On the physiological action of the Calabar bean (Physostigma venenosum, Balf.) / by Thomas R. Fraser.

With the Author's compliments.

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ON THE

PHYSIOLOGICAL ACTION OF THE CALABAR BEAN

(PHYSOSTIGMA VENENOSUM, BALF.).

BY

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XLVIII.—*On the Physiological Action of the Calabar Bean* (Physostigma venenosum, *Balf.*).

By Thomas R. Fraser, M.D., Assistant to the Professor of Materia Medica in the University of Edinburgh. Communicated by Professor Christison, M.D., D.C.L., V.P.R.S.E.

(Read 17th December 1866.)

In 1855, the Professor of Materia Medica in the University of Edinburgh, in a paper read before this Society, directed the attention of physiologists to some of the remarkable properties of the Calabar bean.* In 1862,I presented a graduation thesis to the University of Edinburgh on the "Characters, Actions and Therapeutic Uses of the Ordeal Bean of Calabar." The principal results I had obtained at that time were that this substance causes death by either syncope or asphyxia, the latter being due to an effect on the spinal cord and on the respiratory centres; that the symptoms resemble those of cardiac or pulmonary embarrassment, according to the quantity of the poison administered, and to its rate of absorption; and, also, that the topical application of this agent to the eyeball, or to its neighbourhood, produces a marked and rapid contraction of the pupil and various disturbances of vision.† Since then, and more especially because of the peculiarity of the last of these conclusions, a lively interest has been taken in this substance. Its actions on the eye have been investigated by nearly all the leading ophthalmologists of Europe and of America, and its general physiology has occupied the attention of many distinguished students of biology. Nor have these labours been barren of practical results. Ophthalmic medicine has adopted this agent as one of its important remedies, and there can be little doubt that general medical practice will soon include in its Pharmacopœia a drug of so great energy.‡

The present investigation was undertaken for the purpose of extending and supporting my previous results, with some of which subsequent observers have disagreed; but I purpose to take an opportunity of examining these discrepancies with some detail in a different place. The effects which follow the topical application to the eyeball will be merely alluded to in this paper, as this portion of the subject has not been completed. Enough has, however, been done to convince

* Proceedings of the Royal Society of Edinburgh, vol. iii. p. 280; and Monthly Medical Journal, vol. xx., 1855.

† Edinburgh Medical Journal, 1863, and pamphlet.

‡ Since this sentence was written the *Physostigmatis Faba* has been admitted into the edition of the "British Pharmacopœia," published in 1867.

me of the insufficiency of the views hitherto advanced, and to suggest the advisability of extending my observations.

Preparations.

In 1863, I separated from the kernel, from the spermoderm of the bean, and, also, soon after, from the excrement of a lepidopterous insect which feeds on the kernel,* an amorphous active principle, possessing the general properties of a vegetable alkaloid, for which I proposed the name Eserinia, derived from Eserĕ, the usual name of this ordeal-poison at Calabar; and with it a few experiments were made, some of which have been published. Shortly afterwards, I succeeded in obtaining this alkaloid in, apparently, a state of greater purity, and as a crystalline substance, to which I gave the name Eseria. A crystalline acid, having a similarity to, and being probably identical with, tartaric acid, was also obtained from the kernel at that time. In the present investigation, however, an extract, prepared by acting on the finely pulverised kernel with boiling alcohol (85 per cent.), has been used. This preparation contains a considerable proportion of fatty matter, which prevents its complete solution in water; and, as the division into separate doses of a mere watery suspension would lead to many inaccuracies, it was found necessary to weigh the requisite quantity, separately, for the majority of the experiments. This extract is hygroscopic, which further required that it should be dried and kept in an exsiccator in order to ensure an unvarying preparation.†

Subjects of Experiment and Comparative Effects of Doses.

With few exceptions, the experiments were made with the common frog (*Rana temporaria*), birds, and various mammals. It was found that fatal results were produced with the smallest quantity on birds; and that the largest doses, in proportion to weight, were required by amphibia. A dose of one-sixteenth of a grain proved rapidly fatal to a pigeon weighing nine ounces and three-quarters; whereas a frog, which weighed 726 grains, has recovered from three grains of extract—a quantity sufficient to produce death in a dog of average size.

A. Action through the blood.

As I have already, in a previous paper, described with considerable detail, the general symptoms which follow the administration of physostigma, it will be unnecessary to give them here. It has also been shown, on the same occasion, that the more rapid the absorption of the poison the more quickly are fatal effects produced, and that the active principle may be absorbed by any living

* On the Moth of the Esere, or Ordeal Bean of Old Calabar. The Annals and Magazine of Natural History, May 1864, pp. 389–393.

† The varying potency of an extract possessing the property of absorbing moisture may unfit it for therapeutic purposes, but the tincture I have already recommended (*op. cit.* sect. iii.) will prove a sufficient substitute, and it has the great advantage of constancy of strength.

tissue. From the following experiment it is proved that prolonged digestion with gastric juice does not impair the energy of Calabar bean :—

Experiment I.

A gastric fistula was formed in a healthy dog, and, some days afterwards, and while the animal was in good health, 500 grains of gastric juice were withdrawn from the stomach. Four hundred grains of this were mixed with half a grain of extract of physostigma, received in a flask with an arrangement to impede evaporation, and placed in a water-oven at a temperature of 98° F. The digestion was continued for twenty-four hours, when the fluid was placed in a capsule and evaporated at 85° F. The resulting extract was finely pulverised, heated with alcohol of 85 per cent., filtered, and again evaporated to dryness. Contact with distilled water removed an acid fluid, which was made alkaline by excess of magnesia, and agitated in a bottle with chloroform. The chloroformic solution was removed by a separating funnel and evaporated, and the resulting brown extract was suspended in distilled water. A drop of this was applied to the conjunctiva over the right eyeball of a rabbit, whose pupil, before the experiment, measured $\frac{1}{8}\frac{3}{0}$ths × $\frac{1}{8}\frac{5}{0}$ths of an inch. In eight minutes, the pupil was $\frac{5}{8}\frac{5}{0}$ths × $\frac{1}{8}\frac{3}{0}$ths; in fifteen minutes, $\frac{5}{8}\frac{6}{0}$ths × $\frac{5}{8}\frac{8}{0}$ths; in twenty minutes, $\frac{4}{8}\frac{4}{0}$ths × $\frac{5}{8}\frac{6}{0}$ths, and it continued in this contracted condition for many hours. The remainder of the fluid was injected under the skin of a young pigeon, and caused its death in eight minutes.

Several small pieces of hard-boiled white of egg were placed in a flask with the remaining 100 grains of gastric juice, and digested under exactly the same conditions, and at the same time, as the extract of physostigma. They were found to be completely dissolved in less than ten hours. There could, therefore, be no doubt as to the activity of the gastric juice which had been employed.

This merely confirms the result before obtained, of fatal effects following the introduction of the poison by the digestive system.

I believe that Brinton first demonstrated that a poison which had been administered by the blood may be excreted by the stomach and intestines.* This was proved with tartar emetic; and, more recently, Taylor has published evidence showing that arsenic also may appear in the stomach although it had not been administered by the alimentary canal.† I took an opportunity of examining if a similar event occurs in poisoning with physostigma.

Experiment II.

Five grains of extract, suspended in water, were injected into the right jugular vein of a dog, and caused the death of the animal in eleven minutes. The stomach was immediately removed, and its contents, along with some of its mucous coat, obtained by scraping, were partially dried at a low temperature, and then boiled with successive portions of spirit (85 per cent.) acidulated with tartaric acid. The tincture was concentrated by distillation, and then evaporated to dryness. The extract was treated with distilled water, filtered, and agitated with ether until the fatty matters were removed. The remaining watery solution was made alkaline by the addition of carbonate of sodium and shaken with ether; and the ethereal solution was distilled. A yellowish, alkaline, amorphous residue was obtained, weighing three-fifths of a grain, and having a disagreeable animal odour. A minute portion of this extract was mixed with two

* Cyclopædia of Anatomy, article "Stomach;" Lancet, 1853, vol. ii. p. 599; and Lectures on the Diseases of the Stomach, 2d edit., 1864, p. 54.

† Guy's Hospital Reports, vol. vi. p. 397.

drops of distilled water and applied to the conjunctiva of a white rabbit, in the presence of my friend, Dr CRUM BROWN. Before the application, both pupils had a diameter of $\frac{1}{8}\frac{3}{0}$ths of an inch, in a full light. At first a little irritation was caused. In thirteen minutes, the pupil had contracted to $\frac{5}{8}\frac{5}{0}$ths, and in eighteen minutes to $\frac{3}{8}\frac{3}{0}$ths; the other pupil still remaining at its original diameter of $\frac{1}{8}\frac{3}{0}$ths. This extreme contraction continued for upwards of an hour; but in two hours the pupil was $\frac{7}{8}\frac{7}{0}$ths, and by the following morning it had resumed its original diameter.

It would, therefore, appear that physostigma, when administered by a vein, finds its way into the stomach—a method of poison-excretion which has been established in the cases of antimony and arsenic.

Although this investigation has for its principal aim the determination of the exact method in which physostigma acts, and the demonstration, as far as possible, of the histological structures which it influences, it may be necessary to describe, at this place, the general symptoms which follow the administration of a poisonous dose. In the case of mammals, I have already entered fully into this subject in a previous paper, from which I extract the following descriptions:*—

"When a *small* fatal dose is administered to one of the lower animals, a train of symptoms is produced usually in the following order:—A slight tremor is first seen, especially at the posterior regions, and this extends forwards to the anterior extremities and the head. The limbs yield immediately afterwards, the posterior becoming generally first paralysed, and the animal lies extended in a state of almost complete muscular flaccidity. A few attempts may be made to recover the normal position, but they are usually ineffectual. The bowels, in most cases, are evacuated, and urine is passed. The pupils generally *contract;* as the symptoms advance, the respiration becomes slow and irregular, with a distinct stertor accompanying both inspiration and expiration, and frothy mucus escapes from the mouth. Muscular twitches occur, and often continue after respiration has ceased. Reflex action cannot be produced by either pinching or pricking the skin. By-and-by the eyelids do not contract when touched or even when the eyeball is pricked. On lifting by the ears, the limbs hang inertly, and the only sign of life is an occasional gasping inspiration, which also soon ceases, and the animal appears dead.

"Consciousness is preserved during the whole time, until the power of expression is lost. During incomplete paralysis, proofs of sensation may be obtained by pinching the ears or pricking the skin. Immediately after death the pupils dilate.

"On opening the body the various muscles which are cut contract. The diaphragm and muscles of the extremities may be excited to action by pinching the phrenic and sciatic nerves, and the contractility of the muscles generally is retained for some time after death. The heart is found acting regularly, and the intestines exhibit distinct vermicular action. The heart may continue its action

* *Op. cit.* sect. ii.

for one hour and a-half after death. Its chambers usually cease to contract in a definite order, the left auricle first losing its spontaneous action, then the right and left ventricles, and, after an interval, the right auricle. The large veins in the thorax are found distended. . . . The lungs are engorged—in two experiments this had proceeded to such an extent that detached portions sank in water. . . .

"When a *large* fatal dose of the kernel is administered, the hind limbs almost immediately yield, and the animal falls. It lies flaccid, and in any position, on the table, and exhibits muscular power only by a few twitches. The pupils contract; in a few cases fluid escapes from the nostrils and mouth, and the lachrymal secretion is increased. Reflex action cannot be produced by irritation, and the respirations, after a few gasps, cease.

"The pupils dilate immediately after death. On opening the body, muscular twitches occur. . . . The heart is found distended and passive; irritation, however, produces contraction for about ten minutes after death. The vermicular action of the intestines is very much diminished, and can scarcely be observed. . . . The mesenteric arteries and veins may be readily distinguished by the colours of their contents."

The following will serve to illustrate the symptoms with frogs:—

Experiment III.

Three grains of extract of physostigma, suspended in twenty minims of distilled water, were injected, by WOOD'S syringe, into the subcutaneous cellular tissue at the back of a light-coloured frog, weighing 430 grains. For four minutes it appeared perfectly unaffected and jumped about normally; after which time some increase occurred in the respiratory irregularity which is always found in frogs. In seven minutes, the respiratory movements of the chest had ceased; but those of the throat continued for other four minutes (eleven after injection). About this time, the movements of the animal were sluggish; the fore legs gradually began to separate until they no longer supported the chest and head; and the posterior extremities were affected in a like manner, and soon after lay extended and flaccid. Weak voluntary movements, however, continued until fifteen minutes after the exhibition of the poison; and, for some time after this, irritation demonstrated the continuance of reflex power. In half an hour, the skin of the frog had undergone a marked change, having become of a dark brown colour. Although now apparently dead, it was not, in a strict physiological sense, really so. Motor nerve-conductivity was retained for many minutes longer; the diastaltic function was not abolished, and, hence, it was possible to show that afferent nerve-conductivity also continued; and the muscular tissue, for many hours, contracted when stimulated, and, in the case of some of the heart chambers, spontaneously and successively did so, for a shorter period.

Into all these, and many other points, it is necessary to enter with detail, and several of them may be overtaken in a somewhat connected manner by examining the cause of what is the most prominent, as well as one of the earliest, of the phenomena described. This is obviously the condition of gradually increasing paralysis.

Action on the Voluntary Muscles.

The peculiar successive tremors, which are observed in warm-blooded animals, at first sight suggest that the paralysis caused by Calabar bean is due to an affection of the muscular system; and the condition of general flaccidity, which so rapidly follows its administration to frogs, appears to favour, as it certainly does not contradict, this opinion. Without pretending that such was the order followed in this investigation, it will, as a matter of convenience, be advisable to examine, in the first place, the effects which are produced on voluntary muscles.

Experiment IV.

A full-grown active rabbit had injected into the subcutaneous tissue of its right flank, three grains of extract, suspended in eleven minims of distilled water. Tremors occurred in two minutes; the anterior extremities soon after yielded; and, in four minutes and thirty seconds, the animal fell, the muscular trembling having increased in vigour and having become general over the body. Respiration ceased in five minutes after the injection, but muscular tremors continued during other three minutes. When the thorax was opened the heart was found dilated and passive. Twenty-four minutes after the administration, galvanic stimulation of the sciatic nerves caused powerful muscular contractions; within thirty-six minutes, these nerves were completely paralysed, though application of the electrodes to any of the voluntary muscles produced marked contractions. These contractions became gradually weaker, but could be distinctly excited until one hour and thirteen minutes after the poison had been exhibited.

The general result in all the other experiments which were performed on warm-blooded animals was the same. Muscular contractility remained after destruction of the function of motor nerves; and this also occurred, in even a more marked manner, with frogs.

Experiment V.—(*Temperature of Laboratory about* 53° *F.*)

By means of Wood's syringe, I injected three grains of extract, in fifteen minims of distilled water, into the lower portion of the abdominal cavity of a frog which weighed 473 grains. The usual phenomena quickly occurred. In sixteen minutes, the sciatic nerve and the neighbouring muscles of the left thigh were exposed and found active.

The muscles were now of a very blue colour, quite distinguishable from their normal appearance; and this colour change was discovered in the serous and fibro-serous tissues also. In about four hours, motor nerve-conductivity was universally destroyed. The heart contracted rhythmically, and at a very reduced rate, until twenty-six hours after the administration, after which, the auricles contracted more frequently than the ventricles, and continued to do so until the heart's action ceased, seventy-three hours after the poison was injected; and, by microscopic examination of the web, it was found that a more or less feeble circulation was all this time maintained. Until this stage, no apparent change occurred in the readiness and vigour with which the striped muscles contracted when directly galvanised; their reaction continued to be alkaline, and they were perfectly flaccid. Soon after the stoppage of the heart's action the blue colour, which has been already mentioned, began to disappear, and in ninety-six hours (four days) the muscles were quite pale. No stiffness was yet observable, and galvanism still induced faint contractions. Rigor mortis commenced soon after this, but its progress was extremely slow, as galvanism produced dimples at the electrodes until 110 hours. When the frog was again examined, at 129 hours after the injection of physostigma, no muscular contraction could be produced by powerful galvanism; rigor mortis was complete; and the reaction of the muscles was found to be acid. Galvanism could produce a very faint contraction of the cardiac muscle,

limited to the points of stimulation, until about the time up to which feeble indications of retained contractility could be obtained in the voluntary muscles.

Experiment VI.—(*Temperature of Laboratory between* 52° *and* 54° *F.*)

To a frog, weighing 379 grains, four grains of extract were administered in the same way as in the preceding experiment. Motor nerve-conductivity ceased in two hours and sixteen minutes, by which time the exposed muscles were found to have become blue. The cardiac action continued rhythmical, though much reduced in frequency, until twenty-seven hours and fifteen minutes, after which, the auricles alone contracted spontaneously till forty-four hours, and then, spontaneous cardiac action entirely ceased. During all this time, the muscles were flaccid, contracted vigorously on the application of weak galvanism, and had an alkaline reaction and a blue colour. Soon afterwards, they became paler and slightly stiff, but it was not until seventy hours after the administration of the poison that galvanic stimulation failed to produce any contraction; and then rigor mortis, with an acid reaction of the muscles, set in.

These three experiments distinctly prove the absence of any paralysing effect by physostigma acting through the blood on striped muscle.

Rigor mortis is delayed for an unusual period after apparent death in cold-blooded animals, and its appearance, in mammals and birds, is certainly not hastened. In both classes this change in the condition of muscles is only indirectly affected by this substance, and that through its influence on the cardiac contractions. When the blood supply of the muscles is stopped their function is suspended, and rigidity follows; but the resulting rigor does not seem to be due, in any other than this indirect method, to the action of physostigma.

This may be more clearly demonstrated by detailing one of many experiments in which a portion of the frog was protected from the influence of the poison.

Experiment VII.—(*Temperature of Laboratory between* 52° *and* 54° *F.*)

The right iliac artery was exposed, by removing a portion of the sacrum, and tied in a frog, weighing 878 grains. Two minutes afterwards, three grains of extract, suspended in ten minims of distilled water, were injected into the subcutaneous cellular tissue at the right shoulder. In a few minutes, a condition of general paralysis existed, and shortly afterwards the skin of the tied limb was much paler than that elsewhere, this contrast becoming more marked as the experiment advanced. In an hour and twenty minutes, the sciatic nerves being exposed, it was found that the left was completely paralysed; while galvanism, applied to the right nerve, or that of the limb protected from the action of physostigma, produced active muscular contractions. The muscles of the tied limb were pale as contrasted with those to which the poison had access, and the latter were distinctly blue in colour. The non-poisoned muscles continued active until forty hours; but when examined at forty-nine hours they were acid and stiff, and did not contract when galvanised. In the poisoned parts, the functions of the motor nerves were destroyed in three hours and ten minutes; the non-poisoned, or right, sciatic continued active until thirty-two hours. It was possible to distinguish the heart's impulse on the thoracic walls, and to determine the frequency of its contractions. During the three days that immediately followed the poisoning, these steadily continued at a rate varying from seventeen to twenty-one; and on exposure, at the end of that time, fifteen feeble beats per minute were occurring. Soon after, the usual irregularities were observed, but the circulation was maintained until eighty-two hours after the injection of physostigma, as the microscope demonstrated. During all this period, the muscles everywhere, except in the tied limb, were flaccid, blue and of alkaline reac-

tion, and contracted, though latterly with diminished vigour, when galvanised: those of the tied limb were now putrefying. In 100 hours, the poisoned muscles had lost much of their blue colour, and contracted slowly and partially. In 120 hours, they were slightly stiff, and galvanism produced merely a slow surface depression at each electrode, which continued for a short time after their removal, and gradually disappeared. Such contraction could still be obtained 124 hours, or more than five days, after the injection of the Calabar bean. A similar dimpling could be produced on the heart till nearly the same time, and, therefore, long after it had lost its power of spontaneous contraction.

This experiment affords a very simple means of comparing the effect of mere absence of blood supply with the action of Calabar bean on the irritability of striped muscle. In the former case, irritability was destroyed, and the rigor of death initiated, at some time between forty and forty-nine hours. In the latter, subjection of the muscles during eighty-two hours to the influence of a blood stream conveying Calabar bean was not attended with the slightest injury; their irritability disappeared, however, forty-four hours after the circulation had been stopped by the action of this substance on the heart. Muscular paralysis was in both cases due to stasis of the circulation. It has, however, rarely happened that this irritability has continued so long as five days, in fatal cases of physostigma poisoning. The special circumstances for its production appear to be lowness of temperature and protracted continuance of the cardiac action.

These results may be seen with greater clearness if we tabulate the more important points of the above experiments, and of a few others.

Table of the Periods at which Muscular Contractility was lost, after the administration of Physostigma, and after Blood-stasis by Ligature of Vessels.

Experiment.	Weight of Frog and of Dose, in grains.	In Parts to which the Poison had Access.			In Parts cut off by Ligature.	
		Time when Circulation stopped.	Time when Muscular Contractility was lost.	Interval between stoppage of Circulation and loss of Muscular Contractility.	Nature of Operation.	Interval between local stoppage of Circulation and loss of Muscular Contractility.
V.	473 to 3	73 h.	110 h.	37 h.		
VI.	379 „ 4	28 h.	68 h.	40 h.		
VII.	878 „ 3	82 h.	124 h.	44 h.	Left iliac artery was tied.	In less than 49 h., and in more than 38 h.
VIII.	490 „ 3	52 h.	94 h.	42 h.		
IX.	292 „ 2	21 h.	75 h.	54 h.		
X.	212 „ 1·5	48 h.	104 h.	56 h.		
XI.	400 „ 2	34 h. (nearly)	74 h.	40 h. (about)		
XII.	460 „ 2	80 h.	120 h.	40 h.		
XIII.	620 „ 2	45 h.	88 h.	43 h.	Left iliac artery was tied.	44 h. 8 m.
XIV.	690 „ 3	50 h. 6 m.	72 h.	22 h. (nearly)	Left iliac artery was tied.	In less than 24 h., and in more than 19 h.
XV.	620 „ 5	0 h. 34 m.	33 h.	32 h. 26 m.	Right iliac artery was tied.	In less than 33 h., and in more than 29 h.

After this evidence, it is almost superfluous to remark that physostigma-paralysis cannot be caused by an action on striped muscle, as at least one observer of note has maintained.* Although the effects on muscle have been the first considered, it may be proper to remark here that idio-muscular irritability is the last vital property to disappear in death by Calabar bean, especially as this result has been foreshadowed in several of the experiments already given. Its loss is, moreover, only indirectly caused by physostigma, and the evidence is sufficient to show that it follows the cessation of the blood supply, which is necessary for its manifestation, in tolerably definite periods. As the circulation sometimes ceases more abruptly than at others, so does the loss of muscular irritability sometimes occur more quickly, and without much previous gradual diminution of activity. In the former case, rigor is well marked and comparatively prolonged; in the latter, and chiefly with frogs, it is slight, and the very partial nutritive activity which has been for many hours maintained by a sluggish blood-stream, favours the almost immediate occurrence of decomposition, and, therefore, of a short period of rigor mortis, when the circulation has finally stopped.

In the experiments with mammals and birds, an early and constant symptom was the occurrence of successive muscular contractions of a non-co-ordinate character; and this formed a striking contrast with the flaccid and motionless condition of the muscles which persisted throughout the poisoning of cold-blooded animals. Generally speaking, these contractions were very feeble, and consisted of slight spasmodic twitches, which, in mammals, usually began at the neck and then extended over the body, and which at first involved detached portions of the panniculus carnosus muscle only, and then apparently every muscle of the body and extremities. In the slighter cases, and, I think, where a small dose was being but slowly absorbed, a mere tremulous movement was caused of the head, body and extremities, similar probably to the "tressaillements" which Claude Bernard describes as occurring during curare poisoning,† and which have likewise been noticed with that substance by Watterton, and by Martin-Magron and Buisson.‡ In one or two of my experiments, however, this muscular action became so strong, that the animal appeared as if under the action of a poison which produces convulsions. The twitches always became more marked when the poisonous effects were fully developed, they gradually diminished in strength as death approached, and they continued in a slight form for many minutes after it. Exposure of the muscles to the air, and irritation with a knife, during the autopsy, increased their strength, and even originated them in muscles and parts

* Nunneley on the Calabar Bean, &c. Lancet, 1863, p. 23, and Pamphlet.

