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.

MR. PRESIDENT AND GENTLEMEN,—When I was honoured by the request to bring under your notice some subjects bearing upon pharmacology, I found myself placed in the difficult position of having too many good things to choose from. Within my reach were the fruits—seldom altogether ripe, but without exception temptingly attractive—of numerous investigations, conducted both in this country and abroad, in the field of pharmacological research. At my disposal, also, were the methods by which these fruits had been cultivated—the refinements of experimentation, and the mechanical appliances by whose aid, within recent years, results of surpassing beauty and interest have been obtained, and much progress has been made in the establishment of a sound basis for therapeutics. The consideration of either of these subjects, however, would have required much more time than could be found within the limits of two lectures. It was for this reason that I selected two subjects that admit of briefer discussion, while at the same time they possess a sufficiently independent interest to allow of their being treated apart from the general subject in which they are included.

Definition of Antagonism.—The connection between the chemical properties and the physiological action of active substances occupies a position on the border-land of pharmacology, for it is placed between pharmacology and one of the sciences most intimately related to it. The subject which I propose this evening to bring before you is placed, on the contrary, in the centre of this region, seeing that it is chiefly concerned with the relationships that exist between different groups of well defined pharmacological facts.

Presupposing a definite knowledge of the modifications produced in normal physiological conditions by a certain number of active substances to have been acquired, antagonism is concerned with the opposing influence which the action of one or more of these substances is able to exert upon that of any of the others—with the opposing actions, for example, of morphia and atropia on the pupils and minute blood-vessels, of morphia and quinia on the circulation, of prussic acid and atropia on the vagi nerves, and of physostigma and atropia on the iris and on visual accommodation. When several of the actions of one substance are counteracted by those of another, the antagonism becomes a more general one than in the examples I have cited; and when, among the different counteracting actions that occur in general antagonism, there are included any by which the fatal effect of one or other of the substances is usually produced, the one substance may act towards the other as a physiological antidote.

Physiological antidotism is, therefore, a very different thing from chemical antidotism. In all probability, however, the origin of the one may be referred to the same cause as that of the other. Soon after it become known that injurious effects follow the introduction of certain substances into the system, attempts were naturally made to remedy these effects, and also to discover counteragents or antidotes to the hurtful substances. The success attending these attempts was of necessity closely related to the existing state of knowledge regarding the physiological action and the physical properties of active substances. When the effects of poisons were referred to supernatural manifestations, it was chiefly charms and superstitious rites that were trusted to as protectives and remedies. At a somewhat more advanced period in the progress of human knowledge, vague notions of physiological laws and processes supplied the indications of curative treatment; and bezoars, alexipharmics, Mithridates, and theriacæ, were employed almost indiscriminately as universal antidotes. Still later, chemistry suggested that, as the physical properties of poisons may be modified by various reagents, so may their effects be prevented by the administration of suitable substances.

The recommendations derived from chemistry were at first only of the crudest description; but, as the science advanced, many valuable hints were obtained, and now the class of the chemical antidotes includes a large number of efficient counteragents to poisons. Their operation, however, appears to be limited to the chemical changes which they produce on the poison while it remains in the alimentary canal. As soon as the poison becomes absorbed into the blood, it seems to pass beyond the antidotal influence of the chemical counterpoison; for no example exists of a chemical antidote neutralising a poison after absorption. This may be explained by the fact that the chemical antidotes known to us are never sufficiently stable bodies. Their affinities are numerous; and so, after their entrance into the blood, they dissipate the chemical energy on which their value depends by forming combinations with the elements of the blood and tissues, in place of reserving that energy until the absorbed poison is reached and neutralised.

