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LOCAL ACTION OF POISONS.

BY

CHARLES COGSWELL, M.D., L.R.C.S.E.

PHYSICIAN TO THE ST. PANCRAS ROYAL GENERAL DISPENSARY,

ONE OF THE SECRETARIES TO THE MEDICAL SOCIETY OF LONDON,

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Some time since, following in the track of M. Poiseuille, I entered largely into the investigation of endosmose, with the hope of being able to apply the results to the explanation of the mode of action of medicines. How different was the character of the conclusions from what I anticipated, has been shown in a paper read in December last before the Medical Society of London. Continuing the inquiry, with an especial reference to the admirable researches of Professor Graham on the "diffusion of liquids," I have been led to conclude that the membrane, or other porous partition, does not, as generally supposed, take an active part in the production of endosmose, although it may exercise a modifying influence according to its structural peculiarities. The dynamic cause would seem to be a force existing in the liquids themselves, and the same as that which gives rise to their mutual diffusion when placed directly in contact with one another. Professor Graham, in summing up the results of most interest that follow from his inquiry, includes "the assistance which a knowledge of liquid diffusion will afford in the investigation of endosmose. When the diffusibility of the salt in a liquid," he says, "is known, the compound effect presented in an endosmotic experiment may be analyzed, and the true share of the membrane in the result may be ascertained."

It is doubtless satisfactory to know that if two given salts, such as sulphate of magnesia and nitrate of potash, differ in their action on the economy, there is a physical law by which that difference can be in some measure accounted for. Apart from the development of this fundamental principle, the issue of my attempt conveys rather a disappointment. Opium

and tobacco have not, as the French author conceives, the power of altering the properties of membranes in a way that can be considered analogous to their effects on the living system. So far from putting a stop to endosmose, as if by a narcotizing or paralyzing action on the membrane, they display, on the contrary, much greater energy in the endosmometer than many inorganic salts to which no such action is attributed. The law of endosmose fails to assist us just where the difficulty commences in the case of such agents as especially affect the phenomena of motion in animal life, and leaves us still under the necessity of observing these phenomena empirically, with no better insight into their cause than we had before.

Among the agents of this class which, by a convenient term now fully recognised (Pereira), are said to operate "dynamically," but few have as yet been proved to be capable of producing local impressions on the part to which they are applied, and the purport of the present paper is to show that the number can be greatly extended. Poisons are divided by Professor Christison, with reference to their local action, into those which chemically corrode the part to which they are applied; those which inflame it without injuring its organization; and those which produce local nervous impressions unaccompanied by any visible organic change. The examples of the third class which he admits as well authenticated, in his standard work on poisons, may be briefly stated as follows:—

I. *Monkshood*, when chewed, causes numbness and tingling of the lips and tongue, lasting for some hours. (Brodie.)

II. *Hydrocyanic acid*, confined in a tube, with a finger over the open end, causes numbness of the finger. (Robiquet.)

III. If one of the hind legs of a frog be immersed in *hydrocyanic acid* for about half an hour, the leg becomes paralyzed. (Coullon.)

IV. If an infusion of *opium* be injected between the skin and muscles of the hind leg of a frog, the leg becomes paralyzed. (Monro *secundus*.)

V. An infusion of *opium* injected into the intestine of a rabbit put a stop to the peristaltic motion of the part with which it came in contact. (Wilson Philip.)

VI. *Ticunas* applied to the outer coat of the intestine of a guinea-pig caused an instantaneous and complete suspension of the peristaltic movement. (Morgan and Addison.)

There is another instance given by Fontana, which, on the authority of so experienced a toxicologist, may perhaps be allowed to rank with the preceding. He found that the poison of the viper, when applied to the tongue, caused a long-continued perception of numbness of that organ. (Treatise on the Venom of the Viper, &c., 1787.)

