LECTURE

ON

THE ANTAGONISM BETWEEN THE ACTIONS OF ACTIVE SUBSTANCES.

Delivered before the Royal College of Physicians, Edinburgh.

BY

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LECTURE II.—(*Concluded.*)

Limits to the Antagonism between Atropia and Physostigma.—As both atropia and physostigma possess a number of separate actions, it was not unreasonable to anticipate that several of them are not mutually antagonistic; and, therefore, that combinations of certain doses of the two substances may be administered whereby the non-antagonist actions will be produced in sufficient degrees of energy to be able to cause death. The possibility of a fatal result ensuing after the combined administration of the two substances in certain doses is also rendered probable by many facts which show that several of their actions are of a similar nature. When a dose not greatly above the minimum-lethal of the one is counteracted by a moderate dose of the other, these similar actions are not produced in sufficient intensity to become, even in combination, important toxic actions. When, however, a dose considerably above the minimum-lethal of the one substance is given along with a large dose of the other, the similar actions may be produced in such intensity as to assume the importance of lethal actions.

Guided by these considerations, I anticipated that the counteracting influence of atropia upon the lethal action of physostigma is successfully exerted only within a limited range of doses, and that this range may be determined by experimental research. The task of making this determination was undertaken because it seemed likely that results would thereby be obtained of the greatest interest and novelty, in connexion not only with this special instance of counteraction, but also with the general subject of physiological antagonism and its important and direct bearing on the principles of therapeutics.

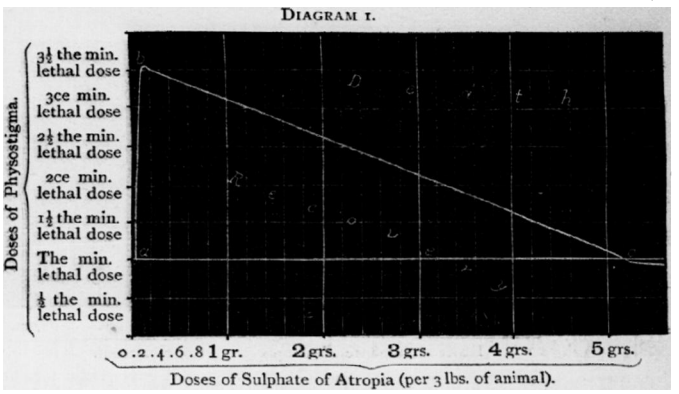
In order to define the limits of the counteracting influence of atropia upon the lethal action of physostigma, three series of experiments were made. The chief objects of the first two of these were to ascertain the maximum dose of physostigma that can be successfully antagonised by atropia, and the range of doses of atropia that can successfully antagonise lethal doses of physostigma. In each series, a constant interval of time was maintained between the administration of the two substances; but in the first atropia was administered five minutes before physostigma, while in the second physostigma was administered five minutes before atropia. In both of these series, experiments were made, in the first place, with the minimum-lethal dose of physostigma; and, in combination with it, various doses of atropia were administered, ranging from one that was too small to prevent the lethal action, through a number that were able to prevent death, until a dose was found whose administration resulted in death. Similar experiments were made with a dose of physostigma one-and-a-half times as large as the minimum-lethal, then with one twice as large as the minimum-lethal, and so on, at the same rate of progression, until a dose was reached that was too large to be successfully antagonised by any dose of atropia.

The chief object of the third series of experiments was to ascertain within what limits of time between the administration of the two substances successful antagonism occurs. In the experiments of this series, a constant dose of physostigma was given along with various doses of atropia; and 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. On this plan, two sets of experiments were performed, in one of which atropia was given before physostigma, and in the other after it; and subsequently these two sets of experiments were connected together by a third, in which atropia in various doses was administered simultaneously with the same dose of physostigma as was given in the two other sets of experiments. I found it necessary to make all the experiments of these three series on rabbits, as it was impossible to obtain a sufficient number of dogs or other convenient animal. The rabbits used were as nearly as possible three pounds in weight; but, when they were lighter or heavier than three pounds, a correction was made, so that each dose represented three pounds weight of animal. The two substances were administered by subcutaneous injection.