Reputed Examples.—In order perfectly to neutralise the injurious effects that follow the introduction of active substances into the living economy, it would appear to be necessary that the physiological functions of the affected organism should be modified. The early though undoubtedly crude notions that originated the employment of alexipharmics, Mithridates, and theriacæ, to a certain extent recognised this principle. The two latter of these compounds contained opium, along with an immense number of other ingredients; and so their indiscriminate employment as antidotes may have led to the first suggestion, or at least to one of the earliest applications, of an antagonism whose recognition dates from a remote period of medical history. I refer to the antagonism between opium on the one hand, and belladonna, hyoscyamus, and stramonium, on the other. One of the earliest records of a belief in the existence of this antagonism is to be found in the *Stirpium Adversaria Nova*, published in 1570 by Pena and De Lobel, where the statement is made that some Italian pedlers, who gained much notoriety by employing the root of the belladonna-plant to quench thirst, were in the habit of administering opiates to remedy the evil effects that occasionally were thereby produced. Tracing the history of this antagonism down to the present time, we find that during the seventeenth and eighteenth centuries, and at the commencement of the present century, several cases were reported, more especially by Horstius, Faber, Boucher, and Joseph Lippi, in which opium was administered with apparent benefit in the treatment of poisoning by belladonna. Within more recent times, many modern authors, as Angelo Poma, Anderson, Cazin, Benjamin Bell, Behier, Lee, Norris, and Constantin Paul, have published evidence, derived from cases of poisoning in man, that appear to favour a belief in its existence. I need scarcely point out that evidence of this kind is usually surrounded by numerous causes of fallacy. It is not surprising, therefore, that observers of such recognised ability as Drs. John Harley and L. Orfila should have come to the conclusion, after a careful examination of the record of each case, that the evidence derived from clinical experience is insufficient to establish the reality of this antagonism; or that Dr. Fraigniaud and others should besides assert that the association of opium with belladonna, in place of producing a diminution, produces an increase, of the toxic power of both substances. For my part, I feel inclined to believe that, while the existing evidence is insufficient distinctly to prove that opium is able to prevent the fatal effect of belladonna, hyoscyamus, or stramonium, or these latter substances that of opium, it is still sufficient to render it extremely probable that a general antagonism does really exist—to the extent, at any rate, of the primary lethal action of morphia being preventable by the physiological action of the other substances which I have named. A properly devised series of experiments would in all likelihood justify the opinion of those who, with no little courage, have practically affirmed their belief in the existence of this antagonism.

The rapid development of pharmacology has led to the acquisition of definite knowledge regarding the manner in which many active substances influence the physiological condition of vital structures; and it has been found that the modifications produced by certain of these substances are of an opposite kind to those produced by others. In this way the existence of many instances of localised antagonism—to several of which I have already alluded—have been established.

The study of pharmacology has likewise led to the differentiation of the special structures by the modification of whose physiological conditions the lethal action of poisonous substances is produced. In a few instances, it has been shown that the nature of the modification produced in the physiological condition of the structure or structures involved in the lethal action of one substance, is apparently contrary to that produced on the same structure or structures by the physiological action of another substance. The establishment of such facts has led to the suggestion of various instances of antagonism, in which it is supposed that the lethal action of one substance may be prevented by the

physiological action of another. Prominent among these are the antagonism between the lethal action of prussic acid and the physiological action of atropia, and that between the lethal action of muscaria and the physiological action of atropia. The elaborate researches of Preyer and of Schmiedeberg and Koppe proved that both prussic acid and muscaria increase the excitability of the vagi nerves, and in this way so seriously affect the cardiac and respiratory functions, that death results when sufficiently large doses are given. Previous investigators—more especially Von Bezold and Bloebaum—had already discovered that atropia exerts an action that is in a remarkable manner contrary to that of these substances; for it paralyses the cardiac inhibitory fibres of the vagi, and likewise the terminations of these nerves in the lungs, and thus accelerates both the cardiac and respiratory movements. Guided by these facts, Preyer made a few experiments which strongly support the opinion at which he has arrived, that atropia is a physiological antagonist to prussic acid, even to the extent of being able to prevent the primary lethal action of that poison; while Schmiedeberg and Koppe have made several experiments which induce them to believe that the lethal action of muscaria may be counteracted by atropia.