With this addition, the dynamic agents ascertained to act locally would be five in number—viz., monkshood, hydrocyanic acid, opium, ticunas, and the poison of the viper. It will be remarked that the evidence always consists in the privation of power, whether of sensation or motion. Many analogous substances will be seen to have the property of causing local paralysis; though with regard to the absence of any concomitant alteration in the tissues, this is a rule the exact limits of which are not easily defined. Even in the recognised instances, I believe it requires to be understood with some qualification. For the present, however, I shall confine my attention to the single question, whether the substance experimented on does or does not affect the phenomena of motion.

But, before proceeding, I must take the liberty of raising a doubt as to the authenticity of the two examples marked V. and VI. in the above list. The authors of the experiments, judging from their own words, seem to infer that the suspension of the peristaltic movement of the bowels was occasioned by paralysis. Thus, Dr. Wilson Philip says, that when he applied an infusion of opium to the external surface of the intestine in a rabbit, he "could not be certain that it at all diminished the peristaltic motion; on injecting it into their cavity, they almost instantly became paralytic." (On the manner in which Opium acts on the Living Body, 1795, pp. 85-6.) And Messrs. Morgan and Addison state, that a very minute portion of ticunas having accidentally come in contact with the still living intestine of a guinea-pig, "the consequence was a complete and instantaneous suspension of the peristaltic motion of that part of the intestine to which the poison was immediately applied; and in repeating the application of the poison to other parts of the intestine in the same animal, precisely the same local paralysis was produced." (On Poisons, p. 63.)

To try these experiments fairly, the bowels ought to have

their vitality as near the natural standard as possible. Having injected a strong infusion of opium through an opening in the small intestine both of the sheep and the rabbit, while the peristaltic movement was active, I observed that the immediate effect was an energetic contraction of the bowel towards the axis, attended certainly with a suspension of the peristaltic movement, but this clearly because the effect of the foreign body had been to *stimulate*, so as to throw the circular fibres of the muscular coat into irregular and excessive action. In a rabbit which was killed purposely to prevent delay in exposing the intestine for this experiment, the part next the opening through which the infusion of opium was injected shrunk instantly to the condition of a mere cord; but in a few minutes afterwards it returned to its former capacity, and at the same time renewed the peristaltic movement. If the living intestine of an animal be gently irritated with the point of a knife, the part acted on, according to my observation, ceases to participate in the peristaltic movement; it contracts, and the result is a furrow or stricture; but by-and-by this disappears, and its previous diameter is restored. A drop of alcohol has the same effect as the knife in producing constriction; so likewise have opium (in strong infusion), hydrocyanic acid, conia, and nicotina. Whatever may be the nature of their ulterior influence, in this primary effect they all agree.

But again, though unable to admit, on the authority of the evidence above quoted, that opium and ticunas have the power of *immediately* paralyzing the bowel, I believe it is very possible that they may have a tendency to do so after an appreciable lapse of time. Such, at least, appears to be the case with conia and nicotina, which, from their physcial constitution, are peculiarly adapted for trying the experiment. Minute portions of these fluid alkaloids being applied to the intestines of newly-killed frogs, the first phenomenon was always a local constriction; but in an hour, more or less, the parts to which they had been respectively applied presented a remarkable bulging outwards, as if they had become flaccid from paralysis. Conia and nicotina applied in like manner to the voluntary muscles of the frog, produced vivid contractions of the fibres at the points of contact. Hydrocyanic acid, opium (in strong infusion), alcohol, chloroform, and the dilute mineral acids, all had the same effect—that of causing the

muscles to contract, which is one we commonly understand in the definition of a stimulus. With regard to the subsequent effect on the voluntary muscles, I was unable to judge by this method. In few words, if there really be any substances which *immediately* paralyze by a local impression on the extremities of the nerves, it would appear that we have as yet no sufficient reason for including opium and ticunas among the number.