In the first series of experiments—where the atropia was administered five minutes before the physostigma—it was found that, when the minimum-lethal dose of physostigma was administered, 0.005 grain of sulphate of atropia is too small a dose to prevent death, but that 0.015 grain is sufficient to do so; and that with any dose ranging from 0.015 grain to 5.2 grains, the lethal action 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-lethal dose of physostigma, successful antagonism was produced by doses of sulphate of atropia ranging from 0.02 to 4.1 grains; with twice the minimum-lethal dose of physostigma, with doses of sulphate of atropia ranging from 0.025 to 3.2 grains; with two-and-a-half times the minimum lethal dose of physostigma, with doses of sulphate of atropia ranging from 0.025 to 2.2 grains; with thrice the minimum-lethal dose of physostigma, with doses of sulphate of atropia ranging from 0.06 to 1.2 grain; and with three-and-a-half times the minimum-lethal dose of physostigma, with doses of sulphate of atropia ranging from 0.1 to 0.2 grain. Successful antagonism could not be obtained above this dose; and accordingly three-and-a-half times the minimum-lethal dose of physostigma is the largest quantity whose lethal action can be prevented in rabbits by atropia administered five minutes previously.

To aid your comprehension of these results, I have prepared a diagram (Diagr. 1) in which they are shown in a graphic form. In this

DIAGRAM 1.



diagram, the doses of atropia are represented by the distance, in a horizontal direction, from the perpendicular line forming the left margin; and they increase at the rate of two-tenths of a grain for every subdivision of the horizontal lines. The doses of physostigma increase from below upwards; the minimum-lethal dose being represented by the thick horizontal line; a dose one-and-a-half times as large as the minimum-lethal, by the thin horizontal line immediately above the thick one; a dose twice as large as the minimum-lethal, by the next thin horizontal line; and so on until a line is reached near the top of the diagram, which represents a dose of physostigma three-and-a-half times as large as the minimum-lethal. The curved line, *a b c*, separates the fatal experiments from those that terminated in recovery;* and accordingly the space enclosed by it represents a region in which recovery always occurs, while the space on its outside represents a region in which death always occurs. With these explanations, the results of the experiments will be rendered apparent by a mere glance at the diagram. It may again be pointed out that the more obvious of these results are, that the maximum dose of physostigma which, in rabbits, can be rendered non-lethal by atropia administered five minutes previously, is about three-and-a-half times the minimum-lethal dose; and that the range of doses of atropia which are able to render non-fatal various otherwise fatal doses of physostigma, diminishes as the dose of physostigma increases. The general nature of these results is well illustrated in the diagram by the triangular form of the region of recovery after lethal doses of physostigma (*a b c*), of which the apex, *b*, indicates the maximum antagonisable dose of physostigma; and the gradual increase in breadth from the apex to the thick horizontal line, *a c*, the gradual increase in the range of doses of atropia that can prevent the fatal effect of doses of physostigma from diminishing from three-and-a-half times the minimum-lethal to the minimum-lethal.

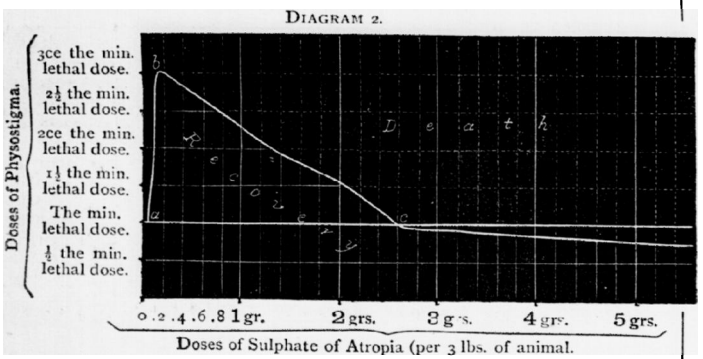
The considerations which led me to anticipate that the counteracting influence of atropia upon the lethal action of physostigma is successfully exerted only within a definite range of doses, and that death may

* In the diagrams exhibited during the lecture, the fatal experiments were marked by crosses, and the non-fatal by dots; but this has not been done in the reduced copies that are here inserted, as the required space is wanting.

be produced when a lethal dose of physostigma, which is capable of being rendered non-lethal by atropia, is given in combination with a somewhat large non-lethal dose of atropia, also led me to anticipate that death may be produced by the combined administration of non-lethal doses of the two substances. I accordingly made some experiments in which half the minimum-lethal dose of physostigma was administered five minutes after various doses of atropia. It was shown by these experiments that death occurs if the dose of atropia be one that is equivalent to about ten grains per three pounds weight of animal, or a larger dose. This result appears a very remarkable one, when it is considered that successful counteraction is produced by much smaller doses of atropia against the poisonous action of doses of physostigma greatly in excess of the minimum-lethal, and that the minimum-lethal dose of sulphate of atropia itself is about twenty-one grains. It, however, may be simply explained by supposing some action or actions of both physostigma and atropia between which there is no mutual counteraction.

