THE PHARMACOLOGY OF APOCYNUM CANNABINUM*

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I

Apocynum is a member of the group of cardiac tonics, and is official in the United States. It has been credited with being the most powerful indirect diuretic known. Descriptions of the drug are given by Paine¹ and two Russians, Gliski² and Gvozdinsky.³ In this country records⁴ of patients suffering from pleuritic effusion have been given, under the influence of Apocynum it was thought that the fluid subsided 'rather quickly.' Hauseman⁵ first suggested that Apocynum might contain a cardiac poison allied to the digitalin group, and in 1883 Schmeideberg isolated two so-called active principles, apocynin and apocynëin. Rose Bradford showed that its principal action was upon the heart. Sokoloff⁶ showed that the drug caused slowing of the heart's action, 'enlargement of the pulse' wave and marked rise of blood pressure. Petteruti and Somma⁷ found different results were obtained according as to whether they used the decoction or the tincture, the decoction acting chiefly on the stomach and intestines causing catharsis and emesis, when this action was

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absent there was diuresis and acceleration of the heart beat. The tincture was stated to be unirritating to the gastro-intestinal tract even in large doses. The emetic and cathartic action of the decoction was attributed to the admixture of the bitter fibre of the wood with the bark of the root.⁸ Further experimental work was carried out by Dortschewski,⁹ Klopotovitch¹⁰ and Lapshin. Since my experiments have been completed, I find that Laidlaw and Dale have been working with a crystalline active principle isolated by H. Finnmere.¹¹ Some apology is, therefore, necessary for the late publication of this paper.

The preparations used in my experiments were (a) *Tinctura Apocyni Cannabini*. One part of the root to ten parts of 60 per cent. alcohol. (b) *Apocynin*.

The animals employed were frogs, rabbits, dogs and cats. Frogs were used for simple injections into the dorsal lymph sac, and for demonstrating the action of the drug on striated and unstriated muscle, the gastrocnemius muscles and a sectional ring of the stomach being used respectively. Perfusion experiments were also performed by tying a cannula into the hepatic vein. The effect of the drug on the heart in situ, and also in connection with recording apparatus, was also observed. The frogs were always pithed, except those used for simple injections.

Observations were made with rabbits on the effects of injecting both large and small quantities of the drug; the action on the vascular system was also determined.

Dogs and cats were employed for obtaining cardiometer and oncometer records; experiments on the urinary flow were performed on dogs.

Chloroform, A.C.E. mixture and urethane were used as anaesthetics. In a few cases no anaesthetic was used, the animals being pithed.

II. ACTION

1. *Vascular System.*

(a) Heart. (i) Frog. The most important action of *Apocynum* is seen in its effects on this organ. In a general way *Apocynum* acts on cardiac muscle in the same manner as it acts on both striated and unstriated muscle. The tonus is always increased, the systole and diastole are greater in amplitude. Cardiac slowing is a marked feature.

On placing on the heart a few drops of a crude extract of the root of *Apocynum* a marked effect is immediately apparent. The beat is slowed and a clear rise of tonus occurs.

Such experiments are of little value, since the effect of a drug applied to the outside of the heart is not necessarily the same as when the drug is given by the circulation, but they suffice to indicate the probable effect.

Fig. 1 shows the movements of a frog's heart recorded by the suspension method, so that the systole is represented by the upstroke. A saturated alcoholic solution of Apocynin was used for injection into the subcutaneous tissues. Section I shows the normal beat. In II is seen an increase of systole and diastole with some slight slowing after a subcutaneous injection of 10 minims of the Apocynin solution. An increased effect is noticed in III and IV after applying the solution directly to the heart. Section V gives the results of placing crystals of Apocynin on the heart. The greatest amplitude and most marked slowing of the beat is seen in the first part of VI, after this, the beat gradually quickens until it becomes very quick and irregular (delirium cordis) and the heart dies in systole.

The experiment illustrated in fig. 1 is particularly interesting, as it shows that the substance Apocynin is active, and that it causes an effect like the tincture. It is also of some interest to observe the delirium cordis, as this is a condition particularly difficult to obtain in the frog.

After a subcutaneous injection of $1\frac{1}{2}$ minims of tincture of Apocynum in the frog, a similar series of events occurred, and death ultimately occurred in systole.

These simple experiments show that the crude extract of Apocynum, the glucoside Apocynin, and the ordinary standard tincture, all give rise to the same series of effects in the frog. The heart beat is slowed and increased in amplitude, later in the action the beat becomes quicker and irregular and death occurs in systole. The development of these effects was also seen in tracings of perfused frog's hearts.