† Leçons sur les Effets des Substances Toxiques et Médicamenteuses, 1857, p. 268.

‡ Action comparée de l'éxtrait de Noix Vomique et du Curare sur l'économie animale. Journal de la Physiologie de l'Homme et des Animaux, tome troisième p. 327, &c.

of muscles from which they had disappeared; and it was then observed that the whole of a muscle seldom twitched at once, but portions of it separately and in succession. I frequently removed a muscle from the dead body, and found that these twitches still continued. In one experiment, where the sartorius had been cut out of a dog, these spasms rapidly followed each other in separate portions of its substance, during ten minutes. Their duration after death varied greatly. Occasionally they ceased before the motor nerves had lost their function, while they frequently continued after their paralysis. The latter effect was well shown in an experiment where seven grains of extract were given to a large dog, by injection into a jugular vein: death, with stoppage of the heart's action and of the respiratory movements, took place in eleven minutes; in twenty-five minutes afterwards, the sciatic nerves were paralysed; and these extraordinary muscular twitches continued for other twenty minutes, or for forty-five minutes after the death of the animal. The central nervous system has no influence in causing or originating these quiverings, for division of a sciatic nerve, before the exhibition of physostigma, did not appear to impede their production. I believe the effect is due to the contact of the poison with the muscular substance itself; and this view is supported by the above facts, and by the circumstance that when a ligature was drawn round the posterior extremity of a rabbit, taking care to exclude the sciatic nerve, the muscles of that limb remained unaffected, after the administration of Calabar bean, while those of the body and of the other extremities were twitching in the usual manner.

Action on the Cerebrum.

A condition of retained consciousness with marked paralysis opposes the idea of the latter symptom being due to coma. Professor Christison has admirably described the coincidence, in his own person, of retained mental vigour with inability for movement. To distinctly prove the absence of any cerebral explanation for this paralysis, a simple experiment was undertaken.

Experiment XVI.

The brain was removed with care from a large frog, and, sometime after this, the animal was found jumping about vigorously.* Two grains of extract, suspended in fifteen minims of

* It appears somewhat startling to assert that complicated movements, of an apparently voluntary character, may continue in frogs after the removal of the brain. I first observed this in an experiment in which the spinal cord had been divided at the base of the skull; and, in describing the condition of the frog in which it was seen, I added a qualifying note ascribing the circumstance to incomplete division of the medulla. Since then, I have occasionally observed the same phenomenon; and the present experiment is conclusive in showing that some of those functions which we are in the habit of ascribing to the cerebral lobes alone, are, in frogs at any rate, shared in by the spinal cord.

May 1867.—Dr Norris enters into this anomaly, and confirms its occurrence, in his admirable paper on Muscular Irritability, in the "Journal of Anatomy and Physiology," No. 2, p. 221, *et seq.* He also refers to Lewes (Physiology of Common Life, vol ii.) as having first prominently announced this curious exception to the generally received views on nerve physiology.

distilled water, were injected into the lower portion of the abdominal cavity. It continued to jump about for four minutes; in five minutes, the first indications of paralysis occurred, at the anterior extremities; and in twenty-five, it was lying flaccid on its belly and chest, without any respiratory movements, but with retained reflex action. The sympoms advanced in their usual order until the complete death of the frog.

An action on the cerebrum cannot, therefore, be the cause of the paralysed condition which is produced. The cerebrum may, notwithstanding, be acted on by physostigma; and the results of several experiments, in which I took various quantities of this substance, appear to favour such an opinion, though, until further investigation, I cannot maintain that the effects produced were not mainly dependent on those perturbations of the circulation which are caused by this poison.

Action on the Spinal Nerves.

1. *Motor or Efferent Nerve-Fibres.*

Experiment XVII.

I injected into the jugular vein of a very large retriever dog, seven grains of extract, suspended in twenty-five minims of distilled water. In three minutes, respiration became gasping; in five, the usual twitching affection of the muscles commenced; and in ten, the dog was lying in a powerless condition. In twenty minutes, respiratory and cardiac action had completely ceased. The right sciatic nerve was then exposed, and galvanic stimulation of its trunk produced vigorous movements confined to the leg whose nerve was stimulated. The same result was obtained when the left sciatic nerve was exposed and stimulated. Both retained their motor conductivity for eight minutes after respiration had ceased; and, for some time longer, the muscles responded to direct galvanic stimulation.

Experiment XVIII.

Five grains of extract were mixed with thirty minims of distilled water, and injected into the abdominal cavity of a large and healthy female cat. Trembling occurred in four minutes, when the cat ran a short distance and fell on her face, after which she lay in any position, flaccid and unresisting. Respiration ceased in ten minutes, but the peculiar twitching of the muscles continued for several minutes longer. The heart was then exposed, and found motionless and full. On galvanising the sciatics, or otherwise stimulating them, the muscles of the posterior extremities contracted vigorously; but no evidence was obtained of the reflex activity of the cord. The sciatic nerves continued active until forty-two minutes after the death of the animal (fifty-two after the administration of the poison); but, when they were galvanised at forty-seven minutes after death, no muscular contraction was produced. The phrenic and brachial nerves also continued active for about the same time.

Experiment XIX.

Three grains of extract, suspended in eleven minims of distilled water, were injected into the subcutaneous cellular tissue in the flank of a full-grown rabbit. Trembling occurred in two minutes, and this continued, with varying strength, until seven minutes; two minutes before which respiration had ceased. The sciatic, phrenic and brachial nerves were galvanised, and found to be active; and such stimulation of the sciatics continued to produce muscular contraction until nine minutes after the cardiac and the respiratory movements had ceased.

Experiment XX.

There was injected into the subcutaneous tissue at the right flank of a rabbit, weighing two pounds, half a grain of extract in fifteen minims of distilled water. The usual tremors rapidly supervened, and in forty-five minutes the animal was dead. During the following thirty-one minutes, galvanism of either sciatic nerve produced contractions of the limb which it supplied.

Experiment XXI.

Half a grain of extract was placed in the mouth of a pigeon. In ten minutes, a profuse flow of saliva and of tears, with occasional passage of fæces, occurred; after which time the bird lay in a helpless condition, with now and then a sudden starting movement. In twenty-four minutes, its respirations had completely ceased. Until eight minutes after death, galvanism of the left sciatic nerve continued to produce movements in the left leg; but in thirteen, the nerve was quite paralysed.

Such experiments were frequently repeated; and in no case did I find that the motor nerves were paralysed before the respiratory movements had ceased, although it has occurred that they have almost immediately afterwards been so. I have found that the interval during which they remain active varies greatly in different animals, and in the same animal according to the dose of poison administered; and I believe that in the latter case the variation is in an inverse ratio. In the rabbit, motor conductivity may be retained for periods ranging from a very few (two or four) to thirty-one minutes. We cannot, therefore, account for either the condition of general paralysis or the cessation of the respiratory movements, which two form the most prominent of the symptoms of physostigma poisoning in warm-blooded animals, by an action on the motor nerves. Experiments XVII., XVIII., XIX., XX. and XXI. are sufficient to prove this. The evidence obtained by experiments with frogs is even more unmistakable. Complete destruction of all the vital functions in this animal never occurred for many hours. In animals of a higher type, the implication of one system so rapidly influences the others that it is often difficult to discriminate between the effects which are caused by the poison and those which are induced as results of the primary action. In the frog, on the other hand, the symptoms advance so slowly from one system to another that it is possible to determine distinctly the sequence of the phenomena which are due to the direct influence of physostigma.

Experiment XXII.

Five grains of extract, suspended in a few minims of distilled water, were injected under the skin over the back of a frog weighing 490 grains. A small quantity escaped in the somewhat vigorous movements which occurred when the frog was liberated. The thoracic respiratory movements ceased in ten minutes, and those of the throat in other four. Twenty-two minutes after the injection, the animal lay on its abdomen in a perfectly flaccid condition; its heart was acting feebly, at the rate of seven per minute; and pinching of the skin anywhere caused but very weak reflected movements. In one hour, no evidence could be obtained by galvanism, or by

any usual irritant, of continuance of the diastaltic function of the cord; but the heart was now contracting nine times in the minute. The sciatic nerves were then exposed; and, on galvanising either of them, movements occurred in, and were confined to, the muscles of the limb whose nerve was so stimulated. Both nerves continued to give this evidence of the conductivity of their motor fibres as long as one hour and thirty-eight minutes after the injection of Calabar bean, or one hour and twenty-four minutes after all respiratory movements had ceased. Shortly afterwards they were found paralysed.

Experiment XXIII.

Into the lower portion of the abdomen of a frog, which weighed 620 grains, a mixture of two grains of extract with ten minims of distilled water was injected. In twelve minutes, the frog was lying in a flaccid condition, and respiration had ceased. In two hours, no reflex movement could be excited. The right sciatic nerve was exposed; and its motor conductivity was found to remain. Galvanism, applied to either sciatic nerve, produced muscular contractions in the limb to which the nerve was distributed, until, but not later than, three hours and twenty-one minutes after the administration of the poison, or three hours and nine minutes after respiration had ceased, and until more than one hour and twenty-one minutes after apparent destruction of the reflex function of the spinal cord. In this experiment, it is important to note, the cardiac action was not greatly affected for more than three hours, as the dose of poison administered was comparatively small.

Experiment XXIV.

Six grains of extract, suspended in fifteen minims of distilled water, were injected into the abdominal cavity of a frog, weighing 350 grains. In eight minutes, no cardiac impulse could be discovered; and the heart was then exposed and found motionless, dark and flaccid. Respiratory movements ceased in eight minutes. It was determined, on irritating the skin with sulphuric acid, that reflex movements could not be obtained two hours and a-half after the injection; but they were produced until nearly this time. *The motor conductivity of the sciatic nerves was retained for twenty-nine hours.*

It thus appears that the motor nerves always remain active after the co-ordinated movements of respiration have ceased, and after the condition of complete and flaccid paralysis has existed for long. On this point, therefore, I cannot agree with HARLEY, who considers that physostigma is a respiratory poison only, and that the early production of asphyxia is caused by paralysis of the motor nerves.*

The protracted interval in the last experiment, between the administration of the poison and the loss of motor conductivity, must be looked upon as a very exceptional one, and as due to the poison having so quickly paralysed the heart that the usual phenomena were not produced. In Experiments XVII., XIX., XXI., XXII., and XXIII., the motor nerves appear to have lost their function sooner than naturally happens in death from cardiac paralysis or from asphyxia. But that they really did so must have remained a mere impression, had it not been that we can, in frogs at any rate, definitely prove a special action on the

* Journal de l'Anatomie et de la Physiologie, 1864, p. 141, *et seq.*; and British Medical Journal, Sept. 3, 1863.

motor nerves, by protecting a portion of the animal from the poison. Such a proceeding cannot be avoided by determining the interval which naturally elapses between the moment of death and the time at which loss of function occurs in these nerves. This interval varies greatly in different classes of animals, and also in different individuals of the same species; and, hence, the data which have as yet been accumulated on this point are not available for such purposes as the present.

Experiment XXV.

The sacrum was excised from an average-sized frog, and, in that manner, the lumbar nerves and the abdominal aorta were exposed. The aorta was ligatured above its bifurcation into the two iliacs, and, immediately afterwards, an average poisonous dose of extract was placed in the frog's mouth. In ten minutes, respiration had ceased; but the frog continued jumping about for other four minutes, when it quietly and gradually subsided on its abdomen and chin. Reflex movements could be excited by irritating the skin anywhere until one hour and seven minutes after the administration; but, for some time before this, a great increase in the strength of the stimulant was required. The skin of the posterior extremities had now become paler, while that of the body, anterior to the ligature, had assumed a much darker colour than it had before the experiment; and the exposed heart was found beating twenty per minute, with regularity and in proper rhythm. The brachial nerve was then laid bare, and was found active; *but this condition ceased two hours and eleven minutes from the commencement of the experiment, and both brachials were then perfectly paralysed.* At this time, weak galvanism applied with closely approximated poles to sections of the spinal cord produced no effect; but when the lumbar nerves below the ligature were galvanised they caused vigorous contractions of the posterior extremities. *On the following morning, this motor nerve activity still remained, in the parts protected from the poison:* but the contractions were now feeble, as muscular rigor was commencing below the ligature; and, in a few hours longer, the muscles separated from the circulation ceased to contract. The muscles of the poisoned portion, in which the motor nerves had been long paralysed, were still quite flaccid, alkaline and irritable; and rigor mortis did not occur in them until the following day.

Experiment XXVI.

The right iliac artery and the right ischiadic vein were tied in a frog, weighing 620 grains; and five grains of alcoholic extract of physostigma, suspended in thirty minims of distilled water, were injected into the abdominal cavity. In twenty minutes, voluntary movements had completely ceased, there were no respirations, and the frog lay in a perfectly flaccid condition. Fifty minutes after the administration of the poison, the left sciatic nerve was exposed. Very weak galvanism of the nerve-trunk caused contractions of the limb; and continued to do so, on occasional observations, till two hours and ten minutes from the commencement of the experiment, or till fifty minutes after the respirations had ceased. In other fifteen minutes, however, the nerve was found to be completely paralysed. The right sciatic nerve, which had been protected from the influence of the poison, by ligature of the blood-vessels of the limb, was examined in a similar manner. *Its motor conductivity continued unimpaired for at least five hours longer than that of the poisoned nerve.*

These are examples of numerous experiments which were undertaken for the special purpose of determining whether Calabar bean has any action on the spinal nerves. They prove undoubtedly that it has the power of destroying their motor conductivity; but it has also been demonstrated that this is not the cause of

paralysis and death in mammals, or of complete loss of voluntary power in frogs. The next question which suggests itself for solution is the somewhat interesting one of the portion of nerve acted on; for, in the case of more than one toxic substance, it has been determined that loss of motor nerve-function does not of necessity imply that both the periphery and nerve-trunk have been affected.

Experiment XXVII.

Immediately after ligature of the left ischiadic artery and vein, two grains of extract were placed in a subcutaneous cavity at the back of an active large frog. Before twenty minutes, respiratory movements had ceased; while the heart was then acting rhythmically, at the rate of thirty beats per minute. One hour after the administration of the poison, the right (or poisoned) sciatic nerve was exposed, and found active; but in other twenty minutes, strong galvanism applied to any portion of its trunk could not produce contractions in the muscles to which it was distributed, and an examination of the brachial nerves proved them also to be paralysed. The left sciatic nerve was, however, perfectly active. When it was galvanised, movements, confined to that limb, were produced in the muscles below (or distal from) the ligatures. *These ligatures were on the thigh; but stimulation of the nerve above them, or of the lumbar nerves on the same side, was followed by energetic muscular contractions below the points of ligature.*

The muscles were everywhere active, and continued so for several days; and those of the non-poisoned limb were the first to pass into rigor mortis. The sciatic nerve of the non-poisoned limb, and the lumbar nerves of the same side, continued active for many hours; but their loss of function occurred several hours before that of the muscles below the ligatures.

This evidence, which has been frequently confirmed, is in favour of the view that the motor paralysis caused by physostigma is due to an action on the nerve endorgans, or peripheral terminations, and not to one on the trunk. We may obtain even more distinct proof, by a slight modification of this experiment.

Experiment XXVIII.

An incision was made down the centre line in the right posterior extremity, from the back of the knee to the ankle, of a frog, weighing 876 grains; and in this way the gastrocnemius muscle was completely exposed. It was carefully dissected from its connections, excepting that its origin and insertion, and the nerve fibres entering it, were untouched. All its blood-vessels were ligatured, and the cut through the skin was closed by sutures.

Immediately after the above operative procedure, three grains of extract, in fifteen minims of water, were injected under the skin of the back. Reflex movement could not be excited an hour and five minutes afterwards, while the heart still continued to contract. Both sciatic nerves were then exposed. Galvanism of the left produced no contraction; while galvanism of the right caused energetic movements of the limb, which, moreover, did not extend to the toes. Five hours after the administration of the poison, this condition continuing, the left gastrocnemius was exposed, and the right again laid bare by cutting the sutures. Galvanism of the right sciatic demonstrated visibly contraction of the right gastrocnemius, but of no other muscles of that limb; and no result followed stimulation of the left sciatic, although the left gastrocnemius muscle contracted vigorously when the poles were applied to its surface.

It is thus shown that some of the endorgans of a motor nerve may have their conductivity destroyed while others remain active during the retained

vitality of the nerve trunk, and that this contrast in condition depends on the access or not of the poison—a clear demonstration of the power of physostigma to paralyse the nerve terminations. This action has been hitherto overlooked.

Calabar bean is, therefore, now added to that very limited class of neurotic agents which affect the motor endorgans. Indeed, only two substances, as far as I am aware, were previously known to possess this remarkable action. For a considerable time after the brilliant, and perhaps unequalled, researches of CLAUDE BERNARD,* curare stood alone as such a substance: when KÖLLIKER discovered that conia has a similar action;† and his observations have been recently confirmed by GUTTMANN.‡

Physostigma is, however, peculiar in the method in which it so acts; a very prolonged contact with the nerve terminations, and a long continued circulation of poison-bearing blood, being apparently necessary. In warm-blooded animals, this paralysis of the motor endorgans may, therefore, be easily overlooked; but in frogs, with localised poisoning, it is conspicuously displayed, as in the experiments which have been given.

It is interesting to remark the different conditions which are produced in the functional vitality of nerves and muscles when physostigma is administered to a frog after the vessels of one of its limbs have been ligatured.

Experiment XXIX.

Immediately after ligaturing the right ischiadic artery and vein of a frog, which weighed 609 grains, two grains of extract, in fifteen minims of distilled water, were injected into the subcutaneous tissue of the back.

One hour and twenty-five minutes afterwards, the heart was found beating seventeen times per minute.

The two gastrocnemii muscles, with their femur attachments, and a portion of each of these bones, along with the sciatic nerves from their terminations in the gastrocnemii to the lumbar plexus, were then removed. These parts were so arranged, that an interrupted current from one DANIELL'S cell and DU BOIS REYMOND'S induction apparatus, could be transmitted simultaneously through either both nerve trunks, or both muscles, by the turn of a key.

a. Examination of the Nerves (one hour and fifty-four minutes after the administration of the poison).—The galvanic current was first passed through the sciatic nerves. Distinct tetanus of the non-poisoned muscle was caused when the secondary coil stood at 63° on the scale; the poisoned was at perfect rest. The current was gradually strengthened by advancing the secondary coil; when this reached 53°, but not before, the poisoned muscle was thrown into tetanus.

b. Examination of the Muscles.—Immediately afterwards, the current was passed directly through both muscles. The poisoned gastrocnemius contracted when the secondary coil reached 63°; the non-poisoned did not do so until this was advanced to between 52° and 53°: that is to say, the poisoned muscle was thrown into tetanus by a weaker current than was required to produce the same effect in the non-poisoned muscle.

* Leçons sur les Sub. Tox. &c., 1857, pp. 238–413.

† Verh. d. phys.-med. Ges. zu Würzburg, 1859, vol. ix., part 2, p. 55, *et seq.*; Virchow's Archiv. x., p. 235; and other papers.

‡ Berliner Klin. Wochenschr., No. 5–6, 1866. Quoted in RUTHERFORD'S Report on Physiology; Journal of Anatomy and Physiology, No. 1, 1866, p. 155.

Experiment XXX.

A similar experiment was performed on another frog, also poisoned with two grains of extract, but weighing only 464 grains.

a. Examination of the Nerves (two hours and twenty minutes after the injection).—The galvanic current was passed along portions of both sciatic nerves simultaneously. When the secondary coil reached 52°, the non-poisoned gastrocnemius was thrown into tetanus, the poisoned remaining inactive. It was then slowly advanced; and at 30°, faint contractions occurred in the poisoned gastrocnemius, of a partial character, as if only a few muscular bundles, and not the whole muscle, were contracting, and which continued for a few seconds only, and did not recur although the secondary coil was advanced, after an interval for rest, to 0° (the strongest current from this arrangement). The stimulus was then applied to the trunk of the non-poisoned nerve above the position of the ligatures, and, therefore, where it must have been in contact with the poison; contraction again occurred when the secondary coil was at 52°.

b. Examination of the Muscles.—When the secondary coil reached 55°, tetanus was produced in the poisoned gastrocnemius; and at 54°·5, the non-poisoned muscle was thrown into tetanus.*

It would thus appear that motor nerve excitability or conductivity is diminished and then destroyed by physostigma (this change being produced at the endorgans), while retained for a long time thereafter in those parts of the same animal which have been guarded from the access of the poison. It is also seen that the effect on idio-muscular contractility is exactly converse; that property being uninjured by the mere presence of physostigma, while diminished and destroyed by stoppage of the circulation.

It is usually asserted that division of a nerve, previous to the exhibition of any substance that affects its vitality, is a sufficient method for determining the position of its primary implication, and, therefore, sufficient for determining the direction in which this extends. This proceeds upon the supposition that when it is the nerve trunk near its origin that is first affected, extension of the poisoned condition to the distal portion will be delayed by intermediate division of the nerve. BERNARD attempts in this way to prove that the primary paralysis of the motor nerve endorgans by curare extends from them, along the trunk of the nerve, towards the cord.† The paralysis of the motor nerves after strychnia is said to proceed in a direction exactly the reverse,—from the origin to the periphery.‡ It appeared of some interest to examine this question with Calabar bean, for with it we would not expect that previous division of the trunk should delay the implication of the nerve endorgans, as this precedes the paralysis of the trunk.

Experiment XXXI.

I exposed the two sciatics of a frog for a short distance, and both equally, and divided the left nerve with a very sharp pair of scissors. A fatal dose of Calabar bean was then administered. When reflex movement could no longer be excited (one hour and two minutes after the administration), the right sciatic was galvanised; but no contractions were caused. The left was stimulated, at the cut extremity of its distal portion, with the same current, and active movements of the left leg and toes followed. The galvanism was repeated, at intervals of five minutes,

* In Experiments XXIX. and XXX. I have thankfully to acknowledge the valuable assistance I obtained from Dr RUTHERFORD.

† *Loc. cit.*, p. 312. ‡ *Ibid.*

for other twenty minutes; with the same negative result in the case of the uncut nerve, and with continuation of activity in the cut one. The energy of the contractions then gradually diminished; but the distal portion of the cut nerve was not paralysed until twenty-eight minutes after the loss of motor nerve conductivity in the portion of its trunk proximal to the spinal cord, as well as in all the other nerves of the body.

Experiment XXXII.

In a second experiment, the distal portion of the divided nerve retained its conductivity forty-five minutes longer than the undivided nerve.

Another experiment contains some further results, which are worthy of being shortly mentioned.

Experiment XXXIII.—(*Temperature of Laboratory*, 56° *F.*)

Performed in August 1866.

I exposed a small and equal portion of each sciatic nerve in a frog weighing 515 grains, and cut through the right nerve-trunk. One grain and a-half of extract was then injected into the cellular tissue under the skin of the back.