The question here involved is one well worthy of attention, because it is intimately concerned with some of the fundamental doctrines respecting the mode of action of medicines. In the first place, it is of great moment in relation to the Brunonian doctrine, that all agents capable of affecting the living body act on the excitability as *stimulants*. Secondly, it enters into the arguments which bear on the long-standing controversy between the advocates of sympathy and absorption. If the immediate effect of a narcotic on the muscular fibre be simply to excite it to contract, this removes any obvious ground for having recourse to sympathy to explain the phenomenon. It is simply a case of muscular contraction on the application of a stimulus. Whereas the production of paralysis at the first moment of contact admits of some other mode of interpretation; and thus we find Messrs. Morgan and Addison claiming the supposed paralysis of the bowel, from the application of ticunas, as a proof in favour of sympathy.

The following experiments were performed for the most part on one of the hinder extremities of the frog, with only an occasional exception, the remarkable result obtained by Dr. Monro from injecting opium between the skin and muscles, and which I have repeatedly verified, having suggested the idea of trying other poisons in the same manner. For testing the irritability of the muscles, I used a frog battery, consisting of a pair of flat zinc and copper rods, about six inches long, connected at one end by a moveable joint, so as to allow the free ends to be separated or approximated at pleasure. It was not at first my intention to employ the mineral acids; but finding that the effects of muriate of aconita appeared to differ in kind, as well as degree, from those of the simple alkaloid, I concluded on submitting them also to the experiment.

The Mineral Acids.

Sulphuric.—A solution composed of one part of the commercial acid to ten of water was injected beneath the skin of the left leg of a frog. For about four minutes the animal used all the limbs vigorously in leaping, but after that it allowed the left foot and leg to drag behind. General depression followed, and in three hours the animal could no longer be affected by stimulants. Shortly before this, it had slight muscular twitchings of the right hinder extremity. On examination, the skin of the left leg was found whitened in some places, and was easily torn; and the muscles below were yellowish, indurated, and unexcitable by the frog battery. The muscles of the left thigh, and those of the opposite limb, had a natural appearance, and contracted under the galvanic stimulus.

Nitric and Muriatic.—The same experiment, with the acids similarly diluted. In a few seconds the animals lost the use of the leg, and began likewise to show symptoms of constitutional depression; but all the effects, including the local paralysis, passed off after some hours. There were no convulsions. The animal on which the muriatic acid had been tried was killed the next day, that the muscles might be examined. The left gastrocnemius was whitened, hard, and unexcitable on the outside, where it had been directly acted on by the acid; but the anterior or inner half looked natural, and preserved its irritability. This, perhaps, explains the temporary paralysis of the muscle, and the apparent recovery of its functions.

Alcohol.

Ten drops of rectified spirits of wine having been injected beneath the skin of the left leg, in about half a minute the whole extremity was paralyzed, while the animal retained perfect command over the other three. Ten minutes after this it was perfectly insensible. The muscles being exposed, and tried with the frog-battery, those of the left leg and thigh contracted very feebly for about half a minute only, but in the right they were much more excitable, and continued also to be susceptible for several minutes.

The experiment being repeated with only half the quantity of spirits, the animal partially lost the control of the limb and

became rather torpid, but the effects all passed off in a few hours.

Ether.

Two Trials.—The same experiment, with five drops of sulphuric ether. The effects resembled those of the same quantity of spirits of wine—viz., paralysis of the leg, (becoming sensible in about half a minute,) general prostration, and recovery after some hours.

In one of the animals the injection was repeated with ten drops of ether. This time the leg was paralyzed in about fifteen seconds, and the general system became more depressed. In twenty-four hours the animal had regained its wonted activity, but was still deprived of the power to use the leg.

Chloroform.