The second series of experiments—in which, as you may remember, the physostigma was administered five minutes *before* the atropia—yielded essentially the same results as the first series, excepting that the region of successful antagonism was found to be a more limited one. This difference is apparent when the diagramatic representation of the experiments of the second series (Diagr. 2) is compared with that of the

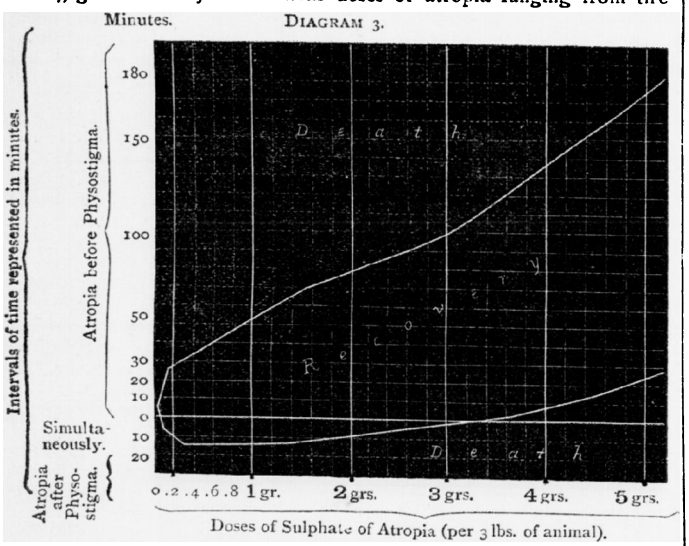
DIAGRAM 2.



first (Diagr. 1). In both series, the general result was obtained that the range of the doses of atropia capable of preventing the lethal action of physostigma diminishes according as the dose of physostigma is increased.

In the third series of experiments, I endeavoured to determine what influence the interval of time separating the administration of the two substances exerts upon the production of successful antagonism. I contented myself with making this determination in the case of one constant dose of physostigma (one-and-a-half times the minimum lethal), given in conjunction with doses of atropia ranging from the

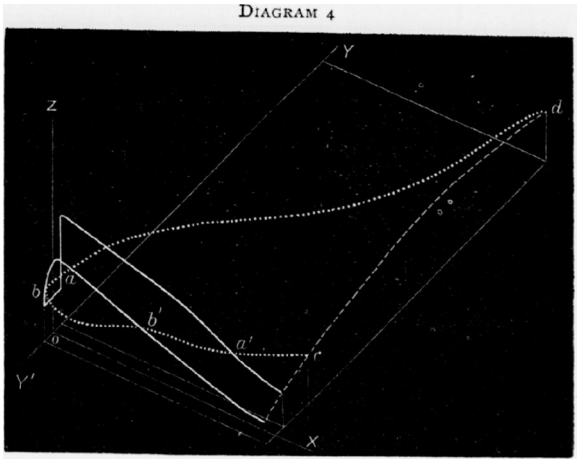
DIAGRAM 3.



one-hundredth of a grain to five grains. The general results of this series are represented in the diagram (Diagr. 3). Without occupying your time with details, I would merely point out that successful antagonism was found to occur with a greater range of doses of atropia, and with a greater range of intervals of time, when atropia is given before physostigma, than when it is given after it (shown in the diagram by the much greater extent, laterally and vertically, of the region of recovery above the thick horizontal line representing simultaneous administration, than below that line). In the latter case, the length of the intervals of time is obviously limited by there being a limitation to the time within which the dose of physostigma that was given itself produces death. In the former case, the intervals are not subject to a similar curtailment, seeing that the doses of atropia administered were all considerably below the minimum-lethal dose.

In the three series of experiments that have now been described, I have pointed out the limits of antagonism—firstly, when atropia is administered five minutes before physostigma; secondly, when atropia is administered five minutes after physostigma; and, thirdly, when atropia in various doses is administered at various intervals of time before and after one-and-a-half times the minimum-lethal dose of physostigma. You will observe that in each series, of the three quantities (namely, dose of physostigma, dose of atropia, and interval of time),

DIAGRAM 4



In this diagram, doses of physostigma are indicated by the distance (parallel to the axis of *z*) from the plane, YOX; doses of atropia, by the distance (parallel to the axis of *x*) from the plane, ZOY; and intervals of time between the administration of the two substances, by the distance (parallel to the axis of *y*) from the plane, ZOX, points on the Y side of this plane indicating atropia administered *before* physostigma, and points on the Y' side indicating atropia administered *after* physostigma. I am indebted to my friend Dr. Crum Brown for the drawing from which this woodcut has been made.

