AN ADDRESS CONCERNING THE ANTAGONISM OF DRUGS.¹

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By SYDNEY RINGER, M.D., F.R.S.,
Holme Professor of Clinical Medicine in University College, and
Physician to the Hospital.

RECENT investigations render it probable that alkaloids or extractives formed from food in the gastro-intestinal canal, or from the tissues of the body, cause many of the diseases we are called upon to treat. These alkaloids or extractives arise from physiological or morbid changes, and if in undue quantity, or if not quickly eliminated, they may act like poisons introduced into the system from without. Some of these ptomaines and leucomaines produce effects similar to vegetable alkaloids, as, for instance, atropine, muscarine, or curare. Indeed, muscarine can be obtained, not only from the fungus *agaricus*, but also from animal tissues. Now muscarine, even in poisonous doses, we can effectually antagonise by atropine.

I shall show you to-night that some inorganic and organic poisons can be completely antagonised, normal function being restored. The study, then, of the antagonisms of poisons becomes of much interest and importance, as we may confidently expect, as the result of further research, that we shall be able to obviate the effects, not only of inorganic and organic alkaloids, etc., introduced into the system, but the effects of ptomaines or leucomaines engendered in the animal body. Probably some of our successes in treatment are already due to our drugs antagonising these products.

A short time ago an interesting controversy arose regarding the reciprocal (mutual) antagonism of drugs. On one side it was maintained that drugs might be mutually antagonistic, whilst other observers denied this statement. The former maintained that the effect of a drug might be antagonised by a second drug, which, if increased in quantity, would manifest its own individual effects, but these effects could be removed by increasing the quantity of the first drug. To take an example, atropine will antagonise the action of muscarine, and muscarine the action of atropine on the heart. To take another instance, atropine will antagonise the action of jaborandi on the submaxillary gland, and *vice versa*; if after atropine has antagonised the action of jaborandi, a further quantity of jaborandi is administered, it will overcome the action of atropine and salivary secretion will return.

Roszbach disputed this, and maintained that whilst one drug increases another depresses or suspends function, and the drug which increases function can never overcome the effect of a drug that has abolished function. He admitted that when atropine arrests the secretion of the sweat-glands, pilocarpine may produce perspiration, but he asserts that this occurs only with a small dose of atropine just sufficient to paralyse the secretory nerves, but not the secretory cells of the gland, and that pilocarpine stimulating the cells may produce perspiration. But he maintains that a larger dose of atropine paralyzes both the secretory nerves and the secretory cells, and after this stage no amount of pilocarpine will excite perspiration.

I shall show you conclusively that drugs can be reciprocally antagonistic. I shall demonstrate that the effect of a toxic dose of calcium chloride on the detached ventricle of the frog's heart can be quite antagonised by a toxic dose of potassium chloride, and *vice versa* that a toxic dose of potassium chloride, sufficient not only to arrest spontaneous beats, but sufficient to prevent a strong induction shock exciting any contraction, can be antagonised entirely by a toxic dose of calcium chloride, and by the careful apportionment of the two salts their antagonism can be so nicely balanced, that the ventricle will beat spontaneously and quite naturally. Moreover, I shall show that a toxic dose of potassium chloride will antagonise a toxic dose of veratria, and *vice versa* a toxic dose of veratria will antagonise a toxic dose of potassium chloride, and these two substances may be given with such equipoise as completely to antagonise each other, so that the ventricle will beat quite naturally and spontaneously. So that in the case of calcium chloride and potassium chloride, and again in the case of veratria and potassium chloride, we may have in the circulating fluid two of each series present in toxic doses without either

poison exerting any apparent influence on the ventricle, which goes on beating spontaneously and normally, but if one salt were administered singly, it would powerfully affect the functions of the ventricle to an extent incompatible with life.

Concerning the antagonisms to which I wish to draw your attention to-night, I will refer first to a physiological antagonism. If the ventricle of the frog, or of the eel, or of the tortoise, is fed with saline solution (.66 per cent.), contractility soon ceases, and cannot be induced by a strong electric shock. On the addition of a lime salt, even in very minute proportions, as 1 part of lime-salt to 10,000 parts of saline solution, contractility immediately returns, but the contraction is abnormal, for the dilatation of the ventricle is greatly prolonged, so that the whole contraction lasts much longer than natural. The addition of a small quantity of a potassium salt, as for instance, potassium chloride, 1 part in 15,000 of circulating fluid, obviates this effect of the calcium salt, accelerates dilatation, and induces a perfectly normal beat, and with such a solution good contractions are sustained for several hours. Here, then, we have an antagonism between lime and potassium salts, affecting, however, only one part of a contraction—namely, the relaxation of the contracted muscle.

Not only are the salts of these two substances—potassium and calcium—antagonistic in physiological doses, but they are likewise antagonistic in toxic quantities.

