sorption of thrombi. I incline to the opinion myself that it is due to the fibroid consolidation which sets in sooner or later in most of these cases, and not, as Harrison suggests, to simple atrophy. But whether this is the case or not, there is no doubt of its occasional occurrence, and it is certainly encouraging that although many of the cases operated upon are now 4 years old, definite recurrence has only been noted in one.

The question of the recovery of the bladder depends partly upon the condition of the patient as regards general nutrition, partly upon the extent to which the muscular coat has been ruined by overdistension, cystitis, and the repeated use of catheters. Nineteen cases in all failed, but in four of these either the whole obstruction was not removed, or no attempt was made to close the suprapubic opening; in two others there was already a fistula owing to the previous removal of a vesical tumour, and another was a very feeble old man who became insane shortly after. These, at least, must be deducted, and in several others there were mitigating circumstances. It cannot, however, be too plainly stated that the real reason why the bladder failed was that the operation was performed too late. Sir H. Thompson has written that habitual catheterism for retention in cases of enlarged prostate for two years will permanently destroy the power of the bladder to empty itself; and although McGill has shown that this is by no means so invariable or so positive, it is certainly one of the strongest arguments in favour of early operation that the chief palliative measure that replaces it, may within two years—*will*, according to Sir H. Thompson—so ruin the bladder that it can never recover.

The final question is whether the operation does not involve too great a risk to life, and how far it will compare in this and in the degree of comfort it confers with palliative measures, such as suprapubic and perineal drainage. For it has been said that nearly the whole benefit derived from it is due to the temporary relief from cystitis or to the extraction of calculi, and not in more than the remotest degree to the removal of the obstructing mass. In answering this the perineal operation must be considered separately from the suprapubic. It is not a matter of option which of the two should be performed; one may be required, or the other, or both; and fortunately in the majority of instances it is fairly easy to tell beforehand which should be selected. Even, however, if owing to some misleading feature, there does happen to be a mistake in the diagnosis, and the perineal operation is performed in a case better suited to the other, exploration with the finger can do no harm, and the presence of the incision, supposing it is not wanted for drainage, adds little or nothing to the gravity of the operation.

Of the thirty-eight cases of perineal operation undertaken for this purpose and not as an afterthought during lithotomy, only three died, and one of these was 80 years of age already, and in another the method adopted was unsuitable. Simple division, I grant, is not of much value unless followed by prolonged drainage; but undoubtedly in suitable cases perineal prostatectomy, without necessitating an appreciably greater risk, confers upon the patient a degree of relief with which that following mere cystotomy or drainage offers no comparison. The patient in a large proportion of cases recovers complete control over his bladder, and even in the failures, even in those instances in which a fistula is left or in which the sole benefit gained is the easier introduction of a catheter, he is no worse off than if the formation of a permanent fistulous opening and nothing more had been the object in view.

The suprapubic operation stands on different ground. Taking all the cases together, the mortality is approximately 20 per cent.; if the last half only, it is still 15 per cent.; and although this will fall lower, especially in the hands of those who are practised in the performance of the operation, it is probable that it will always remain higher than the other. On the other hand, it must be remembered that the majority of the patients operated upon were practically *in extremis*, and that it is very doubtful whether a very large proportion would have survived much longer, or even so long, had the operation not been done.

The real issue lies between suprapubic prostatectomy and the continuous wearing of a cannula, which, in spite of the enthusiastic comments of those who were suffering tortures

before it was introduced, is scarcely preferable to micturition by the natural route. Each has, I believe, distinctly its own field. Enlargement of the prostate by itself requires neither, and fortunately the majority of patients suffering from this complaint pass through life without its ever becoming necessary to raise the question. In a certain proportion, however, complications set in sooner or later; and to many patients there comes at length a time when their constitutions are still sound, but there are clear indications that the local conditions are surely and rapidly growing worse. The catheter has to be passed more and more often; occasionally there is a little difficulty, and, what is still more important, it no longer gives relief—the desire to pass water is as great after the instrument is withdrawn as it was before; cystitis breaks out every now and then; attacks of congestion causing hæmaturia and retention occur with greater frequency; the urine is becoming offensive; the residuum is growing larger, and the night's rest is seriously broken. For these and such as these prostatectomy, by one route or the other, according to the special conditions present, certainly affords a far better prospect than either cystotomy or drainage, and without sensibly greater risk. Permanent cure is possible, and even the failures are as successful as the successes claimed for the other methods.

On the other hand, if this chance is lost, if, as only too often happens, the patient has allowed himself to drift on, using a catheter more and more frequently without realising what the end must be, until his kidneys are diseased or cystitis has destroyed the muscular power of the bladder and made it small, hard, and rigid, the conditions are absolutely different. When the capacity of the bladder is much reduced, and it cannot be distended; when it has lost its power, whether this arises from prolonged retention, repeated inflammation, or the persistent use of catheters; and when, under careful treatment and watching, it shows no sign of recovery, it is useless attempting to remove the obstruction; cure is impossible, and the risk, if there is the least nephritis, much too great. Palliative measures only can be employed; as much benefit can be derived from drainage as from the most complete enucleation; and no surgeon would undertake a grave operation when one less dangerous to life would answer equally well.