(ii) Mammalian heart. Experiments were undertaken to demonstrate the effect of small doses of Apocynum on the isolated mammalian heart.

Fig. 2 represents the records of an experiment in which the drug was introduced (5 c.c. Tinct. Apocyni, 1 in 6,000) into the side tube of the perfusion apparatus so that after considerable dilution with the Ringer's solution in the apparatus all the drug would rapidly pass through the isolated heart. In other words, five minutes after the injection, no Apocynum would be in the circulating fluid. Section I shows the heart beating normally. II shows the effect five minutes after injection; the rate of the beat is the same, but the amplitude of the systole is increasing. Tracings III and IV show still later effects, 20 and 25 minutes after injection the rate of beat still remains about the same, 42 to the minute. In V, a record taken 30 minutes after injection, the heart is beating much more slowly and ventricular beats are being lost, so that two auricular beats are shown to each ventricular beat, and in the later portion of the tracing the ventricular beats entirely cease for a time. This stage is rapidly succeeded by that of delirium cordis in which the heart beats very rapidly and the tonus of the cardiac muscle rises (VI, VII, and VIII). The heart ultimately stops in systole (IX and X) fifty minutes after the injection.

It may be noted here that the death of this heart, which is typical of many experiments, results from a very small dose of the drug, in spite of

FIG. 1.

Heart. Frog. I.—Normal beat.
II.—After subcutaneous injection of 1:100,000 alcoholic solution Apocynin.
III.—After applying solution of Apocynin directly to the heart (1st time).
IV.—" " " " (2nd time).
V.—After applying crystals of Apocynin directly to the heart.
VI.—Continuation of V. Delirium cordis and death.

FIG. 2.

Rabbit's Heart. Isolated. I.—Normal beat, perfused with Ringer's solution.

II.—Five minutes after injecting by side tube 5 c.c. 1 in 6000 Tincture Apocynum.

III and IV.—Later stages.

V.—Dropping of ventricular beats.

VI and VII.—Rising tonus.

VIII, IX and X.—Arrhythmia, delirium cordis, and death in systole.

Scale $\frac{1}{3}$ linear.

the facts that the administration was of short duration, that the small quantity of fluid containing the drug was quickly washed away by the constant flow of fresh saline solution during the whole of the experiment, and that only one dose was given. Evidently not all the drug administered is removed by the constantly flowing saline solution, but it would seem that some part of the dose remains behind in a kind of fixed combination with the cardiac muscle, and that it is this portion of the drug which is responsible for the production of the ultimate toxic effects. This may be taken as an example of cumulative action. I would like to compare this drug with strychnine or atropine which, when administered, induce a certain definite action but are rapidly excreted. Apocynum, on the contrary, is fixed by the heart, and continues to produce an effect on the heart when no drug is present in the coronary circulation.

In other experiments the heart was perfused with the Ringer's solution, but after a short time this was replaced by a saline solution of the drug, so that the heart was bathed during the remainder of the experiment with a diluted tincture of Apocynum (1 in 6,000): this is a condition which would approximate in a remote degree to that prevailing during life while any drug was continuously and regularly administered, and which was absorbed gradually into the circulation. Such experiments showed what may be regarded as the therapeutical action of the drug, systole was augmented, diastole prolonged, and the tonus was unaltered; later the poisoning action was shown by the acceleration present. The acceleration was further increased; so rapid was the heart that diastole was incomplete, the heart beats followed one another too rapidly for complete diastole to occur. Marked arrhythmia was present and tonus was increased, a condition which only occurs when the heart is beginning to die. In some tracings, groups of two following beats were seen, so that there is a greater interval between each group of two following beats than between the individual beats of each group. This is a condition which appears in that form of irregular pulse known by the names of coupled beats, allorhythmia, pulsus bigeminus (twin pulse), and pulsus biferiens. It is well known clinically that this type of pulse may at any time appear during the administration of Digitalis, especially when the effect is becoming cumulative, and it seems also that this is one of the toxic effects of Apocynum. Experimentally, this form of heart beat is only seen when the heart muscle has been rendered 'hyperirritable' by a drug of the digitalis group. One heart died in a state of extreme contraction, having been at work for three hours.

Some further experiments were performed with the cardiometer. Cats anaesthetised with urethane were used for this purpose, and the drug was given directly through the circulation. Apocynum in small doses increases the output of blood from the heart; the effect comes on slowly, but is very prolonged. This effect is, of course, the true criterion of a cardiac tonic, an increased cardiac output being the true sign of stimulation.

