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OBSERVATIONS AND EXPERIMENTS

ON THE

MODE IN WHICH VARIOUS POISONOUS AGENTS ACT ON THE ANIMAL BODY.

By MR JAMES BLAKE.

(*From the Edin. Med. and Surg. Journal, No. 142.*)

THE subject of the following researches is one, the importance of which is fully attested by the attention it has received from physiologists. The action of poisons on organized beings has always been considered as a valuable means for elucidating some of the more important phenomena they present; and the facilities which this class of substances affords us of destroying or modifying some of the more complex functions of animals, renders them valuable agents in attempting an analysis of these functions. These circumstances have invested with so much interest the question as to the manner in which poisons produce their effects; and although many researches have been undertaken with the view of elucidating this question, the conflicting opinions still entertained on this point, afford sufficient proof that much still remains to be discovered in this branch of physiology.

Of the many opinions that have been entertained on the manner in which poisons produce their effects, there are only two which it is now necessary to notice, as they express the views of by far the greater number of physiologists of the present day.*

* In using the word poison in these researches, I would be understood as apply-

According to one of these opinions, before a poison can produce any general effects, it is essential that it should be mixed with the blood circulating over the body, and thus brought into contact with the nervous tissue, or, at least, that the poison should, in some manner, be strictly applied to the nervous centres.

The other opinion to which I have alluded is, that these poisons modify or destroy the functions of the nervous system, by an impression made on the nerves of the part, to which they are directly applied, and which, being transmitted to the nervous centres, may destroy these functions independently of any contact of the substance with the nervous tissue generally.

In bringing forward a series of experiments in order to elucidate this question, I would not be understood as laying claim to any credit for originality in these experiments, as most of them have been performed by former physiologists. My only reason for here detailing them is, that in these researches they have been observed with a definite object in view, and in order to furnish data which are not to found in those already published. The same remark will apply to the conclusions I have drawn from those experiments which are in accordance with the opinions entertained by many distinguished physiologists, although opposed by some of our highest toxicological authorities, and also I think by the greater number of physiologists in this country. As the opinion which would ascribe the general effects of a poison to an impression made on the part to which it is directly applied, is in opposition to the conclusions to which a careful investigation of the subject has led me, I shall take a short review of the evidence adduced in support of this opinion. This is of two kinds; that afforded by direct experiment, and that deduced from the consideration of certain pathological and physiological facts.

I. I shall at once proceed to notice the latter, leaving any remarks on the experimental evidence until I shall have related those experiments which I have performed on the subject.

The most important pathological facts brought forward are;—*1st*, the sudden manner in which certain morbid effluvia have been stated to affect the human body; *2dly*, cases of sudden death taking place after the receipt of a slight wound; and *3dly*, the production of tetanus by the mere local irritation of a nerve. *1st*, The facts brought forward in support of the first statement are derived from the sudden effects which are stated to have been produced by the effluvia proceeding from certain fomites of plague. Instances are reported in which persons have fallen down, and instantaneously expired, whilst conveying these supposed fomites from the ships. The validity of these statements cannot, I think, be allowed, after

ing it exclusively to those substances which appear to destroy life by their effects on the nervous system.

the valuable information which has lately been communicated to the public on this subject by Dr Bowring, who has been an eye-witness of the disease in its worst forms, and who has been led to conclude that it is not infectious. Should the report in question have any foundation, it will probably be owing to mere coincidence of sudden death taking place at a moment when the person was so employed. *2dly*, The same remark will apply to cases brought forward of sudden death produced after the receipt of a slight injury. Such cases must be exceedingly rare, as Professor Cooper, a gentleman who has had most extended opportunities of observing such cases, did they really exist, informs me that he has never met with an instance of death suddenly following a slight injury. *3dly*, In regard to tetanus I would observe, that we are not justified in concluding, that the whole of the morbid phenomena are the result of the mere local irritation of a nerve. It is highly probable, that some pathological state has been propagated from the injured nerve to the nervous centres, before the violent symptoms which characterize this disease manifest themselves. Were the symptoms the mere result of the local irritation of a nerve, we might expect to produce them at pleasure, by merely irritating the nerve; but it is well known that this is not the case. In every instance it is necessary that a certain time shall elapse between the local injury and the appearance of the disease, which time is probably required, in order that the pathological condition above alluded to may be produced. It would thus appear that we have no pathological facts which lead to the conclusion, that poisons act by an impression made on the nerves of the part to which they are directly applied.

