Hence, putting Δ for a in the integrated result above, we have for the potential at σ

$$\frac{2\pi a}{T\Delta}\left(\epsilon^{a\mathrm{T}\Delta} - \epsilon^{-a\mathrm{T}\Delta}\right)\mathrm{F}\mathrm{T}\sigma .$$

That this may be constant, $= 2\pi a\mathrm{V}$ suppose, so long as $\mathrm{T}\sigma < a$, we must have

$$(\mathrm{T}\Delta)\mathrm{V} = \frac{2}{\mathrm{T}\sigma}\Big[(\mathrm{T}\sigma + a)\mathrm{F}(\mathrm{T}\sigma + a) - (\mathrm{T}\sigma - a)\mathrm{F}(a - \mathrm{T}\sigma)\Big];$$

which gives at once

$$\mathrm{V} = \text{constant} = 2, \text{ suppose,}$$

and

$$\mathrm{F}x = \frac{1}{x},$$

the gravitation law.

And as the operator becomes, for $\mathrm{T}\sigma > a$, by expansion

$$2a\left\{1 - \frac{a^2\Delta^2}{1.2.3} + \frac{a^4\Delta^4}{1.2.3.4.5} - \ldots\right\}$$

while

$$\Delta^2 \frac{1}{\mathrm{T}\sigma} = 0,$$

we have for the external potential the usual expression

$$\frac{4\pi a^2}{\mathrm{T}\sigma}.$$

5. An Experimental Research on the Antagonism between the Actions of Physostigma and Atropia. By Dr Thomas R. Fraser. (With a diagram.)

(*Abstract.*)

In a Preliminary Note, read before this Society on the 31st of May 1869 (see *Proceedings*), a number of experiments were described, which proved that the lethal action of certain doses of physostigma can be prevented by the administration of atropia.*

* June 1871.—While this Abstract is passing through the press, the author has received a paper by M. Bourneville, in which the above result is satisfactorily confirmed by experiments on guinea-pigs.

Further, it was pointed out, that antagonism between any two substances, in the sense of the lethal action of the one being preventible by the physiological action of the other, had not previously been shown to exist by any certain and satisfactory evidence. In the various instances where experiment seemed to indicate the existence of such an antagonism, sufficient proof was not given that the dose of the substance whose action appeared to be antagonised was certainly a lethal one. The conflicting opinions and doubts this fallacy has given origin to, have induced the author to follow a plan whereby it may be completely avoided.

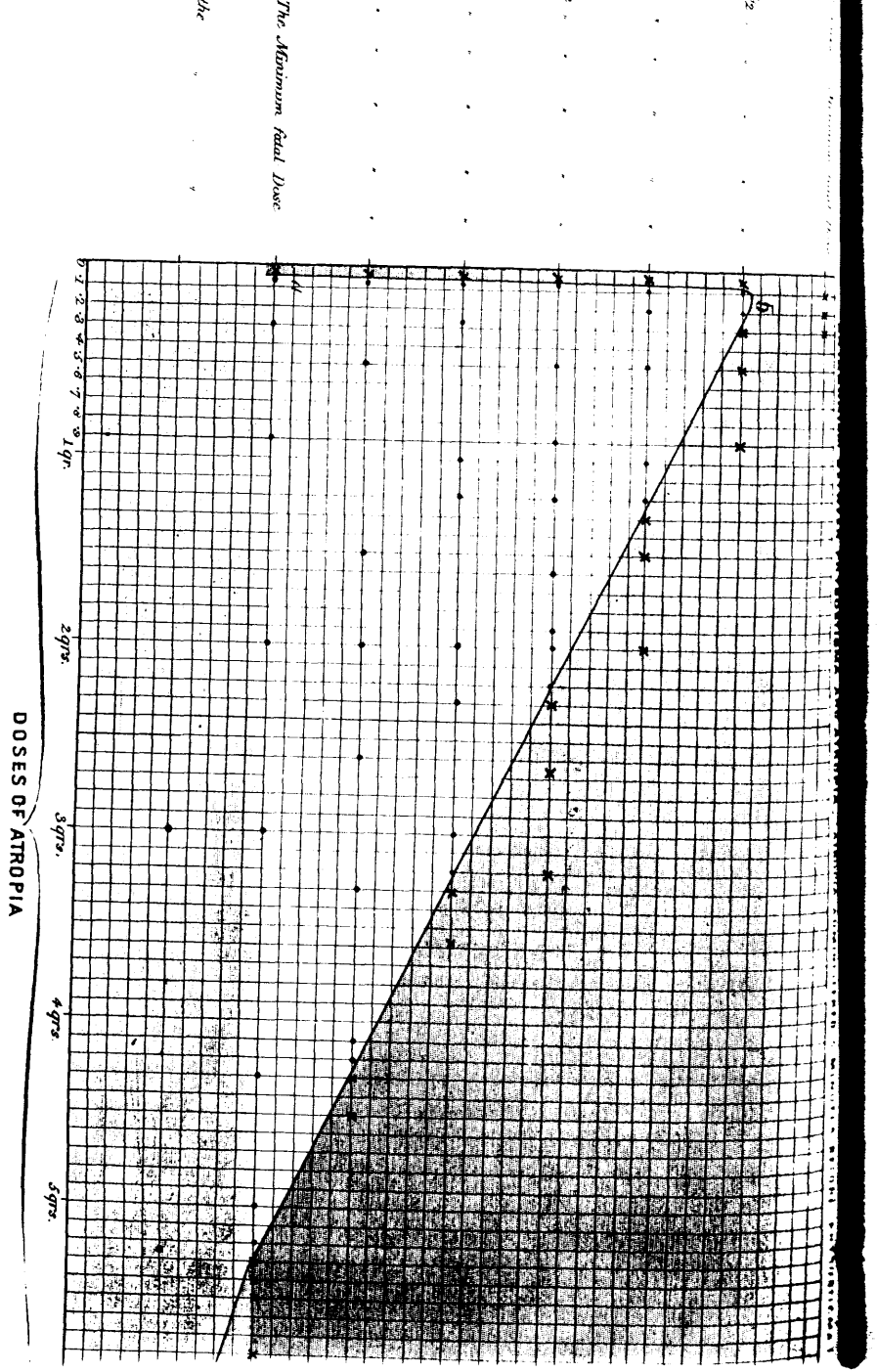
In the first place, the minimum fatal dose of physostigma for the species of animal employed was accurately determined by a number of preliminary experiments: so that the weight of the animal being ascertained, it was an easy matter to be certain of the dose that could kill it. Then, in those experiments where an animal recovered after the administration of a dose of atropia given in combination with a dose of physostigma, equal to or in excess of the minimum fatal, it was killed many days afterwards, and when the effects of the two substances had completely disappeared, by a dose of physostigma, equal to or less than that from which it had previously recovered. *Therefore, when the administration of atropia prevented an otherwise fatal dose of physostigma from causing death, a perfect demonstration was obtained of the power of atropia to produce some physiological action or actions that counteracted some otherwise lethal action or actions of physostigma.*