REPORTS TO THE SCIENTIFIC GRANTS COMMITTEE OF THE BRITISH MEDICAL ASSOCIATION.

REPORT ON THE PHYSIOLOGICAL ACTION OF THE ACTIVE PRINCIPLES OF URECHITES SUBERECTA.

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My attention was directed to this plant by reading two interesting papers¹ by Mr. J. J. Bowrey, Government Chemist in Jamaica, on its chemical constituents and their poisonous action. Mr. Bowrey's experiments on animals, while proving the extreme toxicity of the active principles which he had isolated, did not in any way indicate their mode of action, nor the pharmacological group to which they belong. For the purpose of carrying out a more detailed investigation, he very kindly prepared for me a supply of the active substances, and it was with these that the following research was made.

The urechites suberecta belongs to the natural order *Apocynaceæ*, and grows abundantly in Jamaica and other West Indian islands, where it is known as the "savannah flower" or "yellow-flowered nightshade." It is usually a climbing

¹ Bowrey, *Proc. Roy. Soc.*, xxvii, 309, 1878, "On the Physiological Action of the Poisonous Principle of Urechites Suberecta"; *Journal of the Chem. Soc.*, xxxiii, 252, 1878, "The Poisonous Principle of Urechites Suberecta."

plant, but is sometimes found standing unsupported in small clumps. The flowers are conspicuous by their size and bright yellow colour. Sir Hans Sloane² says: "The whole plant is very milky. It grows in the Savannahs everywhere, and is in flower most part of the year, making a very pleasant sight." It is notoriously poisonous. According to Bowrey, "it is supposed to have been the chief poison used by Obeah men in the time of slavery. The most wonderful tales are current of the power of these men, and it is even stated that they could so administer their poisons as to kill immediately or after the lapse of days or weeks." Further, Sloane states that "it may be so ordered as to kill a person in many days, months, or years." Regarding its medicinal properties, Descourtiz gives an account of its being used in venereal diseases, in dropsy, leucorrhœa, chlorosis, blennorrhagia, and other affections. The milky juice is also reputed to "take away warts and cure ringworms and freckles." For most of these uses there is no rational foundation, but Descourtiz notes that "it provokes an abundant secretion of sweat and urine," and, as this is borne out by the results of pharmacological investigation, it doubtless would prove efficacious in certain cases of dropsy.

In cases of poisoning in man, violent vomiting, purging and griping, and slight convulsions in various parts of the body have been noted.

According to Bowrey, the flowers and all the green parts of the plant are very bitter and acrid. When chewed they cause a feeling of swelling in the mouth, while the powdered dried leaves bring on violent and prolonged sneezing if snuffed into the nostrils. From the leaves he separated out two active substances, and named them "urechitin" and "urechitoxin" respectively.

Of urechitin the fresh leaves contain at least one-half per cent. When isolated it is in small perfectly white crystals, insoluble in cold water and in cold spirit of less than 40 per cent. alcoholic strength, very slightly soluble in boiling water, quite soluble in strong alcohol. It is a glucoside, and has the formula $C_{25}H_{45}O_{18}$.

Urechitoxin also occurs in small colourless crystals, soluble in 1,500 parts cold water, much more soluble in alcohol. It is a glucoside, having the formula $C_{15}H_{20}O_5$; about 3 per cent. is obtainable from the dried leaves, and about one-half per cent. from the fresh. Both substances are intensely bitter when in solution; urechitin being insoluble in water is tasteless in the solid form. A solution of urechitoxin, 1 in 40,000 water, tastes excessively bitter, and if left in contact with the mucous membrane of the mouth it causes tingling and a feeling as if the parts were swollen.

Both substances give characteristic chemical reactions, and, on decomposition, yield a white crystalline body, which Bowrey has named "urechitoxetin." He states that it is physiologically inactive, and this I can confirm from my experiments.

Bowrey's experiments with these bodies are of extreme interest, and were directed to determine their toxicity, and whether there is any truth in the current reports regarding the power of the plant to kill at long intervals after administration. To three cats he gave $\frac{1}{10}$ grain (6.5 milligrammes) urechitin by the mouth. One recovered after vomiting, one died after eight hours, the third died after forty-nine hours.

The symptoms noted were violent vomiting, general feebleness, and death in convulsions. In cats urechitoxin in doses of $\frac{1}{10}$ to $\frac{1}{5}$ grain generally proved fatal after some hours with similar symptoms.