The principal physiological facts which have been supposed to support the opinion, that poisons may produce their effects on the system, without being generally applied to those tissues, the function of which they appear to destroy, are derived from the instantaneous manner in which some poisons have been stated to act. The support derived from this fact, however, has been founded on erroneous views which have been taken, of the time required for the blood to circulate from one part of the system to another; and also from the statements of the instantaneous action of the more powerful poisons, being deduced from incorrect observations. The following facts will, I trust, substantiate the correctness of these remarks, by showing that a sufficient time always elapses between the application of a poison and the appearance of its first effects, to allow it to enter the circulation, and to be directly applied to the tissue, the functions of which are affected.

II. In order fairly to enter on the investigation of the question which is the more immediate object of these researches, it is necessary that correct ideas should be entertained of the time re-

quired for the blood to circulate from one part of the system to another. I shall therefore commence by relating some experiments which tend to elucidate this important point, more particularly as the conclusions to which they lead are not in accordance with the opinions generally entertained on the subject.

As the introduction of a poison into the circulation is the first phenomenon that follows its application to a part, the following experiment, by affording a proof of the permeability of the tissues, shows how readily this may take place : it also offers a striking example of the rapidity with which the blood circulates.

(Exp. 1.) A drachm of the strongest *Liquor Ammoniacæ*, mixed with five drachms of water, was injected into the jugular vein of a dog. A glass rod which had been dipped in hydrochloric acid was held immediately under the nostrils, in order to detect any ammonia that might escape from the lungs. Four seconds after the introduction of the first drop of the solution of ammonia into the veins, it was plainly detected in the air expired from the lungs by the white vapours that were formed on its coming into contact with the vapour of the hydrochloric acid. It would thus appear that in four seconds, this substance must have passed from the jugular vein through the right side of the heart, and reached the capillaries in the lungs ; have permeated the parietes of these vessels, and escaped through the whole length of the air tubes.* Analogous experiments have been recorded by Magendie, and other physiologists, in which oil holding phosphorus in solution was injected into the veins, phosphoric acid being detected in the breath a few seconds after its injection.†

Having shown the facility with which the tissues are permeated, I shall now endeavour to elucidate the question as to the rapidity of the circulation, by tracing various substances, from one part of the vascular system to another. My experiments on this point have been much facilitated by the manner in which certain substances have been found to act on different parts of the vascular system.‡ The effects of these substances have been detected

* As the principal interest attached to these experiments depended on the accuracy with which the time of the occurrence of the phenomena was observed, I would remark, that every precaution was taken in order to obtain correct data on this point. I would also state that Dr Sharpey, Professor of Physiology in the London University, sanctioned by his presence the most important of these experiments ; and I with pleasure avail myself of this opportunity to return him my thanks for the valuable assistance and advice he has on all occasions so kindly afforded me.

† These observations are confirmed by experiments performed on delicate membranes when removed from the body. The rapidity with which these are permeated by different solutions, affords a decisive proof of the facility with which this process may go on, particularly when we consider that the most delicate membranes that can be used for these experiments are probably many hundred times thicker than the parietes of the capillary vessels.

‡ The proofs of the local action of these substances has been derived from an extensive series of researches on the subject, which will shortly be brought before the

the instant they take place, by the use of the hemadynamometer, an instrument which indicates, by means of a column of mercury, the pressure sustained by the parietes of the blood-vessels, and which immediately becomes modified on any change being produced, either in the action of the heart, or in the capillary circulation.

