THE PHARMACOLOGICAL ACTION OF DIGITALIS, STROPHANTHUS AND SQUILL ON THE HEART¹

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It not infrequently happens in the treatment of disease that although certain drugs appear to be indicated, they do not produce their usual effects. In some instances this is due to the poor quality of the preparations prescribed, and, for certain drugs, this contingency cannot be foreseen and provided against at the present time. In many pharmaceutical preparations the active principles have been well and carefully studied, and chemical methods have been devised for estimating them exactly; in others, such as anti-diphtheritic serum, chemical methods are not at present available, and they are therefore standardized physiologically. This method is the only reliable one for the standardization of digitalis, strophanthus, squill, ergot, and Indian hemp.

1. Towards the expenses of this research a grant was made by the British Medical Association, on the recommendation of the Scientific Grants Committee of the Association.

The group of cardiac tonics is characterized by the content of one or more glucosides as the active principle. These glucosides cannot be prepared in a pure state ; first, because their chemistry is so little known, and, secondly, because the different chemical processes suggested for their extraction produce different substances, or at all events substances with very different activities. The quality of the active constituents varies not only in different seasons, and in plants grown in different soils, but also in different parts of the same plant. Moreover, in the attempt at isolation much of their potency is lost, so that these so-called active principles require standardization even more than the galenical preparations. Thus in the Pharmacological Laboratory of Cambridge University several 'digitalins' and 'strophanthins' have been shown to be worthless, and one beautifully crystalline 'digitoxin' was quite inert.

It is necessary therefore, before any comparative investigations with these drugs can be attempted, to obtain an indication of the strength of the preparations to be used. With this object in view, I obtained good average samples of the drugs, digitalis, squill, and strophanthus, which were available in March ; and tinctures were prepared from these, exactly according to the directions in the British Pharmacopoeia of 1898. This is certainly a matter of considerable importance, for other tinctures, obtained from equally good specimens of the crude drugs, but less carefully prepared, were decidedly less toxic in their action. I shall in future refer to these galenicals as the standard tinctures.

STANDARDIZATION

Experiments were first made with the carefully prepared tinctures in order to ascertain their relative potency and toxicity, and to form a standard with which other tinctures could be compared. These drugs have a specific action on the heart, and the type of action is the same on every vertebrate animal, so that, just as we standardize diphtheria toxin by determining the minimal lethal dose necessary to kill a guinea-pig, so we can standardize the members of the digitalis group

by determining the minimum amount of the drug necessary to kill some animal. Guinea-pigs may be employed for these experiments, but as frogs answer every purpose, I eventually standardized my preparations by determining the smallest dose of the drug which, when injected into the dorsal lymph sac of a frog, caused death by arresting the heart in systolic contraction.

Physiological standardization is, of course, not new ; it has been suggested by Gottlieb¹ that digitalis preparations be standardized ; by Houghton² that preparations of ergot be assayed by marking the gangrene after feeding roosters with the drug ; by Barger and Shaw³ that the activity of the digitalis group be determined for the frog's heart ; and by Dixon⁴ and Cushny that digitalis, strophanthus, squill, ergot, and Indian hemp should all be standardized ; and Dixon has suggested methods by which these may be effected. Of course it is not suggested that the dose of any of these drugs necessary to kill a frog bears any direct relation to the dose necessary to produce an effect on man. But supposing that 5 minims and 1 minim are found to be the minimal lethal doses of two tinctures respectively for a frog of 25 grammes weight, then in order to obtain corresponding effects, a man should take as a dose five times as much of the latter as of the former. Dixon and I⁵ suggested standards with which to compare commercial tinctures, and as it is these standard tinctures which have been employed in these experiments, I give their relative toxicity.

