XVII. *On the Physiological Action of the Bark of* Erythrophleum Guinense, *generally called Casca, Cassa, or Sassy Bark.* *By* T. Lauder Brunton, *M.D., F.R.S., and* Walter Pye, *Esq.*

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Several months ago we received from Mr. Monteiro a piece of Casca bark, which he had obtained with great difficulty from a native at Bembe during his residence in Angola. This bark is used by the natives as an ordeal, persons suspected of theft, witchcraft, or other crimes being made to drink an infusion of it. If it causes vomiting only, the person is acquitted; but if it causes purging, he is considered to be guilty, and is either allowed to die of the poison or at once killed. Among some tribes a practice prevails of making the accused, after drinking the infusion, walk in a stooping posture under half a dozen low arches made by bending switches and sticking both ends into the ground. Should he fall down in passing under any of the arches, he is at once considered guilty, and, without waiting for a purgative effect to be produced, he is at once put to death.

All the natives agree in their description of the effect produced on a person poisoned by this bark. His limbs are first affected, and he loses all power over them, falls to the ground, and dies quickly, without much apparent suffering.

The same bark, or one having precisely similar effects, is used as an ordeal in Sierra Leone, under the name of "red-water bark," and in Ashantee, under the name of "doom." In both these places the test of vomiting or purging only seems to be employed, and not that of stumbling, as described by Mr. Monteiro; but, according to C. A. Santos, the missionaries describe the bark as causing vomiting, glazing of the eyes, and loss of the power of contracting the muscles throughout the body; so that, when the poison has fairly commenced its action, the sufferer is incapable of standing or walking, and the head rolls heavily about the breast and shoulders.

Appearance of the Bark.—The pieces given to us by Mr. Monteiro were from 8–12 inches long, about 4 inches broad, and $\frac{3}{8}$ of an inch thick, dark brownish red in colour, and deeply grooved externally. Their appearance agreed exactly with the description given by C. A. Santos, in the 'American Journal of Pharmacy,' April 1849, p. 96, of the bark which he terms Saucy bark, or Gidu.

Chemical Reactions.—When treated with alcohol it yields a dark brownish-red tincture, and boiling water gives an infusion of a similar colour, which deposits a pale brownish-red precipitate on cooling; but at the same time the supernatant fluid remains turbid from suspended particles, which do not subside, and which are not removed by filtration. It becomes clear when heated, but the turbidity returns on cooling. The

tincture, when evaporated, leaves a resinous-looking extract, and when mixed with water gives a pale brownish-red precipitate. The watery solution of either the alcoholic or aqueous extract becomes much darker in colour after exposure to air.

An aqueous solution gives a brownish-black precipitate with ferric perchloride, indicating the presence of some form of tannin. It also gives a precipitate with tincture of galls or tannic acid, mercuric chloride, stannic chloride, gold chloride, silver nitrate, and lead acetate, either neutral or basic. If the precipitate produced by neutral lead acetate be removed by filtration, the addition of basic lead acetate to the filtrate causes very little further turbidity. Platinum chloride causes little or no precipitate.

These reactions closely agree with those given by SANTOS and PROCTER.

SANTOS states that, by passing the dilute tincture through animal charcoal, washing, drying, and boiling in absolute alcohol, he obtained a crystalline substance which was poisonous; but PROCTER failed to obtain a poisonous substance, although he got crystals which were non-poisonous.

From the small quantity of bark at our disposal, we have not attempted to isolate any active principle, as we feared our supply would not be more than sufficient for the investigation of its physiological action.

Professor LIEBREICH, however, has lately succeeded in separating a crystalline substance, which is exceedingly poisonous.

General Action.—Its action on the lower animals has been investigated by SANTOS and LIEBREICH. The former found that a decoction of the bark caused alternate dilatation and contraction of the pupils, appearance of delirium, violent retching, vomiting, symptoms of tetanus, and, finally, death. The crystalline principle obtained from the bark by LIEBREICH caused vomiting and sudden death, without previous loss of consciousness. Death is attributed by him to paralysis of the heart.

In our own experiments on dogs and cats we have observed vomiting, weakness, and death during a convulsion from the effects of the drug, whether introduced into the stomach or injected under the skin, into the peritoneal cavity, or into the veins.

GENERAL ACTION ON MAMMALS.

ACTION ON CATS.

Experiment I.—February 23.

Effects of a very Large Dose.

Four and a half cubic centimetres of a saturated alcoholic solution of Casca* were injected into the abdominal cavity of a half-grown kitten weighing 746 grammes. At three minutes after the injection it began to walk stiffly, and a peculiar jerk occurred in the hind legs each time they were lifted. Respirations 60. At 5′ after injection it

* This solution was prepared by extracting the bark with alcohol and evaporating to dryness. The solid extract thus obtained was dissolved in warm alcohol in such quantity that on cooling a deposit occurred. The solution was then filtered and the filtrate employed for experiments.

seemed giddy, and rolled over on trying to walk. Fæces were passed. Respirations 80, gasping. At 10′ it was lying on its side with its mouth wide open; respirations 120. At 10′ 30″ the respirations were 160, gasping. At 11′ it made feeble and unsuccessful attempts to vomit; the respiration became intermittent; there was an oscillating movement of the eyeballs, and the pupils were widely dilated. At 12′ the respiration became slower, as well as irregular. At 16′ it was 60, irregular and laboured. At 21′ the respiration appeared to be entirely diaphragmatic. At 24′ there were strong, ineffectual attempts at vomiting, followed by sudden stoppage of respiration, and death in a condition of emprosthotonos. The pupils at that time were widely dilated.

On opening the thorax immediately after death, the ventricles were found firmly contracted; but they recommenced to pulsate, and continued to do so for a few minutes spontaneously. They responded by a single contraction to irritation for $3\frac{1}{2}$ hours after death. By this time the heart looked quite dry and glazed, and rigor mortis was well marked in the muscles. The lungs were pale.

Experiment II.—February 22.

Effects of a Moderate Dose.

Three cub. centims. of the same alcoholic solution were injected into the abdominal cavity of a cat weighing 2238 grammes. At 25 minutes afterwards the animal vomited; and this was repeated at 35′ and 41′. At 41′ the cat seemed weak; respirations laboured, 60 per minute; pulse 100, regular. At 55′ respirations 80, shallow, irregular. At 75′ respiration deeper and more laboured. At 85′ the gait was staggering, and the limbs were moved with a jerk at the end of each step; respirations 40, more regular; pulse 100, regular. Four hours after injection the animal was sleepy; when roused it walked feebly; there was no further vomiting. Its condition remained unaltered as long as it was observed; and it died between eight and twenty hours after the injection.

On post mortem examination rigor mortis was well marked. The abdomen contained some yellow serum. The stomach contained no solid food, but about two ounces of a greyish turbid alkaline fluid.

Experiment III.—April 28.

Seven cub. centims. of a similar solution to that used in Experiments I. and II. were injected beneath the skin of a moderate-sized, well-nourished cat. In fifteen minutes the animal vomited for the first time, and this vomiting was repeated four times within the next hour and twenty minutes. During the rest of the day it remained quiet, without further vomiting, and with no paralysis or disturbance of muscular movements. It appeared to be quite comfortable.

On the following day it remained sitting in one position, and refused its food and milk. There was no vomiting, and no urination or defæcation. When disturbed, it would immediately return to its former position in a mechanical manner.

On the following day it passed a very small quantity of fæces; it was not observed to

urinate, and, as before, it neither ate nor drank any thing. It vomited once, very slightly.

From this time forwards, for a fortnight after the administration of the poison, the cat remained in this condition, neither eating nor drinking, although tempted to do so with milk and meat; and even when a live mouse was placed before it, it merely pricked up its ears, and looked eagerly at it, but did not touch it, nor did it pass urine or fæces once for the last eleven days.

It sat always in one position unless disturbed, and though it got steadily weaker, did not lose flesh in the way an animal starved would have done. The temperature on May 2nd was 38° C.

Five days after the poison was given a subcutaneous abscess formed over the right scapula and ribs. No other lesions were ascertained during life. The abscess did not form at the seat of puncture.

It died, apparently from exhaustion, fourteen days after the poison was administered.

Post mortem Examination.

Rigor mortis well marked.

Subcutaneous tissue contained a fair amount of fat.

There was a large, sloughy, subcutaneous abscess in the situation mentioned above, and another localized collection of pus a little higher up in the skin of the neck. No other superficial abscesses were found.

The muscles were pale and rather dry. There was general congestion throughout the body of the larger venous trunks, but apparently not of the smaller ones.

Abdomen.—The omentum contained rather a large quantity of fat.

The stomach was quite empty, pale and contracted.

The small intestine contained a small quantity of bile-stained mucus; it was otherwise empty.

The large intestine contained bile-stained mucus, and in its lower half a considerable quantity of fæces, also bile-stained. The mucous membrane appeared perfectly healthy.

The bladder contained only a few drops of high-coloured urine, but had not contracted at all firmly. It had the appearance of a bladder which has been dried when inflated, and the air then let out.

The kidneys were pale, although the renal vein was much distended.