(Exp. 2.) The following experiment furnishes an example of the time required for a substance to pass from the jugular vein to the capillaries of the pulmonary artery. It had been ascertained that soda and its salts possess the property of arresting the capillary circulation in the lungs. When this effect is produced, no more blood is sent into the left side of the heart and arterial system, and it follows, that the pressure sustained by the parietes of the arteries must be instantly diminished. Fifteen grains of soda dissolved in six drachms of water were injected into the jugular vein of a dog. Six seconds after the first portion of the injection was introduced, the pressure in the arterial system began to diminish, and the mercury in the hemadynamometer speedily sank to zero, although the pulsations of the heart still continued.*

(Exp. 3.) An experiment the reverse of the former was performed by connecting the hemadynamometer with the venous system. When the passage of the blood through the lungs is arrested, it is evident that the venous system must become congested, and thus the pressure supported by the parietes of these vessels will be increased. In this instance six seconds elapsed between the introduction of the substance into the veins, and any perceptible increase in the pressure.

It would appear from these experiments that soda when introduced into the jugular vein affects the capillaries in the lungs in from four to six seconds; a space of time rather greater than that required by ammonia to traverse this distance. This might arise from two causes; either that the diffusive power of some substances is much greater than that of others, and that they thus may be transmitted from one part of the column of blood to another, independently of its progressive motion; or that in some animals the circulation is going on much more rapidly than in others. The

public.—Since the above was written, the experiments in question have been published in a memoir read at the Institute of France.

* The time at which marked effects are produced might not be the moment at which the substance is applied to the tissue affected; a slight interval probably elapses between the arrest of the capillary circulation in the lungs and the diminished pressure in the arterial system. The time, therefore, in which these effects were observed is probably a second or two later than that on which the soda reached the capillaries. The importance of taking into consideration even these apparently trifling circumstances will be acknowledged, when it is shown that an interval of two or three seconds forms a considerable fraction of the whole of the time required for the circulation to be completed in.

next points between which I shall endeavour to trace the passage of a substance are the jugular vein and carotid artery.

(Exp. 4.) The following experiment, although it does not afford a direct proof of the time occupied by a substance in passing from one of these vessels to the other, yet shows that it cannot, in this instance, have exceeded seven seconds. A tube, furnished with a stop-cock, was inserted into the carotid artery of a dog, the point of the tube looking towards the heart. A solution, containing seventy-five grains of chloride of barium in six drachms of water, was introduced into the jugular. Blood was allowed to escape from the carotid artery three seconds after the introduction of the salt into the vein, and was received into a vessel (No. 1) for four seconds. Another vessel (No. 2) was then substituted, but as the action of the heart was already arrested, a small quantity of blood only escaped from the arteries into it; the blood from the left side of the heart was afterwards added to it. The blood from the right cavities of the heart was collected in another vessel, (No. 3.) The quantities of blood contained in these different specimens were as follows: No. 1. contained four fluid drachms; No. 2. twelve drachms; and No. 3. twenty drachms. Each specimen was evaporated, carefully incinerated in platinum vessels, treated with hydrochloric acid, filtered, precipitated with sulphate of soda; the precipitate was collected, washed with diluted nitric acid, dried and weighed.

The following are the results: The quantity of sulphate of baryta furnished by No. 1 weighed 3.33 grains; that from No. 2, weighed 4.62 grains; and from No. 3, 0.90 grain. If from these data we calculate the quantity contained in equal quantities of blood in the different specimens, it appears that No. 1 contained 3.33 grains in four fluid drachms; No. 2 contained 1.54 grains in an equal quantity; and No. 3 but 0.18 grain in the four drachms. This proves that the blood which contained the greatest proportion of the salt had already passed through the arch of the aorta before the action of the heart was arrested, or in less than seven seconds after the introduction of the salt into the jugular vein. If we consider that when the first vessel was removed, a considerable quantity of the salt had already entered it, we must conclude that the moment of its first escape from the carotid could not have been later than five seconds after its introduction into the jugular vein. The very slight trace of the salt found in the blood from the right cavities shows how completely the blood had been renewed.