The minimal lethal doses are as follows :—

Tinct. Digitalis	=	2½ m.	for a 20 gram. frog.
Tinct. Squill	=	2½ m.	„ 20 „
Tinct. Strophanthus	=	½ m.	„ 17 „

Hence the relative toxicity of the three standard tinctures of digitalis, squill, and strophanthus is such that the first two are about equal in potency, while strophanthus is nearly nine times as toxic as

1. Gottlieb, *Berlin Medical Congress*, XIX, 1901.
2. Houghton, *Therapeutic Gazette*, Vol. XXVIII, p. 450, July, 1898.
3. Barger and Shaw, *The Year-book of Pharmacy*, 1904.
4. Dixon, *Pharmaceutical Journal*, July 29, 1905.
5. Dixon and Haynes, *Medical Magazine*, January, 1906.

either. Fraser¹ finds that the M.L.D.* for strophanthin per 100 grains of frog or rabbit equals 0·00005 grain, and says that strophanthin is a little more active than the pure alcohol extract of strophanthus seeds. He states that it is 300 times more powerful than Merck's purest digitalin, and 3,000 times more powerful than an English digitalin. As, however, these glucosides are known to vary enormously, this observation is of little value without the M.L.D. of the digitalins being stated.

It may be objected that although the strophanthus is so much more toxic than digitalis when the drugs are injected hypodermically, the results will be different when the drugs are administered by the mouth. Such variation is not unusual: for example, a single dose of lead, if taken by the mouth, is very slightly toxic, because it is not absorbed to any extent; but the same dose injected hypodermically will produce symptoms of poisoning. And, again, arsenic is infinitely more poisonous than iron when the two are administered by the mouth, because the arsenic is absorbed and the iron is not to any extent. But if the two are injected, there is not much difference between their toxic effects. Hence it might be objected that strophanthus given by the mouth is less effective because of deficient absorption. I decided, therefore, to determine how far the comparative toxicity held when the drugs were given by the stomach. For this purpose certain experiments were conducted on mammals.

INTRODUCTION OF DRUGS INTO THE STOMACH

Well grown cats were decerebrated by pithing without the previous induction of anaesthesia. Tracheotomy was performed immediately afterwards, a tube placed in the trachea and artificial respiration maintained. A cannula was introduced into the right carotid artery and connected with a mercury-manometer. By this means a constant blood pressure was obtained without the disturbing influence of an anaesthetic. The stomach was then exposed by a small

1. Fraser, *Transactions Royal Society*, Edinburgh, Vol. XXXV, Part IV, 1890; Vol. XXXVI, Part II, 1891.

* M.L.D. = Minimum lethal dose.

incision in the linea alba about two cms. long, and five c.c. of the undiluted standard tincture was injected with a fine hypodermic needle through its wall. Short records of the blood pressure were then taken every five minutes.

In the case of digitalis no effect was noticed on the blood-pressure during two hours ; with squill after the same lapse of time, there was also no rise. But with strophanthus, even after one hour's action, the heart went into the condition known as *delirium cordis*, and after beating very rapidly and irregularly for thirteen minutes it suddenly ceased to act, and after death was found in fibrillary twitchings. There was no rise in blood-pressure at any time.

One is bound to conclude, therefore, that tincture of strophanthus, whether given by the mouth or hypodermically, is very much more toxic than the other two drugs in this group. And here is an explanation of a clinical effect not infrequently observed, that a case of cardiac disease which is not improving under digitalis, may immediately improve when tentatively placed upon strophanthus. The patient thus receives a dose five or ten times as potent as that he was previously taking.

The problem of absorption by the gastric mucous membrane is of considerable importance. Under normal conditions, no water or dilute saline solutions appear to be absorbed by the stomach, but volatile substances, such as alcohol or arsenic, are absorbed with ease ; as they are from all parts of the intestinal canal. It might therefore be objected that the digitalis and squill had little chance of being absorbed, and this is no doubt true ; the experiments are only of comparative value. Nevertheless they show conclusively that strophanthus, even under these conditions, was absorbed, although there was no evidence of the absorption of either digitalis or squill. I wish then to draw attention to the result that not only is strophanthus much more toxic than the other two drugs, but also that it is absorbed with at least equal facility from the mucous membranes.

CHANGES IN THE STOMACH WALL

These experiments also showed certain changes in the gastric mucous membrane. Digitalis caused an intense congestion and

corrosion of the tissue, which in one place was necrotic. Squill had a somewhat similar but much less marked effect. Strophanthus made hardly any impression at all. It must be remembered, however, that the stomach was subjected to the action of digitalis and squill for a period of time nearly twice as long as that during which strophanthus was acting.