If to a solution capable of sustaining the ventricular contractions we add a toxic dose of potassium chloride, the contractions speedily cease, even when the ventricle is strongly stimulated. Now, on adding a toxic dose of calcium salt, the potassium chloride is antagonised, and if the calcium salt is added in suitable quantity, complete contractility is restored, and the ventricle beats spontaneously and normally; and *vice versa* if we add to the circulating fluid a toxic dose of calcium chloride, we greatly prolong the duration of the contraction, and especially retard relaxation, but on the addition of a toxic dose of a potassium salt, these lime effects are obviated, and normal spontaneous contractions ensue.

Here, then, we have instances where two substances in toxic doses so antagonise each other that natural beats occur; whilst either substance, added alone to the circulating fluid, powerfully affects the functions of ventricle to an extent incompatible with life.

We are able, however, to analyse the antagonism between these salts more minutely still. During a contraction, four distinct sets of changes occur in the muscular tissue of the ventricle namely, changes occurring during the latent period, during the period of contraction, during the period of relaxation, and reparative changes, independent of those permitting relaxation. Now potash salts, like veratria salts, greatly retard these reparative changes, so that in a ventricle poisoned by potassium chloride, these reparative changes are very slowly performed, and hence, after the completion of contraction and relaxation, if a subsequent contraction is soon induced it is a very weak one, or if the stimulus is too soon applied to the ventricle no contraction may occur, and cannot be induced till a short time has elapsed, and then the amount of contraction depends on the length of the diastolic pause. This effect of potassium chloride on the reparative changes a calcium salt completely obviates.

We see, then, that a potassium salt accelerates relaxation but retards reparation, in both these respects being antagonised by a calcium salt, and *vice versa*. Another antagonism between potassium and calcium salts still remains to be noticed. If a ventricle be allowed to remain without contracting from a few seconds to a minute, then, on exciting it the first contraction is weak, and the subsequent contractions grow gradually stronger till normal contractions occur. This staircase character of beats depends, I believe, on the action of the potassium salt in the circulating fluid, and the degree in which it occurs is in proportion to the relative amount of potassium chloride in the circulating fluid. A calcium salt, as calcium chloride, quite obviates this effect. If sufficient calcium chloride be added, no matter how long the ventricle remains without contracting, the staircase character of the beats is prevented, or is very slight indeed.

Strange as it may appear, veratria affects the ventricle much after the manner of lime salts. Thus, added to simple saline solution, it will restore contractility, and further, like lime, it greatly prolongs the duration of the contraction, and especially delays relaxation of the contracted ventricle, and, like lime and potassium salts, we find veratria and potassium salts are mutually, or reciprocally, antagonistic.

For instance, the addition of veratria to the circulating fluid produces either great irregularity in the contractions, or very great delay in dilatation, according to the temperature of the room. This irregularity a toxic dose of potassium quite removes, and good spontaneous contractions return. Further, if the ventricle is greatly

¹ This lecture was illustrated by experiments on the detached ventricle of the frog's heart placed in a Roy's tonometer, the contractions being recorded on a revolving cylinder.

weakened or arrested by adding a toxic dose of potassium chloride, veratria quite antagonises the potassium chloride effects, and restores spontaneous and normal contractions.

Barium and calcium salts, as might be expected from their chemical relationship, have many actions in common. It is interesting to observe that, although lime salts and barium salts both broaden the beat, causing fusion and contracture, barium salts effect this more powerfully than calcium salts; yet, after barium has produced its effects, on the addition of a calcium salt, instead of obtaining the sum of their united action the effects common to both salts become less. In other words, lime takes possession of the muscular tissue, excluding the action of the barium salts. It would appear, then, that two substances affecting the same tissue in the same way, when administered therapeutically, one will not necessarily intensify the action of the other, but may replace the other, and we get the action of only one substance, and this, whilst having a greater affinity for the tissue, may induce a less physiological effect. These results are very interesting, and I venture to think have considerable importance, both physiologically and therapeutically. Thus we have seen that barium and calcium both exert an influence in the same direction, but the barium molecule is the more active in respect of its influence on the ventricular contraction. If, however, we bring both molecules into action simultaneously, we see that the resultant effect, instead of being greater than with either component, is less, the lime displacing the barium and inducing its less physiological disturbance. The relation of this subject to practical medicine is very clear and important, for on the question of the combination of drugs we must remember that the joint action of two drugs functionally similar is not necessarily greater than that of either separately, and may be even weaker than one of them given separately. I have said necessarily, for in some instances two substances having the same action do increase the action of either separately, so that we get the sum of their joint action. This is the case with lime and veratria.

So far we have seen that substances may be antagonistic in two ways. The first we may term physiological, for instances where two substances inducing an opposite physiological effect on a tissue may be so adjusted that the poisonous action of both is prevented. In the other case the antagonism is probably chemical, and one substance may by a stronger chemical affinity displace another poison, and this may occur, and indeed is most likely to occur, when both substances are chemically related and have a similar physiological effect. But there are other ways in which a substance may act as an antidote.