The following observations will show the time required for a substance to pass from the jugular vein to the termination of the coronary arteries. This may be ascertained by availing ourselves

of a property which some substances possess of suddenly paralyzing the heart when mixed with the blood circulating over its parietes.

Examples of such substances are found in infusion of tobacco, oil of tobacco, the *Upas antiar*, arsenic, oxalic acid, nitrate of potass, and hydrocyanate of potass, all of which, whether they act on other textures or not, have the property of speedily destroying the irritability of the heart, and thereby rendering it unable to contract in its contents.

(Exp. 5.) On injecting a solution of these substances into the veins, an interval varying from seven to fourteen seconds has been found to elapse between their introduction and the arrest of the heart's action. The cessation of the action of the heart has generally been ascertained by the use of the hemadynamometer, but in one experiment, in which the thorax was opened, artificial respiration being performed, the motion of the heart was seen to be suddenly stopped, seven seconds after the introduction of the first portion of a solution of nitrate of potash (one of those substances which exert this affect on the heart) into the jugular vein.

I shall now relate an example illustrating the space of time required for a substance to pass from the commencement of the aorta and to be generally diffused into the systemic capillaries. The manner in which this can be observed, is by injecting a substance, which had been ascertained to arrest the capillary circulation, into the axillary artery of the right side, the point of the syringe looking towards the heart: when pushed with force, the injection is thrown back into the aorta, and thus becomes distributed over the body. The hemadynamometer furnishes an index of the moment in which the capillary circulation becomes affected, for the pressure in the arteries becomes instantly increased. When a substance capable of exerting such an action on the capillaries is injected, it is found that these vessels become affected in an interval varying from four to seven seconds after its first introduction. It has already been shown in Exp. 3, that the interval which elapses between the introduction of a substance into the jugular vein, and its appearance in the carotid artery, may not be more than five seconds. From this point four seconds may be required before it is distributed to the systemic capillaries; thus giving an interval of nine seconds, which may intervene between the introduction of a substance into the jugular vein, and its general diffusion throughout the body.

(Exp. 6.) I shall conclude the observations I have to bring forward on this part of the subject, by relating one experiment which shows the time required for a substance to pass from the aorta through the whole of the vascular system, back into that vessel, and thence through the coronary arteries over the parietes of the heart. A substance capable of paralyzing the action of the heart was injected into

the axillary artery, so as to pass into the aorta. Under these circumstances, a space of time, varying from thirty-five to forty-five seconds, has been found to elapse between the introduction of the substance and the cessation of heart's action. I would remark, however, that all those substances which act in this manner on the heart also possess the property of impeding the passage of the blood through the capillaries for a time varying from fifteen to twenty-five seconds, so that these experiments furnish no exact indication of the time in which a substance which does not possess this property may pass between the points above alluded to. From those experiments in which the phenomena would be observed with the greatest accuracy, I conclude, that the time required for a substance which does not act on the capillary tissue, to pass from any part of the vascular system back to the same point again, varies in dogs from twelve seconds to twenty seconds. These conclusions are in perfect accordance with those arrived at by Hering from a series of carefully conducted experiments on horses, in which he found that the whole round of the circulation was completed in about twenty-five seconds.

Having now the requisite data by which to determine the time in which a substance can be circulated over the body, I shall proceed to relate some experiments which have been performed with a view of discovering if a sufficient interval elapses between the application of those poisons which have been shown to act on the nervous system, and the first symptom of their effects, to allow them to be brought into contact with the nervous tissue throughout the body. Experiments have been tried with concentrated hydrocyanic acid, woorara, nicotine, conia, and strychnia,—poisons which have been shown to produce the most rapid effects on the animal economy.