In the preliminary note referred to, it was suggested that, as both atropia and physostigma are capable of producing a number of different actions, several of which may not be mutually antagonistic, and that, as both substances are capable of producing several actions of a similar kind, considerably less potent to cause death than those by which their fatal effects are usually induced, it would probably be found that a region exists where the non-antagonised and the similar actions are present in sufficient degrees of activity to be themselves able to produce fatal results. This anticipation has proved to be correct. A large number of experiments have been made, by which the region of the successful antagonism of fatal doses of physostigma has been defined with considerable exactness. The smallest and the largest doses of atropia that are able to pre-

vent death after the administration of different fatal doses of physostigma, and the maximum fatal dose of physostigma that is capable of being rendered non-fatal by atropia were ascertained, and it was found that beyond these various points death may be produced by combined doses of the two substances, either by some non-antagonised action belonging to one or other of them, or by a combination of similar actions belonging to both.

As the above results could be obtained only by performing a very large number of experiments, rabbits were the animals selected, it being impossible to obtain a sufficient number of dogs, or other convenient animal. The weight of animal employed was, as nearly as possible, three pounds; and when below or in excess of this a correction was made, so that each dose represented three pounds weight of animal.

In one portion of this investigation, experiments were performed in which physostigma was given five minutes after atropia, both substances being injected under the skin. In the first series, the dose of physostigma was the minimum fatal, and the doses of atropia ranged from one that was too small to prevent the lethal action of this dose of physostigma, through a number of gradually increasing doses of atropia that were able to prevent death, until a dose was found whose administration resulted in death. Similar series of experiments were made with doses of physostigma one and a-half times, twice, two and a-half times, thrice, and three and a-half times as large as the minimum fatal. With the minimum fatal dose of physostigma, it was found that while ·01 grain of atropia is too small to prevent death, ·015 grain is able to do so; and that with any dose ranging from ·015 grain to 5·2 grains the lethal effect of this dose of physostigma may be prevented; while if the dose of atropia be 5·3 grains or more, the region of successful antagonism is left, and death occurs. With one and a-half times the minimum fatal dose of physostigma, successful antagonism was produced with doses of atropia ranging from ·02 grain to 4·2 grains; with twice the minimum fatal of physostigma, with doses of atropia ranging from 025 grain to 3·2 grains; with two and a-half times the minimum fatal of physostigma, with doses of atropia ranging from ·035 grains to 2·2 grains; with thrice the minimum fatal of physostigma, with doses of atropia ranging from ·06 grain



to 1·2 grain; and with three and a-half times the minimum fatal dose of physostigma, with doses of atropia ranging from ·1 grain to ·2 grain. Successful antagonism could not be obtained above this dose, and, accordingly, three and a-half times the minimum fatal dose of physostigma would appear to be about the largest quantity whose lethal action may be prevented by administering atropia five minutes previously.