In one hour and thirty minutes, no variety of stimulation could excite reflex movements: and when the left, or uncut, sciatic was then gently galvanised, faint contractions of the left toes were all that was produced; while the same interrupted current caused vigorous contractions when applied to the distal portion of the cut nerve. This condition continued, the contractions produced by the left (uncut) nerve becoming gradually fainter, until three hours and twenty-two minutes after the poison had been injected, when this nerve became perfectly paralysed, as well as all the other motor nerve fibres and the proximal portion of the cut sciatic. The distal portion of the cut (right) sciatic seemed all this time quite unaffected; and when it was galvanised, the muscles with which it was connected contracted with vigour. This condition lasted for fifteen minutes, *when galvanism of the uncut nerve again produced a faint twitch of several of the left toes.* By-and-by, it recovered all its former activity, and the return to vitality was shared in by the other temporarily paralysed nerves. On the following morning the frog was perfectly well and jumping about.

From such data it cannot be concluded that the motor nerve fibres are paralysed by a centripetal progression of the poison. There seems only to be a connection between the rapidity of paralysing effect, on the one hand, and the subdivision of nerve substance with facility of contact of poison, on the other; as the motor trunks were undoubtedly affected when it was impossible that they should be influenced by an extension of the poisonous action from their endorgans. I cannot advance any very satisfactory explanation of this delay in the action. Probably it is caused by the irritation of the vaso-motor nerves in the trunk of the sciatic, which the section of the latter at first produces, and which is followed by contraction of the capillaries in the parts supplied by them.* During this contraction, a much smaller quantity of poison-bearing blood is brought in contact with the endorgans of the cut than with those of the uncut nerve, and, as a very prolonged contact of the poison appears necessary, this may be sufficient to account for the delay; while the recovery from the irritation of the section, which soon

* Such contraction has been directly demonstrated by LISTER and others after division of the sciatic nerve. See "An Inquiry regarding the parts of the Nervous System which regulate the contraction of the Arteries;" Philosophical Transactions, 1858, vol. cxlviii., p. 607.

occurs, again allows of a free circulation and of consequent paralysis of the motor endorgans of the divided nerve.

2. *Afferent Nerve Fibres.*

The discussion of the influence that those fibres in the spinal nerves that conduct impressions to the cord exert in producing paralysis, will be a short one, as it can be readily shown that their effect is negative. It will be sufficient to notice that in mammalians it was always possible to obtain evidence of their activity as long as the functions of the spinal cord were retained, and that, therefore, they were in no wise concerned in the production of the general flaccidity and loss of motor power which is caused by Calabar bean. The same evidence was obtained in frogs, and could in them be distinctly shown by localization of the poisoning. In place of the function of these nerves being lessened, I believe that it is generally increased, so that movements may be excited more readily after the action of the poison than before it.

Experiment XXXIV.

I tied the right ischiadic artery and veins of a frog weighing 573 grains, and suspended it by the lower maxilla. Soon after, a silk thread was drawn over various parts of the skin, including the right leg, without exciting any reflex movement. On dipping the feet, separately, into dilute sulphuric acid (five minims of oil of vitriol to twelve ounces of water) reflex movements occurred with each, after 80 beats of a métronome set at 100 in the minute. I then injected into the abdomen two and a-half grains of extract in fifteen minims of water. In one hour and three minutes, on the left foot being dipped into the acid, reflex movements occurred in the right in 190 beats of the métronome; but no movement followed in the left limb in 200 beats, nor when the poisoned foot was placed in stronger acid (10 min. to 12 oz.), while this caused energetic contractions of the non-poisoned portion of the right limb. The reflex activity of the spinal cord was, therefore, very greatly diminished, and still the afferent nerves continued active. The silk thread which was formerly employed was now drawn over the skin of the right leg below the ligatures, and, as before, it produced no diastaltic movement. *On applying it, however, to the skin of the left leg and of the other poisoned regions, twitches constantly occurred in the toes of the right leg, and only occasionally, and of a very feeble character, in the poisoned region.* This was repeated, at intervals, during the next ten minutes, with the same result. After this, the thread ceased to excite diastaltic movements; but the spinal cord had now lost its vitality, and no movement could be produced even when it was directly galvanised.

The afferent nerve fibres, in this experiment, retained their original activity longer than the efferent, and at least up to the time at which they could not be tested, because of the loss of the diastaltic function of the spinal cord. The increase of excitability in the afferent fibres, where these had been acted on by blood conveying physostigma, cannot be due, in the slightest degree, to any spinal cause, for the effect did not occur in the right leg, to which access of the poison had been cut off by ligature. Besides, measurement of the rapidity with which reflex movements followed the application of a stimulus to either poisoned or non-poisoned parts gave such proof of marked depreciation having occurred before the afferent excitability had been increased as is sufficient of itself to eliminate any spinal influence.

Action on the Spinal Cord.

Having now excluded the encephalon, muscles and spinal nerves, we are led to conclude that the production of the paralysis by physostigma is due to an action on the spinal cord. Such an opinion was originally expressed by myself after a careful general consideration of the symptoms, but no subsequent investigator has coincided with my theory except Laschkewich,* from whose excellent paper I have derived more than one hint for the further and special examination of the spinal effects of Calabar bean.

I quote the following experiment from my previous paper on this subject, as it affords an excellent example of those general paralytic symptoms that first induced me to refer the principal neurotic action of physostigma to the spinal cord.

Experiment XXXV.

"Five and a-half grains of the fine powder of the kernel were made into pills, and swallowed by a buck rabbit, eight months old.

"A slight degree of paralysis was seen in the posterior regions, in ten minutes, and, soon after, they yielded, the anterior portion of the trunk remaining supported by the fore-limbs. In fifteen minutes, the fore-legs gave way, and fæces were passed. In twenty minutes, the respirations became noisy, reflex action was not abolished, and the pupils contracted. In thirty minutes, the rabbit submitted to be placed in any position. In thirty-five minutes, the respirations became extremely noisy, and accompanied with muscular spasm. Fæces and urine were passed, and reflex action could not be induced by puncturing the skin. General, but slight, muscular spasms now occurred frequently; the eyelids did not contract when the eyeball was pricked, and the respiratory stertor ceased. In forty minutes, a general spasmodic contraction of the muscles occurred, and, in forty-one minutes, all respiratory movement had ceased.

"*Autopsy*, immediate. The cut muscles contracted. The heart was acting at the rate of seventy-two per minute; and this ratio gradually diminished till it ceased, thirteen minutes after death. The brain was rather darker than usual, and no change could be perceived in the spinal cord. The cerebro-spinal fluid was in abnormal abundance. The large veins were distended, and the right chambers of the heart were engorged with dark blood. . . . The vermicular action of the intestines was well marked, and all the viscera contained an abnormal excess of dark blood. The muscular system was flaccid, but contractions could be caused by irritation of the nerves."

This experiment formed one of a series undertaken to discover the smallest dose which could produce death in a full grown rabbit.† The quantity employed, five and a-half grains of the kernel, was the smallest that could do so.

As evidence of the same character, I add the following from many subsequent experiments :—

Experiment XXXVI.

One grain and a-half of extract, suspended in fifteen minims of distilled water, was injected into the abdomen of a small collie dog. The animal was rapidly affected with inability to

* Virchow's Archiv. Februar, 1866.

† *Op. cit.* sect. v. experiment viii.

stand, tremors, lachrymation, defæcation and urination; and in eleven minutes all respiratory movement had ceased. The spinal cord was immediately exposed, but the strongest galvanism, consistent with localisation of the current, applied to various portions of its substance, failed to excite any movement of the body. A sciatic nerve was then exposed; and slight stimulation of it produced vigorous contractions of the limb, but no reflex movement. Lastly, the thorax was opened; and the heart was found contracting thirty-two times in the minute, in perfect rhythm and with regularity, although the diastolic pause was somewhat prolonged. Thirty-nine minutes after death, the cardiac beats were ten per minute, and the sciatic and other nerves could still transmit excito-motory impressions to their muscles.

Such data are sufficient, after the former results, to prove the action of Calabar bean on the spinal cord of mammalians, as far as it is possible to do so. Where larger doses are given, the evidence is not so distinct; as, along with complete loss of reflex function, the heart is found paralysed at death; and it is well known that, in the animals in question, stoppage of the circulation is rapidly followed by loss of reflex function. Still, from the above, and from other experiments which will follow, it can be conclusively proved that physostigma has a special and primary action on the cord.

Experiment XXXVII.

Performed December 1866.

After tying the left femoral artery and vein of a frog, weighing 430 grains, I injected two grains and a-half of extract into the cellular tissue of the back. In an hour and twenty-two minutes, the reflex function of the cord, as tested by stimulation of the skin by galvanism and by sulphuric acid, was completely destroyed; but the exposed heart was found acting regularly and rhythmically, though only at the rate of twelve beats per minute. The two gastrocmenii muscles, with their attached sciatic nerves, and the portions of femur into which these muscles are affixed, were then removed. The poisoned nerve and muscle were arranged in the usual manner on Du Bois Reymond's modification of Helmholtz's myographion—an apparatus designed to measure the rates of conduction along nerve fibres. The curved lines produced by stimulation of two portions of the nerve, differing in length by one inch and a-half, were found to correspond so exactly that the period during which the impression travelled over the one inch and a-half of poisoned nerve could not be measured. The non-poisoned nerve gave the same result.

This experiment was undertaken to determine whether physostigma gradually lessens the rate of conduction in motor nerves, as curare is stated to do.* It was worthless to answer this question, as was also another immediately afterwards performed with the same result; for the frogs employed were in too irritable a condition: but its value is evident in considering the action of physostigma on the spinal cord. *For the diastaltic function of the spinal cord was completely destroyed, while the poisoned and non-poisoned motor nerves were in so equally active a condition, that the difference between the times in which impressions travelled along two portions of the same nerve, differing in length by one inch and a-half, could not be measured in either, even by a delicate instrument specially adapted for this purpose.*

* A. von Bezold; Monats Bericht der Berlin: Akad. 1859.

In the further investigation of the effect on reflex movements, there is no process which yields so conclusive results as that in which frequent measurements are made of the interval that elapses between the application of a stimulant to the extremity of an afferent nerve and the resulting reflex contraction.*

Experiment XXXVIII.

The spinal cord was divided at the occiput of a frog, weighing 460 grains. It was suspended by the lower jaw, and the reflex activity tested by dipping the web of both posterior extremities into dilute sulphuric acid (ten minims oil of vitriol to twelve oz. of water). The exact time which elapsed between the contact of the foot and the resulting reflex movement was ascertained by the beats of a métronome, set at 100 in the minute. Before the administration of the poison, the reflex movement occurred in twelve beats. Two grains of extract, in water, were injected into the abdomen.

In	5 minutes,	reflex movement occurred in	15 beats.
	10 „	„	31 „
	15 „	„	40 „
	20 „	„	57 „
	25 „	„	69 „
	30 „	„	82 „
	35 „	„	106 „
	40 „	„	134 „
	45 „	„	165 „
	50 „	„	181 „
	55 „	„	192 „
	1 hour 5 min.	no reflex movement after	250 „
	1 „ 15 „	strong acid caused no movement.	

The sciatic nerves were then exposed; and weak and carefully localised galvanism applied to either trunk caused energetic contractions of the limb below the portion stimulated, which could be obtained until two hours after the injection of the poison.

It seemed important to ascertain the coincident changes that take place in the heart's action; and for this purpose several experiments were undertaken, of which the following is an example. By a slight adjustment of the frog's body, the cardiac impulses are easily seen and counted.

Experiment XXXIX.

A frog, weighing 460 grains, was suspended by its lower jaw. The average of the cardiac contractions, during ten minutes, was forty-five per minute. The two feet were alternately stimulated, every five minutes, by contact with dilute sulphuric acid (10 minims of oil of vitriol to 12 oz. water); a vessel containing the acid being gently raised so that the fluid covered the whole foot. A métronome, set at 100 in the minute, was employed to determine the interval between the application of the irritant and the resulting reflex movement.

* This method of examining reflex activity seems to have been first recommended by Von Türck in 1850 (Ueber den Zustand der Sensibilität nach theilweiser Trennung des Rückenmarks); and its value has been brought more prominently into notice by Dr J. Setschenow (Physiologische Studien über die Hemmungs-mechanismen für die Reflexthätigkeit des Rückenmarks im Gehirne des Frosches, Berlin, 1863).

15 minutes before poisoning, the right foot was drawn up in 13 beats.
10 „ „ left „ „ 11 „
5 „ „ right „ „ 9 „

Two grains of extract, in 15 minims of water, were now injected into the subcutaneous tissue of the back.

In 5 minutes, the left foot was drawn up in 14 beats.
10 „ right „ „ 22 „
15 „ left „ „ 36 „ the heart contracted per minute, 36
20 „ right „ „ 28 „
25 „ left „ „ 39 „ „ 18
30 „ right „ „ 52 „
35 „ left „ „ 49 „ „ 18
40 „ right „ „ 72 „
45 „ left „ „ 60 „ „ 17
50 „ right „ „ 76 „
55 „ left „ „ 88 „ „ 15
1 h. & 0 min. right „ „ 99 „ } During this interval, the heart's impulse could not be counted, but the frequency of its contractions was probably much lower than 15 per minute.
1 „ 5 „ left „ „ 115 „
1 „ 10 „ right „ „ 111 „
1 „ 15 „ left „ „ 138 „ the heart contracted per minute, 16
1 „ 20 „ right „ „ 169 „
1 „ 25 „ left „ „ 186 „ „ 20
1 „ 30 „ right „ „ 192 „
1 „ 35 „ left „ twitched slightly in 230 „ „ 20

After this, no reflex movement occurred when either foot was dipped in much stronger acid; but galvanism applied to the exposed sciatics caused vigorous movements, which occurred only in the limb whose nerve was stimulated. The cardiac contractions, in half an hour, became as frequent as twenty-five per minute; and, on the following morning, the thorax was opened, and rhythmical contractions were perceived, at the rate of twenty-four per minute. A microscopic examination was at this time made of the web, and a circulation was discovered in its capillaries.

A few experiments were undertaken in order to eliminate the possible effect of Calabar bean on the motor nerves in producing this gradual depression of reflex activity.

Experiment XL.

The femoral artery and vein in each posterior extremity of a frog, weighing 540 grains, were ligatured, and the animal suspended by the lower maxilla. Both feet were simultaneously dipped in dilute sulphuric acid (10 min. of oil of vitriol to 12 oz. of water); and the interval between the contact and the resulting reflex movement was measured, as before, by the beats of a métronome.

15 minutes before the poison was injected, reflex movement occurred in 10 beats.
10 „ „ „ 9 „
5 „ „ „ 11 „

I then injected three grains of extract, in ten minims of water, under the skin of the back.

In 10 minutes, reflex movement occurred in 28 beats.
20 „ „ 24 „
30 „ „ 71 „

In 40 minutes, reflex movement occurred in 80 beats.
50 „ „ 101 „
1 hour and 5 minutes „ 118 „
1 „ 15 „ „ 136 „
1 „ 20 „ „ 150 „
1 „ 30 „ „ 200 „
1 „ 40 „ no movement in 200 „

A stronger acid was substituted (20 min. to 12 oz.).

In 1 hour and 50 minutes, reflex movement in 111 beats.
2 hours 0 „ „ 160 „
2 „ 10 „ „ 173 „
2 „ 20 „ „ 198 „
2 „ 30 „ no reflex movement in 220 „
2 „ 35 „ strong acid caused no reflex movement.

The heart was exposed; and it was found contracting in proper rhythm, nineteen times per minute. The sciatic nerves were active.

On the following day, the heart was contracting twenty times per minute; and galvanism of the sciatic nerves caused feeble muscular contractions in the posterior extremities, but no diastaltic movement. The frog ultimately died.

Experiment XLI.

After ligature of its left femoral artery and vein, a frog, weighing 495 grains, was suspended as in the previous experiments. The reflex activity was tested with the following result:—

Métronome, 100 to 1 minute; acid = 5 min. to 12 oz. water.

At 20 minutes before poisoning, the left leg was drawn up in 24 beats.
15 „ „ right „ „ 19 „
5 „ „ left „ „ 28 „

Three grains of extract, in water, were then injected subcutaneously at the back.

In 5 minutes, the right leg was drawn up in 24 beats.
10 „ left „ „ 30 „
15 „ right „ „ 36 „
20 „ left „ „ 56 „
25 „ right „ „ 72 „
30 „ left „ „ 90 „
35 „ right „ „ 150 „
40 „ no movement when either foot was kept in contact with the acid during 200 beats.

A stronger acid was substituted, of the strength of 10 minims of oil of vitriol to 12 oz. of water.

In 45 minutes, the right leg was drawn up in 89 beats.
50 „ left „ „ 104 „
55 „ right „ „ 108 „
1 hour left „ „ 172 „

A still stronger acid, 20 minims to 12 oz., was now used.

In 1 hour 5 minutes, the right leg was drawn up in 85 beats.
1 „ 10 „ left „ „ 118 „
1 „ 15 „ right „ „ 138 „
1 „ 20 „ left „ „ 140 „

In 1 hour 25 minutes, the right leg was drawn up in 145 beats.
1 „ 30 „ left „ „ 158 „
1 „ 35 „ right „ „ 160 „
1 „ 40 „ left „ „ 180 „
1 „ 45 „ right „ „ 197 „
1 „ 50 „ no reflex movement of either after 250 „ *

Both sciatic nerves were found to be active when directly stimulated, but the contractions were confined to the limb whose nerve was galvanised.

This, and the experiment which precedes it, are conclusive in showing that the diminution, and then destruction, of the diastaltic function are not interfered with when physostigma is only prevented from acting on peripheral portions of the reflex apparatus. When, however, it is permitted to act on the nerve endorgans, but is prevented from reaching the centres, the effect is very different.

Experiment XLII.—(*Temperature of Laboratory*, 53° *F.*)

I opened the abdomen of a frog, and, with great care, tied, and, in some instances, cut through, all the blood-vessels that entered the spinal canal from the lower edge of the scapula to the coccygeal extremity of the sacrum, and then divided the spinal column at the higher of these points. By this means, the blood was only prevented from reaching a limited portion of the cord; so that, though unable to convey physostigma to the reflex centre for the posterior extremities, it could still do so to those extremities themselves, and to all other parts of the body. Voluntary movements of the limbs and of the body, anterior to the divided portion of the cord, occurred when the frog was set free; and irritation of the posterior parts was promptly followed by reflected movements confined to them. The heart, which the operation had partially exposed, was contracting sixty-eight times per minute.

A large dose of extract was administered by the mouth. In twenty minutes, only very faint reflex movements could be excited when the anterior feet were irritated, while gentle stimulation of the posterior caused energetic reflex movements; and the heart was acting at the rate of eighteen per minute. In little more than an hour, the diastaltic function was completely abolished in the anterior half of the body, while the conductivity of the brachial nerves remained; and, still, a slight pinch or weak galvanism of the posterior webs was followed by pretty active reflex movements. The heart had now stopped. *The diastaltic activity of the posterior half of the body continued for two hours after it had disappeared in the anterior.*

The mere prevention of the access of physostigma to a segment of the cord, while it was allowed to act directly on all other parts of the body, had, therefore, the effect of delaying the loss of reflex function in the parts connected with that non-poisoned segment. We have, already, frequently seen that protection of the endorgans and of portions of the nerve trunks from the poison does not delay or at all influence the gradual impairment and final destruction of the reflex function that ensue on its access to the cord. The conclusion is only logical, that Calabar bean produces a destruction of the diastaltic power by an action on the spinal cord.

It is not superfluous to observe that I do not in these experiments ignore the effect on the cord of mere stoppage of the circulation. When the heart is quickly

* In all these experiments, the parts which had been dipped in the acid solution were immediately washed with distilled water. The destructive action of the acid was thereby reduced to a minimum.

paralysed, as frequently happens, reflex movement will, on that account alone, be soon impossible. Experiments in which the heart is so affected are nearly worthless as far as the investigation of the spinal action of physostigma is concerned, and it would be needless to detail them. With the object of bringing forward as clear evidence as possible on this subject, I have selected experiments in which the cardiac action was only impeded, and in which it continued after the abolition of reflex power.

It is well known that strychnia causes an exaggeration of the reflex activity. Whether this is produced by an action on the spinal centre, or by one on the afferent nerves, is yet a question in dispute;* but it is obvious that a substance that diminishes this function at the cord, will also diminish the reflex activity consequent on the administration of strychnia, whatever be the special part of the reflex circle affected by that administration. Such a result is produced by physostigma, and therefore, adds to the many proofs of its spinal action.

Experiment XLIII.

I placed a small drop of solution of strychnia (Brit. Pharm.) on the back of a frog. This produced tetanus in four minutes; when a considerable dose of physostigma extract was inserted into the animal's mouth, the manipulations necessary for which excited a series of violent emprosthotonic spasms. Four minutes after the Calabar bean was exhibited, a decided diminution occurred in the frequency and severity of the convulsions; and, in nine minutes, they had lost their tetanic character. In forty minutes, it was difficult to excite even a faint reflex movement by pretty strong galvanism of any part of the body; and, soon after, reflex action had completely disappeared, even when the exposed sciatic nerves were galvanised.

By comparing the last experiment with one in which the strychnia effects were not interfered with, it is easy to show what part the Calabar bean played in thus interfering with the peculiar action of strychnia.

Experiment XLIV.

A frog was selected of the same weight as the last, and in every other respect as nearly resembling it as possible, and a small drop of solution of strychnia (Brit. Pharm.) was placed on its back. Tetanus occurred in four minutes; and violent convulsions of a tetanic character followed each other at intervals, and could be excited by the slightest touch, during the next six hours, after which the observations were stopped.

This evidence may be still further increased, if we produce well-marked paralysis by physostigma and then administer strychnia without causing its peculiar action.

Experiment XLV.

A frog was selected of the same weight as those employed in the two preceding experiments, and a dose of extract of Calabar bean was inserted under the skin of its back. This acted with considerable rapidity, so that, in twelve minutes, respiratory and voluntary movements had ceased, and reflex action was sluggish. A small drop of solution of strychnia (Brit. Pharm.) was then placed on a wound made through the skin of the back. Twenty minutes after this, reflex movement could still be excited; but during all this time no tetanic convulsion, nor even exaggeration

* Marshall Hall, Brown-Séquard, Bonnefin, Martin-Magron and Buisson maintain that strychnia causes tetanus by an action on the spinal cord; Claude Bernard and Stannius are the principal champions of the opposing theory of its action on the sensory nerves.

of reflex action, had occurred. Thirty-eight minutes after the strychnia had been applied, the diastaltic function had disappeared, though galvanism of the exposed sciatics still caused muscular contractions, and though the heart was beating at the rate of twenty-eight per minute.

The subject of opposing physiological actions has been a favourite one with many writers on poisons, and "antagonistic" effects have been largely discussed, as might be expected from their interest and practical applications. Nicotia,* aconitia† and curare‡ have been proposed as counter agents to strychnia, and atropia has been proposed as one to morphia.§ Calabar bean has been, before now, pointed out by myself and others as an opponent in action to strychnia; and, as with curare, its application to the treatment of tetanus has been recommended. I believe that no other drug so directly diminishes reflex action, and is, therefore, so likely to be employed with advantage in tetanus, as physostigma. Curare opposes spasm by paralysing motor nerves, nicotia by destroying muscular contractility; but physostigma attacks (if we may use the word) the spinal cord which is necessarily implicated as the centre of every diastaltic action. There seems to be no reason why it should not always prove a certain cure in traumatic tetanus. Its success in strychnia poisoning will probably depend on the quantity, in relation to the case, that has been administered; as this poison may be considered to have two fatal doses—a smaller, where death is caused by asphyxia or exhaustion, and a larger, where, even if its tendency thereto by asphyxia or exhaustion shall be averted, it will still certainly occur, by the special action of the poison on the histological structures it attacks.‖ Such a substance as Calabar bean may be employed with advantage to prevent death after the administration of the smaller quantity.

Physostigma has lately been proposed as a physiological antidote for atropia poisoning; and KLEINWÄCHTER has had the courage to employ it for this purpose, principally on the ground of its anti-mydriatic property.¶ As will be afterwards shown, these two substances appear to act in opposite modes on the ganglionic system of the blood-vessels; but the nature of their effects on the cerebro-spinal system is such as to make it irrational to anticipate any success in their employment as counter-agents.