The same experiment, with five drops of chloroform. The animal at first drew up the limb, but in four or five seconds it allowed the leg to lie extended, and three minutes afterwards, on its attempting to move, the whole extremity was observed to be straightened out and rigid. The first indication of the local effect was attended with hurried breathing and commencing stupor. In twenty-five minutes it turned over on the back, without using the left limb, the stupor increasing. In seven hours no sign of life could be elicited, and the blood was stagnant in the capillaries of the feet; the muscles of the left leg and thigh were unexcitable by the frog-battery, but those of the opposite limb all contracted distinctly, though feebly, when thus stimulated.

Hydrocyanic Acid.

The same experiment with ten drops of Scheele's acid. The animal leaped briskly on all the four extremities for about five minutes, but it then began to grow torpid, and in about two hours no longer manifested any sign of consciousness. During this time there was no evidence of local paralysis. The muscles, being tested by the galvanic stimulus, were found to be excitable in both the hind limbs, but possibly to a less degree in the left.

Two other trials were made with a preparation containing twelve per cent. of real acid. In about half a minute the whole extremity was paralyzed, while the animals enjoyed the perfect

use of the other three, but they quickly gave evidence of general prostration, and in between two and three hours were dead to outward appearance. In these instances the muscles of the left extremity were excitable under the frog-battery, but distinctly less so than those of the right.

The singular effects of the acid on the respiratory organs and the blood, in these and other experiments, have already been noticed in a communication laid before the Medical Society of London. (See The Lancet, October 16, 1852.)

Opium.

Dr. Monro's infusion, above alluded to, was made by digesting a drachm of opium in an ounce of water for twenty-four hours, and filtering. Ten, twenty, or forty drops introduced between the skin and muscles of one of the hind legs of frogs, caused local paralysis and general torpor, terminating, when he used one of the larger quantities, in convulsions and death. An infusion prepared in the same manner was employed in the following experiments.

Two frogs were selected, of equal growth, but one of them much stouter and stronger than the other. Five drops of the infusion, injected beneath the skin of the leg, produced no obvious effect on the former; but in the weaker animal, the leg was paralyzed in seventeen minutes. The latter at the same time was somewhat stupified, and in fifteen minutes more it had a convulsion.

The experiment was then repeated on a vigorous frog, with twenty drops of the infusion evaporated to about half the quantity. In eight minutes the animal began to drag the foot, and two minutes afterwards it appeared torpid. On a smart shock being given to the table, it was convulsed, but without the left limb (the one experimented on) being implicated in the movements. In four hours, the animal manifested no outward signs of life. The muscles of both the hinder extremities were found to contract very distinctly under the frog-battery, with no great difference on either side, but, if anything, they were judged to be less susceptible in the left leg.

Morphia.

The same experiment with a grain of muriate of morphia dissolved in a few drops of distilled water. For an hour and

a half the only effect observable was some degree of general torpor, both the hind limbs being used with equal freedom. At this time the animal on being disturbed had a convulsion, during which the left leg was not thrown into action, but lay extended and powerless. The convulsions recurred at intervals for several hours, with the same exemption of the left leg, but in eleven hours this one was observed to be convulsed as much as the right. In twenty-four hours the animal appeared to be dead. The muscles of both the hinder extremities contracted slightly under the galvanic stimulus, with no very evident difference in point of energy. I thought, however, that those of the left leg (or the one operated on) were rather the more excitable.

In another experiment there was no local effect, and the animal only showed a disinclination to move for several hours.

Codeia.

The same experiment with half a grain of codeia, pulverized and diffused in water. In a quarter of an hour the animal seemed to be partially deprived of its control over both the hinder extremities. A few minutes afterwards it threw them both out in a general convulsion, on recovering from which it was totally unable to draw up the left leg. The convulsions recurred with less and less frequency and violence for nearly twenty-four hours, the vital powers becoming gradually exhausted. During each paroxysm the left leg was agitated in common with the other three, but afterwards it remained extended.

In twenty-four hours the body was found apparently lifeless, with both the hind limbs extended. In the right the muscles twitched spontaneously on being exposed to the air, and contracted also when stimulated by galvanism; but in the left they could not be excited to contract.