(Exp. 7.) Half a drachm of concentrated hydrocyanic acid was prepared by passing sulphuretted hydrogen over the bicyanide of mercury. The gas being previously dried by passing it over chloride of calcium, the acid was collected in a receiver surrounded by a freezing mixture. It was used immediately after its preparation. In order to insure a marked effect being produced, the whole of the acid was poured, on the tongue of a strong dog, weighing about eighteen pounds, the head being kept elevated. Eleven seconds elapsed between the application of the poison and the appearance of any morbid symptom. The respiration then became affected. The animal was dead thirty-three seconds after the administration of the poison. If a tube be introduced into the trachea, through which the animal can breathe, a longer interval elapses between the application of the poison and the appearance of its effects. This is probably owing to the acid not being inhaled with the breath; for on account of the extreme volatility of

the strong acid, it is converted into vapour the instant it comes into contact with so warm a surface as the mouth, and in this state it is applied to the capillaries in the lungs, and rapidly absorbed. It thus has a shorter distance to pass through before reaching the nervous centres than when it enters the capillaries of the mouth, and circulates through the right side of the heart.

(Exp. 8.) A tube being introduced into the trachea of a dog, a drachm of the strong acid was poured on the tongue of the animal. Sixteen seconds elapsed before any symptom of the action of the poison manifested itself, and the animal died about forty-five seconds after the application of the poison. These experiments have been repeated twice, and always with the same results. They show that, in these instances at least, a sufficient interval has always elapsed between the application of the acid, and the moment when its first effects were produced, to allow of its being brought into contact with those tissues on which it appears to act.

(Exp. 9.) The woorara is a poison which has been stated to produce instantaneous effects when introduced into the circulation. As it is not very rapidly absorbed, the readiest way of testing its action was by injecting it into the veins. Five grains of the poison dissolved in five drachms of water were injected into the jugular vein of a dog. Twenty seconds elapsed before any symptom of the action of the poison could be observed. Violent convulsions were then produced, and the animal was dead about forty-five seconds after the introduction of the poison. This experiment has been repeated three times, and has constantly furnished analogous results; the time required for the poison to produce its first effects varying from sixteen to twenty-three seconds.*

(Exp. 10.)—The active principle of the hemlock, or conia, is a poison which has been stated by Dr Christison to produce effects so rapid, that an appreciable interval did not elapse between the introduction of the poison and the death of the animal.—(See Transactions of the Royal Society of Edinburgh.)

Having obtained a considerable quantity of conia from an alcoholic extract of the seeds of *Conium maculatum*, and which exactly resembled in physical and chemical characters that described by Dr Christison, I proceeded to try the following experiment, using a large dose of the poison, in order to insure a marked effect the moment it should begin to act.

Ten drops of conia, neutralized with a small portion of diluted hydrochloric acid, were injected into the femoral vein of a dog by

* The poison was procured for me by my respected Professor, Dr A. T. Thompson, whom I have to thank for the valuable assistance he has afforded me whilst conducting these experiments.

means of a finely pointed glass syringe.* Fifteen seconds elapsed between the introduction of the poison and the appearance of any symptoms of its action. The respiration was then violently affected, and the animal was dead thirty seconds after the injection of the poison;—thus affording a proof of its virulence; for by no other substance that I have used has death been produced in so short a time. This experiment has been repeated four times, and in no instance have any symptoms manifested themselves in less than fifteen seconds.

(*Exp. 11.*) The next substance whose action I have tried is nicotina, or the active principal of tobacco. Two drops were injected into the jugular vein of a dog. The first symptoms of its action manifested appeared fifteen seconds after the injection. The animal was dead in about one minute and a half after the administration of the poison.

When this substance was applied to the tongue, an interval of twenty seconds elapsed before any marked symptoms manifested themselves.

(*Exp. 12.*) The striking effects produced by nux vomica are such as enable it, the moment on which these are first produced, to be carefully appreciated. A solution containing twelve grains of the alcoholic extract was introduced into the jugular vein of a dog. Convulsive movements were observed twelve seconds after the introduction of the first portion of the injection. The animal died in about a minute and a half.