* Rev. SAMUEL HAUGHTON, Dublin Quarterly Journal of Medical Science, August 1862.

† E. WOAKES, British Medical Journal, October 1860, &c.

‡ HARLEY, Lancet, 1856; L. VELLA, Comptes Rendus, 1860; CLAUDE BERNARD (opposes the view of counteraction), Leçons, &c., p. 377.

§ GRAVES, Clinical Lectures on the Practice of Medicine; ANDERSON, Effects of Belladona in Poisoning by Opium, 1854; LOPEZ, American Medico-Chirurgical Review, vol. iv. 1859; Dr W. F. NORRIS, American Journal of Medical Science, Oct. 1862; CAMUS (experimentally disproves this asserted antagonism), Gazette Hebdr., 11 Août 1865, and Canstatt's Jahresbericht, &c., Fünfter Band, 1866, p. 123.

‖ It has been found that frogs, after fatal doses of strychnia, may die *without any convulsions*, if care be taken to protect them from all causes of excitation—MARSHALL HALL, Aperçu du Système Spinal, p. 170; CLAUDE BERNARD, Lectures on Experimental Pathology and Operative Physiology, Medical Times and Gazette, 1860, v. ii., p. 25.

¶ Berliner klin. Wochschr, 38, 1864.

To argue from pupil effects alone of an antagonism between the actions of morphia and atropia, I believe to be absurd, while we know almost nothing of how iridal changes are produced by poisons. We shall never have antidotes to active substances until we can produce within the body chemical changes in their composition of such a nature as shall render them inert. By originating a secondary, and apparently counter, action, we may sometimes ward off death; but only where that would have been due to one of the symptoms of a small dose: we do not prevent the fatal action on the tissues of a large dose; and we run the risk of adding a second active substance, which cannot produce any effect without causing a tissue change, and which may, therefore, hasten and render more certain a previously doubtful, fatal result.

The most conspicuous symptom that is caused by physostigma is paralysis; and this necessarily depends on an effect produced on the nervous system, or on the muscular system, or on both. I believe this investigation is sufficient to show that it is due not to an action on the cerebral lobes, on afferent or efferent spinal nerves, or on muscles, but to one on the spinal cord, as a reflex centre. This spinal affection is the result of a primary and special action of Calabar bean; but it is more or less favoured by a simultaneous depression of the heart's action, as will be more conveniently illustrated in the special examination of the cardiac effects.

Action on the Heart.

The heart is affected in a marked manner by Calabar bean; and this has a more or less direct influence in causing death, according to the dose that may have been exhibited. With a large dose, the animal dies by cardiac syncope. With a smaller one, the heart beats are only diminished in frequency, and, as the circulation continues, the spinal cord is more and more affected, until its diastaltic function is destroyed and asphyxia caused. The latter effect is proved in the previous portion of this investigation, and it will be sufficient for the purpose of illustrating the former to quote one of my already published experiments with warm-blooded animals.

Experiment XLVI.

"The skin was raised in the left flank of a large black-and-white female cat, the needle-point of Wood's hypodermic syringe was inserted into the subcutaneous cellular tissue, and ten minims of a syrupy extract were injected" (equivalent to about four grains of the preparation usually employed in this investigation).

"In two minutes, trembling occurred; and, in three, the cat fell. Fluid escaped from the mouth, the pupils contracted, and urine was voided. In five minutes, the respirations became hurried, noisy and laboured. Reflex action could not be excited by severe stimulation, nor did the eyelids contract on irritation of the conjunctiva. The animal became perfectly flaccid, the only symptom of life was an occasional gasp, and this ceased entirely, seven minutes after the administration.

"*Autopsy*, immediate. The pupils were observed to dilate. A few contractions occurred in the muscles that were cut. *The heart was perfectly quiet, and without the slightest action.* . . . . On removing the pericardium, irregular movements occurred in the heart, and a partial contraction could be produced by irritation, fifteen minutes after death. The vessels of the

thorax and abdomen were well filled, and could be readily distinguished by the colour of their contents. On incising the left ventricle, blood of the usual arterial hue escaped; and on incising the right, dark blood appeared. Both were allowed to run side by side, when the contrast was distinctly shown."*

We have now to describe the various changes that are undergone by the heart before its contractions finally cease, and to examine the mechanism by which these changes are produced. For the former purpose, several experiments were performed on frogs whose hearts were exposed before the administration of the poison.

Experiment XLVII.—(*Temperature of Laboratory*, 58° *F.*)

A large frog, which weighed 730 grains, was fixed down on its back in such a manner that the circulation in the limbs was not to any extent impeded; and the heart was exposed by the removal of a portion of the sternum. This operation can easily be performed without injuring any large blood-vessel, and, indeed, without causing any loss of blood further than a temporary oozing from the cut surfaces. A few minutes afterwards, its heart-beats were frequently counted, and found to average seventy per minute. I then injected one grain of extract, mixed with a little water, into each thigh (two grains in all).

5 minutes afterwards, cardiac contractions	= 64 per min.	
10 „ „	= 58 „	
15 „ „	= 43 „	Respirations ceased, except an occasional gasp.
20 „ „	= 39 „	
25 „ „	= 41 „	No respiratory movements.
30 „ „	= 37 „	
35 „ „	= 24 „	Contractions feeble.
40 „ „	= 22 „	
45 „ „	= 22 „	Skin much darker than originally.
50 „ „	= 19 „	
55 „ „	= 13 „	
1 hour 0 min. „	= 14 „	
1 „ 5 „ „	= 12 „	Heart equally dark in systole and in diastole.
1 „ 10 „ „	= 10 „	
1 „ 15 „ „	= 9 „	
1 „ 20 „ „	= 9 „	
1 „ 30 „ „	= 10 „	
1 „ 40 „ „	= 10 „	Galvanism of sciatics caused neither direct nor reflex contractions. Muscles dark bluish, and active.
1 „ 50 „ „	= 8 „	Surface of heart opal blue in colour.
2 hours 0 „ „	= 8 „	Cardiac contractions extremely feeble.
2 „ 10 „ „	= 8 „	Skin deep olive-brown: the frog was originally a pale one.
2 „ 30 „ „	= 12 „	
3 „ 0 „ „	= 18 „	Spinal nerves still perfectly paralysed.
3 „ 30 „ „	= 21 „	
4 „ 0 „ „	= 24 „	Cardiac contractions quite synchronous, and diastole prolonged.
4 „ 30 „ „	= 26 „	A faint twitch occurred when the left sciatic was galvanised.

* *Op. cit.* section v. experiment iii.

The frog was now left in a cold and moist place until the following morning, when it was found jumping about actively, with its heart contracting forty-eight times per minute. It continued in very much the same condition for other two days, when it was killed.

This experiment is especially interesting because of the very near approach to death that was made. A decided effect was produced on the heart's action, as it was reduced in frequency by from seventy to eighty beats in the minute: respiratory movements were stopped; reflex spinal action was completely prevented; and the spinal motor nerves were, for many minutes, paralysed: and yet the animal revived; and regained all its lost functions except that of the heart, which only partially recovered itself. Such a result could never have been obtained with a warm-blooded animal, as death would soon have been produced by asphyxia, however long the heart might continue to contract. It is well known that the frog may live for many days after the removal of its lungs, as the respiratory function of those organs is shared in by the skin of this animal. The effects of the poison that was given in this case—and the dose was a very small one in proportion to the weight of the frog—had gradually disappeared, and the different tissues had returned to their former vitality, after having been acted upon for some time by a nearly normal blood-stream. Had the circulation ceased, or had the effects on the tissues been greater, and, therefore, more permanent, this return from pseudo-death could not have occurred.

Experiment XLVIII.—(*Temperature of Laboratory*, 58° *F.*)

The heart of a frog, weighing 396 grains, was exposed. After allowing a few minutes for recovery from shock, the number of the cardiac contractions was determined at intervals of five minutes, during twenty minutes, and found to vary little from forty-two beats per minute. One grain of extract, in a few drops of water, was then injected into the subcutaneous tissue of each thigh (two grains in all).

2 minutes afterwards,	cardiac contractions	= 36 per min.	
4 „	„	= 24 „	
6 „	„	= 20 „	Contractions seem feeble, and heart is not so pale during systole as is normal.
8 „	„	= 17 „	
10 „	„	= 17 „	
12 „	„	= 15 „	Heart walls seem nearly as dark during systole as during diastole.
14 „	„	= 14 „	
16 „	„	= 14 „	
18 „	„	= 15 „	Frog is helpless and flaccid.
20 „	„	= 14 „	
25 „	„	= 14 „	Almost no difference of colour during systole, and a great prolongation of diastole.
30 „	„	= 12 „	
35 „	„	= 13 „	
40 „	„	= 12 „	
45 „	„	= 8 „	The ventricular contractions seem more feeble than the auricular.

50 minutes afterwards, cardiac contractions = 8 per min.

1 hour „ = 8 „ { The ventricular contraction is scarcely perceptible.

1 „ 5 min. „ are irregular; there being three ventricular contractions per minute, and six auricular.

This irregularity continued for other ten minutes, and then became greater, only one contraction per minute, of the most feeble character, occurring in the ventricles for two and sometimes three in the auricles. During the period of inaction, the heart rested in diastole.

1 hour 20 minutes after poisoning, cardiac contractions = 0 per min.

1 „ 40 „ „ „ = 8 „ { All the chambers contract, with long intervals, and in a vermicular manner.

1 „ 50 „ „ „ = 12 „

2 hours „ „ = 12 „

2 „ 10 „ „ „ = 12 „

3 „ 15 „ „ „ { Again irregular, and exactly as at one hour and five minutes after the poisoning.

3 „ 40 „ „ „ The irregularity was still further increased, the ventricles being occasionally quite motionless, in a dilated condition, for one minute, while both auricles contracted six and sometimes eight times. The contractions consisted merely of feeble wave-like movements of the different chambers. The surface of the heart, and, still more, the pericardium had for some time assumed a blue colour.

When the heart was again examined, twenty-two hours after poisoning, there was no spontaneous movement. It was then gently stimulated by an interrupted galvanic current, and a very feeble contraction of all the chambers followed, which did not repeat itself, but which could be reproduced by a renewal of the stimulation. For some time after these irritations, feeble and irregular contractions occasionally occurred, one ventricle contracting, and, after several minutes, two or three auricular movements following, but with considerable pauses. Forty-eight hours after the administration, the heart was motionless, dark and dilated; gentle galvanism produced no effect, except that the ventricles became rather paler, but a moderate current caused a contraction of all its chambers, succeeded by perfect quiet.

In sixty hours, the heart was pale and quiet, and no movement could be produced by galvanism. Notwithstanding the paleness of its walls, the heart was not contracted, as its chambers contained a considerable quantity of dark, fluid blood. The colour of its walls was, therefore, due to contraction of their capillaries, caused either by the rigor of death, or, as I am more inclined to believe, by the galvanic stimulation they had been so frequently subjected to. At this time, all the muscles were stiff.

Experiment XLIX.—(*Temperature of Laboratory, 57° F.*)

The average number of cardiac contractions in a frog, weighing 415 grains, was fifty-five per minute. Two grains and a-half of extract, in fifteen minims of distilled water, were injected into the subcutaneous tissue of each thigh (five grains altogether).

2 minutes afterwards, cardiac contractions = 52 per min.

4 „ „ = 50 „

6 „ „ = 24 „

8 „ „ = 19 „

10 „ „ = 15 „

12 „ „ = 14 „ No chest respiratory movements.

14 minutes afterwards, cardiac contractions = 14 per min. Systole not quite so pale as originally.

16 „ „ = 13 „ Frog is quite flaccid; it cannot turn from its back, but occasional faint struggles occur.

18 „ „ = 11 „ Contractions very feeble.

20 „ „ = 10 „ Heart as dark during contraction of the ventricles as during dilatation of them.

22 „ „ = 8 „ Irregular and non-synchronous; the auricles sometimes contracting nine or eleven times per minute.

24 „ „ = 8 „ of ventricles, 10 of auricles.

26 „ „ = 8 „ „ 14 „

28 „ „ = 7 „ „ 14 „

30 „ „ = 8 „ „ 14 „

32 „ „ = 0 during one minute, and then a few feeble contractions in the auricles, and again a pause.

34 „ „ = 0 per min.

36 „ „ = 0 „

38 „ „ = 0 „ of ventricles, 3 of auricles.

40 „ „ = 8 „ „ 12 „

42 „ „ = 8 „ „ 16 „

45 „ „ = 8 „ „ 16 „

50 „ „ = 9 „ Synchronous.

55 „ „ = 9 „ Skin extremely dark.

1 hour 0 min. „ = 8 „ No reflex movement on stimulation.

1 „ 10 „ „ = 8 „ Galvanism of the sciatic nerves

1 „ 15 „ „ = 8 „ causes faint twitches of the toes.

1 „ 20 „ „ = 8 „ All the spinal nerves are paralysed; the muscles remaining active and blue.

2 hours 0 „ „ = 8 „

3 „ 0 „ „ = 8 „

The observations were now interrupted until twenty hours after the exhibition of the poison, and, at this time, the frog was quite flaccid and dark; the heart was contracting sixteen times in the minute, and the striped muscles were irritable, but otherwise the animal was quite dead. Twenty-eight hours after the exhibition of Calabar bean, the cardiac contractions were seventeen per minute; and at thirty hours they were ten. In forty hours, the heart was found perfectly still, dark and somewhat dilated. Direct galvanism produced a slow contraction of the portion of cardiac muscle included in the circuit; it did not excite a normal heart beat. The striped muscles contracted very sluggishly when galvanised. This idio-muscular contractility was retained in the heart until sixty-nine hours, and in the striped muscles till seventy hours after the administration of the poison. They then became pale, stiff and acid.

In this experiment, a large proportion of the extract had not been absorbed, but escaped from the thighs when the skin was incised to allow the sciatic nerves to be exposed. The effects cannot, therefore, be regarded as those produced by five grains, but must be held to have been caused by a much smaller quantity. Indeed, where three grains were absorbed by a frog of nearly the same weight, the action on the heart was much more decided and marked.

Experiment L.—(*Temperature of Laboratory, 60° F.*)

The exposed heart of a frog, weighing 469 grains, was found to contract, on an average, sixty-seven times in the minute. One grain of extract, in five minims of water, was then injected into each thigh, and a third grain was injected into the stomach by means of a narrow caoutchouc tube (total three grains).

2	minutes afterwards,	cardiac contractions	= 60	per min.
4	„	„	= 54	„
6	„	„	= 34	„
8	„	„	= 30	„
10	„	„	= 21	„
12	„	„	= 13	„
14	„	„	= 11	„
16	„	„	= 8	„
18	„	„	= 0	„
20	„	„	= 0	„
22	„	„	= 0	„
24	„	„	= 0	„
28	„	„	= 0	„
30	„	„	= 0	„

Very feeble. Heart not quite so pale, now, in systole.

Frog jumped about when set free, but soon fell on its back, and remained there.

Colour of frog has changed from yellowish brown to dark bronze. of the ventricles, 2 of the auricles.

After this, an occasional auricular contraction occurred, but no spontaneous movement was seen of the ventricles. The heart rested in diastole, and was of a dark colour with a bluish tinge. For twenty minutes after this, a slight stimulus excited a few rhythmical contractions, followed, in a few seconds, by rest in diastole, but capable of being reproduced in the same way. One hour and ten minutes after the administration, no reflex movement could be excited; but the sciatic nerves continued active for longer than thirty hours—the rapid stoppage of the circulation having prevented that prolonged contact with the poison that is necessary for the paralysis of the endorgans. The striped muscles remained contractile until more than forty-eight hours, and contractility was also retained by the cardiac muscle during this period.

A possible source of fallacy is introduced into these experiments by the operations that they require. It seemed, therefore, of some importance to test the effects on the frog's heart of mere exposure to the air. For this purpose, a portion of the sternum was removed from an active frog, in exactly the same manner as in the last four experiments, with the following result:—

5	minutes afterwards,	cardiac contractions	= 62.	
10	„	„	= 61.	
20	„	„	= 62.	
30	„	„	= 59.	
40	„	„	= 60.	
50	„	„	= 59.	
1 hour	0 minutes,	„	= 55.	
1 „	30 „	„	= 57.	
2 „	0 „	„	= 60.	
2 „	30 „	„	= 56.	
3 „	0 „	„	= 58.	
3 „	30 „	„	= 59.	
4 „	0 „	„	= 59.	

It is almost needless to remark that the change in the systolic colour of the heart, from pale to dark, did not occur. The heart's surface was prevented from drying by an occasional drop of water; and this was also done during the experiments in which physostigma was administered.

We have now sufficiently described, as proposed (p. 29), "the various changes that are undergone by the heart before its contractions finally cease;" and from the data given, these may be summarised in their order of occurrence as follows:—

1st, Diminution never preceded by increase, of the frequency of the contractions, with prolongation of the period of rest; 2d, Feebleness of the contractions, with no change of colour on the occurrence of systole; 3d, Irregularity of rhythm, the auricles contracting more frequently than the ventricles, and, for intervals, contracting alone; 4th, Stoppage of all the heart's chambers—If the poison be absorbed quickly and in large quantity, the fifth and sixth effects may not occur; 5th, Renewal of contractions, either by all the chambers at once, or by one or more in the first place; 6th, Gradual recovery to a low rate of action, and continuance at this for from a few minutes to several days; 7th, Stoppage *in diastole* of spontaneous contractions; and 8th, Loss of the idio-muscular irritability of the heart, rigor and change of reaction from alkaline to acid.

This method of affecting the heart distinguishes physostigma from the great majority of cardiac poisons, which may be well represented by *Antiaris toxicaria*,* *Tanghinia venenifera*,† *Digitalis*,‡ *Helleborus niger*, *H. viridis*§ and the green resin obtained from *Nerium Oleander*.‖ These produce first irregularity and acceleration of the heart's action, then a diminished frequency, *caused by protraction of the ventricular systole*, and, finally, stoppage of the contractions by "*cessation of the dilatation of the ventricles*, which then remain contracted, white and perfectly empty."¶ In producing cardiac paralysis, physostigma acts in a manner exactly the reverse. It causes no acceleration, it diminishes the frequency of the contractions *by prolonging the ventricular diastole*, and it produces the final stoppage *by cessation of the contraction of the ventricles*, which then remain dilated, dark and full of blood. Very small doses of digitaline and the alcoholico-aqueous extract of *Nerium Oleander* are said to act on the heart in a manner which seems to resemble closely that of Calabar bean,** but no other cardiac poisons appear to share in its peculiarities.

It now remains that we examine the mechanism by which these changes are produced, and endeavour to determine what tissues or structures are influenced by physostigma to effect them. For this purpose, it will be necessary to investi-

* Kölliker, Vulpian, Claude Bernard and others, in various papers.

† M. Eug. Pélikan et Dr Dybkowski; Recherches physiologo-toxicologiques sur l'action de quelques poisons du cœur; and Comptes Rendus, 1865, p. 1209.

‡ *Ibid.* § *Ibid.* ‖ *Ibid.*

¶ On the Application of Physiological Tests for Certain Organic Poisons, and especially Digitaline, by C. Hilton Fagge, M.D., and Thomas Stevenson, M.D. Guy's Hospital Reports, 3d series, 1866, vol. xii. p. 47.

** Nouvelles Recherches sur le poison du *Nerium Oleander*. Note de M. Eug. Pélikan. Comptes Rendus, 1866, p. 237.

gate the possible influences of the cerebro-spinal nervous system, whether exerted through the vagi or through the spinal nerves, and the possible influences of the sympathetic system, whether exerted through the great sympathetic trunks and their branches or through the ganglia contained in the heart's substance. Any effect on idio-muscular contractility has been already abundantly disproved; but it will be necessary to observe how far the impairment and cessation of respiration may explain the cardiac effects in warm-blooded animals.

The paralysis of the heart in diastole and the diminution in the frequency of its contractions by protracted periods of rest in a *dilated condition*, as well as the frequent renewal of its action after a long pause in diastole, might, in the first place, suggest that the inhibitory function of the vagi nerves was being exerted. On this account, it may be advisable to examine their condition during Calabar bean poisoning.

Experiment LI.

An active frog was selected, of the weight of 863 grains, and its heart and two vagi nerves were exposed. The latter were separately tested by galvanism, and each produced stoppage of the heart's action, in diastole. A few minutes afterwards, the average of the heart's contractions was ascertained to be fifty-eight in the minute. Three grains of extract, in a few drops of water, were injected into the subcutaneous tissue of the two thighs—one-half into each.

2 minutes afterwards,	cardiac contractions = 54 per min.		
4 „	„ = 47 „		
6 „	„ = 40 „		
8 „	„ = 37 „		
10 „	„ = 36 „		
12 „	galvanism of the left vagus produced stoppage in diastole.		
14 „	cardiac contractions = 34 per min.		
16 „	„ = 33 „	Contractions feeble.	
18 „	„ = 30 „	Heart dark in systole, as well as in diastole.	
20 „	„ = 24 „		
25 „	„ = 20 „		
30 „	„ = 19 „		
35 „	galvanism of the left vagus produced stoppage for one minute.		
40 „	cardiac contractions = 15 per min.		
45 „	„ = 18 „		
50 „	„ = 14 „	Marked pause between auricular and ventricular contractions.	
1 hour 0 min.	„ = 12 „		
1 „ 5 „	galvanism of the left vagus produced stoppage of all the chambers.		
1 „ 10 „	cardiac contractions were irregular, on being renewed; only twelve ventricular now occurring to eighteen auricular, per minute.		
1 „ 20 „	cardiac contractions continue, with the above irregularity.		
1 „ 30 „	cardiac contractions still irregular; galvanism of the left vagus produced stoppage of all the chambers, but a stronger current was required than before.		
1 „ 32 „	galvanism of either sciatic nerve caused movements confined to the limb whose nerve was stimulated.		
1 „ 40 „	cardiac contractions continue irregular, as above.		

1 hour 50 min. afterwards,	galvanism of the left vagus produced stoppage of all the chambers; and the heart remained at rest, in diastole, for ten minutes, when a feeble auricular contraction occurred, and, soon after, a ventricular.
1 „ 55 „	galvanism of either sciatic nerve caused merely faint twitches of the toes.
2 „ 10 „	cardiac contractions = 18 per minute; very feeble, but rhythmical.
2 „ 15 „	strong and continued galvanism of the left vagus produced no effect on the cardiac contractions.
2 „ 18 „	strong and continued galvanism of the right vagus, which had not been irritated during the experiment, produced no effect on the cardiac contractions.
2 „ 20 „	strong galvanism applied to either sciatic nerve produced no effect.
2 „ 40 „	cardiac contractions stopped. Irritation could produce a few contractions for only a few minutes longer.

From this experiment it is apparent that the vagi retain their inhibitory power over the heart during the whole period that its action is being modified by physostigma. Ultimately, however, they are themselves paralysed, as might be anticipated from the analogies that exist between them and the spinal nerves; and, as this and many other similar experiments prove, the functions of the vagi and of the spinal motor nerves are lost simultaneously, or nearly so.

To illustrate this in warm-blooded animals, it is necessary to exhibit so small a dose of the poison that death shall be caused by asphyxia, and the heart afterwards continue to contract, however irregularly.

Experiment LII.