The chief interest, however, attaches to his observations on the effects of minute doses given daily to cats over long periods. Several experiments were made, but the most striking are those in which $\frac{1}{1000}$ grain (0.065 milligramme) urechitoxin was given every day by the mouth. One cat died on the twelfth day. It exhibited no symptoms except dullness, inactivity, and loss of appetite, but suddenly took a convulsive attack and died in two hours. Another had the same dose daily for eleven weeks, at the end of which time

it also died after a short illness; in this case there were no previous symptoms, and it gained weight up to the day of its death. The total amount given during the eleven weeks was only $\frac{1}{10}$ grain (4.2 milligrammes). Bowrey concludes that there is some truth in the stories told of the poisoning by Obeah men, and that minute doses, frequently administered, might cause death without suspicion being aroused.³

Since Bowrey's research was published, a number of other investigations have been made, but they differ very widely in their results, and have greatly served to confuse our knowledge of the real physiological action of the plant.

Ott⁴ experimented with a liquid extract of the leaves. He compares its action to that of aconite, and advises the use of digitalis as an antidote in cases of poisoning. Vowinkel⁵ used a decoction and tincture of the leaves. He failed, however, to grasp its true action. He states that atropine is an antidote to it, and that it, in its turn, is an antidote to curare. Minkiewicz⁶ isolated two substances, which he names urechitic acid and urechites glucoside. He did not know Bowrey's methods, and seems only to have obtained decomposition products of the active principles, which were not remarkably poisonous.

I may here state that my investigation shows that urechitin and urechitoxin are muscle poisons, acting very especially on the heart muscle. They may, therefore, be included in the so-called digitalis group, although there are certain respects in which they differ from the digitalis action.

EXPERIMENTS WITH URECHITIN.

Frogs.—The urechitin was given dissolved in small amounts of 60 per cent. alcohol (but generally in a quantity insufficient to exert an appreciable alcohol action on the animals).

When $\frac{1}{10}$ to $\frac{1}{5}$ milligramme ($\frac{1}{1000}$ to $\frac{1}{200}$ grain) was injected subcutaneously, it proved fatal after a period of from one to several hours. The symptoms are similar to what occurs in the case of digitalis and other heart poisons, and have been so often described that it is unnecessary for me to enter into full details. The animals gradually became more and more sluggish, the colour of the skin became darker as the blood gradually ceased to circulate through it, and finally there was no reaction whatever on stimulation. These symptoms arise from stoppage of the heart, and consequent slow death of the

³ It is difficult to obtain detailed information regarding Obeah practices. They rest largely on the credence given to superstitious practices and vulgar quackery by the uneducated in every country, but there seems little doubt that among them secret poisoning is included. Benjamin Moseley (*Medical Tracts*, London, 1800) states that Obi had its origin, like many customs among the Africans, from the ancient Egyptians, Ob meaning a demon or magic. Villiers-Stuart (*Jamaica Revisited*, 1891) says that Obeah in the West African dialects signifies serpent, and that the Obeah men in Jamaica carry (but in greatest secrecy, for fear of the penal laws) a stick on which is carved a serpent, the emblem being a relic of the serpent worship once universal among mankind, and also that they sacrifice cocks at their religious rites. Moseley gives the following account: "Obi, for the purposes of bewitching people or consuming them by lingering illness, is made of grave dirt, hair, teeth of sharks and other animals, blood, feathers," and so on. Mixtures of these are placed in various ways near the person to be bewitched. "The victims to this nefarious art in the West Indies among the negroes are numerous. No humanity of the master nor skill in medicine can relieve the poor negro labouring under the influence of Obi. He will surely die, and of a disease that answers no description in nosology. This, when I first went to the colonies, perplexed me. Laws have been made in the West Indies to punish the Obian practice with death, but they have been impotent and nugatory. Laws constructed in the West Indies can never suppress the effect of ideas, the origin of which is in the centre of Africa." "A negro Obi-man will administer a baleful dose from poisonous herbs, and calculate its mortal effects to an hour, day week, month, or year." The missionaries Waddell (*Twenty-nine Years in the West Indies and Central Africa*, 1863) and Blyth (*Reminiscences of Missionary Life*, 1851) confirm this account. They are all agreed that similar practices prevail in West and Central Africa, and that Jamaican Obeah men use poisons. Mr. Bowrey informs me that he has examined many Obeah charms, and confirms Moseley's account of them. He thinks, however, that among the negroes the knowledge of poisons has been rapidly dying out, "doctor's medicine" and the much-advertised patent medicines having largely replaced the drugs of the native practitioners. The belief in Obeah is still, however, almost universal among the black population. According to Sir Spencer St. John (*Hayti, or the Black Republic*, second edition, London, 1889) secret poisoning is a lucrative occupation in the neighbouring island of Hayti, certain of the people having an intimate knowledge of indigenous poisonous plants and being expert poisoners.

⁴ Ott, "The Physiological Action of Urechites Suberecta," *Therapeutische Gazette*, 1880.