The vagina and uterus contained a large quantity of a greenish smeary fluid, which, under the microscope, was seen to be muco-pus. The mucous membrane had, here and there, patches of injection on it (*vide infrà*); near the orifice of the vagina the secretion had quite the character of ordinary pus, but no abscess existed there.

The diaphragm was pale, flabby, and very transparent (*vide infrà*).

Thorax.—The lungs were congested, but otherwise natural.

The heart was very pale and flabby; all the cavities contained moderate quantities of blood.

Microscopical Examination.

Kidneys: epithelium not degenerated.

Heart: muscle-fibres very granular; in many places hardly a trace of transverse striation could be seen.

Voluntary muscles (rectus abdominis) also granular (well marked, but not quite so much as the heart).

Bladder: muscular coat not degenerated.

Intestines: muscular coat not degenerated.

Remarks on Experiments I.–III.

Experiments I. to III. show the effects of the poison on cats when administered in three decreasing doses.

It will be seen that, during life, the most prominent symptoms of a rapidly poisonous dose were in their order of constancy:—1, vomiting; 2, respiratory difficulty; 3, abnormal muscular movements.

After death the condition of the heart and great vessels and of the lungs are most noteworthy.

Vomiting.—This was a constant symptom in all the cats we experimented on, unless they were placed under special circumstances. The vomit consisted, first, of whatever food might be contained in the stomach, and then of a white frothy mucus. On no occasion did it ever have the appearance of intestinal (fæcal) vomiting.

In Experiment I. no actual vomiting occurred. In this case the stomach was found to be empty of food after death; and the absence of the symptoms in this case was doubtless due to the rapid paralysis caused by the very large dose administered.

Respiratory Difficulty.—This is a constant symptom, except when very small doses are administered.

On reference to Experiment I. it will be seen that at one time the respirations rose to 160 per minute. This, however, was exceptional. From 40 to 60 respiratory movements per minute is probably the average rate after administration of a moderately poisonous dose.

Abnormal Muscular Movements.—These are of two kinds; thus, immediately after the administration of any dose, large or small, there is very generally produced a peculiar twitching of the muscles of the limbs, especially of the hind legs. This is especially seen when the animal is walking.

When large, rapidly poisonous doses are administered, symptoms of general muscular paralysis and loss of coordination are developed *pari passu* with the dyspnœa and frequency of the vomiting. The animal rolls and staggers as it walks; its head falls on the ground; and, finally, it falls over on its side and is unable to stand. Death always occurs a very few minutes after the development of these last phenomena.

Appearance of the Heart post mortem.—As a rule, post mortem examination of the heart shows a moderately firm contraction of the ventricles, with a somewhat distended

condition of the auricles. The ventricles, however, were never found to be completely emptied of blood, and on one or two occasions the heart was found to be moderately distended, the left ventricle containing well arterialized blood.

On several occasions, but here also with one or two exceptions, a remarkable vitality of the auricles was noticed (Experiment I.).

The post mortem appearances of the heart and their physiological value will be noticed more particularly in the section which treats especially of the action of that organ.

The lungs were, in all cases in which they were noticed, found to be pale, except in Experiment III. (see Experiment XXXI.).

One of the most noteworthy phenomena is the action of a small dose upon a cat in causing an utter refusal to take either food or drink, and that, notwithstanding this total abstinence from nourishment, the animal should live such a long time, should show considerable muscular power (being able to jump from the floor upon a chair up to the day before its death), and should have still retained so much of its subcutaneous and omental fat. Another point to be noted is the occurrence of subcutaneous abscesses, none of which were near the point where the poison had been injected.

This long continuance of life and retention of strength seem to us to indicate that the processes of tissue change had been retarded by the poison; and the granular condition of the striated muscles appears to indicate a diminution especially in the processes of oxidation.

Action on Dogs.

Experiment IV.—May 9.

The effect of the poison on dogs was investigated in the same manner as it had already been on cats in Experiments I.–III. It will be seen that the results do not differ in any noteworthy point from those previously obtained.

Six cub. centims. of the solution were injected beneath the skin of a dog weighing 8 lbs. It vomited for the first time twenty minutes afterwards, and this vomiting continued at gradually increasing intervals of from 15 minutes to three quarters of an hour for the next four hours. At the end of that time the animal was very restless, and continued to be so while it was observed. On the following day its gait became staggering; and, finally, it lay flat on its belly, and died about thirty hours after the drug was administered.

GENERAL ACTION ON BIRDS.

Birds are affected very readily by the poison, and the symptoms produced in them are similar to those observed in mammals. This will be seen by the results of the following experiment.

Experiment V.

A full-grown pigeon had nearly 1 cub. centim. of the solution injected beneath the

wing. In ten minutes a quivering motion of the wings was noticed; in a quarter of an hour its feathers were puffed out, its gait was staggering; twenty-four minutes after injection it began to vomit. This was repeated four minutes afterwards more violently, and several times subsequently. Forty minutes after the injection it was unable to stand; and from that time to its death, one hour and thirty-five minutes after injection, it lay flat on the table, occasionally attempting to vomit unsuccessfully. For the last forty minutes its respirations were hardly visible, but it moved when roused. Violent expiratory movements came on just before the respiration finally ceased.

GENERAL ACTION ON FISHES AND FROGS.

In fishes and frogs there is but slight susceptibility to the poison, and the effects produced by it are similar in the two classes. The most obvious general symptoms are muscular paralysis and cessation of respiration, preceded by spasmodic movements. It will be seen later, however (Experiment XVIII.), that the particular action of the drug on the heart is well shown in frogs.

Experiment VI.—February 21.

One third of a cub. centim. of the solution was injected beneath the skin of a medium-sized frog. In two minutes slight tonic contraction of the limbs was observed; in four minutes it was jumping rather actively, but fell over on its back; in twelve minutes the respiratory movements had become almost imperceptible; and from this time the reflex movements of the limbs on irritation gradually got weaker and weaker, and finally ceased thirty-three minutes after the injection.

After death, the ventricle was found firmly contracted, the auricles and venous trunks engorged.

Experiment VII.—February 21.

Experiment VI. was repeated with double the dose. The frog was slightly larger than the one first used; but reflex action ceased within a few seconds of the same time after injection. The general effects were almost the same as in Experiment VI., save that five minutes before reflex movements ceased there were four spasmodic inspirations.

Experiment VIII.—April 18.

The effect on fishes was tried. First, 55 cub. centims. of a $\frac{1}{300}$ watery solution of casca were added to 3 litres of water in which a gold-fish weighing 3 ounces was swimming. At the end of three hours no effect was produced on the fish. 1·3 cub. centim. of the alcoholic solution were then injected into the side of the fish, a little in front of the tail. In five minutes it began to roll from side to side; the respirations were catching. For the next ten minutes it lay chiefly on its side, occasionally swimming about actively.

At the end of twenty-five minutes from the time of injection it appeared to have nearly recovered itself, and 1 cub. centim. more of the alcoholic solution was injected.

In three minutes from this time it lay completely over on its side, having spasmodic twitchings of its fins; in five minutes the respirations again became rapid and gasping; in ten minutes the reflex movements were very weak, but respiration and reflex action did not entirely cease before thirty minutes after the second injection.

GENERAL ACTION ON INVERTEBRATA.

The following experiments (Nos. IX. and X.) show that the drug exerts very little, if any, poisonous action on the Invertebrata.

Experiment IX.

A leech was placed in a watery solution of casca nearly as strong as could be made with cold water. At the end of two hours and a half it seemed but little affected, but was found dead on the following morning.

Experiment X.

Nearly 5 cub. centims. of a concentrated alcoholic solution of casca were injected beneath the back of a common snail. The animal showed no signs of poisoning, and on the following morning appeared to be uninjured.

ACTION ON INFUSORIA.

Experiment XI.

In Experiment XI. we investigated its action on Infusoria by placing a drop of tank-water containing some infusorians under the microscope, and adding a drop of a $\frac{1}{300}$ solution of the watery extract of casca. At the end of two hours no alteration in the movements of the animalcules was observed; and it may therefore be concluded that the drug exerted little or no action on them.

The action of the drug on germination and oxidation processes, and on different ferments and ferment organisms, was investigated in Experiments XII.–XX.

On germination the casca infusion was found to exert no effect.

Experiment XII.

A few mustard seeds were placed on flannel in two saucers, and kept moist in a warm place, the one with an infusion of casca, the other with water. The seeds began to germinate at the same time in each, and no difference was observed in the growth of the shoots for three days afterwards.

Effect on the Development of Bacteria.

Experiment XIII.

This experiment, which was repeated on two other occasions, shows that a weak solution of the alcoholic extract possesses the power of hindering the formation of *Bacteria*,

a property not shown by the watery extract, as is shown in Experiment XIV. This difference in the properties of the two extracts does not show itself in the general action of the drug on animals; but the power of the alcoholic extract to prevent the development of *Bacteria*, while it is without action on them after their development, is interesting, as substantiating the results of BUCHHOLZ's experiments on this subject with other drugs*.

Three pieces of fresh muscular tissue were placed in bottles on March 22nd. The first contained a watery solution of the alcoholic extract of casca, the second a $\frac{1}{200}$ solution of sulphate of quinia, and the third distilled water. On March the 29th the bottles were opened; and while the bottle containing water was very offensive, and the water was crowded with *Bacteria*, neither the quinine nor casca solutions contained any *Bacteria* at all.