Half a grain of extract, suspended in ten minims of distilled water, was injected under the skin on the back of a full-grown and active rabbit. The usual symptoms followed; and, in thirty-four minutes, the animal was dead, all respiratory movement having ceased. Immediately afterwards, the heart was exposed; and it was found contracting in normal rhythm, twenty-two times in the minute. The right vagus was divided; and the end proximal to the heart was galvanised, with the effect of producing an immediate stoppage, in diastole, for several seconds. The vagi were tested, occasionally, during twenty minutes after the rabbit's death, and their cardiac inhibitory function, as well as their excito-motory power over the stomach and œsophagus, continued active all this time; and, for the same period, the sciatic, intercostal, phrenic and other spinal nerves retained their motor conductivity. Twenty-two minutes after death, the heart was contracting eight times per minute. Galvanism of either vagus could now neither stop the cardiac action nor excite œsophageal or gastric movements. The sciatic and other spinal nerves were tested at twenty-five minutes after death, and found to be perfectly paralysed.

It is, therefore, quite possible, as far, at least, as conveyance by the vagi nerves is concerned, for Calabar bean to act on the heart by exciting the cardiac inhibitory centre in the medulla oblongata. But, if this be the method of its action, the prevention of this possible influence, by division or previous paralysis of the vagi, or by destruction of the medulla oblongata, should render it impossible for Calabar bean to produce its usual effects on the heart.

Experiment LIII.

The heart and the two vagi nerves were exposed and the latter divided in a frog, weighing 700 grains, and, a few minutes later, the cardiac contractions were found to have an average of sixty-six in the minute. Two grains of extract, in ten minims of distilled water, were then injected into each thigh (altogether four grains).

2	minutes afterwards,	cardiac contractions	= 60	per min.
4	,,	,,	= 60	,,
6	,,	,,	= 53	,,
8	,,	,,	= 46	,,
10	,,	,,	= 39	,,
12	,,	,,	= 31	,,
14	,,	,,	= 27	,,
16	,,	,,	= 24	,,
18	,,	,,	= 22	,,
20	,,	,,	= 18	,,
22	,,	,,	= 16	,, — All the chambers are of dark colour, even in systole.
24	,,	,,	= 13	,,
26	,,	,,	= 14	,,
28	,,	,,	= 12	,, — Ventricular contraction is extremely feeble.
30	,,	,,	= 10	,,
35	,,	,,	= 9	,,
40	,,	,,	irregular; six ventricular for twelve auricular.	
42	,,	,,	stopped in diastole, for thirty-five seconds.	

The heart then resumed its previous unrhythmical action of six ventricular to twelve auricular movements in the minute, and continued to contract, with various changes of irregularity, for many hours longer.

It would needlessly occupy space, were I to narrate any other of the many experiments that were performed with frogs whose vagi had been divided; as the results, and even the details, were in all of them very much the same. It might be proper to instance, at this place, an experiment of the same character on a warm-blooded animal, but I content myself by referring to Experiment LXI., at page 49.

In curare we possess an agent that, within a few minutes after its exhibition, produces complete paralysis of all the motor nerves, including the vagi.* It will, therefore, act as effectually as division, in preventing any inhibitory influence being exerted on the heart.

Experiment LIV.

A small dose of curare was inserted under the skin of a frog's back. Ten minutes afterwards, the animal was perfectly paralysed. At twenty minutes, its heart was exposed, and observed to be contracting fifty-four times in the minute. The vagi and sciatic nerves were tested by galvanism, and their conductivity was found to be completely destroyed. Three grains of extract of physostigma, in water, were injected into the two thighs. The usual cardiac effects were produced within the time that might have been expected, from such a dose; irregularity of the rhythm having occurred in forty-four minutes, and final paralysis, with all the chambers dark, full and dilated, in a few minutes later.

* Claude Bernard, Leçons sur les effects des Subs. Tox. &c., p 352; Kölliker, *loc. cit.*; Martin-Magron, Journal de la Physiologie, 1859, p. 649, &c.

These are sufficient to prove that Calabar bean influences the heart neither by an action on the inhibitory centres nor by one on the nerves that connect those centres with it. I think they are also sufficient to exclude the rest of the cerebro-spinal nervous system: as the only other spinal nerves connected with the heart, by the branches of the great sympathetic trunks or otherwise, are either sensory, or at any rate afferent, nerves that form through the cord reflex arrangements with the vagi and vaso-motor nerves; or excito-motory ones whose action is to increase the frequency of the heart's contractions, but whose function is only periodically exerted, and is quite unnecessary for the continuance of the ordinary rhythmical occurrence of those contractions.* But, to remove the possibility of any doubt on this point, the following experiment was performed:—

Experiment LV.

The spinal cord was divided between the occiput and first vertebra of a frog, weighing 376 grains, and a wire was passed down the spinal canal, so as to produce complete paralysis, and into the cranial cavity, so as thoroughly to break up and destroy the brain. A short time thereafter, the heart was contracting at the rate of forty beats per minute. One half of three grains of extract, in twenty minims of water, was injected into each thigh.

2	minutes afterwards,	cardiac contractions	= 37	per min.
4	"	"	= 31	"
6	"	"	= 28	"
8	"	"	= 26	"
10	"	"	= 25	"
12	"	"	= 24	"
14	"	"	= 22	"
16	"	"	= 20	"
18	"	"	= 17	"
20	"	"	= 14	"
22	"	"	= 13	"
24	"	"	= 12	"

* Dr Power observes, in the sixth edition of Carpenter's "Principles of Human Physiology" (page 217, note), that "the essential cause of the rhythmical action of the heart must still remain an unsolved question." The exact influence of the various nerves that connect the heart with the central nervous systems, appears to be quite as imperfectly ascertained, judging by the contradictory statements and deductions of eminent physiologists. Legallois and Philip Wilson, and, afterwards, Budge, Schiff, Reid, Weber, Moleschott, Von Bezold and others, have shown that a connection certainly exists; but they have left the details of the question unsettled by the great differences in many of their opinions, as, for example, on the cardiac functions of the vagi. Von Bezold, in 1863, attempted to prove the existence, in the spinal cord, of an excito-motory centre, whose stimulation increases not only the number of the beats, but also the blood-pressure—the latter being due to augmented force in the heart's contractions. Ludwig and Thiry opposed this opinion, and asserted that the increased blood-tension is really an effect of excitation of the vaso-motor nerves. In a recent investigation (Comptes Rendus, 25 Mars 1867), MM. E. and M. Cyon give their adherence to the views of Ludwig and Thiry. They also attempt to show that the spinal cord, through the sympathetic system, supplies the heart with nerves that possess the power of directly accelerating its contractions, and that are antagonistic to the vagi, in that, while the latter diminish the frequency and increase the force of the contractions, the spinal "nerfs accélérateurs," on the other hand, increase the frequency and diminish the force.—*April* 1867.

26 minutes afterwards, cardiac contractions = 9 per min.

28 „ „ = 9 „ { Very feeble. Heart dark during systole.

30 „ „ = 7 „

35 „ „ irregular; four ventricular for six auricular.

Irregular and unrhythmical contractions continued for many hours afterwards. The final stoppage was in diastole.

It may now be useful to examine what connection exists, as cause and effect, between the impairment and cessation of the respiratory movements and the interference with, and stoppage of, the cardiac contractions, especially as so deservedly distinguished a physiologist as HARLEY has asserted that Calabar bean is a respiratory poison purely, which causes death by destroying the conductivity of the motor nerves of respiration. CHRISTISON, in his investigation, was the first to observe an action on the heart, and he believes that death is caused by paralysis of that organ. My former results were, so far, in accordance with this statement; but they also show that death may often be due to asphyxia, and while I agree with HARLEY in this, I believe him to be in error when he asserts that paralysis of the motor nerves is the cause of such death. The data that have already been given are sufficient to prove that motor nerve conductivity is always retained, in warm-blooded animals as well as in cold, for many minutes after the complete stoppage of respiratory movements, and that such stoppage is due to destruction of the reflex and co-ordinating functions of the medullæ spinalis and oblongata. To complete this evidence, it will be sufficient to show that no connection of cause and effect necessarily exists between the impaired respiratory movements and the cardiac paralysis.

Experiment LVI.

In a large retriever dog, it was found that the mean number of respirations was ten, and the mean number of cardiac contractions 126, during seven minutes immediately preceding the injection of six grains of extract, suspended in water, into the right jugular vein.

1 min.		after the injection, the respirations	= 10,	cardiac contractions	= 78	per min.
1 „	30 sec.	„	„	= 11,	„	= 54	„
2 „	2 „	„	„	= 9,	„	= 40	„
3 „	0 „	„	„	= 9,	„	= 8	„
7 „	0 „	„	„	= 10,	„	= 20	„
9 „	0 „	„	„	= 10,	„	= 16	„
10 „	0 „	„	„	= 9,	„	= 9	„
10 „	30 „	„	„	= 0,	„	= 0	„

This experiment gives the result that, in one minute and thirty seconds after the poison was administered, the number of cardiac contractions had fallen to less than one-half, while the respiratory movements had increased by one per minute; and it distinctly shows the absence of any respiratory change to cause the marked effects that were produced on the heart's action.

Experiment LVII.

A frog, weighing 460 grains, had its heart exposed by removing a small portion of the sternum. It was acting at the rate of forty-eight beats per minute, while the respirations were seventy-two. Five minutes afterwards, the heart was contracting at the rate of forty-five per minute, while the respirations were seventy-four. One grain and a half of extract, suspended in water, was injected under the skin of each thigh (three grains in all).

In 5 min.,	heart = 36 per min.	Respirations = 74 per min.	
10 „	= 28 „	„ = 64 „	
15 „	= 22 „	„ = 63 „	
20 „	= 14 „	„ = Frequent gasping movements, which cannot be counted.	Contractions weak; and heart continues dark during systole.
25 „	= 13 „	„ =	
30 „	= 12 „	„ An occasional gasp.	
40 „	= 10 „	„ have stopped.	
50 „	= 10 „		
1 h. 0 „	= 8 „		Contractions very feeble.
1 „ 10 „	= 8 „		
1 „ 15 „	= 0 „		Stopped in diastole.
1 „ 20 „	= 0 „		
1 „ 30 „	= 12 „		
1 „ 40 „	= 12 „		
1 „ 50 „	= 12 „		
2 „ 0 „	= 10 „		
2 „ 30 „	= 8 „		Contractions irregular; two auricular for one ventricular.

These two experiments prove distinctly that Calabar bean has a direct influence on the heart, that is quite independent of the indirect influence it exerts on that organ by arresting the respiratory movements. Such arrest does, doubtless, assist the action on the heart, especially during the later stages of the poisoning, by impeding the circulation; and in mammals, when a small dose has been exhibited, such comparatively slight diminution as is first produced in the frequency of the heart's contractions must even be partly caused by the early retardation and cessation of the respiratory movements that constantly occur.

The cardiac action of physostigma is, thus, quite independent of the cerebro-spinal nervous system, and is not a mere effect of the paralysis of respiration. It must, therefore, be caused by an action of a direct nature on the cardiac ganglia, which seem to be the only constant exciters of this organ, however its contractions may be *regulated* by other nerves. The peculiar changes that the heart's action undergoes—the diminution in the frequency of its beats, then their stoppage or irregularity, sometimes followed by renewal of rhythmical contractions, or of independent movements in all the chambers, or in one only—prove that Calabar bean first diminishes the vitality of the exciting ganglia, and then paralyses them. Their influence is, at any rate, maintained until spontaneous movements cease; for, if we divide the ventricles from the auricles at a late stage of the poisoning and when the contractions are unrhythmical, those chambers alone

that are still in connection with the great exciter ganglia in the auriculo-ventricular septum will continue their spontaneous movements.

The action is not a very powerful one, and its characteristics may be explained because of that; for the effects of physostigma on the heart appear to be similar to those of *weak forms* of at least two of the ordinary cardiac poisons—of digitaline in minute doses, and of the alcoholico-aqueous extract of *Nerium Oleander*, which is merely the green extract mixed with various impurities, without which it has the ordinary actions of the larger class of those substances that affect the heart.*

ACTION ON THE BLOOD-VESSELS.

The question of the action of Calabar bean on the condition of the vascular system is intimately connected with that of the cardiac effects; and must, therefore, be considered also, that we may complete the examination of the influence of this substance on the circulation. For this purpose, I instituted two sets of experiments. In the first (1), the blood-tension in the arterial and venous systems was observed; and in the second (2), the calibre-changes of the smaller blood-vessels and of the capillaries were investigated.

1. *Examination of the Blood-Tension, and of the Coincident Changes in the Cardiac and Respiratory Movements, and in the Temperature.*

In these experiments, the tension in the arterial system was determined by dividing one of the carotid arteries and connecting the end proximal to the heart with a modification of POISSEUILLE'S hæmadynamometer, in which two indicating columns were connected with the reservoir. The tube of one of these had an extremely small orifice where it dipped into the mercury, and it, therefore, registered the mean pressure only. The orifice of the other had the same diameter as the rest of the tube, and the contained mercury had, therefore, immediately communicated to it every change of pressure, and oscillated synchronously with the heart's beats. The venous pressure was ascertained by a simple hæmadynamometer having one registering column. The indicating columns were divided into inches and tenths of inches

In the experiments where the temperature was observed, a delicate thermometer was inserted into the subcutaneous tissue at the flank of the animal, and retained there, under the charge of an assistant, during all the time of the experiment.

* PÉLIKAN, *op. cit.*, Comptes Rendus, 1866.

a. *Arterial Tension only.*

Experiment LVIII.

A large and vigorous retriever dog was placed on a table, and tied down by its four limbs.*

Time.	Time after Administration.	Mean Pressure.	Pressure Oscillates between	No. of Cardiac Contractions.	No. of Respirations.	Notes of Operations and of Symptoms.
H. M. S.	M. S.			Per Min.	P r Min.	
3 16 0 P.M.	...	...	...	...	20	The right carotid artery was exposed and connected with the hæmadynamometer.
3 16 30	...	6·8	5·2 & 9·0	...	...	
3 19 0	...	7·0	5·0 9·0	86	18	
3 20 30	...	6·9	5·3 9·3	...	18	
3 22 0	...	7·2	5·3 9·3	108	19	
3 24 0	...	7·0	5·1 8·9	...	...	
3 26 20	...	...	...	...	...	Two grains of extract, in forty minims of distilled water, were injected into the subcutaneous tissue of the abdomen.
3 26 30	...	6·8	5·5 9·0	102	...	
3 26 50	...	...	...	...	...	The injection of the poison was completed.
3 29 0	2 10	6·9	4·9 9·2	93	19	Dog is perfectly quiet.
3 33 0	6 10	6·8	4·5 9·2	90	18	A few struggles occurred.
3 35 0	8 10	6·7	4·9 8·5	75	17	
3 38 30	11 40	7·5	5·0 10·0	90	19	Somewhat violent struggles.
3 41 0	14 10	7·8	5·5 9·3	90	15	Muscular twitches over nearly all the body.
3 41 30	14 40	8·0	...	...	17	
3 42 0	15 10	8·4	7·0 10·0	...	21	Muscular twitches have increased in violence.
3 43 0	16 10	8·9	7·0 10·0	...	22	
3 44 0	17 10	8·8	7·5 10·4	...	...	
3 45 0	18 10	8·5	7·0 9·3	106	...	
3 46 0	19 10	8·3	7·0 9·3	104	31	
3 48 0	21 10	8·2	6·5 9·5	98	38	Twitches are now much feebler; great lachrymation and salivation.
3 50 0	23 10	8·15	7·5 9·5	...	9	
3 52 0	25 10	7·9	6·5 9·4	96	40	
3 55 0	28 10	7·65	6·5 9·9	96	37	
3 57 0	30 10	7·55	6·5 8·6	...	30	Urine and fæces passed.
3 58 0	31 10	...	...	...	34	Respirations noisy, from mucus in the trachea.
3 59 0	32 10	7·3	6·0 8·5	100	28	Very fluid fæces passed.
4 0 0	33 10	7·2	6·3 8·5	112	25	
4 3 30	36 40	7·1	6·0 8·0	112	22	The twitches have very much diminished in force.

* I have much pleasure in acknowledging the valuable assistance I derived in this series of experiments from my friend, Dr Gamgee. I am also indebted, for essential aid in all or several of them, to Dr Brunton, and to Messrs Paton, Ritchie, Finlay, Caton, Hogg, Holden, Wright, Hardie, Gairdner, Glascott, Lucas, M'Ewan, Howieson, Crombie and Young. Without the co-operation of these gentlemen, it would have been quite impossible to obtain the many simultaneous observations which are contained in these experiments, and to which much of their value is due.

Experiment LVIII.—continued.

Time.	Time after Administration.	Mean Pressure.	Pressure Oscillates between	No. of Cardiac Contractions.	No. of Respirations.	Notes of Operations and of Symptoms.
H. M. S.	M. S.			Per Min.	Per Min.	
4 6 0 P.M.	39 10	7·0	...	...	24	
4 7 0	40 10	6·9	6·0 & 7·8	116	23	
4 10 0	43 10	6·8	5·8 7·5	120	22	The twitches are now few, faint and occasional.
4 16 0	49 10	6·8	5·6 7·3	128	23	
4 17 30	50 40	6·7	5·8 7·3	...	22	The dog appears almost perfectly well.
4 19 0	...	6·9	5·5 7·5	124	...	It was deemed advisable to administer a second dose at this stage.
4 22 0	...	...	...	...	...	Commenced the injection of four grains of extract, in thirty minims of distilled water, into the subcutaneous tissue of the right flank.
	Time after Second Administration.					
4 22 30	...	...	...	122	21	The injection was completed.
4 23 0	0 30	6·8	5·8 7·5	...	22	
4 24 0	1 30	6·7	6·0 7·5	...	23	
4 27 0	4 30	7·0	5·8 7·5	120	22	Strong muscular twitches have reappeared.
4 28 0	5 30	6·75	6·0 8·0	116	21	Liquid fæces passed, and urine "jetted" out in a full and abundant stream.
4 30 0	7 30	7·0	...	...	21	
4 30 30	8 0	7·35	...	...	...	
4 31 0	8 30	6·9	6·3 8·3	120	...	Respirations are rather laboured.
4 33 0	10 30	6·9	6·0 8·0	...	22	
4 34 0	11 30	7·1	6·0 8·0	118	...	
4 35 0	12 30	7·2	6·3 8·0	...	...	
4 37 0	14 30	7·4	6·0 8·0	...	23	
4 38 0	15 30	7·3	6·5 8·3	116	22	
4 42 0	19 30	7·6	6·0 8·3	120	24	Twitches are so strong as to cause frequent slight spasms.
4 44 0	21 30	7·15	6·4 7·8	112	25	
4 46 30	24 0	7·2	6·5 8·5	...	...	Urine and fæces discharged copiously.
4 47 0	24 30	7·5	6·5 9·5	...	23	
4 48 0	25 30	7·8	6·0 11·0	92	26	
4 49 30	27 0	7·3	5·6 10·0	30	...	
4 50 0	27 30	7·1	...	...	...	
4 50 15	27 45	6·9	...	...	...	
4 50 30	28 0	6·7	5·0 8·5	...	23	
4 50 31	28 1	6·2	...	...	...	
4 50 35	28 5	5·9	...	...	...	
4 50 38	28 8	5·8	...	...	...	
4 50 40	28 10	5·4	4·0 7·0	40	...	
4 51 0	28 30	5·4	4·0 4·7	...	...	The twitches continue with considerable strength.
4 51 30	29 0	6·9	...	...	25	

Experiment LVIII.—continued.

Time.	Time after Second Administration.	Mean Pressure.	Pressure Oscillates between	No. of Cardiac Contractions.	No. of Respirations.	Notes of Operations and of Symptoms.
H. M. S.	M. S.			Per Min.	Per Min.	
4 52 0	29 30	7·2	6·0 & 9·0	...	...	
4 53 0	30 30	7·1	5·9 9·0	...	...	
4 54 0	31 30	6·3	5·9 8·2	...	...	
4 55 0	32 30	6·3	5·0 8·0	24	...	
4 55 20	32 50	5·6	4·0 8·0	...	...	
4 55 30	33 0	6·1	5·0 8·0	...	...	
4 56 0	33 30	5·0	4·5 7·0	...	21	
4 57 0	34 30	4·6	3·5 5·8	22	...	
4 57 15	34 45	4·0	3·5 5·5	...	...	
4 57 30	35 0	4·4	3·5 6·0	...	...	
4 58 0	35 30	4·4	3·0 6·0	...	27	The respirations are extremely shallow and gasping.
4 59 0	36 30	4·0	3·0 5·0	...	...	
4 59 30	37 0	3·5	2·5 4·5	...	...	
5 0 0	37 30	2·5	1·0 3·0	...	...	
5 0 30	38 0	1·8	1·0 2·5	18	4	Respirations are mere gasps.
5 1 15	38 45	1·6	1·0 2·0	...	4	
5 1 30	39 0		1·0 1 5	...	...	Mercurial column has fallen into the reservoir.

In the autopsy, which was immediately made, the heart was found dilated with dark blood. Occasional contractions occurred for twenty minutes after death. The sciatic, intercostal and phrenic nerves were active, and galvanism of a vagus nerve excited vermicular movements of the stomach. The intestinal peristalsis was feeble. Galvanism of the cervical sympathetics produced no contraction of the pupils. A quivering movement continued in the striped muscles for many minutes.

The first portion of this experiment shows that after the administration of the poison a very distinct rise occurs in the arterial tension, while the number of the cardiac contractions rapidly diminishes during this rise, and before the frequency of the respirations has been affected. The second, and larger, dose did not influence the arterial tension so powerfully, nor did it exert so immediate an action on the frequency of the heart's beats. Both doses were administered in such a manner that their absorption was comparatively slow; in the following experiments, physostigma was directly injected into the circulation, and its action was, therefore, more rapidly and energetically produced.

b. *Tension of the Arterial and Venous Systems.*

Experiment LIX.

Performed on a large retriever dog, vigorous and in perfect condition.

Time.	Time after Administration.	Arterial Tension.		Venous Tension.	No. of Cardiac Contractions.	No. of Respirations.	Temperature.	Notes of Operations and of Symptoms.
		Mean Pressure.	Pressure Oscillates between					
H. M. S.	M. S.				Per Min.	Per Min.	°	
2 58 0	...	...	...	...	...	...	...	The right carotid artery was exposed, and attached to the hæmadynamometer.
3 1 0	...	...	...	...	...	...	...	The left jugular vein was attached to the second hæmadynamometer.
3 2 0	...	5·8	4·3 & 7·0	...	...	...	...	
3 3 0	...	6·0	5·0 7·0	2·8	...	...	...	
3 4 0	...	6·0	4·5 7·5	2·4	...	...	...	
3 5 0	...	6·0	4·6 7·0	2·2	...	...	...	
3 6 0	...	6·2	5·0 8·0	2·2	...	...	...	
3 7 0	...	7·0	5·0 8·0	1·9	...	...	...	
3 8 0	...	6·1	4·0 7·0	1·7	...	...	...	
3 8 30	...	5·5	5·0 7·0	...	...	...	...	
3 9 0	...	6·3	3·3 7·0	1·7	120	...	...	
3 10 0	...	5·9	3·0 6·7	...	...	8	99·2	
3 12 0	...	5·4	4·0 6·5	1·8	...	...	99·8	The dog seems perfectly calm.
3 13 0	...	5·9	4·0 7·0	...	126	10	...	
3 14 0	...	5·6	4·5 6·5	...	132	...	100·0	
3 15 0	...	5·6	4·5 7·0	...	...	10	...	
3 15 30	...	5·5	5·0 7·0	...	...	...	...	
3 16 0	...	6·6	5·0 7·0	1·8	...	12	99·9	
3 16 15	...	...	...	...	...	...	...	Commenced the injection of six grains of extract, in twenty minims of water, into the right jugular vein.
3 16 30	...	...	...	...	...	...	...	The injection was finished.
3 17 0	0 30	6·0	4·0 7·0	2·8	120	...	...	
3 17 30	1 0	4·3	...	...	...	...	...	The muscles are twitching; fæces passed.
3 17 35	1 5	4·9	...	...	...	...	...	
3 17 45	1 15	6·5	4·0 11·0	...	...	...	...	
3 17 50	1 20	7·0	5·0 11·5	...	...	...	...	
3 18 0	1 30	8·4	5·2 11·9	3·4	78	10	99·9	Urine passed; saliva is escaping from the mouth in large quantity.
3 18 30	2 0	8·5	5·5 12·0	...	...	...	...	
3 19 0	2 30	7·9	5·0 10·0	3·4	...	...	...	The twitches are now severe, and have a spasmodic character.
3 19 15	2 45	7·3	5·0 9·0	...	54	11	100·2	
3 19 30	3 0	6·5	4·5 8·0	3·4	...	...	...	No movement of the eyelids when the cornea or conjunctiva is touched.
3 20 0	3 30	5·4	4·0 8·0	3·1	40	...	100·4	The muscular twitches have become less marked.