⁵ Vowinkel, "Ueber die Einwirkung von Urechites Suberecta auf den thierischen Organismus."—*Inaug. Diss.* Berlin, 1885.

⁶ Minkiewicz, "Beitrag zur Kenntniss der in Urechites suberecta enthaltenen wirksamen Substanzen."—*Inaug. Diss.* Dorpat, 1888. Also in Kobert's *Arbeiten des pharmacologischen Instituts zu Dorpat*, v, 1890.

² Sloane, *A Voyage to the Islands of Madeira, Barbadoes, Jamaica, etc.*, vol. 1, 206, 1707, fig. 2, tab. 130. The plant is also figured in the *Botanical Magazine*, vol. xxvii, No. 1064, 1808, and by Descourtiz in the *Flore pittoresque et médicale des Antilles*, vol. vii, 88, Paris, 1829. Botanical descriptions are given by Grisebach, *Flora of British West Indian Islands* (London, 1864), and by others.

FIG. I.
FROG'S HEART TRACING WITH WILLIAMS'S APPARATUS.
URECHLIN 170 10000 000 PARTS CIRCULATING FLUID

FIG. II. RABBIT UNDER ETHER. TRACING FROM CAROTID ARTERY.
URECHITIN AT 11.45 2 MILLIGRAMS
11.51 2 "
12.1 2 "
12.5 2 "

FIG. II CONTINUED.

FIG. III. RABBIT UNDER ETHER URECHITIN, 1 MILLIGRAM AT 12.40 P.M.
TRACING FROM CAROTID ARTERY

FIG. III CONTINUED

FIG. IV. URECHITOXIN

FIG. IV CONTINUED

THE TRACINGS ARE REDUCED TO ONE-THIRD OF THEIR ORIGINAL SIZE.

nervous system. On examination, the ventricle was found in strong systole, very small and contracted and quite bloodless, the auricles being, in strong contrast, in full diastole, and much dilated with venous blood. The reaction of the heart muscle was acid; the voluntary muscles were more or less diminished in electric irritability.

On exposing the heart in pithed frogs, the series of phenomena characteristic of cardiac poisons in frogs was readily observed. Systole and diastole both become fuller for a short time after administration of the poison, and the heart may in consequence beat very slightly slower. Soon the ventricular diastole is seen to be lessened, while the systole becomes even more marked. Owing to incomplete diastole, the ventricle carries on the circulation imperfectly, taking in and giving out less blood. Next, only certain bundles of the cardiac muscle extend during the diastolic period, and do so irregularly, thus giving rise to the well-known "pouching." Finally, the ventricle stops in complete contraction, quite bloodless and irresponsive to stimulation. The auricles become very much dilated with venous blood, which they attempt in vain to force into the contracted ventricle; they go on trying for some time to contract on the contained blood, but soon stop in full diastole.

The following experiments will serve to show how long the process takes with different doses. When very small amounts, such as $\frac{1}{10}$ to $\frac{1}{20}$ milligramme, were given no characteristic action was observed. The previous administration of atropine did not alter matters in any way.

Experiment 1.—Frog, 22 grammes: Brain destroyed, heart exposed; beats, 24-25 per 30 seconds.

1.40 Urechitin, $\frac{1}{10}$ milligramme in 2 minims of 60 per cent. alcohol under skin of flank.

1.50. Heart, 25 per 30 seconds.

1.54 Heart, 24 per 30 seconds; diastole not quite so good.

1.56. Heart, 24 per 30 seconds; slight irregularities in contraction of the ventricle.

1.58. Heart, 22; pouching well marked.

1.59. Diastole almost nil; ventricle white and contracted but still making slight movements; auricles very dilated.

2.0. Ventricle entirely ceased to dilate, fully contracted, white and bloodless.

Experiment 2.—Frog, 28 grammes: Brain destroyed, heart exposed; beats, 17 per 30 seconds.

12.48. Urechitin $\frac{1}{10}$ milligramme in 2 minims under skin of flank.

1.0. Heart, 16.

1.20. Heart, 16.

1.30. Heart, 16; diastole is not nearly so good; the ventricle receives and drives out very little blood; auricles dilated, cannot fully empty themselves into contracted ventricle.

1.35. Heart, 16; *in statu quo*.

2.0. Ventricle is now completely stopped in systole.

Observations were also made on the isolated frog's heart with Williams's apparatus, an instrument by means of which the heart beats can be graphically recorded and the pressure maintained by the heart measured in millimetres of mercury. These fully confirmed my previous results. The tracing (Fig. 1), taken from a heart under the influence of urechitin, shows very well the characteristic effects of a muscle poison (of the digitalis group) on the heart. The beats become slower and more ample, and a much higher pressure is maintained. On continuing the circulation of the poison through the heart this, which corresponds to what we may call the therapeutic stage, passes into the stage of poisoning (as shown in the tracing), when the beats become bigeminous or otherwise irregular, and the heart ultimately stops in systole, no contraction being registered. Very minute amounts of urechitin administered in this way suffice to kill the isolated frog's heart. Thus, 1 part urechitin in 200,000 parts circulating fluid brought the heart to a complete standstill in 9 minutes; 1 to 1,000,000 in 21 minutes, 1 to 2,000,000 in 55 minutes, 1 to 5,000,000 in 83 minutes, 1 to 8,000,000 in 75 minutes, and 1 to 10,000,000 in 120 minutes.