The bottle containing the casca solution was again examined on May 14th, and was found, as before, quite free from *Bacteria*. Long before this a thick crust of *Penicillium* had formed on its surface.

Experiment XIV.

A piece of fresh cat's liver was placed in a solution of casca of the same strength as that used in the preceding experiment; but the watery extract was used instead of the alcoholic. At the end of two days the liquid was found to be crowded with *Bacteria*.

This experiment was afterwards repeated with muscular and other tissues with the same result.

Effect on the Life of Bacteria.

The effect of the drug on the life of *Bacteria*, when developed, was tried in Experiment No. XV. For this purpose an infusion of hay was made, and found to contain many rod-shaped *Bacteria*. To a drop of this infusion a drop of a $\frac{1}{20}$ solution of both the alcoholic and the watery extracts of casca was added at different times, and the movements of the Bacterians carefully watched under the microscope. They did not, however, seem in any way affected by the addition.

For the sake of comparison a $\frac{1}{100}$ solution of quinia sulphate was added to the hay-infusion. The Bacterian movements were found to be instantly stopped.

Effect on Red and White Blood-corpuscles.

In Experiment XVI. the action on the red and colourless blood-corpuscles of the newt was investigated. The effects produced by the addition of dilute solution of casca to the blood were cessation of amœboid movements and rounding of the white corpuscles, with an irregular shrinking of the nucleus, and general crenation of the red ones. These effects were probably due to the action of the tannic acid contained in the extract.

* Archiv f. exper. Pathologie u. Pharmakologie, iv. p. 1.

Effect on Ciliary Motion.

The drug appears to have no action on ciliary motion; for when (Experiment XVII.) two preparations of ciliated epithelium were made, the one being placed in ·75 per cent. salt solution, and the other in a $\frac{1}{300}$ solution of casca extract, it was found on microscopic examination that the movements of the cilia ceased in about the same time in both specimens.

Effect on Processes of Oxidation.

It, however, does appear to exercise an inhibitory action on oxidation processes generally. This point was investigated in the following manner:—

Experiment XVIII.—April 20.

Four thin slices of potato were placed in two saucers, and were just covered, the one with distilled water, the other with a $\frac{1}{300}$ watery solution of casca. When a drop or two of the tincture of guaiacum was added, either to the liquid or to the potato slices, the bluing produced was much fainter in the case of the saucer containing the casca than in that containing distilled water. The results of the experiment on organized and unorganized ferments were negative, neither the development of the yeast-plant (Experiment XIX.) nor the digestion of fibrin by pepsin (Experiment XX.) appearing to be in the least degree hindered by the addition of the drug.

Action on the Digestive System.

One of the most prominent symptoms of poisoning by casca is the violent vomiting which it produces; and, as has already been noticed, its occasional purgative action is used as a test of innocence or guilt. The emetic or purgative action is supposed by some to depend on the administration of a pure infusion, or of one containing the drugs in suspension, and innocence or guilt are thus supposed to be practically decided by the priests, who have it in their power to administer either one or other to the accused.

In order to test this, an infusion was given to one cat, B (Experiment XXI.), and an infusion containing a quantity of powder to another. The latter, however, contrary to expectation, recovered, whereas the former died. The experiment, however, was vitiated by the fact that the infusion was made from the finely pulverized bark, the only kind we had at our disposal at the time, and consequently contained a quantity of it in suspension, which would not have been the case if the infusion had been made from a coarsely pounded bark.

In order to ascertain whether the vomiting and purging were due to the local action of the drug on the stomach and intestines, or to its action on the nervous system after its absorption into the blood, a comparison was made between the effects of the poison when introduced into the stomach and when injected under the skin. Our experiments show that whereas vomiting was invariably produced by the casca, in whatever manner introduced into the system, purging only occurred when the poison was given by the

mouth, and was never observed after subcutaneous injection. The purgative action is therefore due to the local action of the drug on the intestines.

The following is a brief account of two experiments we made in investigating the action of the drug when injected into the stomach.

Experiment XXI. A.—May 10.

10 cub. centims. of an infusion of the watery extract of the bark, with the dregs which were deposited when the infusion cooled, were injected into the stomach of a large cat. It appeared quite well for forty minutes, and then vomited. Within the next two hours and a half it vomited five times. A little more than five hours after the exhibition of the drug it passed some solid fæces with great forcing, and from that time recovered.

Experiment XXI. B.—May 10.

10½ cub. centims. of a cold aqueous infusion of the pounded bark, containing numerous fine particles in suspension, were injected into the stomach of a small ill-nourished cat. Vomiting came on thirty-five minutes afterwards, and free purging an hour and a half after the injection. During the rest of that day and on the next it was very feeble, but showed no special symptoms, and it died quietly on the morning of May 12.

Comparative Action of the Alcoholic and Watery Extracts.

The action of the alcoholic and watery extracts of casca, when administered subcutaneously to cats in large doses, is almost identical; and their activity as poisons appears to be about equal, the watery extract, if any thing, being rather the more powerful.

Experiment XXII.—April 28.

Two equal quantities of the alcoholic and watery extracts were dissolved in equal volumes of alcohol and water respectively. The quantities were 3 grammes of the extracts and 4 cub. centims. of the fluids. These solutions were injected beneath the skin of two cats of the same size. In the case of the alcoholic extract vomiting came on fifteen minutes after injection, with the other symptoms of poisoning by the drug (*i. e.* respiratory difficulty and staggering gait). The vomiting was repeated violently, and the animal died one hour and fifteen minutes after injection, death being preceded by general convulsions.

In the case of the watery extract vomiting did not come on for thirty-five minutes, but death occurred, with symptoms similar to those of the former case, in one hour after the injection.

In order to ascertain whether the vomiting was due to the action of the drug upon the sensory nerves in the stomach itself, after it had been conveyed to that organ by the circulation, or to its action upon the nervous centre in the medulla oblongata regulating the movements of vomiting, the vagi were cut, and the chief sensory nerves

of the stomach thus divided, before administering the poison. By this procedure the retching and vomiting were either completely prevented or very greatly diminished, the dyspnœa rendering it rather difficult to decide in some cases whether some convulsive movements were due to it or were movements of retching. The vomiting is therefore chiefly, and in all probability entirely, due to the action of the drug on the sensory nerves of the stomach itself, as the retching, if indeed really present, might be due to irritation conveyed to the medulla through the splanchnics after the vagi had been divided.

Experiment XXIII.—March 6.

General Symptoms after Injection, both Vagi having been previously divided.

A cat weighing 3 lb. was chloroformed, and the vagi divided in the neck. In 25 minutes after the operation it had recovered from the effects of the anæsthetic. Its respirations were 18 per minute. Three cub. centims. of a concentrated alcoholic solution of alcoholic extract of casca were injected subcutaneously. Five minutes afterwards the cat had fallen over on its side. The respirations were still regular, 16 per minute. During the next hour, with one temporary disturbance, the animal remained quiet, still breathing quietly and slowly, with no symptoms of sickness and no dyspnœa. It remained on its side the whole time, except when roused. It then staggered a few steps, and again lay down. One hour after the first injection $2\frac{1}{2}$ cub. centims. more were injected. For the next quarter of an hour the animal continued to breathe easily, but appeared weaker. At the end of that time there were some very slight convulsive movements, and then respiration ceased. On beginning artificial respiration one or two gasping inspirations occurred, and then entirely ceased one hour and fifteen minutes after the first injection. On post mortem examination the heart's cavities were found distended. They did not contract on irritation or puncture. The lungs were bright scarlet, and contained a moderate amount of blood. The liver and kidneys were congested; the stomach was pale; the brain was normal.

Experiment XXIV.—April 28.

This experiment was in most points an exact repetition of Experiment XXIII., but the results were even more striking. A well-nourished cat was chloroformed, and both vagi were divided in the neck. When it had recovered from the chloroform a solution of ·3 grm. of the alcoholic extract in 4 cub. centims. of alcohol was injected subcutaneously. None of the ordinary symptoms of poisoning by the drug were produced. There was no dyspnœa and no vomiting, except at one time, an hour and fifteen minutes after the injection, when the animal either coughed or vomited up a small quantity of frothy mucus. When seen the next morning it was to all appearance well, and was killed, to prevent suffering being caused by the secondary effects of section of the vagi, which were found to be completely divided.

Experiment XXV.—May 17.

This experiment was similar to Nos. XXIII. and XXIV. As before, no vomiting was produced by injection of the drug after section of the vagi, but death occurred one hour and ten minutes after the injection, in consequence of dyspnœa occasioned by the section of these nerves.

Action of Casca on Respiration.

Powdered casca, when inhaled, acts as a violent sternutatory. All the men employed by us in grinding or pounding the bark suffered severely from the violent and irresistible fits of sneezing which attacked them; and in one instance these were accompanied by great faintness and tendency to syncope.

When injected into the circulation casca greatly accelerates the respirations (Experiments I., II., XXXIV.).