The members of the digitalis group, when introduced in suitable solution into the eye, eventually give rise to anaesthesia of the conjunctiva and cornea. Digitalis and squill cause intense inflammation before the stage of anaesthesia is reached. Strophanthus, however, produces a local anaesthesia in about fifteen minutes with comparatively little irritant action. It was tried, indeed, as a local anaesthetic in ophthalmic practice before the introduction of cocaine. Further, it is a well-recognised clinical observation that digitalis and squill may give rise to emesis and purging; squill has, indeed, been prescribed as an emetic. Strophanthus induces intestinal disorders much more rarely. The expectorant action of squill is explained as a reflex secretion from the bronchioles, brought about by irritation of the gastric mucous membrane. If this explanation be accepted, digitalis may be assumed to be a more potent expectorant than squill.

Hence the three drugs under consideration all possess an irritant action, which bears no direct relation to the toxicity; that is to say: strophanthus, which is the least irritant, is the most toxic; and digitalis is the most irritant, and has about the same toxicity as squill.

EXPERIMENTS ON THE MAMMALIAN HEART

Having indicated the relative strength of these drugs and certain of their characteristics, I now proceed to the consideration of a comparison of their respective actions on the mammalian heart. For this purpose I employed a modification of Langendorff's method, by which, by perfusion of an excised heart through the coronary vessels, may be obtained, for some hours, a free and regular heart-action. Healthy young rabbits, from six weeks to three months of age, were used for the greater number of these experiments, but the effects were obtained equally well on the hearts of other mammals.

Apparatus. The apparatus employed for these perfusions is of the simplest description. It consists of an oviform glass vessel with openings above and below, the lower opening terminating in a nozzle. To this a piece of rubber pressure tubing is fixed, which, in its turn, is connected with an **S**-shaped piece of glass tubing. This, before each experiment, is loosely packed with glass wool, and this serves the purpose of filter. The pressure tubing is also provided with a **T**-piece, which can be opened and closed at will, and may be employed for the introduction of drugs.

To the lower end of the filter a further piece of pressure tubing is fixed, serving to connect the cannula to which the heart is attached ; this tubing has a regulating screw, so that the supply of fluid to the heart can be increased or diminished at will. The upper opening in oviform flask is fitted with a rubber cork, through which pass two glass tubes ; the one, passing to the bottom of the vessel, serves for the introduction of oxygen ; the other only just passes through the cork, and is connected with a mercury valve for regulating the oxygen pressure. The flask is surrounded by a water-jacket, by means of which its temperature can be kept constant. The cannula is of a bulb form, and is provided with a lateral tube, through which a delicate thermometer is passed.

The fluid used for perfusion was a modified Ringer's solution, as suggested by Sherrington, to which a little dextrose was added.

In experimenting by means of this apparatus with members of the digitalis group, I chiefly employed the standard tinctures diluted 1 in 2500 times. I also observed the effects of introducing single doses into the side tube, and of varying the strength of the dilution of the perfused drugs.

RESULTS

The Rate of the Heart-Beat. The first noticeable effect of the action of these drugs on the heart is on the rhythm. The heart beats more slowly. This effect begins a few minutes after the introduction of the drug, and lasts during the first stage of the experiment, that is, until the tonus has commenced to rise considerably, when the heart-

beat again quickens, and may enter into the condition known as *delirium cordis*. This slowing is mainly diastolic, but as I propose to show presently, a small portion of it is systolic, that is to say, not only is diastole prolonged, but also the length of systole is increased, although the increase is not in any way comparable to that of the diastole. In these experiments it is obvious that the slowing must be induced by an action on either the vagal mechanism or the musculature of the heart. This point can be readily determined by eliminating the vagus-action by a previous exhibition of atropine. In such experiments it was found that the diastolic slowing, which is the characteristic effect of all the members of this group of drugs, did not occur to any extent; and often an atropinized heart, under the influence of digitalis, squill, or strophanthus, will maintain its rate almost unaltered until the second stage, that of acceleration and arrhythmia, is reached—that is, all through the therapeutic stage. It is therefore obvious that the greater part of the diastolic slowing is due to excitation of the vagal terminations in the heart.

Of the three drugs under investigation, compared in equal doses of their respective tinctures, strophanthus is the most effective in producing slowing of the heart-beat; squill comes next, and digitalis has the least effect on slowing (see figs. 6, 7 and 8). After the administration of these drugs, the average diminution in rate during the therapeutic stage, calculated from twenty-four experiments, is:—

1. Strophanthus	...	52 %
2. Squill	...	42 %
3. Digitalis	...	30 %

In other words, it is to be expected in such experiments as these that, given a normal heart rate of 100 beats per minute, the slowest rate reached in the therapeutic stage will be 48, 58, and 70, after the exhibition of strophanthus, squill, and digitalis, respectively. This is represented in the subjoined diagram, in which each pair of columns graphically represents the difference in the rate of heart-beat after the administration of the three drugs respectively.