The action on the rate of the heart beat varies according to the stage of action of the drug. In the therapeutic stage the heart is slowed, and is quickened in delirium cordis, which constitutes the poisoning stage of the drug.

The slowing effect of Apocynum on the heart, as indicated by the pulse and also the influence on the respiration, was shown generally by the following simple experiment, for which I am indebted to Professor Dixon. A small-sized dog was given 5 minims of Tincture of Apocynum subcutaneously. The data given in the following table indicate the changes in the pulse rate and respiration :—

Time		Pulse		Respiration
4.30	...	114	...	20
4.45	...	120	...	16
4.55	...	76	...	14
5.0	...	96	...	16
5.6	...	108	...	20
5.15	...	108	...	16

Similar results were obtained on man.

(iii) Relative toxicity of Apocynum on the heart. For this purpose solutions of various strengths of the substance Apocynin and of the Tincture of Apocynum were injected into the dorsal lymph sac of the frog; Dixon and Haynes¹² having previously shown that this forms a suitable means for determining the relative activity of the cardiac tonics.

Effects of injections of Apocynin :—

EXP. I. 5.30 p.m. 1 c.c. of an 0.5 solution of Apocynin was injected into the dorsal lymph sac of a frog weighing 19 grammes.

5.35 p.m. Reflexes less brisk, respiration quickened, animal crawls about but does not sit up.

5.55 p.m. Respiration jerky, irregular groups of two or three respirations occur in quick succession. Responds only to forcible pricking stimulation.

6.20 p.m. By this time the frog had completely recovered.

EXP. II. 3.45 p.m. 2 c.c. of an 0.5 solution was injected into the dorsal lymph sac of a frog weighing 12 grammes.

4.45 p.m. By this time the frog had fully recovered, having been only sluggish for the first half hour after injection,

Exp. III. 3.50 p.m. A frog weighing 14 grammes was injected with 3 c.c. of 0.5 solution.

3.56 p.m. Frog motionless in dorsal position, pupils widely dilated, responds to pinching toe.

4.10 p.m. Breathing very feeble, struggles at times.

4.25 p.m. Turned on to its feet, pupils contracted.

5.0 p.m. Recovered but slightly, slow in its movements.

Exp. IV. 5.0 p.m. A frog weighing 16.5 grammes was injected with 3 c.c. of a 1.25 per cent. solution of Apocynin.

5.5 p.m. Heart beats 60 per minute.

5.13 p.m. Heart beats 48 per minute.

5.15 p.m. Animal very feeble, does not respond to stimulation. The heart was now exposed, the ventricle was feebly contracting and ceased in diastole at 5.25 p.m. The auricles and sinus venosus still contracted in groups of three beats at a time.

5.35 p.m. Dead.

Effects of injections of the Tincture of Apocynum:—

Exp. I. 4.45 p.m. Frog weighed 20 grammes. 15 minims of the tincture injected.

4.50 p.m. Animal helpless in dorsal position.

5.5 p.m. Slight corneal reflex.

5.20 p.m. Dead.

Exp. II. 4.40 p.m. Frog weighed 12.5 grammes. 7 minims of the tincture injected.

5.5 p.m. Crawls with difficulty.

5.15 p.m. Slight corneal reflex.

5.20 p.m. Dead.

Exp. III. 4.38 p.m. Frog weighed 15 grammes. 3 minims injected.

5.5 p.m. Recovers from the dorsal position with difficulty.

5.30 p.m. Dead; ventricle firmly contracted.

Exp. IV. 3.53 p.m. Frog weighed 17 grammes. 2 minims injected.

4.30 p.m. Dead.

Exp. V. 3.55 p.m. Frog weighed 12 grammes. 1 minim injected.

5.25 p.m. Leaps and falls on its back, recovery difficult, tumbles over.

5.30 p.m. Crawls with difficulty.

5.35 p.m. No recovery from dorsal posture, moves limbs. Hind limbs paralysed before upper ones.

5.45 p.m. Dead.

These simple injection experiments serve to demonstrate the comparative inactivity of Apocynin, and the toxicity of the tincture of Apocynum upon the heart. Smaller amounts than one minim of the tincture had no fatal effect. One minim may therefore be regarded as the minimum lethal dose for the standard tincture of Apocynum.