This acceleration appears to be due to stimulation of the pulmonary branches of the vagus, and not to any action of the drug upon the respiratory centre, as no acceleration is noticed when the vagi are divided before the injection of the casca (Experiments XXIII. and XXIV.).

Action on the Intestines.

Experiment XXVI.

In order to ascertain whether the intestinal secretion was increased by casca, a cat was chloroformed, the abdomen opened, and three loops of small intestine ligatured. Into the middle loop 2 cub. centims. of a concentrated solution of the watery extract of casca were injected, and 2 cub. centims. of water into the other two. The cat vomited about an hour afterwards. At the end of about 5 hours, the animal was killed and the body examined. The upper and middle loops were both dry, and the mucous membrane was normal in appearance, except slight congestion at the place of ligature between the upper and middle loop. The lower loop contained several cubic centims. of turbid greyish fluid.

The intestinal secretion is thus seen not to be increased by the drug.

Action of Casca on Circulation.

Experiment XXVII.

Preliminary Experiments on Frog's Heart.

A watery solution of the alcoholic extract and a standard salt solution were prepared; the hearts of two frogs of about the same size were then removed, and placed for a minute or two in ·75 per cent. salt solution. When they had recovered from the shock of removal, and were beating regularly, one was placed in the casca solution, the other in the salt one. At the commencement of the experiment the heart, A, placed in salt solution was beating at the rate of 6 per 10 seconds; the heart, B, in casca at the rate of 75. Both hearts became weaker and their pulsations slower; at the end of 50

minutes the heart in casca stopped entirely, that in salt solution pulsated feebly at the rate of 3 per 10 seconds. In 15 seconds more it stopped.

In Experiment XXVIII. we repeated the foregoing experiment with a much stronger casca solution. The hearts at the commencement of the experiment were beating at the rate of 4 per 10 seconds. At the end of 30 minutes the heart, B, in casca, which had previously got very slow and weak, stopped, while the standard heart, A, was still beating strongly and regularly at the rate of 4 per 10 seconds.

Experiment XXIX.—March 7.

The heart of a frog whose cerebrum had been destroyed was exposed. Pulse 72 before injection.

h m
11 40. Injected 2 cub. centims. alcoholic solution beneath skin of back.
11 50. Pulse 60; regular.
12 2. Pulse 48.
12 10. Pulse 60. Clonic convulsions.
12 15. Ventricle stopped in systole, firmly contracted in its greater part, with a pouch-like dilatation of a small portion. Auricles still contracting.
12 27. Ventricle firmly contracted. Still partial contraction of auricles. Respiration and slight convulsive movements continue.
12 50. Removed from frog-board. The ventricle is not so firmly contracted. Still respiring and occasionally convulsed.
1 0 P.M. Ventricle relaxed. Slight movements of it have recommenced. 1·4 cubic centim. alcoholic solution again injected.
1 7. Ventricle again firmly contracted. No respiration. Still slight reflex movement.
1 30. Died with heart in same condition.

Experiment XXX.—May 10.

The heart of a frog was exposed, and a little extract of casca placed on it. Pulse 34 per minute.

It had no apparent action.

A watery solution of casca was then poured into the thorax. The pulse became slower, =24 per minute.

The ventricle then expanded irregularly; the diastole at the base being later than that at the apex.

Then the distention became imperfect, the ventricle seeming wrinkled.

The heart then stopped in systole, having two pin-point dilated pouches on it.

These experiments show that a very weak solution of casca applied to a frog's heart, when removed from the body, slows its pulsations, while, after the application of a stronger solution, the pulsations become slow, then the systolic contraction ceases to take place instantaneously over the whole surface of the ventricle; lastly the heart stands still in systole.

When the heart of a frog is exposed, but not removed from the body, and a solution of casca is injected beneath the skin, the heart's action is slowed, and is eventually stopped in systole; previous to its stopping, however, pouch-like dilatations are formed; in this respect the action of casca is similar to that of digitalis and other cardiac poisons.

Experiment XXXI.—April 27.

A cat was chloroformed; a cannula placed in the left jugular vein and one in the trachea. Artificial respiration was commenced, and the thorax was opened. The heart was beating regularly, but it was difficult to count the pulsations. They were counted by one person as 90, by another as 180.

10 cub. centims. of a saturated watery solution of watery extract of casca were injected into the jugular vein. No apparent effect was produced.

7 cub. centims. more were injected in the course of a few minutes. Within about a minute of the last injection the ventricle no longer contracted as a whole, but became pouched, the upper half seeming to overlap the under half so as to produce a transverse fold.

A few seconds afterwards, the lungs, which had hitherto been rosy, became white, and almost immediately the motions of all cavities of the heart completely ceased. On irritation of the ventricle no movement occurred.

Both vagi were divided, but without effect on the heart.

It was noticed that the rosy colour of the lungs returned, although the heart did not again beat. No pulsations were noticed in the pulmonary vessels. The heart was perfectly firm, and seemed to be in systole; but on tying a ligature round the base so as to include the large vessels, it contracted to about one third of its former size.

The action of casca on the mammalian heart is seen from this experiment to be similar to its action on the heart of the frog.

Experiment XXXII.

Action on Blood-pressure in the Frog.

The cerebrum of a large frog was destroyed. A cannula was then inserted into the left aorta, and was connected with a small kymograph, the pulse-wave and oscillation being recorded on a revolving drum.

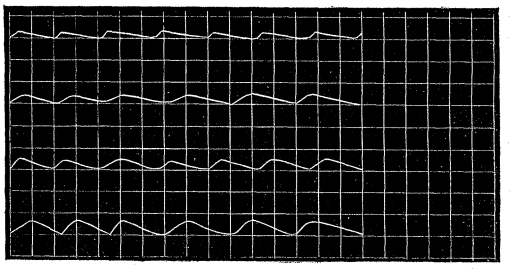
The appended curves give the oscillations of pressure in the aorta, and show that under the influence of casca the blood-pressure in the aorta rises to twice its normal height during systole, although it falls to zero during diastole.

Normal pulse (10 millims.) .....

Pulse three minutes after injection of 1 cub. centim. of a $\frac{1}{300}$ solution of casca into flank .....

Pulse one minute after a second injection of 1 cub. centim.

Pulse three minutes later .....



Experiment XXXIII.—March 31.

Action on the heart and blood-pressure of a large dose of casca. (For action on secretion of urine also, *vide infrà*.)

A bitch, weight 26½ lb., was chloroformed.

A cannula was placed in the trachea.

" " left femoral vein.

" " right ureter.

" " left carotid artery.

The operation was very long, and during it the intestines became much congested.

Time.		Respiration.	Amount of Urine secreted per 10 minutes.	Blood-pressure.	Oscillations.	Pulse.
h. m. s.			minims.			
1 54 57	Normal condition before experiments	....	5	120	10	20
	The rate of secretion of urine was estimated at two successive periods of 10 minutes each.					
2 7 40	4 cub. centims. casca solution $\frac{1}{300}$ injected into femoral vein.					
0 8 10 / 0 10 30	Showing the ordinary effect of the injection of a small quantity	....	....	140	10	20
0 17 40	Urine increased in quantity, alkaline, turbid, not albuminous	....	7	140	10	20
2 27 40	Urine still further increased	....	24	145	10	20
	Is clear; not albuminous.					
2 34 30 / 2 34 40	5 cub. centims. more injected.					
2 35 40	Showing effect of further injection	....	....	160	15	20
2 47 40	Urine secreted, clear as before	....	17	160	15	20
	Clot formed. Lost about 15 cub. centims. of blood.					
2 57 40	Urine as above	....	17	140	25	20
	With the increased dose the pulse-oscillations have begun to be affected as well as the blood-pressure.					
3 0 10	10 cub. centims. more injected.					
3 0 30	Showing the immediate effect of a large dose. The systole and diastole are nearly equal; there is a very powerful action of the heart and increased blood-pressure	....	....	165	40 / 90	10
3 2 40	Showing the later effects of a large dose. The oscillations of the pulse are less, while the blood-pressure is greatly increased. The secretion of urine is much diminished	....	3	200	15 / 20	20
3 7 40	Secretion of urine stopped	....	....	180	10 / 20	16
3 17 40	Urine has again commenced to be secreted, the blood-pressure having fallen somewhat	....	5	150	30	15
3 27 40	Urine secretion again increased	....	13	110	50	12½
3 37 40	.....	....	9	115	30	16
3 37 50	Further injection of 15 cub. centims.					
3 38 10	The blood-pressure is now much affected by the respiration after the injection of a large dose	5	....	150 / 160 / 140	4	30
3 40 0	This is still more marked	5	....	170 / 190 / 150	2	40
3 42 0	The blood-pressure gradually fell, and the pulse was too feeble to write on the kymograph, while there was still a rise of blood-pressure synchronously with the respirations, which stopped at 3 h. 43 min.					

The thorax was then opened, and the heart found beating; respiratory movements recommenced on opening the thorax.

The bladder was found greatly distended; there had been micturition during the experiment, which was probably only overflow.

Remarks.

We append a diagram (p. 652) showing the coincident variations of blood-pressure and secretion of urine, which will be more fully commented on later. (*Vide* effect on urinary secretion.)