In addition to these, many other examples of general or of lethal antagonism have been advanced. Their existence, however, has rarely been inferred from a knowledge that the substances concerned influence the same structures in contrary modes, but has been conjectured from a knowledge of merely the general phenomena that are produced by these substances. The conspicuous spasmodic effects by which the action of strychnia is characterised appear to have suggested the employment, as physiological counteragents, of various substances whose general action includes the production of paralysis; and accordingly the list of proposed antagonists to this alkaloid embraces opium, curara, aconitia, nicotia, bromide of potassium, chloroform, chloral, and nitrite of amyl. Opium and quinia have been proposed as antidotes to each other, on the supposition that the former exalts several of the organic functions, while the latter depresses them; and the physiological actions of iodine and bromine are said to neutralise each other, because the former substance produces sedation, and the latter excitation, of certain general functions.

Among these examples, there are several worthy of further examination; and it is not impossible that their existence may thereby be established. Meanwhile, the criticism of the Professor of Therapeutics at Paris, in reference to the majority of recorded examples of antagonism, appears to be a just one—that "la précision fait souvent défaut dans l'analyse des faits, les inductions manquent de rigueur, et la pratique attend de nouvelles lumières de la part de la physiologie expérimentale et de la thérapeutique rationnelle."

Chief Fallacies in the Evidence regarding the Existence of Antagonism.—This absence of precision may, I believe, with peculiar justice, be said to characterise the evidence by which the existence of such general antagonism as enables one substance to prevent the lethal action of another has been supported. In nearly every instance, too much weight has been placed on a mere modification, or it may be amelioration, of the symptoms, while the establishment of the fundamental fact of these symptoms being the result of a lethal dose has not been sufficiently attended to.

It is doubtful whether, from clinical observation alone, a sufficient degree of precision can ever be obtained. Not only are there difficulties in the way of discovering what dose of poison has been introduced into the system, but even when this dose is ascertained, it is generally impossible to feel assured that it is a sufficient one to produce death. And, further, the effects of the substance administered as a physiological antidote can rarely be accurately observed. The exigencies of treatment demand that every likely method of alleviating the symptoms should be applied; and, among the various remedial measures that are almost always applied, it is difficult, if not impossible, to discover accurately the effects of any single antidote.

How these Fallacies may be avoided.—The only method whereby the existence can satisfactorily be proved of an antagonism, so perfect as that which enables one substance to prevent the fatal effect of another, is by experiment on the lower animals. It is not necessary for me to attempt to show that the fallacies asserted to exist in such experiments have been greatly exaggerated, or that the supposed differences between the results obtained in man and in the lower animals do not possess the importance that has been claimed for them, as, fortunately, nothing remains to be done in this direction since the convincing arguments of Claude Bernard have been advanced and generally accepted.

By testing the existence of antagonism by experiments on the lower animals, the most important of the causes of fallacy to which I have alluded may readily be avoided. In any given species of animal, it is a simple matter to determine he minimum dose of an active substance that can produce death, and the to test the antidotal influence of its supposed antagonist after the administration of an undoubtedly lethal dose of the poison. In this manner, the most convincing proof may be obtained of an antidotal influence; and, inspired with the confidence that is thus gained, the practitioner may with propriety employ the antidote in cases of poisoning in man.

The Antagonism between Atropia and Physostigma.—A plan of this kind was followed in a research which I lately undertook on the antagonism between atropia and physostigma. The experiments were chiefly performed on dogs and rabbits, to whom the substances were administered by subcutaneous injection; and their main purpose was to determine whether the fatal effect of physostigma can be prevented by atropia. Some of the results seem of sufficient interest to justify me in bringing them before you at this time.