From the results of two of the experiments in each of which the frogs died in 35 minutes, one from the effects of Apocynin and the other from the tincture of Apocynum, it appears that 3 c.c. of a 1.25 per cent. solution of Apocynin is about equivalent to 15 minims of the tincture of Apocynum in toxicity. Approximately the 1.25 per cent. solution of Apocynin is

$3\frac{1}{2}$ times less toxic than the tincture of Apocynum. For the sake of comparison, the following table of the minimum lethal doses of the most commonly used cardiac tonics is appended:—

Drug	M.L.D. (in minims) per 100 grammes of frog
Tinct. Digitalis (13)	12.5
Tinct. Strophanth. (13)	1.47
Tinct. Scillae (13)	12.5
Tinct. Apocyni	8.33
Apocynin (1.25 per cent. sol.)	29.15

From this it seems that the tincture of Apocynum is about one and a half times more toxic than the tinctures of Digitalis and Squill, and nearly six times less toxic than the tincture of Strophanthus. The substance Apocynin possesses a fair degree of activity, although it is the least toxic of the series in the above table.

All the experiments show that Apocynum acts on the heart somewhat similarly to Digitalis in causing slowing of the heart beat. The principal action is to raise the tonus or condition of continued contraction of the muscle of the heart, especially in toxic doses the ventricle may be so firmly contracted that it appears quite pale. This is well seen in the frog's heart and also in the mammalian heart when mounted on the perfusion apparatus. If a sufficiently small dose of the drug is administered the first effect usually noticed is a gradual increase in the extent of the heart beat, the increase in the excursions of the recording lever increasing until the vertical height of the tracing becomes two or three times greater than it was before the drug was administered. This increase in amplitude of beat is accompanied by a decreased rate of beat, which is more marked in Batrachian than in Mammalian hearts. The amount of slowing produced varies from rather less than half the original rate up to not more than three times as slow. The heart at this stage is quite regular, relaxation is more complete and so is contraction; under favourable circumstances the contraction of the auricles may equal the contraction of the ventricles in extent. This condition of affairs should represent the most perfect therapeutical effect of the drug.

When this is being most completely manifested a change in the character of the beat more or less suddenly takes place, some quickening and irregularity occur. The ventricular portion of the beat may be dropped, and each chamber of the heart in mammals may contract or not independently of the rest without any order or sequence. This condition of irregularity, combined with extreme rapidity of beat, constitutes the

condition of delirium cordis, and is a toxic effect of the drug. In mammalian hearts the delirium ends in fibrillary twitching. Most of the slowing of the heart beat is due to the action of the drug on the nerve terminals of the vagus in the heart muscle; for if these terminals be paralysed by atropine the slowing produced by the Apocynum is much less decided, although there is a very slight amount seen, which must be due to the direct action of the drug on the muscular tissue of the heart. The slowing effect gives place to a stage of quickening; during this quickening the vagus nerve appears to be paralysed, since no slowing of the beat can be obtained either by electrical stimulation of the nerves or the injection of a drug such as pilocarpin or muscarin, which are known to excite vagal endings. Now, Apocynum is not a paralytic drug; so far as we know, it depresses no nerve endings, and its effect in preventing vagus inhibition has a more ready explanation than the supposition that it paralyses vagal endings like atropin. Apocynum acts essentially on heart muscle by increasing its irritability, and in the later stages of its action, this irritability shows itself by marked acceleration. The vagus nerve is intact, but such is the irritability of the cardiac muscle that it has no longer the power to hold it in check. The acceleration of beat, accompanied in its later stages by irregularity, stimulates that part of the heart known as the excito-motor area, and so the rapidity of beat is increased continually until fibrillary twitchings occur. The amount of work done by a heart under therapeutic doses of Apocynum is increased, or in other words, the output of blood is increased. The increase in the amount of work is due to the combined action of the Apocynum on the nervous and muscular structures of the heart. The increased force of the beat is due to the stimulant effect of the drug on the muscle alone, the stimulant effect on the vagus endings produces some inhibition, so that the heart becomes slower, the diastole is prolonged, and the heart is more completely filled with blood. The systole is also increased, not only in strength, but also in length, so that there results a more complete emptying of the heart in systole.