Urechitin is scarcely soluble in the saline fluids which have been used for circulation through the blood vessels of the frog. Experiments showed that it did not contract the arterioles of frogs in which an artificial circulation was maintained.

Dogs.—Dogs are very susceptible to the action of urechitin.

Experiment 3.—A young spaniel which received 1 milligramme ($\frac{1}{10}$ grain) subcutaneously became very depressed-looking in about 15 minutes, and shortly afterwards vomited. It continued retching and vomiting all day, but next day had apparently quite recovered. The rate of the heart was but little influenced.

Some time after the same dog got 1 centigramme ($\frac{1}{10}$ grain) subcutaneously, with very marked effect, as is shown in the notes of the following experiment:

Experiment 3a.—Spaniel, 8 lbs. weight: In 10 seconds heart beats, 26-28; respiration 8.

2.26. 0.01 gramme urechitin subcutaneously.

2.30 Heart, 16; slightly irregular

2.36. Heart, 14; irregular; respiration, 7; animal depressed.

2.50. Heart, 12; very much depressed; pupils small.

3.0. Heart, 13; can scarcely be felt.

3.15 Heart cannot be felt beating; had an irregular convulsion; pupil dilated. There is evidently marked peristalsis of the intestine as borborygmi can be very distinctly heard.

3.18 Heart, 29; pupil pinpoint; lying on side, half unconscious.

3.35. Heart, 28, regular but not strong; respiration, 8; great muscular feebleness; retched and vomited violently; marked borborygmi.

3.38. Heart beats cannot be felt.

3.41. Died quietly.

The smallest fatal dose in a dog was 2 milligrammes ($\frac{1}{50}$ grain). The animal died in thirty-eight minutes from heart paralysis. It vomited frequently, and showed symptoms of great muscular weakness. The heart was affected in a very decided manner; the beats fell from 144 to 24 per minute, and its action was markedly irregular and intermittent, with frequent long pauses.

The symptoms of acute poisoning with urechitin consist therefore in severe and continued vomiting, great muscular weakness, and marked slowing and irregularity of the heart, which, however, is often rapid in the later stages. In addition, there are symptoms of increased intestinal peristalsis, as shown by slight diarrhoea and borborygmi. There is also an increased frequency of micturition. It is evident from these symptoms, which the *post-mortem* appearances confirm, that the involuntary muscles of the intestinal canal and bladder are specially affected as well as the heart. The vomited matters consisted at first of food, but afterwards were entirely frothy mucus. Sometimes severe dyspnoeic attacks occurred, no doubt from disturbance of the circulation. The minimum lethal dose is small, but death takes place comparatively slowly, the explanation most probably being that it is usually some time before the poison enters into combination with and affects the heart muscle fully. The size of the dose, provided it be lethal, does not greatly influence the time of death, as another dog which received 2 centigrammes ($\frac{1}{5}$ grain) expired only after twelve hours. Some of the animals died quietly, others during an irregular convulsion. It was evident that the convulsions were asphyxial and due to improper circulation of the blood from cardiac paralysis.

The results of *post-mortem* examination were as follows: The condition of the heart varied somewhat; sometimes all four chambers were in diastole, and filled with venous blood; sometimes the left auricle was contracted and empty, the left ventricle being semicontracted and half filled with blood; the right side of the heart was always distended. The auricles twitched for some time after death; the ventricles were motionless and inexcitable to stimuli. The veins were always very full of dark blood, the arteries empty and like thin white cords. The walls of the stomach and bowels were very thick, hard, and contracted, to such an extent that at points the lumen of the bowel was occluded. The bladder wall was also thick and contracted. The voluntary muscles contracted slightly to very strong currents, but they had to a very large extent lost their electric excitability. The lungs were very full of venous blood, the kidneys anæmic. There was great irritation at the point of injection.

Rabbits.—Rabbits required very much larger doses than dogs; 1 or 2 centigrammes caused a good deal of depression and marked slowing of the heart, but the animals had apparently recovered next day; 3 centigrammes and upwards, given subcutaneously, always proved fatal—that is to say, fifteen times the minimum lethal dose for a dog. As rabbits cannot vomit, the symptoms consisted simply in great muscular depression, slowing and irregularity of the heart, and death after several hours, sometimes after marked attacks of dyspnoea.