The experiment was thrice repeated without any material difference in the phenomena.

Narcotine.

Two grains of narcotine pulverized and diffused in water produced no effect when injected beneath the skin of a frog's leg. The same quantity given afterwards to the same animal by the mouth likewise had no effect.

Hyoscyamus.

Three grains of the extract triturated with water having been injected beneath the skin of the left leg, in a quarter of an hour the animal began to drag the foot, and in five minutes more the whole extremity was paralyzed. At the time of the first local effect it appeared lethargic. Two hours from the commencement it was completely insensible. The muscles of the right hinder extremity contracted under the stimulus of galvanism, but in the left they were totally unexcitable.

Atropia.

Half a grain of atropia diffused in water, and injected beneath the skin of the left leg, produced no effect.

A grain was then tried on another frog. After leaping actively for about six minutes the animal began to drag the leg, and appeared languid. Four minutes after this it lay in a state of general prostration, with occasional twitchings of the right hind foot, and power to withdraw it when irritated, but with the whole of the left extremity relaxed and powerless. After remaining thus for about two hours the animal began to revive, and in five or six hours from the commencement it had regained the use of the paralyzed limb, and appeared to be quite recovered. The next morning, however, a new order of phenomena had set in. The animal was quiet unless disturbed, but the slightest agitation threw it into convulsions, in which both the hinder extremities were implicated. Gradually the convulsions became spontaneous and frequent, and as the day advanced death took place apparently from exhaustion.

The *sulphate of atropia* was tried on a third frog. Half a grain having been introduced beneath the skin of the leg, in two minutes the animal began to gasp and labour with the respiratory muscles. In three minutes the leg was paralyzed, and the same train of phenomena ensued as in the last experiment—viz., general torpor, apparent recovery, and then successive fits of convulsions, and death. In examining the body, a slight twitching at the throat, and jerking of the fore legs, were excited by the incisions, and then recurred spontaneously at intervals of four or five minutes. The muscles of the right thigh responded to the galvanic stimulus, but none of the others in either of the hinder extremities.

Nicotina.

The usual experiment on the left leg was performed with a drop of nicotina. The animal immediately drew up the leg, but in a few seconds allowed it to protrude from the thigh, and by the lapse of a minute, the whole extremity was rigidly extended and powerless. In the meanwhile the animal was growing insensible; and in five minutes it could no longer be affected by stimulants. The muscles of both thighs, and of the right leg, contracted under the frog-battery, but in the left leg they were totally unexcitable.

Aconita.

The same experiment with an eighth of a grain of aconita, pulverized and diffused in water. For about two minutes the animal leaped briskly, and had the entire control over the limb, but then began to let it remain extended. There was now evidence of commencing torpidity. In an hour, the animal had scarcely any power of voluntary motion, only shrinking very slightly when irritated, and retracting the eye if it was touched. The phenomena did not entirely cease for nearly forty-eight hours. At this period, the muscles contracted under the frog-battery in both the hinder extremities, but rather less forcibly in the left. Similar results were obtained on repeating the experiment.

Muriate of Aconita.—An eighth of a grain of this alkaloid, nearly dissolved in water by the addition of muriatic acid, was next tried. In less than a minute, the animal's control over the leg was impaired; and presently it dragged the whole extremity in moving from place to place, but still, as in the previous instances, it could use the limb by a strong effort of the will. In five minutes it lay relaxed and insensible. In twenty minutes it had a convulsive quivering over the whole system, not, however, including the limb that was operated on. In half an hour it appeared to be dead.

The muscles of the right hinder extremity contracted under the galvanic stimulus, but not those of the left. The results were very similar on repeating the experiment, including the convulsive movements. Allusion has been already made to these, as marking a difference between the action of the alkaloid, and that of the salt of muriatic acid.

Conia.