FIG. 1. Heart-beats per minute.

N = normal mean rate. D = slowest mean rate after perfusion with Digitalis.

Sq. = " " " " Squill.

St. = " " " " Strophanthus.

It must not be forgotten, however, that although these drugs are being administered in equal doses according to the British Pharmacopoeia, such doses are not proportional to the strengths of the tinctures. As I have previously shown, strophanthus is 8-10 times more toxic than the other two drugs, and if the three were given in proportionate doses, then squill would evidently be seen to be by far the most efficient drug in slowing the heart-beat. The systolic slowing is not of much significance in this connection, and will be further considered under the next heading.

Very occasionally the heart may show an initial acceleration after the administration of any of these drugs, more especially in the case of strophanthus (*c.f.*, fig. 7). This effect never lasts longer than a few minutes, and is generally associated with an increased flow of fluid through the coronary vessels. The explanation of this, which I suggest, is that these drugs exert two main actions on the heart; first, they slow the beat; and secondly, they increase the irritability or the cardiac muscle, and thereby increase the force of the beat. In certain experiments the irritability is increased, just at first, to such an extent that the vagal mechanism is unable to hold the heart in check, and hence the quickening in the rate of the heart. An acceleration from such a cause follows in the usual sequence of events in the

second stage of poisoning by these drugs, when the heart enters into *aelirium cordis*. The associated increase in the flow from the coronary vessels must be explained by the increase in liberated metabolites, as a result of the augmented cardiac muscle work. It is the same effect that Gaskell observed during activity of skeletal muscle—the vessels dilate as a result of the local liberation of metabolites.

With regard to the time taken by the action of the three drugs before the greatest slowing is reached, the averages are as follows :—

1. Strophanthus	...	15 minutes
2. Squill	...	24 „
3. Digitalis	...	63 „

It is thus seen that digitalis takes by far the longest time to produce the maximum slowing.

Experiments on the Atropinized Heart. Excised hearts are perfused in the usual manner, and when the action is regular and constant, a minute dose of sulphate of atropine, 0.0025 grm. in warm saline solution, is introduced into the apparatus through the side tube.

FIG. 2. Heart-beats per minute

N = normal mean rate of atropinized heart ; St. D. Sq. = slowest mean rate after the introduction of Strophanthus, Digitalis, and Squill, respectively.

This immediately produces some quickening, which after a few minutes subsides and the heart resumes its previous rate of action. The drug whose action is to be observed is then perfused as in the

previous experiments, but different results are obtained. The slowing is much less, and the time taken to produce the greatest slowing is prolonged. Thus if the rate before the introduction of the three drugs strophanthus, digitalis, and squill, is 100 per minute, the lowest rate caused by each is 89, 82, and 81, respectively (see Fig. 2).

The period of time which elapses before the greatest slowing is produced is 120 minutes for digitalis and 30 minutes each for strophanthus or squill.

By comparing the results of the action of the drugs on the atropinized heart with those obtained when the heart is not previously atropinized, the following tables have been produced.

TABLE A

Drug	Percentage decrease in rate of heart-beat in beats per minute			
	Without atropine		With atropine	
Digitalis ...	...	30 %	...	18 %
Squill ...	...	42 %	...	19 %
Strophanthus ...	...	52 %	...	11 %

Fig. 3 is a diagrammatic representation of above table.

FIG. 3. Beats per minute

1. Normal mean rate.
2. Lowest mean rate caused by drug on atropinized heart.
3. Lowest mean rate caused by drug on normal heart.

In the second table (B) the period of time in minutes before greatest slowing is produced is shown.