Post mortem, the condition of the chambers of the heart varied considerably as regards systole and diastole; the voluntary muscles were always very remarkably diminished in electric excitability, and intestinal peristalsis had ceased. The conditions generally were practically identical with what was found in dogs.

Blood Pressure.—The experiments were made on rabbits under ether or ether and morphine. The tracings were taken

from the carotid artery with a mercurial manometer, and the urechitin was given by the jugular vein. The results obtained were not always similar, but the differences can be readily understood as they depend on the extent to which the heart was affected. Most frequently the heart beat more slowly, and there occurred a rise of blood pressure, these conditions being maintained for some time, or passing (especially if more urechitin was given) into great slowing and various other irregularities, usually with fall of blood pressure, and finally stoppage of the heart. The tracing from such an experiment is shown in Fig. 2.

In other cases the slowing of the heart was so great that it was unable to maintain the pressure in the arteries, and hence no, or only a slight, rise of blood pressure took place, or frequently there was a marked fall. This condition might last for a considerable time, or the heart might be rapidly paralysed. The pulse waves were exceedingly large and ample, often bigeminous or otherwise irregular. The tracing from such an experiment is shown in Fig. 3.

I quote the details of one experiment, namely, the one from which Tracing 2 is taken.

EXPERIMENT 4.—Rabbit Etherised.—Cannula in Carotid Artery.

Time.	Mean Blood Pressure in Millimetres of Mercury.	Pulse in ten seconds.
11.46	124	22
11.48	129	21
<i>Two milligrammes urechitin.</i>		
11.48½	158	20
11.49	160	18
11.50	145	21
11.53	152	20
11.55	147	19
11.56	151	17
11.57	143	18
<i>Two milligrammes urechitin.</i>		
11.58	180	16
11.58½	160	16
11.59	150	16
12	128	17
12.1	108	16
<i>Two milligrammes urechitin.</i>		
12.2	89	7
12.4	102	9
12.5	122	15
<i>Two milligrammes urechitin.</i>		
12.6	152	14
12.7	136	13
12.8	Falling rapidly	
12.10	Heart stopped	

EXPERIMENTS WITH URECHITOXIN.

Urechitoxin also proved to be a muscle and heart poison, but very much less active than urechitin. It was given dissolved in water.

Frogs.—As with urechitin, the effects are not outwardly very striking. There is a gradually deepening motor and sensory paralysis, due to failure of the circulation, and death occurs from stoppage of the heart. Doses from $\frac{1}{10}$ to $\frac{1}{2}$ milligramme ($\frac{1}{10}$ to $\frac{1}{2}$ grain) proved fatal in one or more hours, according to the amount given.

On the heart the effects vary according to the dose. When a large dose ($\frac{1}{4}$ to $\frac{1}{2}$ milligramme) is administered, the action and results are exactly similar to what has been previously described under urechitin, the ventricle stopping in extreme systole.

When, however, a smaller dose ($\frac{1}{4}$ to $\frac{1}{10}$ milligramme) is given, the heart, after previous changes, finally stops in diastole. Shortly after administration of the poison the heart shows increased systole and diastole, pouching, and other irregularities, but the final result is stoppage in full diastole. Often for a time during the poisoning the ventricular diastole is incomplete, but this condition is recovered from, the heart tends to make long pauses when it is fully dilated, and finally stops in one of these. If, immediately or some time after stopping, the ventricle be stimulated mechanically or by electricity, it passes into complete systole and does not again dilate. Previous administration of atropine did not affect the phenomena in any way, either after a large or small dose of urechitoxin.

Experiments made on the isolated heart with Williams's apparatus gave tracings and a rise of pressure similar to those which have been previously described as occurring with urechitin. It proved to be much less poisonous, however. Thus 1 part of urechitoxin to 100,000 parts of circulating

fluid stopped the heart in six minutes, 1 in 200,000 in eight minutes, 1 in 400,000 in eleven minutes, 1 in 800,000 in forty-two minutes, while 1 in 1,000,000 left the heart still beating after seventy-five minutes.

Circulation of a saline fluid containing urechitoxin in solution, through the blood vessels of frogs, did not cause them to contract, even when the solution was a saturated one (about 1 in 2,000).

Dogs.—In dogs the chief symptoms are vomiting and muscular weakness, with slowing and irregularity of the heart. In some cases, however, the poison (when given subcutaneously) affects the heart very slowly, so that there are no immediate symptoms, and death is considerably delayed. The following experiment shows this:

Experiment 5.—A dog, weighing 36 lbs., received 5 milligrammes urechitoxin ($\frac{1}{4}$ grain) subcutaneously, at 11.25 A.M. At 12.8 P.M. it was running about quite well and cheerful, and 5 milligrammes more was given. All the afternoon no change could be detected until 6.30 P.M., when it was a little depressed looking, and had little appetite for food. All next day it visibly suffering from muscular weakness, and did not eat. It died quietly on the morning of the third day from cardiac failure. *Post-mortem* examination showed the left auricle contracted and empty, the left ventricle contracted and half full of blood, the right auricle and ventricle dilated fully. The veins were over-filled, the arteries empty. The bowel was not specially contracted.