So far as the phenomena of correlation are concerned, this experiment shows that while a small dose of casca slows the pulse, an additional one greatly quickens it. This action of casca closely resembles the effect of digitalis, which first slows the pulse by stimulating the vagus-roots, and then quickens it by paralyzing the ends of the vagus in the heart. It therefore seemed probable that the cardiac ends of the vagus would be found to be paralyzed by large doses of casca.

It was possible that the primary slowing of the heart's action might be due to stimulation of the inhibitory apparatus in the heart itself, and not to the action of the drug on the vagus-roots. Two questions, therefore, were to be settled:—

1st. Is the primary slowing of the pulse due to stimulation of the vagus-roots, or to stimulation of the inhibitory apparatus in the heart?

2nd. Is the secondary acceleration of the pulse due to paralysis of the ends of the vagus in the heart?

To answer these questions the following experiment was performed.

Experiment XXXIV.—March 21.

Action on the Heart and Arterial Pressure of a small dose of Casca.

A dog weighing 8 lb. was chloroformed, and kept under chloroform during the experiment.

A cannula was inserted into the right carotid and into the right femoral vein.

Time.		Blood-pressure.	Pulse in 10 seconds.	Oscillations.	Respiration.
m. s.		millims.		millims.	
	Condition before injection	110	18½	10	
0 55	7 cub. centims. $\frac{1}{300}$ watery solution injected into femoral vein	125	16½	10	
1 0		130	16	10	
1 10	Rise of blood-pressure. Commenced prolongation of diastole	155	14	10	
1 20					
1 45	Systole fairly sharp, diastole very long	140	5	40	
	Commencing fall of blood-pressure.				
2 5	Great fall of blood-pressure and lengthening of diastole.	65	⅓	25	
2 20	Diastole extends over 15 seconds.				
	Systole extends over ½ second; does not vary with respiration.				

TABLE (continued).

Time.		Blood-pressure.	Pulse in 10 seconds.	Oscillations.	Respiration.
m. s.		millims.		millims.	
2 40 to 3 0	Blood-pressure again lower. Diastole further prolonged ..... Diastole 20 seconds. Systole $\frac{1}{3}$ second. Diastolic curve slightly affected by respiration.	45	$\frac{1}{2}$	30	5
3 40 to 3 50	Blood-pressure recovering. Diastole shorter ..... Diastole 5 seconds. Systole $\frac{1}{2}$ second. Respirations affect diastolic curve to extent of 3 millims.	50	2	25	9
4 0 to 4 10	Blood-pressure rising..... Systole and diastole nearly equal. Both affected by respiration to extent of 4 millims.	100	4	35	10
4 20 to 4 30	Blood-pressure nearly at the height of commencement of experiments. Systole sharp	130	5	35	
4 40 to 4 50	Blood-pressure higher. Diastole again prolonged .. Diastole 4 seconds. Systole $\frac{1}{2}$ second. Respirations affect curves to extent of 10 millims.	140	$2\frac{1}{2}$	60	10
5 20 to 5 30	There was again a fall of blood-pressure with great prolongation of diastole similar to that which occurred at 2.5 to 2.20, but less marked	115	1	50	9
6 0 to 6 10	Do., more marked	80	1	30	4
6 20 to 7 30	Gradual fall of blood-pressure. Cessation of heart's action.				

Post mortem (immediately after death).—The heart contained blood, and contracted on puncture. The auricles contracted for three minutes after death.

This experiment shows that the action of a small dose of casca is to raise the blood-pressure and slow the heart at first. Next, when the heart becomes very slow, the pressure falls, and finally the heart ceases to beat and death takes place.

The cardiac pulsations remained slow from the time of the injection of the casca up till death; and although they at one time rose from 1 pulsation in 30 seconds up to 5 pulsations in 10 seconds, they never came at all near to the normal, which in this animal was $18\frac{1}{2}$ pulsations in 10 seconds.

The very slow pulse here indicates that the vagus is probably stimulated by the casca; and the continuance of the blood-pressure at the height of 65 millims., during a cardiac diastole, lasting for 30 seconds, shows unmistakably that the arterioles are strongly contracted by the drug.

ACTION ON VAGUS.

Maximum Irritation.

Experiment XXXV.—March 4.

A cat, weight 4 lb., was chloroformed, and a cannula was placed in the left carotid artery and in the left femoral vein.

Time.		Blood-pressure.	Oscillations.	Pulse in 10 sec.
m. s.		millims.	millims.	
1 0	Normal curve taken 1 minute after connexion of cannula. Oscillation at top of respiratory curve =9, at bottom 2	80	2 / 9	23
2 15	R. vagus ligatured and cut.			
2 18	L. vagus do. do.			
	Condition after section of vagi	100 / 110	2	40
4 40	L. vagus irritated. Coil 5°*	60	18	15
	R. vagus irritated. do.	55	12	12
8 10	Condition subsequent to irritation	110	1	42
	It was thus ascertained that irritation of the strength of coil 5° was almost sufficient to stop the heart's action when applied to the peripheral end of either vagus previous to injection of casca.			
8 10 / 9 12	3½ cub. centims. of casca solution injected gradually into vein.			
10 0	Condition after injection	120	2	40
11 0	A clot formed.			
12 0	Condition after clot was removed	115	4	43
	(Slight improvement of pulse.)			
12 35	Peripheral end of L. vagus irritated. Coil 5°	90	8	35
13 0	Peripheral end of R. vagus irritated. Coil 5°	95	8	35
	Condition between irritations	120	2	35
14 27	Left vagus. Coil 0°	88	5	27
	Right vagus. do.	110	0	0
	Complete stoppage of heart's action without fall of blood-pressure.			
15 20	Experiment repeated with R. vagus. Coil 0°	85	5	26
17 10 / 17 44	Fresh injection of 4 cub. centims.			
18 30	Condition after injection	115	2	40
19 5	Right vagus. Coil 0°. Commencement of irritation	100	3	30
	Latter part „	118	2	36
19 30	Left vagus. do. Commencement „	104	4	30
	Latter part „	120	2	35
20 0	Left vagus. do. Commencement „	121	2	35
	Latter part „	150	2	35
20 30	Condition after irritation	120	2	40
22 0 / 22 25	A third injection of 2 cub. centims. was given.			
24 25	And the central ends of the vagi exposed for irritation.			
24 30	Condition before irritation	120	2	40
25 12	Central end of left vagus irritated. Coil 0°	130	1?	30
	(Blood-pressure increased; pulse nearly extinguished.)			
25 50	Condition after irritation	125	2	34
26 30	Right vagus. Coil 0°	130	1	34
	(Effect as before.)			
27 0	Condition after irritation	120	2	36
28 16	The sciatic nerve was exposed and irritated with coil 5°	135	2	37
28 45	Condition after irritation	120	2	36

This experiment shows that when both vagi are divided the injection of a small dose of casca no longer slows the heart; and therefore the slowing usually observed after

* The mark ° here signifies distance in centimetres between primary and secondary coils in Du Bois Reymond's induction-apparatus.

its administration is due to stimulation of the vagus-roots and not to stimulation of the inhibitory apparatus in the heart itself.

It also shows that a large dose completely paralyzes the ends of the vagus in the heart, so that a strong interrupted current applied to the trunk of the nerve produces no slowing of the cardiac pulsations.

Action of a small dose on the excitability of the Vagus.

As it has been stated that digitalis in small doses increases the excitability of the ends of the vagus in the heart, so that a slight irritation applied to the trunk of the nerve will cause slowing or stoppage of the heart after the administration of the drug, although previously it had no effect, it seemed advisable to ascertain whether or not a similar action was possessed by casca. The following experiment was therefore tried:—

Minimum Irritation of Vagus (peripheral end).

Experiment XXXVI.—April 6.

A cat, weight 6 lb., was chloroformed, and kept under chloroform the whole time of the experiment.

A cannula was inserted into the right carotid artery and into the right femoral vein.

Both vagi were then cut, and the peripheral end of the right vagus attached to Von Basch's electrodes.

Operation lasted half an hour; the cat at first very feeble, afterwards recovered.

Time.		Blood-pressure.	Oscillations.	Pulse.
m. s.		millims.	millims.	
1 50	Condition previous to irritation, both vagi being cut..	120	1–2	40
2 0	Right vagus irritated. Coil 30°. No effect	120 / 125	1–2	42
3 20	Right vagus irritated. Coil 25°. This irritation was sufficient to slow the heart and lower blood-pressure	100	5	20
5 0	Condition previous to injection	155	2	44
	As the cat was stronger, the normal minimum irritability was again tried, and coil 25° was again found to be the weakest which produced any effect.			
6 0 / 6 30	1½ cub. centim. casca solution, as in Experiment XXXIV., injected into femoral vein.			
7 0	Condition after injection	175	2	42
7 30	Vagus irritated. Coil 30°. No effect	175	2	40
8 0	Vagus irritated. Coil 25°. No effect	180	2	42

From this experiment it appears that the excitability of the peripheral terminations of the vagus-nerve is not increased by casca.

Action on the Vagus-roots.