(b) Blood Vessels. The general effect of Apocynum on the blood vessels was shown by the perfusion of a pithed frog. The hepatic vein of a fair-sized frog was displayed, and a small cannula tied into it. This cannula was then connected with a simple perfusion apparatus. One leg of the frog was cut off below the knee, so that the perfusing fluid as it circulated through the body of the frog dripped from the cut end of the limb. The drops were counted at short intervals for periods of one

minute; the frog was first perfused with normal saline solution, and then with a solution of 1 in 60 Tinet. Apocyni. This experiment distinctly showed that Apocynum is a powerful vaso-constrictor, as it diminished the flow from 31 to 6 drops per minute. This effect is a peripheral one, as the brain and spinal cord of the frog were destroyed, so that no central vaso-motor influence was at work. It may be noted that this diminution of flow was not due to any decrease of the action of the heart, as at the end of the experiment this organ was still beating vigorously. The vaso-constriction must be due to the direct action of the drug on the nerve endings or muscular coats of the blood vessels.

The vaso-motor effects of Apocynum were further demonstrated by another experiment.

The record in Fig. 3 was taken from a pithed cat and the blood pressure recorded in the usual way with a mercury manometer, the changes in the intestinal vessels were recorded by an oncometer. Two c.c. of a 1 in 4 solution of the tincture were injected by the side tube into the jugular vein, and at once a very marked rise of blood pressure is seen. This was accompanied by a lowering of the oncometric curve, which indicated a diminution of the intestinal volume owing to the powerful contraction of the intestinal vessels, after this the volume increased owing to the dilation of the organ as a whole, no doubt brought about by the great increase in the cardiac output. The volume of the intestine at about the maximum blood-pressure is the resultant of two factors, namely increase of size from the distension caused by the greater blood-pressure, and decrease of size owing to the great vaso-constriction as shown by the volume pulse. During the supervention of delirium cordis the intestinal volume again underwent decrease; owing to the marked fall in blood-pressure the intestine was less distended and the vaso-constriction factor became evident. At the end of the experiment the blood-pressure fell rapidly and suddenly to zero, and intestinal pallor was noticeable. The administration of Atropin had no effect on the final result as the vagal influence had already been annulled by the Apocynum: this is due to the increased irritability of the heart muscle which can no longer be controlled by the vagus.

In pithed dogs similar experiments were performed with like results. Further experiments were undertaken on the renal vessels, and the same type of constriction as in the splanchnic vessels occurred. In every case, then, in which this drug was perfused through the vessels or given internally, vaso-constriction resulted. To determine whether the drug acts on muscle or nerve endings, the pulmonary vessels of a mammal were perfused. The first effect was a short dilatation, followed by a profound and prolonged constriction; adrenalin, which was first injected, having no influence on the blood flow. Therefore, since we know that the pulmonary vessels are not innervated, the action of Apocynum must be on the muscle fibre. The constriction of the blood vessels produced by Apocynum is well marked, not only during its therapeutic action, but also during the development of its toxic effects. Finally, all the experiments,

such as perfusing a frog's body or a mammal's lung, or recording changes in the volume of kidneys, loops of bowel, and forelimbs, show very conclusively that this drug is a powerful vaso-constrictor. And it is to be noticed that this effect is a peripheral one, due to the direct action of the drug on the muscular tissues of the blood vessels, since the constriction still takes place when the vaso-motor centre in the medulla is destroyed and also when the drug is perfused through blood vessels which have no

FIG. 3.

Cat—pithed. Artificial respiration. Upper tracing taken from intestine enclosed in oncometer; lower tracing records blood pressure. Delirium cordis—death.

2 c.c. $\frac{1}{4}$ strength Tinct. Apoc. introduced per jugular vein at 1st arrow. Atropin at 2nd arrow.

Time 20 seconds.

Scale $\frac{1}{3}$ linear.

vaso-motor nerve endings; the integrity, or otherwise, of the nervous system makes no difference to this action of Apocynum on the vascular tissues.

(c) Blood Pressure. In every experiment where the blood pressure has been taken, certain changes in the tracings of the blood pressure have always been recorded. In a pithed dog an immediate rise of blood pressure

is recorded after the injection of 1·5 c.c. of Tinct. Apocynum. The slowing of the heart beat was reflected in the tracing. This is the therapeutical effect of the drug, but in this case it quickly gave place to rapidity and irregularity of the heart beat and a further rise of blood pressure; this condition is entirely due to the enormous dose of the drug given; it is, of course, never seen when the dose is moderate. The delirium cordis is increased by the further injection of 5 c.c. of the tincture, and the blood pressure ultimately falls to zero.

This experiment was typical, and the same results with similar effects are obtained in cats and rabbits after massive doses of the drug.