In order to illustrate the effects that are produced by physostigma alone, let me, in the first place, describe the symptoms that occur when a lethal dose of the extract of this substance is given to a rabbit. Soon after such a dose is administered, unfrequent and slight twitchings take place over the surface of the animal, and then movements of the mouth and lips occur, as if an accumulation of saliva were being removed. In the course of a very few minutes, there is evident difficulty in going about; gradually, stiff extension shows itself in the anterior, and then in the posterior, extremities; and thereafter the animal stumbles about, or stands shaking with the body elevated on the extended limbs. In a short time, the extended state of the limbs is succeeded by their partial paralysis; great weakness, accompanied with constant tremblings, is present; fluid escapes from the mouth, and soft and pultaceous fæces are passed at frequent intervals. The respirations become infrequent and laboured, and the heart's contractions diminished in their frequency and force; while the pupils contract below their normal size. Soon afterwards, the respiratory movements assume the character of more laboured gasps, the pupils still further diminish in size, and general weak tremors succeed each other; while the flow of saliva, the discharge of semi-liquid fæces, and the incessant fibrillary twitches of the surface continue. By and by, it is a matter of difficulty to distinguish any respiratory movement or cardiac impulse, and they soon altogether cease on the occurrence of death.

Such a train of symptoms is usually produced by a dose of physostigma representing the smallest quantity that can kill a rabbit, and this event occurs in from twenty to thirty minutes. Let us now see how the effects of a considerably larger dose may be modified by atropia.

A rabbit received, by subcutaneous injection, a dose of extract of physostigma considerably greater than the minimum-lethal; and one minute and a half afterwards it received, also by subcutaneous injection, half a grain of sulphate of atropia. In three minutes after the injection of atropia, the pupils measured $\frac{14}{50} \times \frac{11}{50}$ths of an inch, the measurement immediately before the experiment having been $\frac{10}{50} \times \frac{9}{50}$ths. In seven minutes, the pupils measured $\frac{16}{50} \times \frac{10}{50}$ths, the rate of the heart's contractions was considerably accelerated, fibrillary twitches were occurring, and a little restlessness was present. Soon afterwards, the pupils became still more dilated, and the animal had some difficulty in moving about. In twenty-five minutes, this difficulty had become greater—even to such an extent, that often the anterior extremities yielded, and the rabbit fell on the thorax. In fifty-two minutes, the pupils measured $\frac{15}{50} \times \frac{14}{50}$ths of an inch, but no obvious change had occurred in the general condition of the animal. In one hour and ten minutes, however, evidences of recovery were manifested; the rabbit went about with but little difficulty, and frequently a perfectly normal sitting posture was assumed. Indeed, the only symptom of an abnormal character that was now apparent consisted of frequently occurring and well marked fibrillary twitches. From this time the condition of the animal steadily improved, until perfect recovery occurred.

Preliminary experiments had satisfied me that the dose of physostigma extract given in this experiment was at least twice as large as the minimum-lethal. Yet the fatal effect of this large dose was prevented in a remarkable manner by the dose of atropia that was given in conjunction with it. To add to the proof that was thereby obtained of an antagonism between these two substances, I administered to this rabbit, nine days afterwards, a dose of extract of physostigma only one half as large as that from which it had thus recovered. Symptoms of poisoning very quickly appeared, and death occurred in about fourteen minutes.

In another experiment on a rabbit, which I shall briefly describe, a lethal dose of sulphate of physostigmia was allowed to exert its action for a longer period than in the last experiment, before a dose of sulphate of atropia was administered. Previously to the administration of the physostigmia, it was found that the average rate of the cardiac contractions was 38, and that of the respiratory movements 22, in ten seconds; and that the pupils measured $\frac{11}{50}$ths by $\frac{10}{50}$ths of an inch. Fif-

teen minutes after the lethal dose of sulphate of physostigmia had been given, the rabbit was lying on the side, and saliva was flowing copiously from the mouth; unfrequent, laboured, and noisy respirations were occurring; the cardiac contractions were extremely feeble, and at the rate of only nine in ten seconds; and the pupils had contracted to $\frac{7}{50}$ths × $\frac{7}{50}$ths of an inch. In fact, the animal was at the point of death.