The slowness of the pulse which quickly follows the injection of casca, and which we have already shown to be due to stimulation of the vagus-roots, might be caused either (*a*) by stimulation of the central end of the vagus by increased blood-pressure in the

nerve-centres, or (*b*) stimulation by the direct action of the drug itself; (*c*) it was also possible that without actually irritating the vagus-roots the casca might increase their sensibility to other stimuli, reflex or otherwise.

Effect on minimum excitability of the Vagus-roots.

Experiment XXXVII.—March 30.

A cat, weight 4 lb., was chloroformed.

A cannula was inserted into the trachea.

,, ,, left carotid.

,, ,, left saphena vein.

The right vagus nerve was cut, and its central end placed in a VON BASCH'S electrode. The left vagus remained intact. A $\frac{1}{300}$ solution of the watery extract was used.

Time.		Respirations in 10 sec.	Blood-pressure.	Oscillations.	Pulse in 10 sec.
m. s.			millims.	millims.	
0	Condition before experiment	4	105	1–2	38
1 0 to 2 30	The normal excitability of the central end of the right vagus was then tested; it was found that coil 10° produced slight slowing of the pulse and fall of blood-pressure, while the respirations became slower and deeper. This was the slightest irritation which produced any effect	2	100	3	30
3 30	Condition after irritation	2	110	1–2	34
4 0	·5 cub. centim. injected.				
4 30	Condition after injection. Rise of blood-pressure. No alteration of pulse. Respirations quickened and respiratory oscillations increased.	3	140	1	34
5 0	Central end of right vagus irritated. Coil 15°. No effect.	3½	140	1	34
6 0	Central end of right vagus irritated. Coil 10°. Same effect as before injection.	2¼	135	1	38
7 0	Second injection of 1½ cub. centim.				
8 0	Clot formed and removed.				
9 0	Condition before irritation	3	120	2	43
9 30	Irritation with coil 10°. The thorax remained in a state of permanent inspiration during irritation, while the effect on the heart and blood-pressure was *nil*.	0	120	2	40
10 0 to 10 5	Irritation with coil 6°. No effect on heart. Respiration as before.	0	115	2	40
10 8	Condition immediately following irritation. Slowing of pulse. Great fall of blood-pressure. Great oscillation. Systole and diastole of same length, with no pause between them.	3	60	28	12
15 0 to 15 30	Irritation with coil 8°. As before there was no effect on the blood-pressure or pulse, and there was permanent inspiration during the irritation.	0	120	2	40
15 35	Condition immediately after irritation. See remarks on after effect of coil 6°	4	30	15	16 irreg.
16 0	Gradual cessation of after effect	2	100	7	22
16 30	After effect ceased	0½	120	2	35
17 0	Coil 8°. Irritation repeated with same results.				

In this experiment, as well as in several others, the blood-pressure rose without being accompanied by a slowing of the pulse, and this indicates that the latter is not dependent on the former.

The excitability of the vagus-roots to reflex stimuli does not seem to be increased by casca, as a stimulus of the same strength applied to the central end of one vagus had a similar effect before and after the injection of the drug. We would call attention, however, to the very extraordinary effect which succeeded the application of a stronger stimulus, an effect which seems all the more extraordinary from occurring after the stimulus had ceased, and not during its application.

Irritation of the vagus-roots by the carbonic acid accumulated in the blood during the tetanic inspiration, which lasted during the irritation, at once suggests itself as a cause of the slow pulse which followed the irritation; but the fact that the pulse was not affected when the distance of the coil was 10 centimetres, although the thorax was tetanically expanded, seems to indicate that the slowing which followed the stronger irritation from a secondary coil at 8 or 6 centimetres distance from the primary was due to reflex action, which the first irritation had been too weak to produce.

From Experiment XXXV. it will be seen that after the administration of a large dose of casca, irritation of the vagi, instead of producing slowing or stoppage of the heart's action increased the frequency of its pulsations. The acceleration was equally great after irritation of the left, as after irritation of the right vagus. This shows that the accelerator-fibres in the vagus are not paralyzed by casca, and also that accelerator-fibres, though usually, according to BOEHM, contained only in the right vagus, may occasionally be present in the left.

The effect of irritating the other accelerating nerves of the heart contained in the rami cardiaci or in the sympathetic cord was not examined.

ACTION ON CARDIAC GANGLIA, EFFECT ON PULSE, ETC.

Experiment XXXVIII.—June 10.

A moderate-sized cat was chloroformed, and cannulæ were placed in the carotid artery and jugular vein.

A solution of 3 cub. centims. of saturated alcoholic tincture added to 50 cub. centims. of water was used for injection into the vein.

Time.		Blood-pressure.	Oscillations.	Pulse in 10 sec.
m. s.		millims.	millims.	
0 5	Condition before injection	160	25	23
1 20	Injected 1 cub. centim. casca solution.			
1 30	Condition shortly after injection	180	50	14
	Rise of blood-pressure, slowing of pulse.			
2 0	Later, quickening of pulse	165	7	26
3 0	Same effect, more marked	175	5	36
4 0	Commencing slowing of pulse	170	6	30
4 30	,, ,, ,,	140	8	30
5 0	,, ,, ,,	150	14	24
5 5	Further injection of 1 cub. centim. casca.			
5 40	Secondary slowing of pulse with *fall* of blood-pressure.	115	25	16

From this experiment it is seen that after the primary slowing due to stimulation of the vagus-roots and the quickening due to paralysis of the vagus ends in the heart, a second slowing occurs.

This second slowing might be due either to stimulation of the inhibitory apparatus in the heart or to weakening of the cardiac motor ganglia.

The latter seems improbable, from the fact that each systole during this slow period instead of being weak is exceedingly strong, the pulsation in an artery being felt very powerfully when the finger is laid upon it, and the rise of pressure during it being very great, as shown by the oscillation of the mercurial column of the manometer.

In order to ascertain more exactly whether the inhibitory cardiac ganglia were stimulated or not the following experiment was tried.

Experiment XXXIX.

A dog was chloroformed and 7 cub. centims. of a concentrated watery solution of casca were injected into the jugular vein.

The pulse at the time of injection was 37 in ten seconds. In ten seconds after the injection it sank to 20. After the injection of 3 cub. centims. more the pulse rose to 37. After a further injection of 26 cub. centims. more in divided doses it again sank to 16.

This number was, however, uncertain, as the tracing was a very imperfect one.

The injection of 1 cub. centim. of liquor atropiæ, B. P., did not seem to alter the number of the pulse, but the injection of $\frac{1}{2}$ a cub. centim. more seemed to cause it again to become quick.

This seems to indicate that the slowing is due to an action of the casca on the inhibitory ganglia. The imperfection of the tracing renders the result somewhat uncertain; but want of time prohibited us from repeating the experiment, although we greatly desired to do so.

Experiments XL., XLI.—March 15.

The effects on the capillaries of the frog's web were microscopically observed in Experiment XL. after an injection of casca under the skin of the back, in Experiment XLI. when locally applied to the web.

The capillaries were observed with oc. 2 obj. 4 of HARTNACK. In the first case, *i. e.* after the drug had been injected, the results were purely negative. In the second, after application of a drop of strong casca solution to the web, the results were also indecisive. In the capillaries and also in the larger trunks the current was at first slowed, and in some permanent stasis occurred. When slowing only was produced, the partial arrest was followed by reaction, which did not exceed the original rapidity of the circulation. No dilatation or contraction of the vessels was seen to accompany the original slowing.

Although the results of experiments on the frog's web gave no definite information regarding the contraction of the arterioles under the influence of casca, yet no reasonable doubt can be entertained that in mammals they do contract; for this is the only possible explanation of the exceedingly slow fall of the blood-pressure during the intervals

between the beats of the heart when these have become slow, either from the action of the drug or from irritation of the vagus-trunk.

In order to ascertain whether this contraction was due to the action of the drug upon the vasomotor centre in the medulla oblongata or in the vessels themselves, the vasomotor centre in the medulla was separated from its connexion with the vessels by division of the spinal cord in the neck previous to the injection of casca.

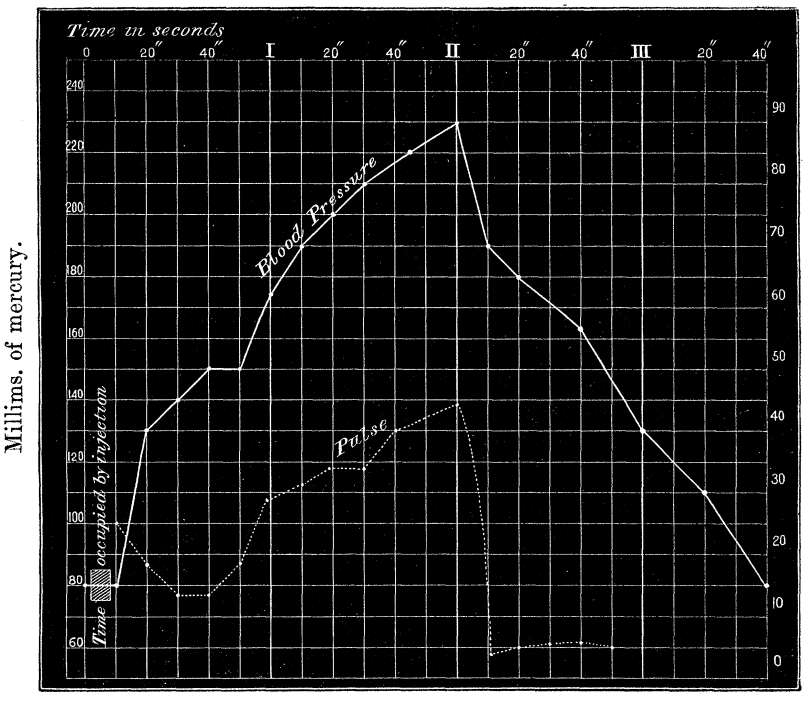
Effect on Blood-pressure after division of Cord.