TABLE B

Drug	Without atropine	With atropine
Digitalis ...	63 minutes	120 minutes
Squill ...	24 "	30 "
Strophanthus ...	15 "	30 "

It thus appears that the drugs, acting on the atropinized heart, cause very much less slowing than they do when acting on the normal heart ; and also that the time elapsing before this slowing reaches its maximum is doubled in the case of digitalis and strophanthus, and prolonged in the case of squill. The inference, therefore, is that this group of cardiac tonics directly excites the terminations of the vagus in the heart, and that this is the chief cause of the slowing. (Compare figs. 6, 7, and 8, with figs. 9, 10, and 11, respectively.) Considerable difficulty was experienced in administering a dose of atropine sufficient to paralyse the vagal terminations without causing the death of the heart. The amount usually administered (gms. 0.0025) sometimes caused a very rapid action, followed by death, in diastole ; but if given slowly and carefully it was eventually found to be sufficient to paralyse the nerves without killing the muscle or affecting the accelerator mechanism. Fraser, in his work on *Strophanthus hispidus*, found that 'the previous administration of atropine did not prevent, nor indeed in any conspicuous manner modify, the production by strophanthus of the changes in the heart's contractions which have been seen to follow its application to frogs to whom (*sic*) no atropine had been administered.' But, on the contrary, with rabbits he found that 'the administration of atropine succeeded in lessening its (strophanthus) effect on the rate of the pulse.'

The Quality of the Heart-beat—It is well known that drugs which excite the ordinary cardiac muscle increase its tonus and both the force and amplitude of its contraction. Examples of such drugs are barium

and veratrine. The increased tonus, however, is not observed with these drugs provided that they are administered in moderate doses, because of the prolonged state of diastole from excitation of the vagus, Squill is by far the most effective drug for augmenting the force of the cardiac systole without increasing the tonus. Both this drug and digitalis, during the first or therapeutic stage of their action, cause more complete contraction and more complete relaxation of the cardiac muscle. Strophanthus causes a very complete systole with no corresponding increased relaxation. (*Cf.* figs. 6, 7, 8).

Fraser finds that 'with a considerable or a large dose of strophanthus the systolic type of change is produced, in which by a direct action on the heart's muscle the capability to relax is diminished, until diastole becomes impossible, and the heart ceases to pulsate, with the ventricles so thoroughly contracted that its cavity is almost effaced.' With small doses, he describes a diastolic type of change, and says that 'whatever be the type, great increase occurs in the movements of the heart by exaggeration of expansion as well as of contraction. This occurs only temporarily where the type is systolic, but throughout, or nearly throughout, the action where the type is diastolic.'

This action of strophanthus may occur in frogs, but it is certainly not the case with the mammals; because in the perfusion experiments, although the dose received by the heart is small, no increased relaxation was observed in any case; whereas in an experiment in which a large dose, 1 c.c. of tincture of strophanthus, was introduced into the side tube, there was at first marked dilation and slowing, soon followed by great rise in tonus, and an increase in force and rate of the heart. The latter experiment, however, is hardly physiological, because such a large dose of strophanthus as is here administered can never reach the heart at any one time in man. The perfusion experiments, in which a small amount of this drug is allowed to act over a prolonged period, more nearly approach the conditions which obtain in life.

Fig. 4 shows the relative increase in the excursion of the lever attached to the heart after exhibition of the three drugs.

FIG. 4. Showing the relative increase of force of heart-beat.

N = normal excursion of lever ; Sq. D. and St. = excursion of lever after Squill, Digitalis, and Strophanthus respectively.

The average increase in excursion is : after squill 13, after digitalis 7.6, and after strophanthus 5.5, the initial excursion being reduced in each case to 10, for the purpose of comparison.

All three drugs cause death of the heart in the systolic phase. This may be said to be invariable ; in twenty-six out of twenty-seven experiments the ventricles were tightly contracted at death, the one exception occurring during the perfusion of digitalis, when the heart died suddenly during diastole, after three hours' action (see fig. 6). And without doubt, in this case, had atropine been given, the heart would have continued to beat till death occurred in systole.

Strophanthus usually causes the heart to die suddenly when the tonus has been greatly increased and the relaxation is very slight. The heart actually stops during the diastolic pause ; and the ventricles then very slowly contract up without beating, until the cavity is obliterated. Digitalis and squill nearly always cause the condition known as *delirium cordis*, preceding death in systole. The heart passes suddenly into rapid irregular twichings which last five or six

minutes to an hour. The ventricles cease in tonic contraction and the auricles continue to beat feebly.

