrated very clearly that some of the actions of adrenaline and morphine must be regarded as being mutually antagonistic, if this there was the most manifest evidence. e.g. acceleration of respiration, effects on heart rate etc. Certain of the obvious effects of the two drugs were of similar nature e.g. production of tonic and clonic effects, protrusion of eyeball etc. No doubt also both drugs possess actions of different nature which are also not mutually antagonistic actions. Therefore, each substance possesses a variety of actions of
Considerable number, the extent of the lethal antagonism between them is limited by the following reasons. When given together in sufficient quantities each constituent acts promiscuously, the sum of the effects of which may, with standing the antagonism of other effects, be sufficient to produce death. Similar actions also will act by summation which in the case of a large dose of one and a small successfully antagonising dose of the other may well be of moment that becomes so when the large dose of the one becomes much larger and the dose of the antagonistic agent is also increased; therefore a dose not much above the minimal will be antagonised by a small dose of the antidote, and a dose much larger than the minimal lethal will not be antagonised by a large dose of the antidote. On account of the reinforcement of similar action, i.e., supposing other factors are left out of account, the actions that are mutually antagonistic are probably to in very varying degree by perfection and certain combinations of doses of the two drugs, will result in such triumphe, or lack of equilibration in the antagonism. Red blood may occur without the agency of non-antagonised, or similar actions playing...
any important part. These considerations afford a full explanation of why the successful antagonism of doses of atropine against the lethal action of morphine only succeeds within a definite limit of doses of morphine and of atropine. The fact that a combination of non-lethal doses may be lethal is also a consequence of the existence of actions which are all mutually antagonistic only so within definite proportions for some time as the limit of antagonistic action is reached, and passed in an action previously under the influence of morphine, antagonism may become much more potent for evil. The summation of the effects of similar actions will also be most marked in combinations of non-lethal doses. It is not necessary to show how equally applicable the foregoing considerations are to the occurrence of a fatal issue which is consequently an e.g. the combined action of half the lethal dose of morphine and one third the minimal lethal dose of atropine, nor is it necessary to deny further the truth of the assertion that the occurrence of death under the action of combined non-lethal doses, is a contradiction of the statement that smaller doses of atropine can antagonize lethal doses of morphine. It was intended to have worked out very fully the
field thus arose up regarding the number and ratio of actions of two drugs which are mutually antagonistic, similar, and non-antagonistic. Morphine and morphine can very favorably account for this observation which was commenced in the Pharmacological Institute Berlin. A large number of experiments were performed on frogs but progress had only got as far as becoming better orientated in the matter when work of greater practical value called forth cessation. It also was anticipated that by studying more carefully the phenomenon of combined action of the two drugs perhaps a greater insight into their combined action could be acquired, in the first place from the establishment of the exact numerical relations of the simultaneous burning in the areas of recovery and death.

The fact of the existence of actions which are mutually antagonistic, similar, and non-antagonistic is of course also the reason why in combined action the appearance is presented as of a new drug. The degree and nature of the antagonism existing with for e.g. small and large doses of morphine will result in correspondence new combinations of actions and therefore in the
production of novel manifestations such indeed are indicated within the range of successful antagonism in the summary that has been given of some of the antagonism experiments. One obvious novel phenomenon was the occurrence of a so-called "psychic attitude." It has also been remarked that one would with difficulty recognize that the action was produced by a combination of chlorpromazine and morphine, although it was as amile easy to recognize the probability of certain actions being the result of chlorpromazine and others as being the result of morphine.
Some general considerations.

The facts which we record and the general results of these experiments are to confirm in the most emphatic way the results obtained by Professor Fraser in regard to the lethal antagonism which he demonstrates. Doses of atropine were able to exercise an antagonist effect on lethal doses of physostigmine. The present experiments account for the circumstances under which they were carried out and the antagonism that have taken place in their continuation are nothing like so complete a study of the antagonism between atropine and morphine as that of Professor Fraser on atropine and physostigmine.

In the case of atropine and morphine the range of doses capable of removing the lethal action of morphine is of much less extent than in the case of atropine, and whereas physostigmine can be antagonised in doses three and a half times as large as the minimal lethal, only two or a quarter times the lethal dose of morphine can be antagonised. In regard to this difference, if the figures of Professor Fraser's experiments be calculated out in the terms of the quidrical system and
a chart similar to the one which accompanies this paper constructed on the basis of this calculation the following points are to be noted. The range of recovery, e.g. for the minimal lethal dose of physostigmine in rabbits is found to be three times greater than the range of recovery for the minimal lethal dose of morphine in white rats. Further the dose of morphine sulphate fatal for rabbits in Professor Fraser's experiments was exactly 3 of that which has now been determined to be the minimal lethal dose for white rats. The question now arises is the apparent accident, or was the range of antagonism in the present series of experiments limited to one third of the range in Professor Fraser's experiments because the animals used were one third as susceptible to the action of atropine? Of course atropine is not the only factor in the antagonism and the reactions which take part in the antagonism of physostigmine may be altogether, and must be in considerable degree, quite different from those which are concerned in the antagonism of morphine. It may well be able justifiable to compare experiments performed in the one case on rats and in the other case on rabbits. The point however is worth
tainty as giving an indication for future enquiry
the possible relationship between the extremely
small range of lethal antagonism of atropine to
morphine and the extreme non-susceptibility of the
white rat.