The following experiment shows the effect of the drug on the blood pressure with the heart atropinised. A rabbit was pithed and connected with the artificial respiration pump; the blood pressure was recorded in the usual way. After two injections of 1 c.c. of an 0·5 per cent. solution of Atropin, the cardiac terminations of the vagus were paralysed, and, consequently, the heart rate increased and the blood pressure rose to some extent; some slowing of the heart beat and a rise of blood pressure occurred after a hypodermic injection of 20 minims of Tinct. Apocynum; delirium cordis eventually prevailed. In this experiment the slowing produced was entirely due to the influence of the drug on the heart muscle alone.

The action of Apocynum on the blood pressure is due to the combined effect of two or more factors. In all the experiments the general effect of Apocynum has been to produce a rise of blood pressure, and this occurs in spite of the slowing of the heart due to the stimulation of the vagal endings. The rise in blood pressure depends on two factors, (1) the increased output from the heart per minute, (2) vaso-constriction. It is when these factors, namely, the cardiac slowing, with the increased strength of beat resulting in augmented output, and vaso-constriction are most in evidence that the drug produces its therapeutical effect. The rise of blood pressure is thus the mean result of the above changes. Sometimes before the typical rise of blood pressure occurs there is a fall in the normal blood pressure; this is due to the sudden stimulation of the vagus overshadowing for the time being the other effects of Apocynum. I have more than once in this way seen the heart die straightway from vagal inhibition. When delirium cordis supervenes the blood pressure undergoes the most extreme variations, or it may at once fall to zero.

Fig. 4. A cat was anaesthetised with urethane and the blood-pressure recorded in the usual manner. The tracing shows a very perfect delirium cordis, in which the vagal influence is entirely eliminated as no slowing effect is produced by the injection of 5 c.c. of an 0·5 per cent. solution of Pilocarpin. Three c.c. of Tinct. Apocynum had previously been injected.

With large doses the irritability of cardiac muscle rapidly increases, and the heart beat quickens; and hence in this stage the blood pressure rises greatly, both on account of increased cardiac output and vasoconstriction. Still later, as the irregularity of auricles and ventricles further increases, they take on their own rhythm; sometimes the auricles

FIG. 4.

may force blood into the ventricles during diastole of the latter, in which case when the ventricles contract the blood pressure rises. Sometimes there is no sequence between auricles and ventricles, and then ventricular contractions fail to keep up blood pressure. At this stage records of blood pressure show great variations, sometimes bounding up to 50 mm. of mercury for half a minute, and sometimes falling almost to zero.

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Besides the action on the heart and blood vessels, Apocynum has some influence on the kidneys. The kind of action the drug has on the excretory function of the kidney is indicated by the following experiment:—Urethane and morphia were injected into a dog, anaesthesia being maintained in the usual way by the A.C.E. mixture. The blood pressure was recorded by a mercury manometer and the artificial respiration pump connected with the trachea. The abdominal cavity was opened, and one ureter was dissected out and a cannula inserted. The urine was collected in a measuring glass every two minutes. Sixteen and eighteen drops of urine passed in equal periods of time, with a rise of blood pressure; twenty-three and twenty-one drops of urine passed in equal periods of time, after the injection of 1 c.c. of a 1 in 10 solution of Tinct. Apocynum.

Observation		Amount of Urine flowing in two minutes
1	...	2·3 c.c.
2	...	2·2 c.c.
3	...	2·1 c.c.
4	...	1·7 c.c.
5	...	1·8 c.c.
6	...	1·3 c.c.
7	...	1·0 c.c.
8	...	1·2 c.c.
9	...	0·8 c.c.
		0·5 c.c. (1 in 2 sol.)
10	...	Tinct. Apocynum injected
		0·6 c.c.
11	...	0·4 c.c.
12	...	0·9 c.c.
13	...	1·1 c.c.
14	...	1·3 c.c.
15	...	1·2 c.c.
16	...	1·3 c.c.
17	...	0·8 c.c.
18	...	0·8 c.c. urine blood-stained
		Sod. sulphate solution
		injected by side tube
19	...	1·2 c.c.
20	...	3·2 c.c.
21	...	3·2 c.c.
		1 c.c. Tinct. Apocynum injected
22	...	4·3 c.c.
23	...	5·5 c.c.
24	...	1·5 c.c.
		1 c.c. Tinct. Apocynum injected
25	...	1·2 c.c. Delirium cordis
26	...	0·2 c.c.
		Death
27	...	0·0 c.c.