Experiment XLII.—May 17.

A large strong cat, weighing 7½ lb., was chloroformed. A cannula was inserted into the left carotid, and another into the jugular vein. The spinal cord was then divided opposite the second cervical vertebra, and artificial respiration kept up.

Time.		Blood-pressure.	Pulse in 10 sec.	Oscillations.
m. s.		millims.		millims.
0 0	Condition after section of cord and previous to injection of casca	80	25	5
0 3 / 0 7	Injected 1 cub. centim. watery solution of casca.			
0 10		80	25	5
0 20		130	18	12
0 30		140	13	20
0 40		150	13	25
0 50		150	18	12
1 0		175	28	5
1 10		190	32	4
1 20		200	34	3
1 30		210	34	3
1 40		220	41	4
2 0		230	44	3
2 10	Sudden alteration in character of pulse, which becomes slow. The curve flat-topped, and both systole and diastole showing numerous secondary oscillations. Blood-pressure falling	190	3½	40
2 20		180	5	30
2 40		165	6	25
3 0	Blood-pressure rapidly falling	130	6	15
3 20	Both pulse and oscillations are very irregular	100	5	?
3 40		80		
3 50		25		
4 0		10		
	There was no more pulsation after this; but the blood-pressure took 1′ 30″ to fall quite to zero. On opening the thorax the heart was found moderately contracted; electrical stimulation of the phrenic nerve caused contraction of the diaphragm.			

The result of this experiment will be seen all the more clearly by the following diagram, in which they have been graphically represented.



The rise of pressure in this experiment was greater than in any other in which the cord had not been divided. This seemed to us so extraordinary that we thought at first that the cord had not been properly divided; but a careful dissection made immediately after death showed us that the division was complete. A year or two ago this result would have been regarded as a proof that the drug acts on the vessels themselves; but recent researches having shown that much more importance must be attributed to vaso-motor centres in the cord and in the periphery than was previously done, we cannot say whether the drug acts on these centres or on the walls of the vessels themselves. The non-contraction of the vessels of the frog's web would indicate that the action of the drug is rather on nervous centres in the cord or neighbourhood of the vessels than on the vascular walls.

In order to exclude all centres except those in the periphery, Experiment XLIII. was performed.

Experiment XLIII.

The sympathetic cord was divided on the right side of the neck of a rabbit and the animal allowed to come out of the chloroform anæsthesia. The ear of the right side was deeply injected while the left ear was very moderately filled with blood. A dose of casca was then administered. The vessels of both ears became pale, those of the right ear equally so with those of the other.

Vessels affected by the Drug.

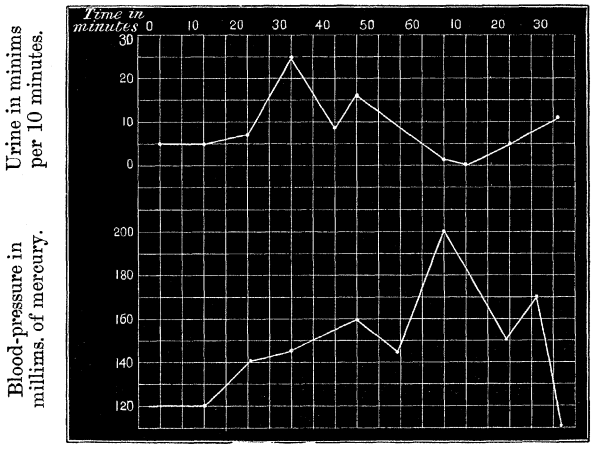
The vessels by which the blood-pressure in the body is chiefly regulated are those of the intestines, those of the skin and muscles being very much less under the influence

of the vasomotor centre in the medulla. As casca acts on the vessels without this centre, however, it was natural to suppose that other vessels than those of the intestines might be affected; and this the curves show to be the case. During the stoppage of the heart (Experiment XLII.) for half a minute the pressure fell only slightly. Now LUDWIG and HAFIZ found that when contraction of the abdominal vessels was produced by irritation of the vasomotor centre in the medulla oblongata, complete stoppage of the heart was followed by a rapid fall in the blood-pressure, the blood finding its way out of the arterial system into the veins through the vessels of the muscles. The slow fall after the administration of casca shows that the vessels of the muscles must be contracted as well as those of the skin and intestines.

ACTION ON SECRETION OF URINE.

A detailed account of our experiment on the action of the drug on the urinary secretion, together with the accompanying effects on the circulatory system, will be found in pages 642 and 643. Underneath is a diagram showing the close dependence of the rate of secretion of urine upon the blood-pressure.

Experiment XXXIII.—March 31.



Remarks.

The results of this experiment, as regards the vascular phenomena of blood-pressure, pulse, &c., have been already fully noticed.

The action of the drug on the secretion of urine is seen to be very marked and characteristic, and the dependence of the secretion on the blood-pressure is well shown in the accompanying chart.

Thus the average rate of urine secreted before administration of casca being 5 minims in 10 minutes, an increase of 50 millims. in the blood-pressure caused by the drug brought the rate of secretion of urine up to 25 minims. When the action of the drug was further pushed there was first decrease and then total suppression of urine, the blood-pressure at the time of suppression being 200 millims. of mercury.

Subsequently as the blood-pressure fell the secretion of urine recommenced.

The physiological explanation of these successive phenomena appears to be that the primary increase of blood-pressure produces arterial fluxion to the kidney; but that if the action of the drug is pushed, the renal vessels become contracted so as to prevent the blood reaching the kidneys, notwithstanding the high pressure in the arterial system. It is worth notice that the urine collected after the secretion had recommenced did not contain albumen.

In this respect the result of this experiment differs from those obtained by Mr. POWER and one of us in our experiments on the action of digitalis; it coincides, however, with those experiments in its general results.

ACTION ON THE PUPIL AND LACRYMAL GLAND.

In order to see if the drug exerted any local action on either of these organs, we (Experiment XLV.) placed some drops of strong watery solution of casca in the eye of a cat, but with purely negative results.

ACTION ON MUSCLE.

Effect on Structure of Muscular Tissue.

The effect on fresh muscular tissue of immersion in casca solution was carefully watched with an oc. 3 obj. 7 of HARTNACK'S microscope without any change in the structure being discovered (Experiment XLVI.). We then (Experiment XLVII., March 22nd) examined the "naked-eye" and microscopical changes produced in muscular tissue by prolonged immersion in a watery solution of the alcoholic extract, the effect of which solution in preventing the development of *Bacteria* has already been detailed (p. 635).

A. The solution in which the muscular tissue had been placed presented, in addition to the absence of *Bacteria*, few noteworthy points; it preserved its original slightly resinous smell, and deposited a fine light-brown sediment, which, under the microscope, appeared as a granular structureless detritus.

B. The muscular tissue to the naked eye appeared hardly altered in consistence: the fibrous sheath was firm; there was no smell. Under obj. 7 HARTNACK the fibres were seen to be very granular, in part only preserving their transverse striation; the general appearance closely resembled ordinary fatty degeneration. Some of the fibres were then soaked in ether for twenty-four hours; on examination after this the granulations had in great part disappeared. Many of the fibres appeared to consist merely of collapsed tubes of sarcolemma; where they were not collapsed they showed plain transverse striæ.

Six weeks later the muscle was again examined; it having remained in the same casca solution all the while, it was now reduced to the condition of a rather tough gelatinous pulp; the sheath of the muscle retained its strength. Under the microscope

there was seen a mixture of granular and fibrous material, with a large quantity of oil-globules and flat crystals, and when treated with ether these were completely removed.

Effect on the Lifting-power of Muscle.

Experiment XLVIII.

The lifting-power of a frog's gastrocnemius which had been placed in a $\frac{1}{300}$ solution of casca was compared with that of a similar preparation placed in salt solution, by attaching the one muscle as quickly as possible after the other to an apparatus for estimating their lifting-power connected with a revolving drum. The irritations were made with electrodes connected with a Leclanché's battery.

The results of our first experiments appeared to show that the drug possesses a stimulating action on the lifting-power of muscle; but on repeating the experiment this result was not confirmed—the conclusion we drew from the whole series of experiments being that muscles which had been immersed in casca and salt solution respectively possessed nearly the same lifting-power.

Effect on Muscle-curves.

Experiments XLIX., L.

Two frogs were injected with casca, and when they seemed dead, nerve-muscle preparations were made of the gastrocnemii. In Experiment XLIX. the preparation was attached to a Fick's pendulum myograph and a tracing taken. In Experiment L. the nerve muscle was made to trace on a revolving cylinder: the curves obtained in these experiments are evidently normal.