These experiments, I think, furnish sufficient proof that the opinion of the instantaneous action of poisons must be founded on incorrect observations. An interval, never less than twelve seconds, has been shown to elapse between the application of a poison and the first symptom of its action; an interval in itself so short as might almost justify its being neglected, particularly in the present state of opinion of physiologists on the rapidity with which the organic processes are carried on; but which becomes of importance when compared with the time actually occupied for the performance of these processes, as it is quite sufficient for a poison to be brought into general contact with those tissues it affects. This being the case, it is unphilosophical to suppose that these effects on the nervous centres are owing to an impression communicated to them by the nerves, and not the result of the direct application of the poison to them.

The following experiment supports these conclusions, by show-

* In order to prevent the contact of the poison with the blood until the moment when the injection was pushed, a small portion of oil was drawn into the point of the syringe, which could thus be introduced into the vein in readiness to push the injection on a signal being given, without any danger of the poison becoming mixed with blood.

ing that the nearer to the nervous centres is the part of the vascular system into which the poison is introduced, the more rapid is its action.

By injecting a poison which acts on the nervous system into the aorta, the distance it has to traverse before reaching the nervous centres is much less than when it is introduced into the venous system. We should thus have an appreciable difference in the interval elapsing between its introduction and the appearance of the first symptom of its effects, whether it be introduced into the artery or the vein.

(*Exp. 13.*) A tube was introduced into the axillary artery of a dog. Five grains of woorara, dissolved in two drachms of water, were injected, so that it should pass into the aorta. The first symptoms of the action of the poison manifested themselves seven seconds after the injection, and the animal was dead in thirty seconds after the introduction of the poison.

On comparing this experiment with Experiment 7, we find a difference of some seconds elapsing in the first appearance of the action of the same poison, according as it is introduced into the nervous or arterial system. Analogous experiments have been performed with other substances, and constantly with the same results.

As the evidence derived from these experiments in support of the theory of general diffusion being necessary for the action of a poison is only presumptive, the present state of our knowledge not allowing us to detect their presence in the nervous tissue, I have endeavoured to strengthen it, by showing that the mere contact of a poison with a large extent of surface is not sufficient to produce any general effects, as long as it is prevented entering the general circulation. The only parts available for these researches are the abdominal viscera, on account of the facility with which they can be insulated from the general circulation, their connection with the nervous system remaining unimpaired.*

(*Exp. 14.*) The abdomen of a dog was laid open. A ligature was passed under the vessels entering the liver, and tied. Three drachms of hydrocyanic acid of Scheele's strength, containing 3.3 per cent. of acid, were introduced into the stomach through an opening made in its parietes. The poison was thus brought into contact with a large surface, freely supplied with nerves, at least with those nerves on which poisons are supposed more particularly to produce these impressions. (See Addison and Morgan on Poisons, page 35.) Under these circumstances, the poison remained in the stomach ten minutes, without producing the slightest general effect. The ligature on the *vena portæ* was then re-

* I am aware that analogous experiments have been performed by Magendie, Segalas, and other physiologists, but as those I have to bring forward differ from theirs, and afford a more complete proof of the fact I wish to establish, I have thought it advisable to relate them.

moved, so as to restore the circulation over the viscera. One minute after the removal of the ligature, the animal began to experience the effects of the poison. The ligature was again replaced; but before this could be effected, a sufficient quantity of the poison had been absorbed to arrest the respiratory movements, and the animal must have speedily perished, had not artificial respiration been had recourse to. After this had been continued eight minutes, the animal was sufficiently recovered to continue the respiratory movements itself. After a short interval the ligature from the *vena portæ* was again removed. The animal was dead in two minutes.

This experiment affords a strong proof of the non-action of poisons when merely applied to the extremities of nerves, for not only did the poison produce no effects before it entered the circulation, but we find the animal recovering from the effects of the poison, with three drachms of hydrocyanic acid still in its stomach.*

(*Exp. 15.*) As it might be objected to this last experiment that the nerves to which the poison was applied were not in their natural condition, on account of the circulation not going on over them; and that they were thus rendered incapable of transmitting any impression that might be made on them, the following modification of the experiment was devised.