Rabbits.—These animals are affected only by very large doses. Smaller quantities than 2 grains produced no visible effect, about 5 grains being necessary to cause death. This is only the case when the urechitoxin is given subcutaneously; when injected into the jugular vein it kills in comparatively small doses, such as 5 milligrammes ($\frac{1}{4}$ grain). The only explanation which I can offer of this absence of action or delayed action (which is also seen in the dog) is, that when the poison is injected locally it is absorbed by the voluntary muscles of the part, which retain it, and only very slowly give it out again into the circulation to act on the heart. When, however, it is injected into the jugular vein, it reaches the heart in sufficient quantity at once to affect it very markedly and cause stoppage. That the voluntary muscles are capable of absorbing substances injected subcutaneously in this way, and of thus delaying their general action on the organism, I have shown in my paper on benzoylcegonin,⁷ and I have found that caffeine behaves similarly.

Blood Pressure.—Urechitoxin acts on the blood pressure and modifies the pulse wave very much in the same way that urechitin does. My experiments were made on rabbits under ether. If the heart be brought slowly under the influence of a small dose of urechitoxin the pulse is slowed and the blood pressure rises. Larger doses are apt to bring on rapidly great irregularities and a fall of pressure, the heart beats being slowed or quickened at different periods of the experiment. The heart in many cases was so much slowed that the blood pressure did not rise, sometimes even fell. In illustration of the action, I quote the details of one experiment in which the drug rapidly proved fatal, and give a tracing (Fig. 4) from another in which smaller doses were given, and the effects were maintained for a much longer time.

EXPERIMENT 6.—Rabbit Etherised.—Cannula in Carotid Artery, and Tracing Recorded.

Time.	Mean Blood Pressure in Millimetres of Mercury.	Heart Beats per Ten Seconds.	Remarks.
12.35	148	17	—
12.36	<i>5 milligrammes urechitoxin per jugular vein.</i>		—
12.36½	157	17	—
12.37	205	14	Pulse large and bigeminous
12.38	210	12	Pulse large and regular
12.39	223	18	Pulse smaller and beating in threes
12.40	163	11	—
12.41	225	28	Pulse smaller and irregular in size
12.42	164	18	—
12.43	144	14	—
12.43½	182	17	—
12.44	131	13	—
12.44½	179	14	—
12.45	121	9	—
12.46	36	—	—
12.50	0	—	—

⁷ *Journal Anat. and Phys.*, 1886.

Here the heart was very seriously affected, and rapidly passed through various stages of great irregularity to stoppage.

Summary.—From the foregoing experiments it is evident that urechitin is a poison of a very active kind, which may be included in the digitalis group. Its action on the frog and frog's heart, the effect on dogs, the comparatively large doses necessary to affect rabbits, and its action on the circulation, point to a similarity between it and all other substances which have now been recognised as essentially resembling digitalis in their physiological actions. Urechitoxin may also, for the present, be included in the same group, which is, as now understood by pharmacologists,^{*} a pretty wide one, and embraces substances which are certainly not quite identical in action. The differences, however, have not been satisfactorily worked out. Urechitoxin, although essentially a muscle and heart poison, shows certain well-marked peculiarities in its action; these, and the finer details of the actions of both substances, I have made no attempt to work out at present, as the primary object of the research was to determine whether the marvellous stories told regarding its poisonous action were true or not. As in most tales of the kind there is a certain admixture of truth and falsehood. If a full lethal dose of the dried leaves, or any other preparation of the plant, be administered, symptoms of poisoning will certainly supervene within a limited period, and death will occur either in a few hours or in a day or two. The circumstances would most probably be such as to arouse a suspicion of poisoning. A single dose of the poison cannot be so administered as to be fatal "after the lapse of days or weeks."

On the other hand, if repeated minute doses can be given—doses insufficient to cause immediate symptoms—there seems to be no doubt, from Bowrey's experiments, that an animal (or man) may remain all the time in apparently good health, and then die suddenly. To effect this, however, these minute doses would have to be given frequently and regularly. It is conceivable that minute amounts of the dried leaves might be so administered without arousing suspicion, if the poisoner had daily access to the food of his victim, and it is quite probable that the Obeah poisoners were often enough able to do this.

The explanation of the long-delayed action and sudden death in such cases is to be found in the well-known cumulative action of digitalis and similarly acting bodies. These substances, after entering the circulation, are absorbed by the heart muscle, and most probably enter into chemical combination with it. The combination seems to be a close one, so that the poison is but slowly excreted. Small repeated doses cause an accumulation of the poison in the heart muscle until a stage is reached when the heart is so thoroughly poisoned that death ensues from cardiac failure. Clinically such accidents, although in a minor degree, are well known and recognised in the case of digitalis.