Experiment LIX.—continued.

Time.	Time after Administration.	Arterial Tension.		Venous Tension.	No. of Cardiac Contractions.	No. of Respirations.	Temperature	Notes of Operations and of Symptoms.
		Mean Pressure.	Pressure Oscillates between					
H. M. S.	M. S.				Per Min.	Per Min.	°	
3 20 15	3 45	5·0	...	...	...	...	...	Excessive lachrymation.
3 20 30	4 0	4·7	2·5 & 6·0	3·2	...	...	...	
3 20 40	4 10	3·7	3·0 6·0	...	...	...	...	
3 20 50	4 20	3·8	3·0 6·5	3·0	...	...	100·4	
3 21 0	4 30	4·3	3·0 6·0	2·9	32	...	...	Cardiac impulse quite perceptible to the touch.
3 21 15	4 45	3·5	2·0 5·0	...	...	...	100·4	The dog is now quite quiet.
3 21 30	5 0	3·0	2·0 5·0	2·8	...	...	...	Third eyelid is protruded slightly, and the eyeball is directed downwards and inwards.
3 22 0	5 30	2·6	2·0 5·5	2·4	24	8	100·3	
3 22 15	5 45	3·1	3·0 5·0	2·2	...	...	...	
3 22 30	6 0	2·5	2·0 5·0	2·1	...	...	...	Cardiac impulse can still be felt readily.
3 23 0	6 30	2·6	2·0 4·5	2·0	22	...	100 3	
3 23 30	7 0	2·7	1·5 5·0	1·9	...	...	...	Respirations are short and jerking.
3 24 0	7 30	2·5	2·0 3·5	1·8	20	10	100·3	
3 25 0	8 30	2 6	2·0 3·5	1 9	12	...	100·3	An occasional faint muscular twitch occurs.
3 26 0	9 30	2·7	2·3 3·0	1·7	16	10	100·2	Respirations are gasps merely.
3 26 15	9 45	2·5	2·0 3·5	...	...	...	...	
3 26 30	10 0	2·4	2·0 3·0	...	...	6	...	No reflex movement on severe irritation.
3 27 0	10 30	2·2	2·3 2·5	1·7	14	...	100 2	
3 27 30	11 0	1·3	2·0	1·6	...	...	100·2	
3 27 40	11 10	...	...	1·0	...	...	...	Cardiac and respiratory movements have ceased.
3 28 0	11 30	...	...	...	...	...	100·1	
3 33 0	16 30	...	...	...	...	...	100·0	
3 35 0	18 30	...	...	...	...	...	99·7	

The exposed heart was found, in the autopsy, to be perfectly quiet; and only one or two irregular non-synchronous movements could be obtained when it was stimulated. All its chambers were full of blood. Slight peristaltic movements were observed in the small intestines.

Experiment LX.

Experiment LX.

Performed on a large and very active Newfoundland-and-retriever cross-bred dog.

Time.	Time after Administration.	Arterial Tension.		Venous Tension.	No. of Cardiac Contractions.	No. of Respirations.	Temperature.	Notes of Operations and of Symptoms.
		Mean Pressure.	Pressure Oscillates between					
H. M. S.	M. S.				Per Min.	Per Min.	°	
2 53 0	...	...	...	...	...	...	...	The arterial hæmadynamometer was connected with the right carotid artery.
2 54 0	...	...	...	...	...	...	...	The left jugular vein was attached to the venous hæmadynamometer.
2 56 0	...	6·0	4·5 & 7·0	...	118	34	98·0	
2 57 0	...	5·8	4·0 7·0	2·4	...	...	...	
2 58 0	...	6·2	5·0 7·5	2·4	...	28	100·1	
3 0 0	...	6·0	5·0 8·0	2·5	...	...	...	
3 3 0	...	6·0	5·0 8·0	2·5	...	...	99·9	
3 4 0	...	6·0	5·0 6·5	...	176	30	...	
3 5 0	...	6·1	4·8 7·0	...	...	...	100·2	
3 6 0	...	6·1	5·0 6·5	...	180	26	...	
3 7 0	...	6·3	6·0 7·0	3·0	...	...	...	
3 8 0	...	6·1	5·0 7·2	3·5	175	...	...	
3 9 0	...	6·0	4·5 7·0	...	...	...	100·1	
3 10 0	...	6·1	5·0 7·0	2·9	160	...	...	
3 10 30	...	...	...	...	...	...	...	Commenced the injection, into the right jugular vein, of seven grains of extract, in twenty-five minims of distilled water.
3 10 40	...	...	...	...	...	...	...	The injection was finished.
3 11 30	0 50	6·0	4·7 7·0	...	...	...	...	
3 12 0	1 10	5·9	4·5 6·5	3·1	108	...	...	Marked twitches occurred.
3 12 30	1 40	6·0	4·5 6·5	3·2	...	...	100·3	
3 13 0	2 50	...	5·0 6·0	3·3	...	25	...	
3 14 0	3 20	5·9	6·0 7·0	3·2	...	...	100·3	
3 14 30	3 50	...	...	3·4	...	...	...	
3 15 0	4 20	5·8	...	4·2	...	22	100·4	
3 16 0	5 20	7·0	5·5 8·0	4·3	42	25	...	Respirations are feeble and short.
3 16 30	5 40	6·5	5·0 8·5	3·8	...	...	100·3	
3 17 0	6 20	6·8	5·5 7·5	3·2	32	...	...	Twitching interferes with, and prevents the counting of, the respirations.
3 18 0	7 20	7·6	6·7 8·9	3·5	32	...	100·5	
3 18 30	7 50	5·0	4·0 5·0	4·2	...	...	...	
3 18 45	8 5	...	...	4·0	...	...	...	
3 19 0	8 20	4·5	3·0 4·0	3·8	24	...	100·5	
3 19 30	8 50	4·0	3·0 4·5	...	...	...	...	Occasional gasps.
3 19 45	9 5	3·1	2·5 3·5	...	...	...	100·3	
3 20 0	9 20	2·6	2·0 2·8	3·5	20	10	...	
3 20 30	9 50	2·4	2·0 2·7	3·2	...	...	100·2	
3 21 0	10 20	2·3	2·0 2·5	2·9	16	13	100·2	
3 21 30	10 50	2·4	2·0 2·4	2·7	...	10	...	Muscles are now *quivering*, not twitching.

Experiment LX.—continued.

Time.	Time after Administration.	Arterial Tension.		Venous Tension.	No. of Cardiac Contractions.	No. of Respirations.	Temperature.	Notes of Operations and of Symptoms.
		Mean Pressure.	Pressure Oscillates between					
H. M. S.	M. S.				Per Min.	Per Min.	°	
3 22 0	11 20	1·9	1·5 & 2·3	2·7	8	...	100·1	
3 22 30	11 50	...	...	2·4	6	...	...	No respiratory movements, except an occasional jerking inspiration.
3 23 0	12 20	2·0	2·0 2·1	2·3	...	...	...	
3 23 30	12 50	1·8	1·5 1·7	2·1	...	...	...	
3 24 0	13 20	1·5	1·5 1·6	2·0	...	...	...	
3 24 15	13 35	...	...	1·9	...	...	...	
3 24 30	13 50	1·5	0·6 1·0	1·0	...	...	...	
3 24 45	14 5	0	0	0	0	0	...	The three indicating columns of mercury have subsided into their reservoirs.
3 25 0	14 20	...	...	...	...	...	100·0	
3 26 0	15 20	...	...	...	...	...	99·0	
3 27 0	16 20	...	...	...	...	...	99·3	

The abdomen and chest were immediately opened: the heart was dilated, full and motionless; and no peristalsis could be observed in the intestines. The diastaltic function of the cord was completely abolished, while motor nerve-conductivity was retained, for at least five minutes after death, in the sciatic, phrenic and intercostal nerves.

The principal results of these experiments are indicated so clearly that it is almost superfluous to point them out. During the first stage, the arterial tension diminishes slightly, the venous tension increases and the cardiac contractions rapidly diminish. The frequency of the respirations was increased in only the first experiment. After this, the arterial tension increases, soon arrives at a maximum considerably above its average before the poisoning, and then slowly diminishes; while the venous tension arrives at a high maximum rather later, and by more gradual stages, than the arterial, and in the same gradual manner declines until death. In neither system is the highest point reached before a very considerable fall has been caused in the frequency of the heart's contractions. The temperature rises during the poisoning, and attains its maximum near the time that the blood-pressures have commenced finally to diminish.

As these marked changes in the circulation could be produced before the respiratory function was modified to any important extent, it did not seem to me at all necessary to repeat the experiments with the addition of artificial respiration.

It is interesting to observe the same phenomena produced by physostigma after the division of the vagi nerves.

c. *Tension of the Arterial and Venous Systems after Division of the Vagi Nerves.*

Experiment LXI.

Performed on a young, full-grown and active retriever dog.

Time.	Time after administration.	Arterial Tension.		Venous Tension.	No of Cardiac Contractions.	No. of Respirations.	Temperature.	Notes of Operations and of Symptoms.
		Mean Pressure.	Pressure Oscillates between					
H. M. S.	M. S.				Per Min.	Per Min.	°	
2 38 0	...	...	...	...	...	...	...	The carotid artery, external jugular vein and vagus nerve of each side were exposed.
2 48 0	...	...	...	...	...	...	...	The venous hæmadynamometer was attached to the left jugular vein.
2 49 0	...	...	...	1·9	118	...	99·8	
2 50 0	...	...	...	1·8	...	...	99·2	The right carotid artery was connected with the second hæmadynamometer.
2 51 0	...	...	...	2 0	...	18	98·8	
2 52 0	...	4·9	4·0 & 6·0	...	102	...	98·7	
2 53 0	...	4·7	3·5 5·5	1·5	...	20	99·2	
2 54 0	...	5·0	4·0 6·0	2·2	108	...	99·0	
2 55 0	...	4·2	3·5 5·0	...	...	...	99·3	
2 56 0	...	...	...	...	80	...	99·2	
2 57 0	...	...	...	...	92	...	99·2	
2 58 0	...	4·5	3·0 5·5	2·1	...	...	...	
2 59 0	...	4·4	3·0 5·0	2·1	...	..	...	
3 0 0	...	4·6	3·5 5·5	2·1	90	16	99·2	
3 1 0	...	...	...	...	...	...	99·3	The right vagus nerve was cut through.
3 1 15	...	...	...	...	...	...	99·3	The left vagus was cut through. The respirations became short and spasmodic.
3 2 0	...	...	...	2·5	60	...	99·4	
3 3 0	...	6·0	5·5 6·0	2·6	...	...	99·3	The mercury in the oscillating column moves very rapidly over short spaces.
3 3 30	...	5·8	5·5 6·2	...	...	...	...	
3 4 0	...	5·8	5·8 6·2	2·5	120	...	99·2	
3 4 30	...	5·9	5·5 6·0	2·5	...	...	...	
3 5 0	...	5·9	5·5 6·0	2·5	125	...	99·2	
3 5 30	...	5·9	5·3 5·8	...	140	...	...	
3 6 0	...	5·8	5·5 5·8	2·5	170	30	99·1	
3 6 30	...	5·7	5·3 5·7	...	166	...	...	
3 7 10	...	5·7	5·7 6·1	...	166	...	99·2	Commenced to inject slowly, into the right jugular vein, seven grains of extract in twenty-five minims of water.
3 7 30	...	...	...	...	...	...	...	Finished the injection.
3 8 0	0 30	5·6	5·0 5·5	...	79	20	99·4	
3 8 30	1 0	5·6	5·0 8·0	...	...	...	...	
3 9 0	1 30	...	4·0 7·0	2·8	50	...	99·3	Respiration spasmodic ; great salivation.

Experiment LXI.—continued.

Time.	Time after administration.	Arterial Tension.		Venous Tension.	No. of Cardiac Contractions.	No. of Respirations.	Temperature.	Notes of Operations and of Symptoms.
		Mean Pressure.	Pressure Oscillates between					
H. M. S.	M. S.				Per Min.	Per Min.	°	
3 9 30	2 0	5·4	4·5 & 7·5	3·2	...	...	99·3	Slight twitches have commenced.
3 9 40	2 10	...	...	3·7	...	...	...	Tears are flowing copiously.
3 10 0	2 30	6·8	5·0 9·0	4·2	45	...	98·5	The respirations cannot be counted, because of the twitching.
3 10 15	2 45	6·9	5·0 9·5	4·5	...	...	...	Fæces passed.
3 10 30	3 0	7·3	5·0 9·5	4·9	...	...	...	Tremors are very strong.
3 10 45	3 15	...	...	5·2	...	...	...	
3 11 0	3 30	6·8	4·5 8·0	5·2	...	...	98·2	
3 11 15	3 45	6·8	4·5 7·5	5·1	...	...	...	
3 11 30	4 0	7·8	6·5 9·5	5 0	...	...	...	
3 11 45	4 15	...	...	5·2	...	...	98·0	
3 12 0	4 30	8·1	6·0 10·0	5 3	42	...	...	
3 12 15	4 45	7·5	6·0 8·0	5·4	...	...	...	
3 13 0	5 30	6·3	5·5 7·5	5·3	56	10	98·2	Respirations are merely gasps.
3 13 30	6 0	5·6	4·0 5·5	...	...	...	...	Neither cornea nor conjunctiva is sensitive.
3 13 35	6 5	4·7	4·0 5·5	5·3	...	...	98·2	Twitches have nearly ceased.
3 13 40	6 10	4·0	...	...	...	...	...	
3 13 45	6 15	3·8	3·0 4·5	5·3	...	...	...	
3 14 0	6 30	3·5	3·0 4·0	5·3	40	an occasional gasp.	98·0	
3 14 30	7 0	3·8	3·0 4·5	5·2	...	...	...	The muscular movements can scarcely be seen, but they can readily be felt.
3 14 45	7 15	3·8	3·0 5·0	4·8	25	Do.	97·7	
3 15 15	7 45	...	...	4·2	...	...	...	
3 15 30	8 0	...	...	3·4	...	...	...	
3 15 45	8 15	...	...	3·0	...	...	...	Urine passed.
3 16 0	8 30	1·5	1·0 1·5	2·4	10	...	...	
3 16 30	9 0	...	...	2·2	...	...	97·6	
3 17 0	9 30	1·0	...	2·2	...	...	...	
3 17 15	9 45	...	...	1·9	...	...	...	
3 17 30	10 0	...	...	1·5	...	...	97·5	
3 17 45	10 15	...	...	1·3	...	...	...	
3 18 0	10 30	...	...	1·0	...	...	97·2	
3 18 30	11 0	..	...	...	...	...	...	
3 20 0	12 30	...	...	...	...	...	97·0	
3 22 0	14 30	...	...	...	...	...	96·8	
3 24 0	16 30	...	...	...	...	...	96·5	

The autopsy was made immediately. Slight, but distinct, peristalsis was observed in the intestines. The heart was dilated and motionless, and its right side contained more blood than in the preceding experiments. The phrenic, intercostal and sciatic nerves were active.

It is, therefore, shown that the same effects are produced on the circulation after the division of the vagi, as when these inhibitory nerves retain their connec-

tion with the heart. The action on the frequency of the heart's beats is well illustrated in this experiment; from their number having been considerably increased before the exhibition of the poison, by the division of the vagi nerves.

The distance over which the mercury travels in the oscillating column seems to be increased as the effects of the poison manifest themselves. This appears from all the experiments in this series, but especially from the second and the last. The division of the vagi, in the last experiment, had abnormally diminished the distance of oscillation; and, yet, it became much greater after the poisoning than it had been previous to the nerve-division. It further appears that this increase in the oscillating distance occurs when the arterial tension is about its maximum. It can only be explained by a very decided increase in the force of the cardiac contractions. I believe that this effect on the heart is altogether a reflex one, due to the resistance to the propulsion of the blood, that the augmentation in the general vascular tension must excite. In a normal condition, a stimulus of this nature might be expected to operate by increasing the *number* and not the *strength* of the cardiac contractions; but any tendency to increased frequency is opposed by the action of physostigma, for we have already seen that this substance diminishes the number of the contractions, by prolonging the diastolic pause. Their strength may, however, continue unchanged; and, during the operation of physostigma, a stimulus may even increase it without affecting the number of the beats, so long as the ganglia that initiate the systolic contraction have their excitability merely lowered without being destroyed and the contractile power of the cardiac muscle continues undiminished.

Before discussing any further the changes of blood tension, it will be advisable to examine the condition of the minute blood-vessels during the action of physostigma.

2. *Examination of the Calibre-Changes in the smaller Blood-Vessels.*

The facility with which frequent measurements may be made of the diameter of any selected capillary or minute artery or vein in the web of the frog's foot, is well known to physiologists, and has been taken advantage of by Wharton Jones,* Bennett,† Lister‡ and others, in examining their condition during inflammation. A more general application of such examination of the capillaries to the investigation of the action of poisons would certainly be of great value. It has proved so in the case of nicotia;§ and we cannot consider any research on the actions of a cardiac poison to be complete unless it be done.

* On the State of the Blood and Blood-Vessels in Inflammation, &c. Guy's Hospital Reports, 1851.

† Principles and Practice of Medicine.

‡ Philosophical Transactions, 1858.

§ Claude Bernard, Leçons, &c., 1857, p. 399.

In my first experiments, the frog was merely tied down in the manner usual when the circulation in its web is being microscopically examined, but it was found impossible to prevent movements so absolutely as was required to retain the selected vessels in the field of the microscope. I ultimately found it necessary to adopt LISTER's recommendation of dividing the spinal cord several hours before the observations were begun.

Experiment LXII.

I divided the spinal cord at the occiput of a light-coloured frog weighing 529 grains, and, six hours afterwards, placed the web of one of its feet on the stage of a microscope. A small artery, a minute branch and a vein were selected and placed conveniently for measurement.*

A = diameter of larger artery; B = diameter of smaller artery; and C = diameter of vein.

Time.	A.	B.	C.	Notes.
15 minutes before administration of Calabar bean	8·0	2·5	6·5	
10 Do.	8·0	2·5	6·5	Circulation free.
5 Do.	8·0	2·5	6·5	
Time after administration of poison.				Four grains of extract, in twenty minims of distilled water, were injected into the subcutaneous tissue of the abdomen.
6 minutes,	7·8	2·5	6·5	
9 ,,	6·5	2·0	6·0	
10 ,,	5·9	1·8	5·7	
12 ,,	6·8	2·0	6·2	Circulation feeble, oscillating sometimes; vessels are crowded.
14 ,,	7·0	2·0	6·5	
15 ,,	8·5	3·0	6·5	
17 ,,	8·5	3·0	7·0	Almost no circulation.
19 ,,	9·0	3·0	7·5	Faint oscillations only in the artery; considerable crowding in all the vessels.
23 ,,	8·5	3·0	7·5	
29 ,,	8·5	3·0	7·5	Complete stasis.
36 ,,	8·5	3·0	7·5	
39 ,,	9·0	3·0	7·5	
1 hour	9·0	3·0	7·5	
2 hours	9·0	3·0	7·5	

Experiment LXIII.

The web of a frog, of 590 grains weight, was placed in the field of a microscope, after the animal had been prepared in the manner described in the previous experiment.

* NACHET's eye-piece No. 1, and object-glass No. 3, were employed; and the measurements represent divisions of an eye-piece micrometer, each of which equals $\frac{1}{100}$th of an inch with the above glasses.

A = diameter of a small artery; B = diameter of a very small vein.

Time.	A.	B.	Notes.
15 minutes before poisoning,	5·0	3·0	
10 Do.	5·0	3·0	
5 Do.	5·0	3·0	
Time after Administration of Poison.			Two grains of extract, in fifteen minims of water, were injected into the left flank.
5 minutes,	5·0	3·0	
10 „	4·7	3·0	Circulation oscillating.
15 „	4·2	3·0	
20 „	4·2	2·9	
25 „	4·0	2·9	
28 „	4·9	3·0	
29 „	5·7	3·0	
30 „	6·0	3·2	Stasis, and crowded vessels.
35 „	7·0	3·5	Slow circulation.
40 „	7·0	3·5	
45 „	8·0	3·5	Faint oscillations.
50 „	8·0	3·5	
1 hour,	8·0	3·5	
2 hours,	8·0	3·5	

The action of Calabar bean on the minute blood-vessels of the frog's web is, therefore, to contract them considerably first, and then dilate them. The contraction may be influenced, to a slight extent, by the reduction in the frequency of the heart's action; but the succeeding dilatation, during a still greater reduction, would lead us to suppose that it is mainly due to a specific effect on the ganglia and nerves that govern the calibre-changes of the vascular system, because it is by their influence that the final dilatation must be produced.

We are now in a position to explain the changes of blood tension that have been described in mammalians. The slight fall that usually occurs in the mean pressure immediately after the poison has been exhibited, I believe to be solely due to the diminution in the rate of the heart's contractions, which has always been caused by that time. The subsequent rise in both arterial and venous tensions before any considerable embarrassment of the respiration, may be satisfactorily explained by such contraction of the smaller arteries and veins as has been demonstrated to occur in the vessels of the frog's web. It cannot be caused by increased cardiac pressure; for the heart is at the time contracting with only one half its normal rapidity, or with even less; while the greater force of each heart beat the increased oscillating distances appear to indicate, is quite insufficient to account for the high degree of blood tension sometimes attained. The subsequent, more or less rapid diminution of pressure in both arterial and venous systems is the evident result of the great dilatation in the minute blood-vessels, assisted by the weakening of the *vis e tergo* that this poison quickly produces.

Action on the Temperature of the Body.

The temperature of mammalians that are being poisoned by Calabar bean rises slightly, so that a thermometer, placed either in the subcutaneous tissue or in the rectum, will indicate a gradual elevation as soon as well-marked symptoms begin to be produced. The effect on the surface temperature has been already shown in Experiments LIX., LX. and LXI.; that on the internal temperature was frequently observed with rabbits, and may be illustrated sufficiently in the following experiment.

Experiment LXIV.

A full-grown rabbit was placed on its back on a board, and firmly secured by a ligature round each leg.

Time.		Time after Administration of Poison.		Temperature.	Respirations.	Notes.
H.	M.	M.	S.	°	Per Min.	
12	5	...		...	...	The bulb of a delicate thermometer, with Fahrenheit's scale, was secured in the rectum.
12	10	...		99·0	...	
12	20	...		98 5	...	
12	30	...		98·4	...	
12	40	...		98·2	...	
12	50	...		98·0	47	
1	0	...		97·5	...	
1	10	...		97·3	...	
1	20	...		97·0	48	
1	30	...		96·5	...	
2	0	...		96·0	48	
2	10	...		95·8	...	
2	20	...		95·7	48	
2	30	...		95·5	48	
2	40	...		95·5	48	
2	50	...		95·3*	48	
2	56	...		...	...	Half a grain of extract, in ten minims of water, was injected into the subcutaneous tissue of the left flank.
3	1	5	0	95·8	...	Faint tremors of legs and of head.
3	5	9	0	96·3	...	Tremors are now general and stronger; and they prevent accurate determination of the respiratory movements.
3	6	10	0	96·5	...	
3	8	12	0	96·0	...	
3	15	17	0	95·5	...	
3	16	18	0	95·3	72	The muscular tremors have greatly diminished. Respirations are shallow and gasping, and they appear much impeded by bronchial secretion.
3	25	29	0	95·0	...	Quiet; except a few occasional twitches.
3	30	34	0	95·0	24	Respirations are very noisy and laboured.
3	32	36	0	94 5	...	The animal is dead.
3	35	39	0	94·0	...	
3	50	54	0	93·0	...	