Besides increasing the force of the beat, these drugs also prolong the beat, that is to say the heart remains in systole for a longer period than normal. This effect is not seen in the majority of the tracings, because the object has been rather to show up the increased force of the beat and the prolonged diastole, but it is shewn quite easily when the tracings are taken on a more quickly moving drum. It is most pronounced with squill, and least with strophanthus. With squill it may at times be so pronounced that nearly all the slowing is systolic.

Relative Toxicity on the Heart Muscle.—The relative toxicity of the three drugs on the heart muscle is determined by comparing the lengths of time elapsing between the introduction of the drug and the death of the heart.

Drug perfused	Strength	Time elapsing before death	Ratio of toxicity
Tr. Digitalis ...	$\frac{1}{2500}$	142 minutes	1
Tr. Scillae ...	$\frac{1}{2500}$	93 "	1.5
Tr. Strophanthi ...	$\frac{1}{2500}$	42 "	3.4

This is not of course a true standard of toxicity ; for it does not necessarily follow that because one drug is twice as toxic as another it kills in half the time. The table supports the experiments on standardization made on the frog, and shows how much more toxic strophanthus is than digitalis.

On the atropinized heart strophanthus is apparently not so toxic, while digitalis and squill have nearly the same toxicity as on the normal heart, both absolutely and relatively.

Drug perfused	Strength	Time elapsing before death	Ratio
Atropine sulphate ...	gm. 0.0025	150 minutes	1
Tr. Digitalis ...	$\frac{1}{2500}$		
Atropine sulphate ...	gm. 0.0025	100 "	1.5
Tr. Scillae ...	$\frac{1}{2500}$		
Atropine sulphate ...	gm. 0.0025	60 "	2.5
Tr. Strophanthi ...	$\frac{1}{2500}$		

Action on the Coronary Vessels—From a consideration of the literature on the subject it has become evident to me that the blood supply to the heart itself has not received adequate attention. In the standard works dealing with cardiac disease, although gross disease, such as atheroma is fully discussed, the state of the coronary arteries in such conditions as hypertrophy and atrophy of the heart, in Bright's disease, and in cases of high blood-pressure, is scarcely noticed. It is obvious that the condition of the coronary arteries and the blood-supply of the heart muscle must be of paramount importance, both in the causation, and as a factor in the treatment of cardiac disease. It has been shown by Schäfer¹ that the coronary vessels have no nerve supply, and this observation has been confirmed by Elliot² who showed that adrenalin, pilocarpine, and muscarin, drugs which excite nerve-endings, do not appreciably alter the calibre of these vessels. And on consideration, it is evident that it is essential that they should not be innervated and so constrict under conditions which influence the general circulation; herein possibly lies an important factor in the cardiac hypertrophy in interstitial nephritis. In this condition the peripheral and splanchnic vessels constrict, owing probably to the need of increasing the blood-pressure in order that more blood may circulate through the excretory apparatus which is diminished in extent by disease. But the coronary vessels do not constrict, and as by the greater pressure in the sinuses of Valsalva, more blood is forced through the heart muscle, it becomes more vascular and therefore hypertrophies in just the same way as any other organ will hypertrophy when its blood supply is permanently increased.

In order to examine the action of these three drugs on the coronary arteries, I adopted the following method of estimating the flow of fluid through these vessels. Perfusion experiments were performed as before described, and the amount of fluid passing through the coronary arteries during one minute was measured in a cylindrical glass graduated vessel at intervals of five minutes. The measurements in cubic centimetres were charted, and curves obtained for each drug. (See Fig. 5).

1. Schäfer, *Proc. Brit. Assoc.*, Cambridge, 1904.

2. Elliot, *Journal of Physiology*, XXXII, p. 401, 1905.

These experiments show that strophanthus has little or no effect—there is a diminution of 0·2 c.c. in sixty minutes. Digitalis causes some gradual decrease in the flow through the vessels—0·6 c.c. in the first sixty minutes, and 1·1 c.c. in three hours. Squill still further decreases the flow by 0·9 c.c. in the first sixty minutes, and 1·5 c.c. in three hours. It acts more quickly than digitalis. These results are here shown in tabulated form :—

Drug			Average decrease in flow per minute	Total decrease in first 60 minutes	Total decrease during action
Squill	...	...	0·0089 c.c.	0·9 c.c.	1·5 c.c.
Digitalis	...	...	0·006 c.c.	0·6 c.c.	1·1 c.c.
Strophanthus	...	...	0·0036 c.c.	0·2 c.c.	0·2 c.c.