only two vary; and, therefore, that the results of any one series may be represented by a diagram on a plane, as in the diagrams I have brought under your notice. A combined representation of the results of the three series of experiments, involving, as it does three variable quantities, will, however, be best effected by a model in three dimensions, such as I now show you. Diagram 4 is an orthogonal projection of this model, in which the three variables are represented on a scale somewhat different from that of Diagrams 1, 2 and 3; but this difference does not cause any difficulty in the recognition of the corresponding parts. The continuous line, *a a'*, represents the boundary of the region of recovery in the experiments where atropia was administered five minutes *before* physostigma (Series 1); the continuous line, *b b'*, the boundary of this region where atropia was administered five minutes *after* physostigma (Series 2); and the dotted line, *c a' b' a d*, the boundary of this region where atropia was administered in various doses and at various intervals of time before and after one-and-a-half times the minimum-lethal dose of physostigma (Series 3). It is obvious that these lines lie upon a curved surface, on whose one side every point represents conditions leading to death, and on whose other side every point represents conditions leading to recovery. The surface, of course, cannot be fully known from the three sections of it that have been obtained by these experiments. It could be known only by greatly increasing the number of the experiments, so as to obtain a number of other curves parallel to and on either side of *b b'* and *a a'*, and of horizontal sections parallel to and below and above *c a' b' b a d*. To obtain a sufficient number of such curves, however, the labour and expenditure of time would be very great, seeing that so large a number of experiments as two hundred and seventy-six were made in order to obtain the curves represented in the diagram. Besides, a tolerably

accurate conception of the form of the curved surface may be gained from the curves of the three series of experiments that have been made.

The region included within this curved surface represents every possible variation in the doses of atropia and physostigma, and in the intervals of time separating the administration of the two substances, that is compatible with the production of successful antagonism between physostigma and atropia. Its existence shows us how an investigation on antagonism may lead to very fallacious results, even when every care has been taken in obtaining a large amount of experimental data. I have already pointed out that, almost without exception, the instances of lethal antagonism asserted to exist cannot be regarded as certainly established, because sufficient care has not been taken in proving that recovery took place after an undoubtedly lethal dose of one of the substances concerned. In attempting to *disprove* the existence of any asserted instance of lethal antagonism, a fallacy of equal importance may originate from ignorance of the fact that the antagonism does not necessarily occur throughout an unlimited range in the doses of the two substances, or in the intervals of time separating their administration: in short, that there is a region of death as well as a region of recovery in connection with probably every instance of lethal antagonism. Unless, therefore, the factors I have mentioned be greatly varied in a large series of experiments, it cannot be positively asserted that the antagonism does not exist. It appears to me that the fallacy to which I have now drawn your attention, has not been sufficiently attended to in much that has recently been written on the subject of antagonism.

Bearing of Antagonism between Active Substances on Therapeutics.—An eminent authority in pharmacology has recently published the statement, that the only method by which the injurious action of a poison can be made to terminate is by the employment of such means as will cause or hasten the elimination of the poison. This statement, fortunately, does not accurately describe our remedial resources. The existence of so undoubted an example of physiological antagonism as that which I have brought before you shows that the toxic action of a morbific agent may be directly opposed by the physiological action of an antidote or remedy; and, therefore, that recovery may be produced not only by removing the cause of the abnormal conditions, but likewise by directly influencing these abnormal conditions themselves in such a manner as to cause their return to a normal state.

It does not seem, however, that, in order to effect this return, the dose of the remedy must necessarily be increased in proportion to that of the morbific agent. This general principle has hitherto been somewhat vaguely recognised as a guide for treatment. The greater the severity of the symptoms, the greater the need for administering the antidote in large doses. When it is remembered that the action of poisons—whether these be the known substances with which toxicology is concerned, or those unknown substances on which the symptoms of many diseases are dependent—is rarely a simple one, but a series of independent actions directly involving many structures, and that the action of the antidote or remedy is in like manner the aggregate of several independent influences, we at once see how improbable it is that each of these several actions should be mutually antagonistic. In the case of the antagonism between atropia and physostigma, only a limited number of the different actions produced by each substance are of an opposite, and therefore counteracting kind; while others of these actions—either of a similar or of a different nature—are not mutually counteracting. Successful antagonism occurs when the doses are so proportioned that the non-counteracting actions are not permitted to acquire an undue prominence. When, however, they are permitted to acquire this prominence, death, and not recovery, occurs; and this result may be induced by an increase, beyond certain proportional limits, of the dose either of atropia or of physostigma. When the dose of physostigma is a large one, therefore, we find that a comparatively small and not a large dose of atropia is the proper one to administer; and, when the dose of atropia is a large one, we find that it can successfully antagonise only a small, and not a large, dose of physostigma.