A similar series of experiments has been made, in which physostigma was administered five minutes before atropia, and the results were essentially the same, excepting that the region of successful antagonism was found to be more limited.

These results may be graphically represented by means of diagrams. The diagram accompanying this abstract is a reduced copy of one exhibited by the author to illustrate the series of experiments above described, in which atropia was administered five minutes before physostigma. The experiments that terminated in death are marked by crosses, and those that terminated in recovery by dots, while the position assigned to each experiment is determined by the doses of physostigma and atropia, calculated, when necessary, for three pounds weight of rabbit. The doses of atropia increase according to the distance, in a horizontal direction, from the perpendicular line forming the left margin of the diagram, and the increase proceeds at the rate of one-tenth of a grain for each subdivision of the horizontal lines. The doses of physostigma increase from below upwards, the same horizontal line always representing the same dose of physostigma. The curved line, *a b c*, separates the fatal experiments (crosses) from those which terminated in recovery (dots), and, accordingly, it defines the region of successful antagonism—a region further distinguished in the diagram by the absence of shading. The *darkly* shaded region is that in which antagonism is not successful, death being produced because the doses of atropia given in combination with one or other of the doses of physostigma employed are either too small or too large. In the *lightly* shaded region, below the horizontal line representing the minimum fatal dose of physostigma, the doses of physostigma are too small of themselves to cause death. The lateral extension of the diagram is, however, insufficient to exhibit the chief interest of this region. Were the diagram extended, it

would show that fatal experiments occur in this region, not only with fatal doses of atropia given in combination with less than fatal doses of physostigma, but also with less than fatal doses of atropia given in combination with less than fatal doses of physostigma.

In this manner, the entire *superficial area* of the region of successful antagonism has been defined, when physostigma is given five minutes after and five minutes before atropia. In addition to this, what may be termed the *thickness* of the region has been determined. For this purpose, series of experiments were made, in each of which the doses of physostigma were the same, and the doses of atropia varied; while with each dose of atropia, several experiments were made which differed from each other by a difference in the interval of time between the administration of the two substances. From the data thus obtained, curves have been constructed; the dose of physostigma serving as the base-line, the various doses of atropia as the abscissæ, and the different intervals of time that separate successful from unsuccessful experiments as the summits of the ordinates. When these curves are brought into relation with a diagram of the superficial area of the region of successful antagonism, in such a manner that the base-lines, representing the doses of physostigma, correspond to each other, and that the ordinates of these curves extend at right angles to those in the diagram of the superficial area, the lateral extension of the region of successful antagonism may be defined. In this way, its lateral as well as its superficial extent has been indicated with atropia and physostigma.

After defining the superficial area and the thickness of the region of successful antagonism, it seemed of interest to ascertain what dose of atropia is required to produce death with a dose of physostigma below the minimum fatal. The experiments performed for this purpose show that when one-half of the minimum fatal dose of physostigma is given five minutes after atropia, so large a dose of the latter substance as 9·8 grains is required in order to cause death; recovery taking place with doses ranging from 3 to 9·5 grains.

The minimum fatal dose of sulphate of atropia given alone was found to be twenty-one grains for a rabbit weighing three pounds.

It is, therefore, remarkable that the $_{2}\frac{3}{0}$ths of a grain can prevent a dose of physostigma, equal to the minimum fatal, from causing death, and that the $_{1}\frac{1}{0}$th of a grain is capable of rendering non-fatal a dose of physostigma, equal to three and a-half times the minimum fatal.

Excepting dilatation of the pupils, these minute doses of atropia, and indeed any dose capable of antagonising the lethal action of physostigma, are unable to produce any symptom recognisable by a mere inspection of the animal. Still, they undoubtedly produce energetic physiological effects—effects, however, which it is unnecessary to describe in this brief abstract. It is sufficient to point out that the notion, which exists in many quarters, that rabbits can scarcely be affected by atropia is an erroneous one.

Without referring to the other results obtained in his investigation, the author pointed out, in conclusion, that unless the antagonism between any two active substances be examined in the manner indicated in this communication, no satisfactory proof of its existence can be obtained. The superficial area of the region should always be defined, otherwise indications of antagonism obtained by one observer will be liable to be discredited by those who subsequently examine the subject. The first observer may succeed in performing an experiment within the area of successful antagonism, and thus feel satisfied of its existence; but his successors may fail in obtaining any proof by so varying the dose of one or other substance as to pass the limits of the region of success (see diagram). Feeling assured that many examples of successful antagonism, besides the one he had the honour of bringing before the Society, will yet be discovered, the author could not avoid the conclusion that the imperfect methods of investigation hitherto pursued are accountable for the absence of success that has attended the numerous researches made on this subject—a subject, it need scarcely be added, of the greatest importance to toxicology and to scientific therapeutics.