It is improbable that the urechites suberecta will ever prove to be of value as a cardiac tonic. I have made no observations in this direction, as it seems to possess in a high degree the objectionable cumulative properties which have been so often remarked in the case of digitalis.

REPORT ON

THE ABDUCTOR AND ADDUCTOR FIBRES OF THE RECURRENT LARYNGEAL NERVE.¹

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CLINICAL and pathological experience (Semon, Rosenbach) has shown that in organic and progressive affections of the recurrent laryngeal nerve the abductor fibres are prone to succumb before the adductor. Freezing the nerve (Gad and B. Fraenkel), the electrical excitability of the human laryngeal muscles after death (Jeanselmie and Lermoyez), and of

those of animals (Horsley and Semon)—all give a similar result; the exactly opposite effect is produced by ether reaching the laryngeal muscles through the circulation (Hooper, Horsley, and Semon). Semon has suggested that possibly the fibres and centres dominating over the two functions are strictly differentiated. Morell Mackenzie considered that possibly the proneness of the abductors to succumb before the adductors in affections of the nerve, especially compression by tumours, was due to the former fibres being superficially and circumferentially arranged in the nerve trunk. Experimental researches have been made by Hooper, Onodi, and Dionisio, and have been referred to at length in the full paper. The general plan on which my research² was conducted was as follows:—

1. The separation and isolation of the different bundles of nerve fibres of which the nerve trunk is composed, electrical excitation of each separate bundle, and observation of the effects produced on the vocal cords by such excitation.

2. Exposure of the different bundles of nerve fibres, under exactly similar circumstances, to the drying influence of the external air, with observation of the relative duration of vitality possessed by the different bundles.

3. (Control) Tracing by dissections, each bundle of nerve fibres separated in the nerve trunk to its termination in the mucous membrane, or in a muscle of the larynx.

4. (Control) Exposure of the muscles of the larynx immediately after death, and direct observation of them during excitation of the separate bundles of nerve fibres, this being controlled by occasional excitation of individual muscles themselves.

5. (Control) Observations of the muscular degenerations which followed division of one or other bundle of nerve fibres in the nerve trunk three weeks after such division.

The difficulties which attended this last set of experiments were very great, so that out of seven experiments three were unsuccessful; however, those that were successful yielded such striking results that, in view of the great difficulties attending them, further multiplication of these experiments has been considered unnecessary. Twice the abductor bundle of fibres was alone divided, and *post mortem* the abductor muscle on the same side as the injured nerve alone found atrophied and degenerated; once the adductor bundle was alone divided, and the adductor muscles on the same side alone found atrophied and degenerated; and once a sensory bundle was divided, in which instance none of the laryngeal muscles showed any sign of atrophy or degeneration.

The conclusions which are drawn from the results of these experiments are:

1. That the abductor and adductor fibres in the recurrent laryngeal nerve are collected into several bundles, the one distinct from the other, and each preserving an independent course throughout the nerve trunk to its termination in the muscle or muscles which it supplies with motor innervation—a condition of things the possibility of which was suggested by Semon more than ten years ago, from the evidence of pathological facts.

2. That while in the adult animal simultaneous excitation of all the nerve fibres in the recurrent laryngeal nerve results in adduction of the vocal cord on the same side, abduction is the effect produced in a young animal by an exactly similar procedure.

3. That when the abductor and adductor fibres are exposed to the drying influence of the air under exactly similar circumstances, the abductors lose their power of conducting electrical impulses very much more rapidly than the adductors; in other words, they are more prone to succumb than are the adductors—a fact which has long been recognised and insisted on by Semon as being the case in the human subject, and in support of the truth of which that observer has adduced many powerful arguments.

4. That, even in the young dog, the abductor nerve fibres, though preserving their vitality much longer than in the case of the adult animal, nevertheless in the end succumb before the adductor fibres.

5. That this death commences at the point of section of the nerve, and proceeds gradually to its peripheral termination, and does not take place in the whole length of the nerve simultaneously.

6. That it is possible to trace anatomically the abductor and adductor fibres throughout the whole length of the recurrent laryngeal nerve to their termination in one or other

² Dogs were, without exception, the animals used, and in every case ether narcosis was produced and continued throughout the whole course of the experiment, at the end of which the animal was killed by an overdose of the narcotic.

^{*} Schmiedeberg, *Archiv f. expt. Path. und Pharmak.*, xvi, 149; *Beiträge zur Kenntnis der pharmakologischen Gruppe des Digitalins*.

¹ Part of the expenses connected with this experimental research have been defrayed by a grant from the Scientific Grants Committee of the British Medical Association. Details were given in full in a paper read before the Royal Society, March 31st, 1892.