* It will be observed that the temperature has gradually fallen in this experiment before the

The inconsiderable elevation of temperature exhibited in these experiments is probably an effect of the general muscular twitching that Calabar bean causes in mammals. It is quite possible that it may be also in part the result of vascular dilatation: but I think the first explanation is sufficient alone; and this additional one seems improbable when we remember that during the dilatation the circulation is extremely sluggish, because of the great diminution in the number of the cardiac contractions that accompanies it.

Action on the Blood.

The blood obtained from animals that have been poisoned by Calabar bean is generally dark in colour, because of the usual cause of death; but if drawn from the left side of the heart after a very large dose of the poison, it has the scarlet hue of arterial blood. It frequently remains semifluid for some time, and then clots loosely. When examined with the spectroscope, no modification has ever been observed in the characters or positions of the normal crurine bands.

In dogs and rabbits, the red blood corpuscles are changed in form, and present various irregularities of outline, among which a well-marked stellar crenation predominates. There can be no doubt that this is an effect produced by physostigma, as I have frequently examined the blood previous to the administration, and found its microscopic characters perfectly normal, and repeated the examination immediately after death, and invariably observed the above modifications. No change is produced in the red corpuscles of birds or frogs, nor in the white corpuscles of any animal I have examined.

For the purpose of detecting any possible effect on the respiratory function of the blood—a subject to which Harley, by his elaborate researches, has directed considerable attention*—two experiments were performed, the results of which agreed very closely. One of these may be given here, but without the numerous details which are necessarily connected with it.

Experiment LXV.

A small quantity of blood was directly removed from the right side of the heart of a Skye-terrier dog, by passing a gum-elastic catheter down the right jugular vein, affixing a syringe with a stop-cock, and withdrawing the requisite amount, according to the ingenious method of Claude Bernard.† The catheter was then detached from the syringe, and, the stop-cock

poison was administered, and apparently because of the constrained position in which it was necessary to retain the rabbit. In other nine experiments of the same description, a similar fall occurred. I endeavoured to find if a stationary, constant point could be obtained, after which the poison might be given; with the following result:—When the thermometer was introduced, the temperature was 97°; in one hour, it had fallen to 96°·3; in two hours, to 95°·6; in three hours, to 95°·3; in four hours, to 94°·7; in five hours, to 93°·3; and in six hours, to 92°. The rabbit was now set free: it was unable to stand; and other four hours afterwards, it was found dead. As this is a very ordinary method of treating rabbits during physiological experiments, it is important to recognise this injury to their vitality, which may occasion many fallacious conclusions if overlooked.

* On the Influence of Physical and Chemical Agents upon Blood; with special reference to the mutual action of the Blood and the Respiratory Gases. Phil. Trans. 1865, p. 687.

† Action de l'Oxyde de Carbon sur le Sang, Leçons, &c., 1857, p. 166.

having previously been closed, a bent steel tube was substituted by which means the blood could be readily passed into a small absorption tube over mercury, without coming in contact with the atmosphere.

The vein was now ligatured, and the dog was poisoned with a moderate dose of the extract. At the moment of death, a second quantity of blood was withdrawn with the same precautions as the first, and it was placed in a similar absorption tube. A nearly equal portion of atmospheric air was added to each tube, and they were frequently shaken during twenty-four hours in a room with a temperature that varied little from 50° F. The gases were then removed and analysed. The following are the results :—

Gases from Blood before Poisoning.		Gases from Blood after Poisoning.	
Volume of blood =	7·77 cub. cent.	Volume of blood =	4·03 cub. cent.
„ air =	47·95 „	„ air =	48·20 „
After contact with the blood for 24 hours, air measures	51·65 c. c.	After contact with the blood for 24 hours, air measures	50·54 c. c.
∴ Apparent exhalation =	3·70 c. c.	∴ Apparent exhalation =	2·34 c. c.
Composition per cent. :—		Composition per cent. :—	
Oxygen, . . .	20·63	Oxygen, . . .	19·93
Nitrogen, . . .	77·82	Nitrogen, . . .	78·77
Carbonic acid, . .	1·55	Carbonic acid, . .	1·30
	100·		100·

These results agree sufficiently to prove that the respiratory function of the blood is not interfered with in physostigma poisoning. Had there been any marked discrepancy, a suspicion of such an action might be raised; but I doubt if this could be really settled without a much more refined method of experiment than was adopted. HARLEY'S results seem open to very many objections, as his usual method permitted of an even greater number of fallacies than were possible in the two experiments I performed. At the same time, his paper is an extremely valuable and elaborate one, and contains many conclusions of the highest interest to physiologists.

ACTION ON THE LYMPH-HEARTS OF THE FROG.

The lymph-hearts discovered by MÜLLER* and PANIZZA† in amphibia, have always been found paralysed at an early stage of the poisoning, in the experiments where their condition was examined. As the pulsations of the pair situated one on each side of the sacrum of frogs may be readily determined without any operation, attention was especially directed to them. The time at which they cease to contract is noted in the following experiment; and the previous increase in rapidity that is there mentioned has been observed on other occasions.

Experiment LXVI.

The lymphatic hearts in the ischiadic region of a frog had an average rate of forty-nine contractions in the minute. Five minutes after two grains of extract had been subcutaneously

* Philosophical Transactions, 1833, p. 559.

† Proceedings of the Royal Society of London, vol. ix. p. 559.

administered, these contractions were seventy-two; in ten minutes, they were seventy; in fifteen minutes, they were sixty-two; and in twenty minutes, they were forty-four. At this time, the frog was flaccid, though still possessing the power of feeble voluntary movement; and its respiration had ceased. One minute thereafter, or twenty-one after the poison had been given, the most careful examination failed to detect any pulsation of the lymphatic hearts, their final stoppage having suddenly occurred.

In many other experiments, these symptoms merely repeated themselves.

Action on the Peristaltic Movements of the Abdominal Viscera.

A close analogy exists between the action on the minute blood-vessels and that on the peristaltic movements of the intestines. In mammalians, physostigma seems, in the first place, to increase the vermicular contractions of all the abdominal viscera, and then to diminish them. For some time, the intestines move with increased vigour; they then contract, so as very considerably to diminish their calibre; and, finally, they assume a condition of dilatation with lessened movement. Peristalsis has been invariably observed to continue after death; but if a large dose has been exhibited, it may be very slight and of short duration. Stimulation of the vagi nerves sometimes increases vermicular movements after death, and it then does so very conspicuously in the stomach. I have never succeeded in convincing myself of the activity of the splanchnic nerves in post mortem examinations; but, as the intestinal movements are then usually sluggish, it is a matter of extreme difficulty to judge of the action of their inhibitory nerves. During the progress of the symptoms in rabbits, I have also observed very energetic peristalsis in the cornua and body of the uterus, and even in the ureters. From the former of these effects I should be inclined to recommend physostigma as an oxytocic. As with those of the heart, the special ganglia of the intestines appear to have their functions retained, with diminished activity, for a considerable period after death; and, as with the cardiac muscle, stimulation produces non-peristaltic movements of those abdominal viscera that possess a muscular structure, long after the nerves that govern their rhythmical contractions have been paralysed.

Action on the Pupil.

In many experiments, the condition of the pupil was carefully observed, and its diameter was measured at intervals by means of a graduated glass scale, each division of which represented one-fiftieth of an inch.

The changes that usually occur in mammals may be briefly described as consisting of a short period of slight dilatation and a succeeding one of contraction; and either the latter gradually increases until death, or the pupil first oscillates once or twice between dilatation and contraction. The latter condition is present at death, and after this the pupil again dilates.

These iridal movements are best seen in rabbits; they are sluggish in dogs, more so in certain birds, and least evident in frogs.

The more important of the results may be conveniently arranged in the form of a table.

Table of Pupil-Changes during Poisoning by Physostigma.

Experiment.	Animals.	Average before Poisoning.	Minimum after Poisoning, and Time of Occurrence.	Time of Return to Average before Poisoning.†	Dilatation over Average, and Time of its Occurrence.	
No. LXVII.	Frog	3 × 4*	1·75 × 3 in 46 min.	Not noted	None noted	
„ LXVIII.	Do.	5 × 7	4· × 5 in 29 „	4 hours	Do.	
„ LXIX.	Do.	5 × 7	4·5 × 6 in 16 „	55 min.	6 × 7 in 1 h. 10 m.	
„ LXX.	Rabbit	13 long diam.	4 in 7 min.	Not noted	None noted	
„ LXXI.	Do.	9 „	4 in 5 „	15 min.	Do.	
„ LXXII.	Do.	10 „	7 in 11 „	23 min.	Do.	In 23 minutes, when the pupil had returned to its average, the animal had nearly recovered from a small dose; the second line marks the effects produced by a second and larger dose, 24 minutes after the first.
	Same rabbit	10 „	6 in 7 „	Not noted	Do.	
„ LXXIII.	Rabbit	10 „	3 in 12 „	Do.	Do.	
„ LXXIV.	Do.	11 „	3 in 16 „	58 min.	Do.	
„ LXXV.	Do.	9 „	3 in 7 „	8 min.	Do.	
„ LXXVI.	Do.	12 „	4 in 8 „	Not noted	Do.	
„ LXXVII.	Do.	13 „	3 in 8 „	Do.	Do.	
„ LXXVIII.	Do.	11 „	3 in 16 min. 30 sec.	17 min. 30 sec.	Do.	
„ LXXIX.	Frog	4 × 6	3·5 × 5 in 24 min.	Not noted	Do.	
„ LXXX.	Do.	5 × 6	4· × 5 in 25 „	2 hours	5 × 6 in 1 h. 46 m.	Eyelids closed, so that it was difficult to see the pupil after 24 minutes. This often happens in frogs.
„ LXXXI.	Do.	5 × 6	3· × 4·5 in 16 „	2 hours	None noted	
„ LXXXII.	Do.	5 × 6	4· × 5 in 30 „	1 hour 47 min.	Do.	
„ LXXXIII.	Dog	21	17 in 28 min.	29 min.	25 in 30 min.	
„ LXXXIV.	Frog	5 × 6·5	4· × 5 in 19 min.	2 hours 5 min.	None noted	
„ LXXXV.	Do.	4 × 5·5	3·5 × 5 in 11 „	22 min.	Do.	
„ LXXXVI.	Do.	6 × 7·5	3· × 5 in 50 „	Not noted	Do.	
„ LXXXVII.	Dog	21	15 in 4 min.	4 min. 30 sec.	25 in 5 min. 30 sec.	
„ LXXXVIII.	Do.	10	4 in 5min. 30 sec.	8 min.	15 in 10 min.	
„ LXXXIX.	Do.	16	3 in 7 min.	9 min. 30 sec.	None before death	
„ XC.	Do.	15	9 in 11 „	16 min.	None noted	
„ XCI.	Pigeon	6	4 in 8 „	Not noted	None noted	
„ XCII.	Do.	6	4 in 28 „	Do.	Do.	General symptoms were very slowly produced.

* The figures represent fiftieths of an inch.

† In warm-blooded animals, the periods entered in this column are generally subsequent to death.

In many other experiments, the pupils are described as having contracted during the poisoning, but the exact changes were not measured. In the Table, Experiments LXXV., LXXVIII., LXXXIII., LXXXVII., LXXXVIII. and LXXXIX. illustrate the rapid change that frequently occurs from contraction to dilatation; and it is obvious that unless special and continued attention be directed to the condition of the pupils, the contracted state will frequently escape detection. HARLEY,* AMÉDÉE VÉE,† NUNNELEY,‡ LASCHKEWICH§ and VAN HASSELT ‖ agree with me in describing contraction of the pupils as one of the effects that follow the internal administration of Calabar bean.

It is, unfortunately, impossible to enter fully into the question of the method in which physostigma produces its effects on the pupil, as the physiology of pupillary changes is yet unsettled, and as even the structural anatomy of the iris is a subject of debate. I am anxious to avoid being committed to any theoretical assertion on this subject, especially as the opinions I previously expressed do not seem so certainly supported by my further experience as to permit of their reassertion.

Many endeavours have been made to arrive at some definite conclusion, and, although this has not yet been attained, as in the state of our knowledge of the anatomy and normal physiology of the iris it could not be, the probable method of action may be indicated with the aid of the following experiment.

Experiment XCIII.

The two sympathetic nerves were exposed at the neck of a white rabbit. Both pupils had a diameter of seven-fiftieths of an inch. The left sympathetic was divided.

In 2 minutes, left pupil = 5, right = 7.

I then endeavoured to fix definitely the strength of the weakest interrupted galvanic current that could so stimulate the portion of the divided sympathetic next to the eye as to produce dilatation of the pupil. For this purpose, DANIELL'S cell and DU BOIS REYMOND'S induction apparatus were employed.

When the secondary coil was at 500, the resulting current produced no effect on the pupil in 30 sec.

" 480, " "
" 400, " "
" 300, " "
" 250, " "
" 200, " "
" 150, the left pupil dilated from 5 to 15, immediately.
" 190, the resulting current produced no effect on the pupil in 30 sec.
" 185, the left pupil dilated from 6 to 15 in 10 seconds.

One grain of extract, in fifteen minims of distilled water, was injected into the subcutaneous tissue of the right flank. In thirty seconds, tremors occurred; and the symptoms rapidly advanced to a fatal termination, fifteen minutes and thirty seconds after the administration of the poison.

* *Op. cit.* p. 140.
† Recherches sur la Fève du Calabar, 1865, p. 22, &c.
‡ *Op. cit.* p. 12.
§ *Op. cit.* p. 300.
‖ Mentioned by DONDERS (Accommodation and Refraction of the Eye: New Sydenham Society, 1864) as having been observed in 1856; and, I am informed by Professor DONDERS, communicated to a scientific society, but not otherwise published by VAN HASSELT.

The examination of the cervical sympathetics was resumed soon after the poison was exhibited with the following results :—

In 2 min.		after the administration, stimulation of the left sympathetic with the secondary coil at		190=0 in 30 seconds.
4	„	do.	do.	185=dilatation from 7 to 15 in 10 sec.
10	„	do.	do.	188=0 in 30 seconds.
10	„ 30 sec.	do.	do.	185=dilatation from 5 to 15 in 10 sec.
12	„ 30 „	after the administration, left pupil = 4, right pupil = 5.		
13	„ 30 „	do.	stimulation of the left sympathetic with the secondary coil at	185=0 in 30 seconds.
14	„ 0 „	after the administration, stimulation of the right sympathetic with the secondary coil at		185=0 „
14	„ 35 „	after the administration, stimulation of the left sympathetic with the secondary coil at		160=0 „
15	„ 30 „	do.	do.	90=0 „

The rabbit was now dead, and both pupils had been for more than two minutes previously in a state of extreme contraction.

In 16 min. 10 sec.	after the administration, stimulation of the right sympathetic with the secondary coil at		30 = 0 in 30 seconds.
17 „ 0 „	after the administration, stimulation of the left sympathetic with the secondary coil at		10 = 0 „
18 „ 0 „	after the administration, stimulation of the right sympathetic with the secondary coil at		10 = 0 „

The left iris was at this time exposed by cutting away a portion of the cornea. The electrodes were applied directly to its surface, near the external margin, when a slight and rapid contraction of the iris (dilatation of the pupil) occurred, instantly followed by a rebound to its previous condition. This effect was frequently produced during many minutes after death, but no distinct expansion of the iris (contraction of the pupil) could be caused when the electrodes were applied in the same way to the pupillary margin. It must, however, be added that the pupil was at this time in a very contracted condition.

We learn from this experiment that the cervical sympathetic is paralysed before the death of the animal, while a portion of the apparatus that is immediately concerned in the contraction of the iris retains its vitality for a considerable period afterwards. The cause of the pupillary contraction during poisoning by internal administration is, therefore, in all probability, to be found among those consequences that naturally succeed the removal of the influence of the cervical sympathetic nerve. Without dogmatising on this subject, and feeling content in the meantime with the mere narration of these facts, I am inclined to think that such changes of the iris can only be explained by considering the influences of dilator and constrictor muscles, and also of a system of contractile blood-vessels.

An animal struggles violently during the action of a poison, and the pupil dilates. It is natural to suppose that, in this case, the excited spinal nerves had produced increased action of the dilator muscle, and that thereby the antagonism of the constrictor had been overcome. But if iridal movements are merely the results of spinal or cerebral nerve-force interfering with antagonism between muscles, how account for the continuation of either dilatation or contraction after

the death of these nerves? Such conditions should not exist when the causes of interference with antagonism have been removed. I, therefore, venture (in common with others, and notwithstanding the anatomical difficulties that exist) to include an arrangement of contractile blood-vessels among the causes that produce iridal movements.

These blood-vessels will possess the function of erectile texture, and will act either in harmony with the dilator or constrictor muscles, or independently of them. The coincidence I have frequently observed between changes of blood-tension and differences in the size of the pupil also leads me to support this view. At the same time, the influence of an erectile tissue is not in itself sufficient to account for all the pupil changes; they can never be explained satisfactorily without also considering the effects of spinal and of cerebral motor nerves, operating probably on radiating and circular muscular fibres whose action is independent of such tissue. The cervical sympathetic appears to be the channel through which the nerves that originate in the cilio-spinal region pass to the iris. Stimulation of this region, or of the sympathetic nerve, produces dilatation of the pupil: and this does not interfere with the supposition of the existence of a contractile vascular network co-operating with a proper dilator muscle; for then the blood-vessels of this network, being governed by branches of the same nerves, would contract along with the dilator fibres, and the result would be a diminution in the size of the iris, and, consequently, a dilatation of the pupil. In the same way, division or paralysis of the sympathetic would result in iridal expansion; the contraction of the pupil being caused by dilatation of the blood-vessels, assisted, it may be, by the simultaneous contraction of a circular muscle.

B. TOPICAL EFFECTS.

When applied to the Nervous System.

It is obvious that when a poison is applied during life to the substance of any of the central nerve-organs, it will produce its specific action on the system in the ratio of the absorbing power of the organ, and therefore very much in proportion to the local blood supply. Other distinct effects are, however, frequently caused by the concentrated form and other peculiarities of the preparation. The watery suspension of physostigma extract caused no peculiar symptom when applied to the cerebrum of mammalians, birds, or frogs; and as its absorption was slow when so exhibited, the constitutional effects were produced only after long periods. When it was applied to the spinal cord of frogs, peculiar twitchings occurred in the muscles directly connected by motor nerves with the part of the cord in contact with the poison. These twitches soon ceased, and no movements were then caused when this portion of the cord was galvanised. The first effect was probably the result of local irritation merely, while the final paralysis was due to a specific action of physostigma.

From the nearly complete absence of blood-vessels in the trunks of the sciatic nerves, it is possible to localise the effects of a poison to any portion of the trunk. A curious result was produced by the topical application of Calabar bean. It has been shown that this poison does not appear to paralyse the afferent nerve fibres when acting through the blood; or, at least, that under its influence the function of the motor nerves is indubitably very much sooner destroyed than that of the sensory. When, however, the poison is applied to a mixed nerve-trunk, the order wherein these effects are produced is reversed, the afferent nerves being paralysed a few minutes before the efferent. This may be shown with great distinctness if strychnia be given after the local action has continued for some time.

Experiment XCIV.

The spinal cord of a frog was divided at the occiput, the sciatic nerves were exposed, and a piece of gutta-percha parchment was placed under each nerve, so as to isolate it completely. A small pad of cotton wadding *steeped in water*, was applied to the *right* nerve, while a similar pad *steeped in a concentrated mixture of extract of physostigma and water*, was placed on the *left;* care being taken to prevent the diffusion of any of the extract beyond the parchment. At this time, a slight stimulation of either nerve, below or above the pads, caused contraction of the limb and general reflex movements.

The pads were kept moist by an occasional drop of water on the right, and one of watery extract of physostigma on the left; and they were retained in their positions for an hour and forty minutes. They were then removed, and the left leg was carefully washed with distilled water, so as to remove effectually any extract that might have been adhering to the nerve. They were both tested with galvanism, when movements of the left leg followed the application of the poles to any portion of the exposed left sciatic; but no reflected contraction occurred when the nerve was stimulated below the position that had been occupied by the pad. No change had occurred either in the afferent or the efferent conductivity of any portion of the right nerve.

A drop of solution of strychnia was now applied to the wound that had been made in the neck by dividing the cord. Seven minutes after this, very weak galvanism of any portion of the right sciatic nerve caused a spasmodic shock of all the body. The same current produced a like effect when it was applied to the left nerve above the part that had been occupied by the poisoned pad; *but when it was applied to the poisoned part,* or *lower down,* the muscles below the point stimulated alone contracted, *no reflected movements being caused.* The same effects were repeatedly observed for other six minutes, before the lapse of which time the action of the strychnia had manifested itself more violently, and rendered the above peculiarities more distinct and exaggerated.

This experiment has been several times repeated, and has always yielded similar results.

If the poisoned pad be permitted to remain in contact with the nerve for a few minutes after the paralysis of its afferent fibres has been caused, the motor fibres also will have their conductivity destroyed.

Experiment XCV.

The sciatics of a frog were exposed, and were treated exactly as in the previous experiment. The afferent conductivity of that portion of nerve to which physostigma had been applied was lost in two hours, but the motor conductivity was yet retained. The application was continued, with the result that the conductivity of the motor fibres was destroyed within other fifteen minutes.

When applied to Striped and to Unstriped Muscle.

Although physostigma, when acting through the blood, does not destroy muscular contractility, the contact of a concentrated preparation is immediately followed by very rapid paralysis of the portion of muscle to which it is applied.

Experiment XCVI.

The two gastrocnemii muscles of a frog, and portions of the sciatic nerves in the thighs, were exposed and separated from contiguous structures. The muscles were completely isolated by pieces of parchment. A pad *soaked in a concentrated mixture of extract and water*, was placed on the surface of the right muscle, and a similar pad *moistened with water*, was placed on the left: the muscles being at the time completely under the control of their sciatic nerves, and being readily excited to contractions by direct galvanism.

Four minutes afterwards, a weak galvanic current was applied to the left nerve, and produced energetic contraction of all the muscles supplied by the nerve; and the left gastrocnemius muscle also contracted forcibly when directly stimulated. The same current was then applied to the right nerve, and caused pretty active movements of the right leg; in which, however, the gastrocnemius only sluggishly participated.

In fifteen minutes, the right or *poisoned gastrocnemius was perfectly paralysed; while the left muscle appeared to be as active functionally as when the experiment was commenced.*

The pad soaked in the extract was then removed from the right muscle and placed on the left. In five minutes, the contractility of the latter was considerably impaired; and in twenty minutes, no contraction could be produced, even when it was stimulated by very strong galvanism.

It was found that when a portion of intestine in energetic peristalsis, had its surface painted over with a concentrated watery mixture of the extract, it became flaccid; and that when a vermicular contraction ran along towards this portion, it stopped at the margin of the portion, and appeared to *skip over* it, as the peristalsis was resumed at the nearest unpoisoned point of the intestine. Soon afterwards, the poisoned portion of intestine could not be stimulated to contract by strong galvanism.

When applied to the Heart.

For the purpose of examining the topical effects on the heart, frogs were generally employed, but warm-blooded animals were in a few instances made use of.