The same experiment with a drop of conia. For a few seconds the animal leaped briskly on all the four extremities, but it then began to drag the left leg, and in about five minutes the whole extremity was paralyzed. It likewise manifested at this time some degree of torpidity, which increased to such an extent that the animal was completely prostrated. After some hours, however, it began to revive, and gradually all the effects disappeared.

Similar results followed on repeating the experiment.

Theine or Caffeine.

It is one of the triumphs of chemistry to have furnished a clue to the cause of the predilection of so large a portion of mankind for tea, coffee, and cocoa, by demonstrating that the two former contain an active principle identically the same in chemical composition, and that a very similar principle (theobromine) exists in cocoa. From the similarity of composition between these principles and taurine, "the nitrogenized compound peculiar to bile," Liebig supposes that their chief use in the economy is to contribute to the formation of bile,—that they serve as "food for the liver,"—though, if I understand him right, he admits that they are also "remarkable for their action on the brain, and on the substance of the organs of motion," (Animal Chemistry, 1842, pp 181, 189). However this may be, there is no more familiar observation in dietetics than that strong tea and coffee are apt to produce vigilance, and, if taken habitually, to engender hysterical and hypochondriacal complaints. It will be seen that popular experience in this respect is supported by the result of a direct appeal to experiment with the proximate principle.

A grain of caffeine (theine) pulverized and diffused in water was put into a frog's mouth. The animal seemed almost immediately to lose a portion of its previous vivacity. In twelve minutes it had a general convulsion, after which the hinder extremities remained half extended, as if from inability to gather them up. In about half an hour it lay stretched out at full length, not moving when undisturbed, but thrown into violent convulsions by a sudden shock, as if it were under the influence of strychnia. In an hour there was no outward

sign of life, the body was rigid, and the blood stagnant in the vessels of the hind feet. The muscles generally were found to be excitable by galvanism.

In another experiment, with but half a grain of caffeine, the phenomena were similar, but the animal recovered.

Next, half a grain diffused in water was injected beneath the skin of the left leg of a frog. In six minutes the animal began to drag the foot, and in half an hour the loss of power extended to the leg. The animal was now slightly agitated by a shock. It soon became unwilling to move, and when disturbed, was thrown into convulsions. In these circumstances it underwent a gradual failure of the vital powers, without appearing to be deprived of consciousness, for nearly twenty-four hours, when no movements could any longer be excited by irritants. The circulation had ceased in the left hind foot, but was proceeding sluggishly in the right.

The muscles being now exposed, presented universally a peculiar purple tint, very different from their usual appearance after death. In the left thigh and the whole of the opposite limb they contracted under the frog-battery, but in the left leg they remained perfectly quiescent. A repetition of the experiment gave very similar results.

The active principle of tea and coffee is therefore a narcotic poison to the frog. In point of destructive energy it is far superior to morphia, and may almost be compared to strychnia and conia. The part of the nervous system affected seemed to be principally the spinal cord, as there did not appear to be any decided loss of consciousness, although in this matter it is difficult to judge in the frog.

The substances here stated to have been submitted to experiment comprise the mineral acids, alcohol, ether, chloroform, hydrocyanic acid, opium, muriate of morphia, codeia, narcotine, hyoscyamus, atropia and its sulphate, nicotina, aconita and its muriate, conia, and theine or caffeine. Many others have been tried, but I have not yet been able to feel so well satisfied with regard to them. As to those results which are given, I believe they are likely to stand the test of examination, the present details being little more than an abstract, which conveys no adequate idea of the time and labour bestowed on the investigation. Leaving out the mineral acids as included among the chemical irritants, and narcotine, the

remaining substances, all of them belonging to the class of so-called dynamical agents, have been found to be capable of producing local paralysis. Of these, the local action of aconita, hydrocyanic acid, and opium, was already known. It is obviously a question whether some of the bodies enumerated do not paralyze the limb chiefly by the influence of their chemical affinities; but this is a subject for a separate inquiry.