The abdominal aorta of a dog was exposed, and a ligature passed around it, immediately above the origin of the cœliac axis and mesenteric arteries. A tube was then introduced into the aorta, directly below the origin of these vessels, so that any injection introduced through the tube must pass into them. A ligature was passed round the vessels entering the liver, and an opening was made in the *vena portæ*, so as to allow the blood to circulate over the viscera, when the ligature was removed from the aorta. Five grains of woorara, dissolved in four drachms of water, were now introduced through the tube, and passed into the cœliac axis and mesenteric arteries. The ligature from the aorta was then removed, and thus the blood containing the poison was circulated over the whole of the abdominal viscera, and applied to the extremities of the nerves, in circumstances favourable for the transmission of any impression that might be made on them by this large dose of poison. Seven minutes, however, elapsed be-

* The explanation that has been brought forward of the sudden action of some poisons by Muller and those physiologists, who consider that the circulation requires one or two minutes to be completed in, and yet who allow that poisons only act when applied to the nervous centres, is shown by this experiment to be incorrect. They state that the poison becomes applied to the brain and spinal chord by diffusion and imbibition through the tissues, independently of its being transmitted by the blood. Yet, in this instance, we have the poison they bring forward as possessing this power of expansion in the highest degree in contact with a large surface of the body without giving any proof of its having reached the nervous centres, independently of its transmission by the blood.—(See Muller's Physiology, translated by Baly, p. 247.)

fore the slightest symptom of the action of the poison manifested itself, and the animal did not die until fifteen minutes after the introduction of the poison; even then it is probable death was produced by the blood containing the poison having escaped from the *vena portæ* into the cavity of the abdomen, from whence a portion of the poison was again absorbed and carried into the general circulation.

Any remarks on these experiments would be perfectly superfluous, the striking nature of the facts clearly showing the point they were intended to illustrate. I would only observe that they are in perfect accordance with a number of facts brought forward by other physiologists.

III. It now only remains for me to notice some experiments that have been brought forward by Messrs Addison and Morgan, in their *Essay on the operation of poisonous agents*, (Lond. 1829,) and which, if free from fallacy, would prove that some poisons can produce general effects from an impression made on the nerves of the part to which they are directly applied. The most important experiment adduced by these gentlemen in support of the local action of a poison is that in which the jugular vein of a dog was exposed in a considerable part of its course. Two ligatures were applied to it, three inches apart; a portion of woorara was introduced into that part of the vessel, comprised between the ligatures, and the upper ligature was then removed. The blood was thus brought into contact with the poison which became applied to the parietes of the vein. In these circumstances, it is stated that the poison rapidly produced its effects; and it is concluded that these effects were owing to an impression made on the nerves of the insulated portion of the vein.

I would observe, however, that there must evidently be some fallacy in this experiment, for had the vein been perfectly insulated in the space comprised between the two ligatures, the only parts by which it still remained connected with the system were at those parts of the vessel beyond the ligatures, and thus, as far as nervous communication was concerned, it was in the same condition as if it had been removed entirely from the body, for a ligature still was around the lower part of the vessel, and one had previously been placed around the upper portion; an assertion quite sufficient to incapacitate the nerves which had been included in it, from performing their functions, and thus there remained no means by which an impression made on the nerves in the insulated portion of the vessel would be transmitted to the nervous centres. As this obvious source of fallacy must have struck the authors of the experiment did it really exist, I conclude that the vein could only have been partially separated from the surrounding tissues. In this case we have a ready explanation of the action of the poi-

son, the free anastomoses which exist between the veins of opposite sides readily permitting the poison to become mixed with blood circulating through the body. Even supposing the complete insulation of the vein, the ready manner in which solutions become diffused through fluids, would forbid the conclusion that the solution of the poison in the blood could be confined to the insulated portion of the vessel. It must speedily become mixed with the blood in the upper part of the vessel, above the point at which it was insulated, and thus could readily enter the general circulation.