A lime salt in the circulating fluid we have seen is necessary for the contraction of cardiac muscle. Now a soluble oxalate destroys function, in part, by combining with the lime in the circulation, and rendering it insoluble and so inoperative. Here, then, we obviate the poisonous effect of an oxalate by adding lime to the circulation. There are still, however, other ways in which we can antidote a poison. A soluble oxalate not only destroys function by withdrawing lime, but is directly to some extent poisonous to the cardiac muscular tissue; and this poisonous action we obviate by the administration of a lime salt, which combines with the oxalic acid, forming an insoluble and therefore inoperative compound. To take another instance, soluble barium salts are poisonous to the cardiac muscle and arrest the ventricle in systole. Now I find that the addition to the circulating fluid of a solution of sulphate of soda will precipitate the whole of the barium, and the ventricle will speedily resume its normal contractility, even though the contractions had been suspended for an hour. The effect of the sodium sulphate is very rapid. Barium salts, one would think, can prove poisonous only to the tissues after more than enough has been absorbed to combine with the whole of the sulphuric acid in the blood and tissues, and it is possible that part of the action of a barium salt may be due to the withdrawal of sulphuric acid from the tissues.

Finally, there is another way by which the poisonous action of some substances can be greatly lessened. Some poisons prevent the changes which take place in the exercise of a function, as, for instance, the contraction of muscle. They do not destroy the structure, they only suspend function, and this power they possess only when the poison reaches a certain percentage of the circulating fluid. If the fluid is diluted, then the percentage amount becoming less the poisonous action is greatly reduced. This is the case with potassium and most other salts. This fact probably explains the effect of bleeding, which has been successfully employed in some cases of poisoning, and is highly successful in uræmia. The loss of blood induces a rapid absorption of the intercellular fluid and water from the gastro-intestinal anal, and so diluting the poison, lessens or removes the symptoms. If bleeding proves unsuccessful the influence of dilution suggest-

transfusion of a saline solution, also the free administration of liquids by the stomach—methods I long ago suggested.

I now bring this demonstration to a close, and I conclude by expressing the hope with which I commenced my remarks, that the antagonisms we have witnessed justify us in confidently expecting that further investigation will discover remedies by which we shall safely antidote the poisons generated in the body, and that these discoveries will enable us to relieve much suffering or even to save life.

BRITISH MEDICAL ASSOCIATION.

FIFTY-FIFTH ANNUAL MEETING.

PROCEEDINGS OF SECTIONS.

INTRODUCTION TO A DISCUSSION ON THE PREVENTION OF PUERPERAL FEVER.

Read in the Section of Obstetric Medicine at the Annual Meeting of the British Medical Association held at Dublin, August, 1887.

By W. S. PLAYFAIR, M.D., LL.D., F.R.C.P.,

Professor of Obstetric Medicine at King's College, and Physician for the Diseases of Women and Children to King's College Hospital.

THE subject which I have the honour to introduce to you for discussion cannot fail, I think, to be of interest to all on whom the responsibility falls of attending women in the trying time of labour. Who that has undergone the distress of seeing septicæmia develop in one of his patients, and who has had to suffer the terrible anxiety which every such case involves, will hesitate to endorse the statement that the prevention of this scourge of midwifery practice is one of the most important duties that can possibly fall to his lot. It will be out of the question that in the short space of a quarter of an hour allotted to me I can endeavour to do more than lay down some few broad general principles that should guide us. To enter into details will be impossible; my object will be fully gained if I am able to inaugurate a useful discussion on a question of such interest to us all, and I cannot doubt that much information of value will be elicited from a comparison of the opinions and practice of the many gentlemen in this room who are qualified to speak on this topic with authority. I am more particularly anxious to-day to insist on the prevention of puerperal disease in private and domiciliary practice. In lying-in hospitals, since the great revolution produced by the general recognition of the importance of antiseptics, a marvellous change has been effected. From being hotbeds of death and disease, in which no woman could be confined without running a serious risk, sometimes hardly less grave than that of a capital surgical operation, in the majority of well managed lying-in hospitals a woman is now actually as safe, if not safer, than if she was confined in a large and luxurious private house, with nurse, physician, and all that money can procure. This is no exaggerated statement. Obstetric literature within the last few years teems with facts and statistics proving the accuracy of what I have said.

The great lying-in institution of Dublin is a case in point. The statistics of similar institutions in London, Paris, St. Petersburg, and every large Continental city, corroborate it. There is nothing in the history of medicine more remarkable than the change which has come over the working of these public institutions since Lister's life-saving principles have been adopted. There the battle is gained. I doubt if such a thing can be found now as a lying-in hospital in which rigid antiseptics is not the rule, and in which similar good results have not followed its introduction.

Although the principle is universally recognised, and, I believe, everywhere practised in public institutions, I very much question if even yet antiseptic midwifery is at all in general use in private practice. It is my lot, as of other consultants, often to see cases in which septic symptoms have developed, and very seldom, heretofore, have I found that the practitioners in attendance followed any of the antiseptic rules which are now so universally and so rigidly enforced in our lying-in hospitals. Perhaps in the near future, when the younger members of the profession enter more largely into work, it will be different; but with the bulk of men now in practice no special care is taken.

Yet, if the work of public charities in which lying-in women are congregated—in which, as the bitter experience of the past so fully