A marvellous change, however, was quickly produced by the administration of sulphate of atropia. Two minutes after seven-tenths of a grain of this substance had been injected under the skin, the respirations were occurring at the rate of 18 in ten seconds, while their character was nearly normal; and the cardiac contractions were strong, and at the high rate of 50 in ten seconds, the rate before the antidote was given having been only nine in ten seconds. Soon afterwards, the pupils dilated and the flow of saliva ceased; and, by and by, the animal again turned from the side, raised the body on the limbs, and then assumed a perfectly normal posture. It was shown that the dose of sulphate of physostigmia from which this animal had recovered was a lethal one, by administering to it, several days afterwards, a dose of equal size, without any atropia. The usual symptoms of physostigma-poisoning were thereby produced, and death occurred in sixteen minutes.

I have said that the antagonism between atropia and physostigma was tested in dogs as well as in rabbits, and in order to illustrate the nature of this antagonism in the former animal, it may be proper to give a few details of one of my experiments. An active young Scotch terrier dog, weighing ten pounds and three ounces, received, by subcutaneous injection, three-fifths of a grain of sulphate of physostigmia, dissolved in a few drops of distilled water. Before the injection, the rate per ten seconds of the cardiac impulses was 32, and that of the respirations 4, and the size of the pupils, in a full light, was $\frac{12}{50}$ × $\frac{12}{50}$ths of an inch. In four minutes after the commencement of the administration, slight tremors occurred, and fibrillary twitches were present. In five minutes, a solution containing three-tenths of a grain of sulphate of atropia was injected under the skin. In two minutes thereafter, the tremors already noted had become more prominent and strong, the limbs were unable properly to support the body, saliva escaped from the mouth, and the eyeballs were unnaturally moist. In five minutes, the pupils were greatly dilated, but now the secretions of the salivary and lacrymal glands were diminished. In seven minutes, the dog lay quietly on the abdomen and thorax; and in thirteen minutes it fell over on the side. An endeavour was made to count the cardiac impulses, but, when the hand was placed over the heart, the tremors referred to became so greatly increased that it was impossible to distinguish the heart's impulse. It was not until thirty-eight minutes, that an attempt to count the heart's contractions was successful, and then it was found that the impulses occurred at the rate of 45 in ten seconds. At the same time, the respirations had a rate of 7 in ten seconds, and the pupils measured $\frac{17}{50}$ × $\frac{17}{50}$ths of an inch. In forty-eight minutes, the condition of the dog had so far improved that, after some efforts, it rose on the limbs, and then lay down in a normal crouching attitude, with the head raised. Soon afterwards, it again got up and walked about the room, with only a little unsteadiness. In one hour and fifty-five minutes, the animal seemed to be perfectly well. On the following day, the dog was active, and in a perfectly normal condition. Nineteen days after the performance of this experiment, the same dog received, by subcutaneous injection, a dose of sulphate of physostigmia, only one-half as large as that from which it had recovered when atropia was also given; and the result was that death was produced in twenty-two minutes.*

Gentlemen, the details of these three experiments will serve, I trust, to convince you that atropia exerts a powerful counteracting influence upon the lethal action of physostigma. I am glad to be able to state that several experiments bearing on this antagonism have been performed by Dr. Bourneville of Paris, which have led to equally satisfactory results. The experiments which I have brought under your notice by no means represent the amount of evidence that may be advanced in support of this antagonism; for results similar to those I have described were obtained in a large number of other experiments. These additional experiments, however, were not undertaken for the mere purpose of increasing the amount of this evidence.

* Full details of these, and other similar experiments, are contained in a paper by the author, in the *Transactions of the Royal Society of Edinburgh*, vol. xxvi, part III, 1870-71, pp. 529-713.

[*To be continued.*]

TESTIMONIAL.—Mr. Clement Hamerton of Navan, F.R.C.S.Irel., has been presented with a carriage, a purse containing £46 : 10, and a highly complimentary address, as a mode of evincing the gratification of his friends at his recovery from a severe and protracted illness.

CRITICISMS OF DR. CHAUVEAU OF LYONS ON THE DISCUSSION AT THE PATHOLOGICAL SOCIETY ON PYÆMIA.