Another experiment brought forward by these gentlemen to prove that a poison does not exert its effects by being taken into the blood, and thus applied to the nervous centres, is one in which they connect the carotid arteries of two dogs in such a manner, that they suppose the blood from the heart of the one dog is sent to the brain of the other. This supposition, however, is entirely opposed to the physical arrangement of the vessels that supply the brain. Were the carotids the only vessels going to this organ the experiment would be a fair one; but in the dog the vertebral arteries are so large as readily to furnish a sufficient supply of blood to the brain, even when the carotids are tied. The only condition in which the blood could pass from one animal to the other is by the pressure of the blood on the parietes of the superior end of the carotid of each dog being less than the pressure on the inferior portion of the carotid of the dog with which it was connected, and the quantity of blood that passed would be in proportion to the difference of pressure on the two ends of the tube connecting the vessels. I have ascertained by direct experiment with the hemadynamometer, that the pressure exerted on the parietes of a tube, inserted into the distant extremity of the carotid, is less by a column of mercury of not more than two or three-tenths of an inch, than the pressure on a tube inserted into the end nearer the heart. If we suppose, therefore, that the pressure in the arterial system of each animal was originally equal, (a fact by no means probable,) it is evident that but a very small quantity of blood can pass from the arteries of one animal to those of the other, and this only whilst both are in the same state. As soon as the poison begins to exert its influence on either animal, the pressure in its arterial system will be diminished, and thus, far from blood containing the poison being sent to the brain of the sound animal, the only effect of this arrangement will be to cause a reflux of pure blood from the arteries of the sound dog into those of the poisoned one. It is not surprising that, under these circumstances, the experiment furnished a negative result. It is evident that from neither of these experiments can any argument be deduced in favour of the local action of poisons.

I shall now draw up a short abstract of the facts which these ex-

periments have been intended to illustrate, observing, that in using the word poisons, I would only now allude to those which appear to act on the nervous system.

1. That the time required* by a substance to permeate the capillary vessels may be considered as inappreciable.

2. That the interval elapsing between the absorption of a substance by the capillaries and its general diffusion through the body may not exceed nine seconds.

3. That an interval always more than nine seconds elapses between the introduction of a poison into the capillaries or veins and the appearance of its first effects.

4. That, if a poison be introduced into a part of the vascular system nearer the brain, its effects are produced more rapidly.

5. That the contact of a poison with a large surface of the body is not sufficient to give rise to general symptoms, as long as its general diffusion through the body is prevented.

* In regard to the statement as to the time required for substances to be diffused through the body I would observe that all my experiments have been performed on full grown dogs. It is probable that these observations might require to be slightly modified in applying them to other animals. It is also evident that a difference must exist in the time occupied by a substance in reaching the capillaries in different parts of the body. The time here given, or nine seconds, is that in which I conclude a substance may be applied over the greater part of the body, more particularly to the central parts of the nervous system. It would appear that seven seconds may suffice for its being conveyed to the capillary terminations of the coronary arteries.

patients have been intended to illustrate, observing, that in using the word poison, I would only allude to those which appear to act on the nervous system.

1. That the time required for a substance to permeate the capillary vessels may be considered as insignificant.

2. That the interval elapsing between the absorption of a substance by the capillaries and its general diffusion through the body may not exceed nine seconds.

3. That an interval always more than nine seconds elapses between the introduction of a poison into the capillaries or veins and the appearance of its first effects.

4. That if a poison be introduced into a part of the vascular system nearer the brain, its effects are produced more rapidly.

5. That the contact of a poison with a large surface of the body is not sufficient to give rise to general symptoms, as long as its general diffusion through the body is prevented.

In regard to the statement as to the time required for substances to be diffused through the body, I would observe that all my experiments have been founded on self-grown dogs. It is probable that these circumstances might require to be slightly modified in applying them to other animals. It is also evident that a difference exists in the time occupied by a substance in reaching the capillaries in different parts of the body. The time here given or less would be that in which a substance may be applied near the greater part of the body, more particularly to the central parts of the nervous system. It would appear that some seconds may suffice for its being conveyed to the capillary terminations of the nervous system.

It is also evident that the time required for a substance to be diffused through the body is not the same in all cases. It is evident that the time required for a substance to be diffused through the body is not the same in all cases.

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