Does a reciprocal antagonism between
atropine and morphine exist? In the literature on the
subject of the actions between atropine and morphine
one frequently finds the statement that morphine
has a lethal antagonism to atropine but atropine
has no such relation to morphine. Professor Bayer
in his work on atropine and physostigmine makes
no allusion to the actions of physostigmine on lethal
doses of atropine. The natural inference from this
silence is that Professor Bayer had made no investiga-
tions in the matter and therefore expressed no
opinion. This silence has however been otherwise
interpreted, among others by Bresadola and Föhrlich,
who state that although Professor Bayer himself did
not formulate the conclusion that the conclusion must
be drawn from his experiments that "a lethal dose of
atropine cannot have its lethal action removed by
any dose of physostigmine. That as they have found
no reciprocal antagonism in regard to single
opium as also this is confirmed by Professor Bayer.
work in regard to the accruing of life. They had drawn the conclusion that antipyrine was as little able to abolish death from physostigmine as physostigmine was from antipyrine. While in the latter point their own and Professor Fraser's results entirely agree, Professor Fraser shows by an extraordinary number of experiments that small doses of antipyrine can be taken in life after 4 minimal lethal doses of physostigmine. So they cannot say any one member of experiments against those of Professor Fraser. They cannot contradict him. Nevertheless they must uphold the correctness of their observations and conclude that the different results are due to the used a different physostigmine preparation. They continue "we cannot forbear to draw attention to the fact that in Fraser's experiments themselves a preliminary contradiction is solved by him. Thus, viz. that while on the one side after lethal doses of physostigmine the animal can be saved by small doses of antipyrine, animals in which just lethal doses of physostigmine and just lethal doses of antipyrine were given in the same series of experiments, and with the same time interval, died." Therefore the "contradiction" is again referred to as removing the proof of the lethal
antagonism. Such a way of stating or rather of mis-stating the facts demonstrated at once a grave misconception of the import of the experiments in which the criticism is passed. The opinion expressed would not be worth giving prominence to were it not uttered by me regarded as expressing with authority, and whose opinions are today widely accepted in Germany and have only recently been republished. The explanation of the misconception is to be found in Rosbach and Folkers' preconceived "general rules" regarding antagonism which did not, it is to be feared, allow of their seeming facts in a light incompatible with their theories.

In the chart the area below the lethal dose of morphine lactate and extending laterally to the right towards the minimal lethal dose of antipyrine sulphate, is on account of the large scale on which the milligrammes of aspirin and the small scale of which lethal dose of morphine are represented a very lengthy one. It has been intended to investigate this area more fully for the following reasons: the relation between the antipyrine and morphine and whatever tissues are involved in the cause of death from a combination of non-lethal doses of the two drugs is one of great
Most investigators have asserted the existence of a lethal antagonism of morphine to atropine. Curiosity was aroused as to where the line a-b, which in the chart separates the areas of recovery and death would cut the zero line of morphine doses. This line a-b gradually approaches the zero line of morphine doses, and might cut this line before coincident with, or beyond the position on it of the minimal lethal dose of atropine sulphate, or fourthly, might cut out the zero morphine line, while and the separation of the areas of recovery and death be abruptly bounded by the perpendicular which marks the minimal lethal dose of atropine (this was a priori not likely). Of the course of the line a-b, the observer will observe that every diminution in the quantity of morphine is accompanied by a diminution in the gradient of this line, and that the diminution in the gradient in the region of the low minimal lethal dose of morphine has become so great as to afford a striking contrast to the sharpness of the gradient in the region of the lethal doses of morphine (see chart 2). At first thought it would seem that this line a-b was likely to gradually swing towards the zero of morphine dosse till the first quantity of atropine...
Chart 11. Knock out

1. Magnesium and morphine combinations as ascertained.
2. Hypothetical interpolation of the descent of the line a-b separating areas of death and recovery towards the minimal lethal dose of morphine.
was reached, which without the addition of any morphia
was unable to cause death i.e., if the minimal lethal dose
of atropine was reached and not coincident with this
position—really just before it—the line a—b would
cut the zero of morphia doses. This would mean
and of course, and because of a—b cut the zero line
of morphia doses it would also mean that the dose
of morphia was compatible with life if given above
with a lethal dose of atropine. But the manner
the descent of a—b requires consideration. If it be
borne in mind that the gradient, which had become
so gradual for half the minimal lethal dose of morphia
would in conformity become yet more gradual still
for a quarter and for others yet smaller fractions
of the minimal lethal dose of morphine every little
calculation was required to make one doubt if the
space required for the descent to the zero line
of morphia to continue, did exist within the limits
fixed by the position of the minimal lethal dose of
atropine, and that at any rate for the merely fractional
doses of morphia (e.g., the minute dose of atropine which
antiaginie morphia) this limit might be exceeded
under the mere effect of the quantity of atropine
having reached the minimal lethal causes the
line a—b separating the areas of recovery and
Seehl abruptly turned particularly down the ordinate to the zero line of morphine dose. This would be the one effectiveness in the whole subject of the antagonism. Here seems no reason why the graphs be so, and a possibility at least that the line a-b would be found to cut the ordinate of the minimal lethal dose of atropine, denoting then of course at a point corresponding with the maximum dose of morphine able to antagonize the minimal lethal dose of atropine. (The corresponding point for atropine is about 1/4 of the minimal lethal dose for the simplest lethal dose of morphine). The line a-b would then continue its descent through the corresponding maximum morphine points till the maximum dose of atropine capable of being antagonized was reached. Turning round this point the line would return through the minimum points of atropine for each lethal dose of atropine, towards the ordinate of the minimal lethal dose, the ordinate of which would then serve to constitute the boundary between the areas of recovery and death.