It is to be noticed that the increase of urinary flow is coincident with the rise of blood pressure. Apocynum is sufficiently irritant in character to cause the appearance of blood in the urine. The administration of a saturated solution of Sodium Sulphate by the jugular vein causes a very much greater diuresis than Tinct. Apocynum; the latter is very feeble as a direct diuretic.

From this it appears that Apocynum causes a feeble increase of urinary flow in the healthy animal; if the action is continued long enough and the dose is sufficiently large, haematuria may result. The slight diuresis is not due to any direct action on the kidney, but is due to the increase of blood pressure and passage of a greater quantity of blood through the kidney; because the flow of urine in normal animals always bears a direct relationship to the condition of the renal vessels and blood pressure. If the renal vessels are much contracted the flow of urine diminishes, but if they are only slightly contracted and the blood pressure is considerably raised, the flow of urine is slightly increased. In patients with cardiac disease and a failing heart, when there is back pressure and venous congestion and oedema of the kidneys as well as in other organs, little urine is secreted. The kidney is particularly sensitive to venous blood, and ceases to excrete as soon as the oxygen reaches a certain point. Now it is just in these cases that Apocynum produces so great a diuretic effect. It acts, then, not by any direct influence on the kidney, but by improving the condition of the circulation and so sending arterial blood once more to the kidneys. The kidney vessels are at the time of diuresis actually constricted, but this constriction must not be very complete, otherwise the diuresis will lessen. As in the case of Digitalis, the increase in urinary flow is due neither to the rise of blood pressure nor to any action on the excreting arrangements of the kidney, but to the increased quantity and quality of the blood which is driven through the kidney owing to the greater force of the heart beat. The diuretic effect of Apocynum is a purely dynamical one, and is quite different to the action of such a diuretic drug as Caffeine, which produces dilation of the kidney vessels as well as a rise of blood pressure; the very marked flow of urine which follows an injection of a solution of Sodium Sulphate (see table) is an example of a third method of diuretic action, and occurs probably because the salt solution has some kind of direct action on the renal epithelium.

2. *Toxic effects.*

The drug has a penetrating bitter taste, which gradually increases until a feeling of nausea supervenes. Large doses have a very toxic effect on the mucous membrane of the alimentary canal.

Experiment. A rabbit weighing 1,350 grammes was taken, and for eight consecutive days 5 minims of Tinct. Apocynum with 10 minims of normal saline solution were injected into the marginal vein of the left ear. On the sixth and seventh days the animal was noticeably ill and exhausted; it was constantly vomiting and had lost some weight. Death occurred suddenly on the eighth day.

On examination the most obvious changes had occurred in the alimentary canal. The whole of the stomach and intestines were closely marked with haemorrhagic spots and areas, chiefly situated on the side of the gut distal to the attachment of the mesentery. On opening the stomach and portions of the intestines these haemorrhagic areas were found to correspond with ulcers of various shapes and sizes in the mucous membrane. The ulceration was general throughout the whole length of the alimentary canal, from the lower end of the oesophagus to the rectum. The ulcers varied in size from 2 cm. square, with complete denudation of epithelium, to mere punctures. These small punctate ulcers easily perforated on washing portions of the gut through from a pressure tap, when the water sprayed out in many small streams.

The main blood vessels appeared to be normal, but some small white sclerotic patches were noticed in the aorta a short distance above the semi-lunar valves. The heart was larger than would be expected. Another small sclerotic patch was noticed in the wall of the left ventricle just below the semi-lunar valves. The remainder of the organs appeared healthy.

Experiment. A second rabbit was used weighing 1,200 grammes. Two minims of Tinct. Apocynum were injected into the ear veins at intervals of one, two or three days over a period of seventy days altogether. At the end of this time the animal was killed. The left ear was oedematous and swollen to three or four times its ordinary size. The left eye was very prominent, and the conjunctiva extremely swollen and oedematous.

On opening the thorax, some slight amount of fluid was found in the pleural sacs, both lungs were oedematous. The pericardial sac was distended with fluid. There was no increase of fluid in the abdominal cavity.

One other effect of Apocynum deserves mention here. The mucous membrane of the alimentary canal, like all other plain muscle in the body, is stimulated; peristalsis is increased, and may give rise to nausea, vomiting, and diarrhoea. This effect is, no doubt, partly local; stimulation of the mucous membrane causing local reflexes through Auerbach's plexus, with resulting peristalsis. But this is not the whole explanation, since Apocynum still causes some increased movements of the alimentary canal even after absorption, or the same effect can be induced by injecting the drug directly into the circulation of an animal.