In Experiment LI. the action on the sensibility to electrical stimuli of muscle and motor nerves was tried, also with completely negative results, by making two nerve-muscle preparations of a frog's gastrocnemii, and immersing one in casca solution, the other in salt solution. The sensibility of the two preparations was then tested by various strengths of a Du Bois Reymond's coil connected with a Leclanché's battery. The two muscles responded quite similarly.

Remarks on the Action of Casca on Muscle.

1. When applied to fresh muscular fibre no change is observed in its histological details.

2. In addition to the absence of the development of *Bacteria* which is noticed when muscular tissue is placed in a watery solution of the alcoholic extract, and which has already been remarked upon, the structural changes which the muscular tissue undergoes appear to consist in a fatty metamorphosis, which at first simulates very closely that of ordinary fatty degeneration, while the later appearances resemble those of the more complete fatty changes which go on after the death of a tissue, large oil-globules and abundant crystals of the fatty acids being everywhere found.

3. It does not diminish the lifting-power of muscle in a nerve-muscle preparation, nor

when the irritation is applied to the muscle itself, and it probably does not increase it; for although apparently positive results were attained on the first occasion when the lifting-power was experimented on, these results were not borne out by further experiments.

4. The muscle-curve given by a nerve-muscle preparation taken from a frog poisoned by a large dose of casca appears to be quite a normal one.

5. It also exerts no action on the sensibility of muscle to electrical stimulation if this sensibility be tried quantitatively by estimating the weakest interrupted current which will produce a contraction.

From all these results, then, it may be concluded that while the drug produces a peculiar and characteristic change on muscular tissue immersed in it for some days, it is not a muscle-paralyzer.

Action on Motor Nerves.

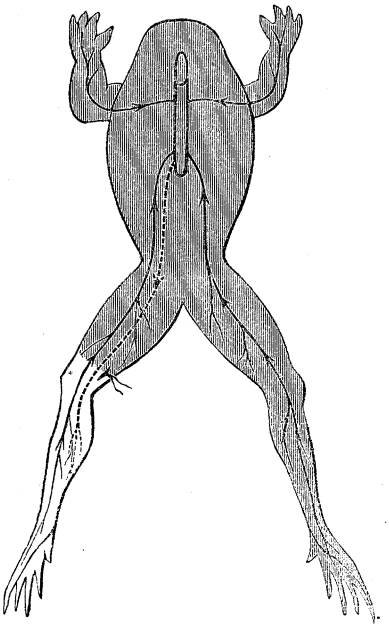
If casca had any paralyzing action on the ends of motor nerves similar to that of curare it would be found that after immersion in a solution of the drug the muscle would respond to electrical stimuli directly applied to it, but not to those applied to the nerve. In Experiment LII., however, the nerve also is seen to preserve its irritability, and therefore we may conclude that casca has no action on motor nerves.

Action on Sensory Nerves.

Effect on Reflex Excitability.

Experiment LII.—March 22.

The cerebrum of a living frog of medium size was destroyed. The circulation through the left leg was cut off by ligaturing the arterial trunks above the knee (*vide* fig.). The



sciatic nerve was left uninjured. $\frac{1}{4}$ cub. centim. of the alcoholic extract was then injected beneath the skin of the back.

The reflex excitability was then tested at intervals of 5 minutes by irritating points above and below the ligature. No difference in the sensibility could be detected.

As the frog was very little affected by the injection, another $\frac{3}{4}$ cub. centim. was injected.

The frog became insensible to reflex irritation in five and twenty minutes; during this time the irritability was tested every five minutes as before; the rates of increase of the insensibility appeared to be equal above and below the ligatures.

In this experiment the poison was applied to the terminations of the sensory nerves above the ligature, but not to those below it. Had it possessed any marked power of diminishing the sensibility of these nerves a stimulus applied above the ligature would have had less effect than one applied below it; but this was not the case.

The poison therefore seems to have no action on sensory nerves, at any rate none of a paralyzing character.

Action on Reflex.

Experiment LIII.

In this experiment the action on reflex was tested by applying a very dilute solution of sulphuric acid to the leg of a frog with its cerebrum destroyed and suspended by its head. Its normal irritability was then tested. The tips of the toes only were immersed in the acid. Contraction was immediate and lasted three minutes (right leg). A $\frac{1}{4}$ cub. centim. alcoholic solution was then injected; the animal immediately hung more flaccidly. Five minutes afterwards, on immersing the tip of the toes of the right leg, slight contraction occurred after 63 seconds. A quarter of an hour later, on immersing half the leg, contraction was immediate and lasted 5 seconds; in ten minutes more a similar immersion produced contraction after 10 seconds, and five minutes afterwards after 15 seconds. Fifty minutes after the injection of the drug the acid solution produced no reflex movements, and only slight ones were excited by pinching. Reflex ceased last in the eyelids one hour and twenty minutes after the casca had been injected.

In Experiment LIII. the reflex excitability disappeared very much more quickly than it usually does.

This might be due to the action of the drug on the spinal cord itself, or to the cessation of circulation caused by the action of the drug on the heart.

In order to decide this the following experiment was made.

Experiment LIV.

The heart of a frog was exposed and casca administered. As soon as the heart had ceased to beat the heart of a second frog was ligatured at the root of the aorta so as completely to arrest the circulation. At first both frogs were able to jump readily; but gradually their movements became more sluggish, and after a jump their legs trailed out behind them and were only slowly drawn up to the body. They became less and

less sensitive to pinching, and insensibility and loss of motor power occurred simultaneously in both.

The diminished power of movement and diminished reflex action observed in the frog after the administration of casca is therefore due to the arrest of the circulation caused by it, not to any action of the drug upon the nervous system.

Antagonism between Casca and Atropia and Chloral Hydrate.

The remarkable result of Experiment XXIV., in which a dose of casca, usually fatal, produced no effect in an animal with divided vagi, seemed to render it probable that such a drug as atropia, which paralyzes the ends of the vagus in the heart, might have an antagonistic action. On trying it, however, it was found that the vomiting caused by the casca was even more violent than usual; and therefore a combination of atropia with chloral hydrate was employed, the chloral being given to lessen the irritability of the vomiting centre in the medulla.

The results were not satisfactory, as will be seen from the two following experiments.

Experiment LV.—May 1, 1876.

About 11.40. Injected 4 cub. centims. of liquor atropiæ under skin of flank of cat A.

12^h. Injected 4 cub. centims. of a saturated alcoholic solution of alcoholic extract of casca under skin of flank of cats A and B.

h. m.	A.	B.
12 30	.....	Sick and vomits. During the intervals between the fits of vomiting seems well.
12 40	Crouching, trembling, and seems about to be sick. Licks its lips. Hind eyelid much drawn up.	
12 52	Very sick; vomiting. Seems more uneasy than B.	Vomiting. Disinclined to move. When disturbed and made to walk its hind legs give a shake as if to shake off something sticking to the feet every time they are drawn up.
1 0	Very sick.	Very sick. Brings up fluid, which appears to be digested meat. Respirations 18 per minute.
1 15	Gives loud squalling cries when retching.	Seems weaker.
1 30	Seems easier; not retching.	Twitch or rather shake of hind legs is very marked.
2 35	Walking about.	Seems unable to move.
2 40	.....	Violent retching; crying. Convulsive extension of legs and emprosthotonos. Then two or three sighing respirations; a pause; one or two respirations at intervals; then death.
4 0	Has been vomiting at intervals. Has a violent fit of sickness and dies in the same way as B.	
	Post mortem.	
	Stomach contains a quantity of food. Heart moderately contracted. Ventricles continue to make slight pulsations, auricles not. Lungs somewhat congested. No congestion of interior of stomach.	Stomach empty, not congested. Heart moderately contracted. Lungs normal.

Experiment LVI.

Cat A. Large.

h. m.
12 3. Injected 30 minims liquor atropiæ subcutaneously.
12 20. Injected 5 cub. centims. saturated watery solution and suspension of casca.
12 30. Vomited.
12 45. Vomiting has been repeated 3 or 4 times. Is lying on its side and cannot stand. R. 144. Alæ nasi working.
12 52. Eyelids much drawn up. Respiration irregular.
12 55. Gasps; seems to try but to be unable to vomit. Emprosthotonic spasms.
12 58. Muscular twitchings. Slow sighing respirations. Death.

Cat A lived 38 minutes after injection of casca.

Cat B. Medium.

h. m.
12 45. Injected 15 grs. of chloral hydrate and 15 minims of liquor atropiæ with 5 cub. centims. of casca.
12 58. Mewing.
12 59. Vomited twice.
1 9. Vomited again.
1 14. Loud violent retching, but no vomiting.
1 15. Involuntary extrusion of fæces and urine. Died.

Cat B lived 30 minutes.

Cat C. Large and strong.

h. m.
12 40. Injected 5 cub. centims. of the same casca solution.
12 49. Very restless.
12 52. Vomited for first time. After this it vomited frequently, but remained restless. T. 37°·1.
1 30. Died rather suddenly, with violent gasping and emprosthotonic spasm.

Cat C lived 50 minutes.

In this experiment the cat which had received the casca alone lived longer than the others.