The definite fact which illustrates that the addition of any dose whatever of morphine to a lethal dose of atropine, or vice versa lethal antagonism to the lethal effects of the atropine can
be found. Nor can there be found anything more than ascertains that such an antagonism exists. The above considerations made it interest to look for the existence of at least a small range of lethal antagonism of morphine to atropine and desire to know whether such an antagonism existed or not. It may be that no such antagonism exists; but there is no proof that it does not, and throughout the preceding experiments the relations of the quantities of atropine and morphine, and the charts, give no evidence to the contrary. The range of the antagonism of atropine to morphine is only from 31300 to 10 a - a range so surprisingly small, that it was easy to miss it altogether. There is no reason to suppose that, should a lethal antagonism of morphine to atropine exist, it would be found to be of a wider range. It is much to be regretted that no opportunity has been found for more fully investigating the limitation of the area below the level of half the minimal lethal dose of morphine, i.e. for definitely establishing the existence or non-existence of a lethal antagonism of morphine to atropine. At the pharmacological institute in Berlin a beginning was made, but the work was left at a point whichmoendship view.
Therapeutic Hearing of the Mouse, etc.

In the first place it has been proved that atropine really possesses the power to sustain life when otherwise death would occur from morphine poisoning. Although the heart is susceptible both to atropine and morphine there is no reason why one may not continue to assert that such an antagonism will also exist in the case of the higher animals and also in man. On the contrary the great amount of experimental evidence that has accumulated especially in regard to dogs (Bing, Heinbach, Vollmar, etc.) of the favourable influence exercised by atropine on, in particular, the heart, blood pressure, and respiration depressed by morphine, receives additional weight from these experiments. The clinical experience of similar occurrence in man also enhances in value. Contrary evidence in regard to individual organs and life itself has lost its weight entirely taken away, for without denying the first whiteness of the evidence it can be interpreted in a way in accordance with the results of the present experiments and as evidence really in support of them.
Without exception, opponents to the程式化的 antagonism, who have themselves experimented (Cohnbarty, Polaszek, Unversicht, Krapstein, etc.), have based their opinions on researches in which they employed doses of atropine very much too large for an antagonistic action to be exercised. Their experiments have usually been performed in the area wherein non-lethal doses of atropine are combined with such doses of atropine that death results. On the other hand, Bing and his pupils have performed their experiments in the area where non-lethal doses of atropine can be combined with certain smaller doses of atropine with beneficial results. Occasionally actual lethal doses of the two drugs have been combined.

The opinions of these opposing factions are correct if limited to the special circumstances of experimentation but are of no general application to the question of antagonism between atropine and morphine.

Briefly, this investigator believes that atropine is to be used and it must be regarded as justified to use it in relieving opium or morphia poisoning if it must be given in very much smaller doses than have usually been advocated. Bing, who has most recently
Ille gluumphung recommmends 10 to 80 mg per report 10 mg per report every half hour. Any dose that is to be given should be given as one administration to delay in giving is only to give the morphine the greater start. And transcap heavily the morpnyne in the struggle. Time has been shown to have an important bearing on the antagonism and giving a dose in instalments is only another special form of delay in administration. Possibly the best dose to give would be one of 1.5 mg. on no account to be repeated. The impatience which seems to be the basis of the general recommendation of repetition is without any justification. The antagonism is a slow process unaccompanied by sudden disappearance of all symptoms of poisoning, and is certainly not accompanied by marked manifestations which have seemingly been anxiously looked for.

In view of the fact that in many cases of poisoning non-lethal, or doses very little over the lethal are the cause, the risk of converting a non-lethal dose of morphine into a lethal one requires emphasis and must be borne in mind.

The experiments have further demonstrated the great importance of warmth in administration.
and have also indicated very distinctly that excessive handling contributes to death, which calls forth a protest against the rigorous mechanical stimuli of patients, and the advocacy both of absolute rest and absolute quiet for such patients. Infancy again seems to be the basis for the rigorous treatment in vogue, for it can hardly be conceived to serve any rational purpose in morphine poisoning.

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Simple view of the interduralism between atrophies and morphine showing area of recovery with morphine alone (white) and when morphine is antagonised by atropine (stippled white).

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