The results of the experiments serve to illustrate the extremely irritant action of Apocynum on the tissues of the body. In the first rabbit to which the larger dose was given, the intestinal ulceration may be regarded as a secondary lesion occurring at the points of elimination of the drug into the intestine. As far as the naked eye appearances go, the frequent haemorrhagic areas point to profound changes in the blood vessels of the intestine, and these changes are certainly correlated with the appearance of the patches of sclerosis seen in the aorta.

Further evidence of the influence of Apocynum on the vascular system is afforded by the lesions found in the case of the second rabbit; these were localised oedema, pulmonary oedema and slight hydrothorax, and distinct hydropericardium.

3. *Muscular System.*

(a) *Striated muscle.* The action of Apocynum on muscle is comparable to that of Veratrine and Barium. The most characteristic action of Apocynum on striped muscle is the delayed relaxation and constantly increasing rise of tonus; in this respect Apocynum exactly resembles Digitalis and Squill. It can be shown that this drug has the same type of action on all forms of muscle, but that the effect on the more delicate cardiac muscle overshadows the others.

(b) *Unstriated muscle.* This is thrown into a state of prolonged contraction, and the tonus is also raised so that in isolated preparations the death of the muscle occurs in contraction. Plain muscle throughout the body is affected in this way. The typical effect on this tissue may be simply observed in ring preparations of the frog's stomach, in which the movements are recorded by the suspension method, so that the down stroke of the tracing indicates the contraction (systole) of the preparation.

Apocynum applied directly to the preparation causes a decided contraction, and the tonus of the muscle is permanently raised; and this

effect is obtained in spite of the fact that the tincture which was here employed contains alcohol, the action of which is to reduce tonus.

This effect on plain muscle may be regarded as representing the type of action occurring in all plain muscle throughout the body. I would observe here, however, that the alimentary canal shows irregular colicky contractions, the spleen and bronchioles are induced to contract, there is marked vaso-constriction and the tonus of the bladder and uterus is increased. The effect of Apocynum on the uterus was determined on the isolated uterus of a cat.

Experiment. Fig. 5. The uterus was suspended with its lower end fixed in an oxygenated saline solution and the movements recorded by suitable levers. The introduction into the saline solution of a trace of tincture of Apocynum causes a great increase in the muscular tonus. The peristaltic movements become less and less and ultimately cease, but the muscle remains in a state of tonic contraction. The uterus in this case was a pregnant one, and 0.2 c.c. of the tincture was administered at the arrow mark.

The type of action shown in the above experiment is very similar to that of digitalis, except that the effect of Apocynum on the uterine muscle is of a much more intense character.

FIG. 5.

Pregnant uterus of Cat. 0.2 c.c. Tincture Apocyni given at arrow produces rise of tonus and decrease in size of contractions. Death in systole.

Full Scale.

III. COMPARISON OF APOCYNUM CANNABINUM WITH OTHER MEMBERS OF THE CARDIAC GROUP OF DRUGS

Apocynum will be compared only with Digitalis, Strophanthus and Squill.

The experiments show that, of the four drugs, Apocynum stands second in relative toxicity on frogs' hearts. Strophanthus has the greatest toxic action, Digitalis and Squill, which are about equal in toxicity, have a less toxic action than Apocynum.

Apocynum has a greater tendency to cause delirium cordis than any of the other three drugs; in several experiments delirium cordis set in almost immediately after the administration of the drug, and in others no so-called therapeutical effects were obtained, also no tracings show generally such wide variations of blood pressure at this stage as those obtained from Apocynum.

This drug is the most irritant of the four towards mucous membranes, as shown by the intense ulceration produced in the alimentary canal after the intravenous injection of moderate doses of the drug. Strophanthus has been shown to be the least irritating to mucous membranes, and is in consequence the most readily absorbed. Apocynum is the most powerful vaso-constrictor of this group of drugs, and its property of constricting the blood vessels stands in direct relationship to what is really the specific action of the drug, that is its ability to increase the tonus of muscular tissue of every kind. In connection with this action, a greater rise of blood pressure is produced by Apocynum than by either Digitalis, Strophanthus or Squill; it is known that Strophanthus produces a comparatively small effect on the blood pressure, Apocynum causes a more immediate and sudden rise of blood pressure than Digitalis or Squill. There is no special difference in the action of these drugs on the kidney, which in each case is an indirect one, but Apocynum appears more likely to produce haematuria owing to its pronounced irritant properties.

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