The conditions of the experiments were varied by the application of the poison to the visceral pericardium, and to the muscular substance of the heart; without, and after, its removal from the body; and by the insertion of the poison into one of the cardiac chambers.

1. *Without its Removal from the Body.*

a. *To the Visceral Pericardium.*

Experiment XCVII.

The exposed heart of a frog was found, during ten minutes, to have an average rate of seventy beats in the minute.

A drop of filtered concentrated solution of the extract was placed on the pericardium.

In 1 minute, heart = 52 per minute.
2 „ = 40 „
4 „ = 36 „
6 „ = 30 „
8 „ = 24 „
10 „ irregular; eighteen ventricular and twenty auricular contractions.
13 „ „ no ventricular and eleven auricular contractions.
14 „ „ „ „
22 „ = 8 per minute; both chambers contract, but the ventricles very feebly.
25 „ = 12 „
40 „ = 15 „ very feeble, but rhythmical.
50 „ irregular; twelve ventricular and fifteen auricular contractions.
52 „ „ no ventricular and eighteen auricular contractions.

The ventricles did not again contract spontaneously, but the auricular action continued for many hours. Voluntary movements were made by the frog until fifty minutes after the poison had been placed on its pericardium.*

b. *To the Heart.*

Experiment XCVIII.

A portion of the pericardium was removed from the exposed heart of a frog; and, during ten minutes that followed this operation, its contractions varied little from forty-five in the minute. A small drop of the same solution of extract as was employed in the previous experiment was placed on the heart's surface.

In ten seconds, heart = 0.

It continued motionless for thirty seconds; then recommenced; but, almost immediately afterwards, the frog struggled violently, and the contractions again ceased for ten seconds.

In 2 minutes, heart = 27 per minute.
4 „ = 21 „
6 „ = 30 „
8 „ = 34 „ Rhythmical and regular.

At this time, a second drop was applied to the heart.

In 30 seconds, a struggle occurred, and the heart stopped for ten seconds. When it recommenced, the contractions were irregular, only five ventricular to ten auricular occurring in the minute.

In 3 minutes, there were no ventricular movements and 6 auricular.
10 „ „ „ 20 „
12 „ heart = 23 per minute; rhythmical but irregular.
20 „ „ = 28 „ „ and regular.
40 „ „ = 28 „ „ „

A third drop was now applied.

In 2 minutes after the third application, heart irregular, { no ventricular movement, and 24 auricular.
8 „ „ „ „
18 „ „ = 7 per minute, { both ventricles and auricles contracting.
25 „ „ = 0 „

* In this and in the other experiments of the series, a drop of water was occasionally placed on the heart to prevent its surface from drying.

Experiment XCIX.

A young rabbit was killed, and its heart was exposed. During four minutes, the contractions were eighty per minute. A concentrated solution of extract was painted over the greater portion of the heart's surface. In one minute, the contractions had entirely ceased; but, a few seconds afterwards, the left ventricle spontaneously resumed its action, and in two minutes after the application, the whole heart was contracting at the rate of seventy-six per minute.

The application was thrice repeated with similar results. Latterly, however, a longer interval occurred between the suspension and recovery of the cardiac contractility. Paralysis of the heart was ultimately caused by continuing these applications.

2. *After Removal from the Body.*

When the heart is removed from the body and placed in a concentrated solution of extract, its contractions immediately become irregular, and then cease. All the vital properties of its structures are paralysed in one or two minutes.

3. *Insertion of Physostigma into one of the Heart's Chambers.*

Experiment C.

A young rabbit was killed by the destruction of the medulla oblongata. In four minutes afterwards, while the heart was contracting at the rate of fifty per minute, two grains of extract, in five minims of water, were injected by WOOD'S syringe into the right auricle. The action of the heart instantly ceased. However, during the next ten minutes, irritation could still cause single laboured contractions.

TOPICAL ACTION ON THE BLOOD-VESSELS AND PIGMENT-CELLS WHEN APPLIED TO THE WEB OF THE FROG'S FOOT.

WHARTON JONES has examined with great care the changes in the calibre of the blood-vessels that follow the application of various substances to the frog's web.* Solution of atropia produces a marked contraction, a result that I have had occasion to confirm; and it, in this respect, resembles ordinary stimuli, such as galvanism, temporary cold and heat, and various irritants. He further established, and LISTER has supported and extended the statement,† that the contractile power of minute blood-vessels is independent of the central organs of the nervous system, though it may be controlled by them. A few substances were found that cause dilatation of blood-vessels, and among them solution of opium.

This antagonism in the actions of opium and atropia, and the well-known difference in their effects on the pupil, whether acting through the blood or acting by topical application, seem to have an important bearing on the question of how far the movements of the iris are due to calibre-changes of its blood-vessels. The examination of the topical effects of physostigma—a much more powerful

* On the State of the Blood-Vessels in Inflammation, &c.; *loc. cit.*

† An Inquiry regarding the parts of the Nervous System which regulate the Contraction of the Arteries; Philosophical Transactions, vol. cxlviii., 1858.

myositic agent than opium—is thus not only of great intrinsic interest, but also likely to be of considerable importance in explaining its action on the iris. In the experiments that were undertaken for this purpose, the condition of the pigment-cells also was observed.

Experiment CI.

The spinal cord of a light-coloured, large frog was divided between the first vertebra and the occiput; and, thirty minutes afterwards, a portion of a web was placed on the stage of a microscope.

An artery and three branches were selected for examination (A, B, C and D); and during ten minutes, their diameters occupied pretty constantly the following divisions of an eye-piece micrometer :—

A = 3; B = 2; C = 2; D = 1·5. The pigment-cells were diffusely stellate.

A small drop of filtered watery solution of extract was placed on the web.

In	2 minutes,	A = 3·0; B = 2·0; C = 2·0; D = 1·5.	Pigment-cells stellate,	Current of blood seems rather more rapid.
	8 „	A = 3·0; B = 2·5; C = 2·5; D = 1·5.	„	„
	15 „	A = 3·5; B = 3·0; C = 3·0; D = 1·5.	„	concentrating.
	20 „	A = 4·0; B = 3·0; C = 3·0; D = 1·5.	„	concentrated : no rays.
	40 „	A = 4·0; B = 3·0; C = 3·5; D = 2·0.	„	„
	50 „	A = 4·0; B = 3·0; C = 3·5; D = 2·0.	„	diffusing a few rays.
	1 h. 0 min.	A = 4·0; B = 3·0; C = 3·5; D = 2·0.	„	rather more diffuse than at commencement of experiment.
	1 „ 10 „	A = 4·0; B = 3·0; C = 3·5; D = 2·0.	„ in nearly extreme diffusion.	Circulation free.
	1 „ 20 „	A second drop of the solution was placed on the web.		
	1 „ 25 „	A = 4·0; B = 3·0; C = 3·5; D = 2·0.	Pigment-cells concentrating.	
	1 „ 26 „	A = 4·0; B = 3·0; C = 3·5; D = 2·0.	„	stellate.
	1 „ 30 „	A = 4·0; B = 3·0; C = 3·5; D = 2·0.	„	again diffusing.
	1 „ 35 „	A = 4·0; B = 3·0; C = 3·5; D = 2·0.	„	in extreme diffusion.
	2 „ 30 „	A = 4·0; B = 3·0; C = 3·5; D = 2·0.	„	„

Experiment CII.

An artery and two branches (A, B, C) and a capillary (D) were selected in the web of frog, which was prepared as in the preceding experiment. Their diameters were found to be the following—A = 7; B = 6·5; C = 4; D = 1 : while the pigment-cells in the field were in a state of extreme concentration, there being no rays visible.

A drop of a filtered, strong solution of extract was placed on the web.

In 10 minutes,	A = 9; B = 8; C = 5; D = 1.	Pigment-cells in extreme concentration.	Circulation active.
20 „	A = 9; B = 8; C = 5; D = 1.	„	extreme concentration. Circulation active.
40 „	A = 9; B = 8; C = 5; D = 1.	„	stellate. Circulation languid.

The observations were continued until two hours after the application; and, up to that time, no further change had occurred, except that extreme diffusion had appeared in the pigment-cells.

Experiment CIII.

A portion of the web of a frog was arranged for microscopic examination, in the same way as in the two preceding experiments. An artery and two branches (A, B, C) were selected for examination, along with several adjoining pigment-cells.

Before the application, A = 4 ; B = 2 ; C = 1·5 : while the pigment-cells were in the stellate form.

A drop of a filtered, strong solution of extract was placed on the web.

In 5 minutes,	A = 5; B = 2; C = 1·5.	Pigment-cells	concentrated, with a few short rays,	Circulation more rapid; and many capillaries that were before empty now contain an actively moving blood stream.
10 „	A = 5; B = 2; C = 1·5.	„	in extreme concentration.	
20 „	A = 5; B = 2; C = 1·5.	„	„	Circulation continues active.
30 „	A = 5; B = 2; C = 1·5.	„	„	„

The action of physostigma on the calibre of the minute and contractile blood-vessels is thus the reverse of that of atropia.

Lister believes that the pigment-cells possess a nerve apparatus that governs their condition in exactly the same way as the smpathetic ganglia and spinal nerves govern the calibre-changes of the smaller blood-vessels.* If this be so, the long continued concentration, which precedes the diffused condition of the pigment in these cells, would imply that their nerves are more sensitive to irritation than those of the vascular system, and that this pigmentary concentration is the result of a stimulating property of the extract, of so slight a character as to have no effect on the ganglia and nerves of the blood-vessels.

When applied to the Eyeball, or to its immediate neighbourhood.

As this investigation has been confined to the lower animals, the action on the iris only can be here discussed. This has been observed in amphibia, reptiles, birds, and mammalians. The pupil contracts within a few minutes after the application of physostigma to the eyeball, to the cutaneous surface in its neighbourhood, or to the nasal mucous membrane; and, if the quantity have been considerable, this may last for two or three days. It is caused much more rapidly, and maintained for a much longer time, than the often varying state of contraction that has been described as a symptom produced by physostigma acting through the blood. There is no reason to doubt that it is as purely an effect produced by contact with the iris as the opposite state that atropia causes; and so limited is the action, that in the same animal extreme physos-

* On the Cutaneous Pigmentary System of the Frog; Philosophical Transactions, vol. cxlviii., 1858, p. 627.

tigma-myosis may exist in one eye, while atropia-mydriasis is present in the other. It is easy to prove the presence of the extract within the eyeball, after its topical application, by removing the aqueous humour and placing it on the conjunctiva of another animal, when the usual effects of Calabar bean on the pupil will be produced.

In addition to this phenomenon, increased lachrymation, and congestion of the conjunctiva, and, I believe, of the iris itself, are produced.

The question of the effects produced on the eye by the topical application of such substances as physostigma and atropia must always be an interesting one to physiologists. Its full discussion would require a special paper, so numerous are the data to be considered, and so conflicting the opinions that have been expressed. Besides, there are some effects that can only be conveniently examined in man, and which must be included in any satisfactory review of this attractive subject. It is, however, quite within the purpose of the present investigation to consider the method in which the iris is expanded by physostigma. I have already expressed an opinion that iridal changes appear to require the co-operation of special radiating and circular muscular fibres, with a system of contractile blood-vessels possessing to a certain extent the properties of erectile tissue. A mere antagonism between the two former muscular arrangements could not alone account for the effects of either physostigma or atropia; and, indeed, the actions of those substances seem to oppose such a theory. All the muscular fibres in the iris are unstriped, and physostigma relaxes while atropia contracts such fibres. Therefore, were these the only causes of iridal movement, physostigma would produce no effect on the pupil; for it would merely render less energetic the contraction of both, and would not thereby disturb their counterbalancing antagonism. For a similar reason, atropia will merely increase the opposing action of both, without causing any iridal movement.

To reconcile their actions with this anatomical arrangement, it is necessary to make one of the following very improbable suppositions—that the circular muscle at the pupillary margin has different physiological properties from the dilator; or that the one set of fibres is regulated by nervous ganglia that can be stimulated by the contact of substances, which paralyse corresponding ganglia whose power is limited to the other set.

Let it be granted, however, that dilator and constrictor muscles with counterbalancing powers exist, and that, in addition, a system of contractile blood-vessels is present, and the ascertained physiological actions of these opposing substances will be rendered available for the explanation of their peculiar effects. Dilatation of the pupil by atropia will then be due to the successful opposition of radiating muscular fibres and contractile iridal blood-vessels, to unaided constrictor fibres; the contact of atropia causing contraction of all unstriped fibres,

including those of the blood-vessels: while contraction of the pupil by physostigma will be intelligibly explained by the universal relaxation of all the contractile tissues of the iris, and the consequent enlargement of its area by the increased accession of blood, which the dilated vessels attract and permit.

The topical action of physostigma on the blood-vessels has been already described, and it certainly supports the view just stated. Confirmatory evidence is also obtained from ADAMÜK's recent experiments on intra-ocular pressure,* which show that this is increased by extract of Calabar bean applied to the conjunctiva and diminished by atropia; for such a difference of effect would necessarily exist, did physostigma augment the blood supply of the iris and atropia decrease it.

The additional effects that follow the topical application to the human eye-ball will be mentioned among the general conclusions.

The following are the conclusions of this investigation:—

A. ACTION THROUGH THE BLOOD.

1. Physostigma has proved fatal to every animal hitherto examined, with the exception of the Eséré moth. In mammals and birds, death is most rapidly caused when the poison is injected into the circulation or when it is brought into contact with a wounded surface. It follows nearly as quickly, when Calabar bean is introduced into a serous cavity; much more slowly when it is exhibited by the mucous membrane of the digestive system. In rabbits, death has been caused by its application to the Schneiderian, the auditory or the conjunctival mucous membrane. The skin of frogs resists the poison for a long time; but, if it be applied for a considerable period, and with proper precautions, distinct evidence of absorption may be obtained, though death has never been caused by such application.

2. The contact of the extract of Calabar bean with the gastric juice of a dog, for twenty-four hours and at a temperature a little above 95° F., did not, in the slightest degree, modify the energy of the poison.

3. A large dose, given to a mammal or bird, rapidly affects the cardiac contractions, and then paralyses the heart. The respiratory movements are quickly stopped, but the symptoms and post mortem appearances are those of syncope. Such a dose, injected into the abdominal cavity of a frog, affects nearly simultaneously the heart and spinal cord, and very rapidly destroys the vitality of both organs. In this case the motor nerves are only slightly, or not at all affected, and may retain their conductivity for about thirty hours. Evidence of

* Centralblatt, No. 36, 1866; and RUTHERFORD's Report on Physiology, Journal of Anatomy and Physiology, No. II., 1867.

the vitality of the afferent nerves may be obtained as long as the retained vitality of the spinal cord permits of its diastaltic function being examined.

4. In mammals and birds, an average dose produces symptoms of asphyxia. When administered to frogs, a similar dose impairs the function of the spinal cord, and diminishes the rates of the cardiac contractions and of the respiratory movements; and, soon after, the latter cease. In periods varying from one and a-half to four hours afterwards, the motor nerves are paralysed; this paralysis implicating their endorgans first, and their trunks afterwards. From this it must not be inferred that the nerve is paralysed by a centripetal progression of the poison; the only fact demonstrated being that a direct ratio exists between, on the one hand, subdivision of nerve substance, facilitating contact of the poison, and, on the other, rapidity of paralysing effect. Indeed, division of the nerve trunk, previous to the administration of Calabar bean, delayed the paralysis of the endorgans. The afferent nerves retain their activity as long, at least, as the functions of the spinal cord are not lost. The spinal cord and the motor nerves are generally paralysed at about the same time.

5. When a small, but still fatal, dose of Calabar bean is administered to a frog, the effects are the same as those in the previous conclusion, until they arrive at the stage of paralysis of the motor nerves; after this, an interval of several hours may elapse before the functions of the spinal cord are completely suspended. During this interval the *tactile* sensibility of the afferent nerves is increased: so that, if the ischiadic artery and vein of one limb have been tied before the exhibition of the poison, a slight touch of the skin in the poisoned region, which before the administration of the poison caused no effect, will now produce faint twitches of the limb whose vessels are tied; while an ordinary excitant, such as sulphuric acid, will show everywhere a marked diminution in the diastaltic activity, as measured by the métronome.

6. *With a still smaller dose, a frog may have its cardiac contractions reduced by from seventy to eight per minute, its respiratory movements completely stopped, and the endorgans of its motor nerves paralysed, and yet afterwards completely recover.* This has occurred when two grains of extract were administered to a frog, weighing 730 grains.

7. In frogs, the voluntary muscles are unaffected by the poison, and may continue to respond to galvanic stimulation during three or four days after its administration. The contrast between this and the effect of Calabar bean on the motor nerves, may be well shown by ligaturing the ischiadic vessels of one limb before injecting the poison. If, when strong stimulation causes no reflex movement, the two gastrocnemii muscles with their attached nerves be so placed that an interrupted current, from one Daniell's cell and Du Bois Reymond's induction apparatus, may be transmitted simultaneously through either both muscles or both nerve trunks, it will be found in the case of the

muscles that when the secondary coil is slowly advanced contractions will occur with the same current in both muscles, or with a weaker current in the case of the poisoned than in that of the non-poisoned one, this varying with the length of time which has elapsed since the limb was deprived of blood; when the current is transmitted through both nerves, contractions will be produced simultaneously in both muscles, or with a weaker current in the non-poisoned one, or contractions will occur in the non-poisoned muscle only, this also varying with the length of time that may have elapsed since the exhibition of the poison.

8. In mammals and birds, the voluntary muscles are affected in a very remarkable manner. At an early stage of the poisoning, faint twitches occur, which gradually extend over the body, and, at the same time, increase in vigour so as to interfere with the respiratory movements. Shortly before death, they again become mere successive twitches, often requiring the use of the hand to discover their existence. After death, if a muscular surface be exposed, these twitches will still be observed, involving usually different muscular fasciculi at different times, rarely the whole of a muscle at once; and in mammals they may persist for more than thirty minutes after death. They are caused by a direct effect of physostigma on the muscular substance. This is shown by their continuing after paralysis of the motor nerves, by their persisting in a muscle cut out of the body, and by their non-occurrence in parts that have been separated by ligature from the circulation.

9. In mammals and birds, when the dose is large, the heart's action is rapidly made slower and then stopped. In dogs, it may diminish to one-half in three minutes, and cease in ten. In frogs also, a large dose, injected into the abdominal cavity, causes rapid and complete cardiac paralysis. A smaller dose causes either a gradual cessation followed by a renewal at a diminished rate, or a gradual fall, from sixty or seventy to four or six beats per minute, followed by a gradual return to a diminished rate of from eight to twenty per minute. At this stage, and for many hours afterwards, the only signs of vitality are this diminished cardiac action and the power of the voluntary muscles to respond to galvanic and other stimulation. In the frog, where alone these last phenomena have been observed, the heart may continue so to contract for three or even five days, provided the temperature of the apartment be as low as 50° F. After stoppage, galvanism may sometimes cause a renewal of rhythmical contractions; but this can rarely be done, and unrhythmical and partial contractions can alone be excited. Cessation of the heart's contractions occurs in diastole, with all the chambers full.

10. The pneumo-gastric nerves retain their inhibitory power over the heart during the whole time from the diminution to the partial recovery of its action. Soon after this, however, they are paralysed; and this occurs at nearly the same time as the affection of the motor nerves.

11. Division of the pneumo-gastric nerves, or their paralysis by curare, or destruction of the medulla oblongata or spinalis, does not protect the heart from the action of physostigma.

12. The lymphatic hearts of frogs poisoned by Calabar bean soon cease to contract.

13. In rabbits, a large dose paralyses the cervical sympathetic nerves, before the death of the animal. A smaller fatal dose merely diminishes their activity.

14. Before the stoppage of the heart, proofs may be obtained of the vitality of its sympathetic ganglia; but, as striped muscle is not affected by Calabar bean conveyed by the blood, we are obliged to infer from the symptoms respectively produced, that the activity of the cardiac sympathetic system is probably destroyed by a large dose, and lessened by a smaller one.

15. The animal temperature, both external and internal, has been invariably observed to rise in rabbits and dogs, but only slightly and for a short period; after which it slowly falls.

16. The condition of the capillary circulation was examined in the web of the frog. Soon after the exhibition of the poison, the smaller arteries and veins contracted slightly; but, after a short interval, this contraction was succeeded by a rapid and permanent dilatation, in which the calibre of the vessels was considerably above their maximum previous to the poisoning. This capillary dilatation appears to occur all over the body, as is shown by a peculiar blue coloration of the voluntary muscles and of the heart, a similar coloration of the serous and fibro-serous tissues, and a congestion of the blood-vessels in the conjunctiva and iris. This change also occurs, in a less marked manner, in birds and mammals.

17. The general results of experiments in which the arterial and venous tensions were examined were, that the arterial tension first diminished slightly, immediately after the administration of the poison, then gradually increased until it reached its maximum—when the number of cardiac contractions had diminished to at least one-half,—and afterwards rapidly fell; and that the venous tension began to increase immediately after the administration, continued doing so until it slowly reached its maximum—when the arterial tension had considerably diminished,—and then fell, though more gradually than the tension of the arterial system. The number of the cardiac contractions when the venous tension had attained its maximum, was about one-third of the average before the poisoning: the respirations were rather less frequent than before, and the temperature had risen a few tenths of a degree.

18. Physostigma causes extreme diffusion in the pigment-cells of the frog's skin, and thus a very marked change occurs in the colour of the animal during the progress of the symptoms.

19. In dogs, the peristaltic action of the intestines is usually destroyed at death; it may, however, continue a short time afterwards. In rabbits, the intes-

tinal movements are frequently increased in activity before death, and generally continue for a considerable time afterwards.

20. The pupil contracts in all cases of rapid poisoning in mammalians and birds. The contraction may, however, be slight and of short duration; and dilatation may then be observed during the greater portion of the experiment, especially if the dose be a small one. Contraction of the pupil is produced in frogs also.

21. Calabar bean acts as an excitant of the secretory system; increasing the action of the alimentary mucous, of the lachrymal, and of the salivary glands.

22. In the frog, the symptoms of poisoning are not materially altered by removal of the brain, or by division of the cervical portion of the spinal cord.

23. Artificial respiration does not prevent death, in mammals, after the exhibition of a poisonous dose. This is a necessary result of the effects of physostigma on both the cerebro-spinal and sympathetic systems.

24. Congestion of internal organs occasionally occurs; but this is by no means an invariable consequence of a fatal dose.

25. The blood is generally dark after death, but becomes arterialised on exposure to the air; its respiratory capabilities are unaltered; it often clots loosely and imperfectly; and, when examined with the spectroscope, the bands of scarlet crurine are found unchanged. In the rabbit and dog, a microscopic examination demonstrates an invariable change in the coloured corpuscles, which have their outlines distinctly crenated. This change is not caused in the blood of birds or amphibia. The white corpuscles remain unaltered.

B. TOPICAL EFFECTS.

1. When the poison is applied to the surface of a frog's brain, no effect is produced; but when it is brought into contact with the spinal cord, a few twitches occur in the extremities, followed by paralysis of the portion of cord acted upon.

2. When physostigma is applied to a mixed nerve-trunk, in a concentrated form and with proper precautions to prevent absorption by neighbouring parts, first the afferent nerve-fibres are paralysed, and afterwards the efferent.

3. Topical application destroys the contractility of striped and of unstriped muscular fibre. The heart's action is stopped by repeated application to its external surface or to the pericardium. If a small quantity be injected into one of its chambers, paralysis nearly immediately follows.

4. The blood-vessels are dilated when a solution is applied to the web of the frog's foot.

5. The effects of the application of Calabar bean to the eyeball are a somewhat painful sensation of tension in the ciliary region, contraction of the pupil, myopia and astigmatism; with, frequently, congestion of the conjunctival vessels, pain in the supra-orbital region, and twitches of the orbicularis palpebrarum muscle.