By J. BURDON SANDERSON, M.D., F.R.S.,
Professor of Practical Physiology in University College.

I HAVE to thank the Editor of the BRITISH MEDICAL JOURNAL for having called my attention to a recently published criticism, by my friend Dr. Chauveau of Lyons, of my communication to the Pathological Society last April on the subject of pyæmia. The criticism in question forms an Appendix (entitled "Le poison pyohémique à la Société Pathologique de Londres") to a course of lectures on the Physiology of Infective Liquids, which has been published during the last three months in the *Revue Scientifique*. In these lectures the author has embodied the results of a lengthened and most important experimental inquiry, which in its general bearing somewhat resembles that in which my colleague Dr. Klein and I were engaged last winter. M. Chauveau's purpose is to demonstrate the close relation which exists between the virulent (or, as I prefer to call them, the infective) diseases and ordinary inflammation. He founds this *rapprochement* mainly on the resemblance between the irritant properties of inflammatory products, and those of the specific morbid poisons; and asserts that ordinary pus induces inflammation in any living tissue with which it is brought into relation, in the same way that a virus reproduces the disease from which it originated under similar conditions. Those of M. Chauveau's experiments which have to do with recent—*i.e.*, living—inflammatory products are in close relation with ours. But, in addition to these, he has made others in that older field of inquiry which concerns the toxic action of pus in various degrees of putridity.

Knowing as I do, by personal intercourse with M. Chauveau, the extreme accuracy of his method of working, and regarding myself as in some measure his pupil (for there are few men from whom I have learnt more pathology), I felt perfectly certain, as soon as I found that we were on the same ground and looking in the same direction, that, if there were disagreement between us, it could only arise from the imperfect manner in which the facts had been presented on one side or the other—in this case on my side.

At the Pathological Society, I founded what I had to say on an entirely new experiment, which I then regarded, and still regard, as a fundamental one. It is to this experiment, or rather to my interpretation of it, that M. Chauveau objects. I shall have no difficulty in showing that his objection arises from a misconception. He describes it in terms which (with the important exception of the words I have put in italics) are correct: "If a pyæmic liquid, introduced into the peritoneal cavity of a guinea-pig, be left there for a couple of days, *during which it does not determine any intense symptom in the animal*, the toxic power of that liquid increases to such a degree that, when taken from the first animal and transported to a second, it manifests the most pernicious activity, and produces symptoms which are very rapidly fatal." This, M. Chauveau adds, was demonstrated to the Society in a "dog, into the abdominal cavity of which six drops of a pyæmic liquid which had resided two days in the peritoneal cavity of a guinea-pig had been injected."

M. Chauveau expresses no doubt as to the strict accuracy of the facts, but thinks I have misunderstood them, and proceeds to recite an experiment of his own, which appears to him to furnish the key to mine. It is as follows. An old horse was sent to the veterinary school with a seton, the discharge from which was extremely fœtid; the animal, however, was in good health; pulse, 32; temperature in rectum, 99.7 deg. Pus was collected from the seton, diluted with twice as much distilled water, and strained. Of this liquid, 15 minims were injected subcutaneously on the right side into the neck of the same animal from which it had been taken. In twenty-four hours, the pulse had increased to 45 and the temperature to 101.8 deg. On the fourth day the animal died. There was an enormous diffuse swelling around the seat of injection, due to "œdematous gelatiniform infiltration" of the subcutaneous tissue. The swelling was gangrenous at the centre, and exhibited elsewhere patches of vascular engorgement or extravasation. There were no internal lesions. Thus, to quote M. Chauveau's own commentary on the facts, "a few drops of the same pus, which when contained in a pyogenic cavity occasions neither local irritation nor any appreciable general disturbance, when injected into the cellular tissue of the same animal destroys it in less than four days; and the inflammation thereby produced is of so violent a character that the circulation stops, hæmorrhagic *infarctus* are formed, the tissues die, and the animal