I cannot avoid thinking that, were our knowledge of the conditions produced by disease as accurate as that of the conditions produced by many active substances, it would, for similar reasons, be found that a remedy which exerts so perfect a counteraction to a disease as to be able to prevent its fatal effect, would aid, and not prevent, the lethal action, when given in a somewhat large dose, even when this dose is considerably below the minimum-lethal. Just as we have seen that the actions of atropia which are not employed in counteracting those of physostigma, may increase the fatal power of a dose of the latter substance to such an extent that death occurs, even when the dose of neither substance is of itself sufficient to cause death.

The occurrence of this anomalous result is well worthy of consideration for another reason. The symptoms that are produced by a dose of physostigma *slightly* below the minimum-lethal are of so serious a character, that it is impossible to predict from their evidence alone whether death or recovery will occur. This can only be done by previously defining the minimum-lethal dose; and, unless this precaution be taken, the greatest errors may arise in judging of the effects of antidotes. Do we not find an analogy between this cause of error and that which frequently characterises the inductions of therapeutists? A disease that produces symptoms of the most serious import, does not necessarily terminate in death, even although this termination be a frequent one. The *dose of disease* present may not be so large as a minimum-lethal one, and still the symptoms may be sufficiently urgent to induce us to consider that they are caused by such a dose. If a remedy be applied in these circumstances—and, in the present state of our knowledge, they are probably always present—what surety can there be that the remedy has cured the disease? or that any remedy which may have been employed is not an efficient counteragent to its fatal effects? or even that the so-called *vis medicatrix naturæ* is not alone sufficient to counteract its lethal action? In presence of these uncertainties in reference to the exact degree of diseased action which is necessary to produce death—the exact dose of the disease that constitutes the minimum-lethal—there is little cause for wonder that scepticism regarding the power of remedies should exist, or that the unfortunate irrationalism of an indiscriminate expectancy should be revived as a therapeutic dogma.

I venture to think, however, that even the few facts which I have this evening brought before you are sufficient to show that a series of abnormal actions which, if unchecked, would inevitably terminate in death, may be so modified by an antidote or remedy, that the tendency to death is averted, and recovery produced. The existence of such an antagonism as that between atropia and physostigma encourages the hope that the power of directly counteracting disease is far from unattainable; and it supplies a strong incentive to efforts designed to determine the conditions of disease and the actions of remedies with an exactitude sufficient to show how the remedial action may be applied as a counteracting influence to the diseased condition.

REMARKS ON THE PROGRESS OF HELMINTHOLOGY, AND ON DR. HAUSSMANN'S OBSERVATIONS RESPECTING TÆNIA IN INFANTS.

By T. SPENCER COBBOLD, M.D., F.R.S.,
Professor at the Royal Veterinary College.

ALTHOUGH I hope shortly to publish a course of lectures embodying some of the most important recent discoveries in helminthology, the progress of research is so rapid, that I crave indulgence for space sufficient to indicate the source and character of such of these scientific inquiries as may be supposed to have an especial interest for the profession.

Dr. Haussmann's observations in the JOURNAL for October 26th are extremely ingenious in the view of supplying a possible explanation of the alleged occurrence of tænia in the new-born infant; but I fear they are altogether inadequate. He makes it appear possible that the segments or proglottides of a tapeworm might actually pass from the maternal perinæum into the mouth of the partially expelled infant; and then, after these portions of the worm have sojourned four days in the baby's intestinal canal, they might be finally discharged on the fifth day—as is supposed to have happened in Mr. Armour's case. Such a circuitous route for these cucurbitini appears to me impossible, when all the circumstances are duly weighed, without laying any stress upon the likelihood of their being partially digested in the infant's stomach. But it is possible that the notice, as recorded in the JOURNAL for August 17th, may, by reason of its brevity, have misled Dr. Haussmann. Here, therefore, I may mention that, through the kindness of Dr. W. S. Playfair of King's College, my attention was early called to the particulars of this case, as given in the *Medical Press and Circular* for February 14th of the present year. Since then I have had an opportunity of consulting the original communication itself; and, from a careful study of Mr. Samuel G. Armour's letter, it is quite clear that the facts are of a very different order from that implied by Dr. Haussmann's conception of them. Thus it is said that, commencing on the fifth day, the child "continued to pass segment after segment for five or six days"