From these results it appears that although, as has been before mentioned, the coronary vessels are not innervated, yet squill and digitalis cause some constriction of them. How can this be accounted for? It might be urged that the vessels were constricted by direct compression from the heart muscle owing to increase of the tone of the cardiac muscle. Against this is the action of strophanthus; for, although it causes even more increase in tonus than the other two drugs, yet the measurement of the fluid perfusing the coronary vessels at the time of death shows hardly any difference from that of the fluid passing through before the drug was administered. Possibly by their irritant action, squill and digitalis cause contraction of the muscular coat of the coronary arterioles; in fact, there seems to be no other explanation of their action. And this is also in harmony with what we know concerning the action of these drugs on other forms of plain muscle.

When injected into the circulation all three drugs cause a rise in blood-pressure—squill the greatest and strophanthus the least—strophanthus having very little action even on innervated arterioles. Squill is recognized clinically as a potent diuretic, this action being due to increased cardiac output combined with a rise in blood-pressure, in producing both of which factors it acts more powerfully than digitalis.

FIG. 5. Graphic representation of three perfusion experiments on young rabbits.

The coronary arteries were perfused with Ringer's solution. The ordinates equal outflow in c.c. per min., and the abscissae time in minutes. Perfusion with the drug, which in each case represents a strength of 1 in 2,500 of the official tincture, commenced at the arrows. Squill and digitalis constrict the vessels about equally, squill being a little the more active. Strophanthus has hardly any action; the initial dilatation it induces is due to products of metabolism from the increased cardiac activity. Perfusion pressure = 25 mms. or mercury.

CONCLUSIONS

In reviewing the results obtained from these experiments, the most striking feature is the superiority of squill over digitalis and strophanthus as a cardiac stimulant. The commercial preparations of this drug show less variability in strength, and so they are more trustworthy. Squill has a more constant action than digitalis: it has, moreover, a greater effect in increasing the work done by the heart, and more effect on the vessels; it is also less irritant to the gastric mucous membrane. Squill is popularly regarded as a stimulating

expectorant, and is a common ingredient of cough mixtures ; but its well-marked cardiac action is very frequently overlooked. No doubt its popularity as a so-called expectorant is chiefly due to the almost invariable custom of prescribing it along with other expectorants, and relief is afforded by its action in allaying the distention of the right side of the heart, so common a condition in bronchitis and other pulmonary affections. But with regard to its reflex expectorant action from irritation of the stomach, digitalis should prove as effective, if not more so, for it is a stronger gastric irritant. I should like to enter a plea for the more extended use of squill in place of digitalis in cases of heart failure : it acts more quickly, more effectively, and does not cause any more, if as much, gastro-intestinal derangement. Every precaution which is observed when digitalis is properly administered should also be observed in the use of squill. It should not be given for many days without intermission, and a close scrutiny must be kept on the pulse rate and on the amount of urine passed. A pulse below 60, and a rapid diminution in the quantity of urine are indications for its withdrawal.

With regard to digitalis, it is a common experience amongst practitioners of medicine that its preparations are often untrustworthy. Dixon and I have shown that some tinctures, at any rate, are only about one third the strength of others. This may be due to the quality of the leaves selected (these show great variation in percentage of glucosides), or to an inexact and careless method of preparation, or to the age of the tincture. The solution of the difficulty is to be found in physiological standardization of these drugs. Preparations should be placed on the market, suitably labelled, stating definitely that at a given date a certain dose killed a frog of so many grams within a limited time. The standard could be fixed, as in these experiments, so that $2\frac{1}{2}$ minims kills a 20 gramme frog within three hours, and the tincture diluted accordingly. Experiments are being conducted at Cambridge with a view to ascertain how long these tinctures retain their potency.

Strophanthus is a dangerous drug. The Pharmacopoeial dose is 5-15 minims, like those of digitalis and squill, yet it is 8-10 times as

toxic as either. It has a powerful action on the heart, and is apt to cause sudden death without warning. In small doses it is no doubt valuable in cases of heart failure associated with marked arterial degeneration, for its action in constricting the vessels is very slight. The dose in the Pharmacopoeia should be reduced. In this connection it is interesting to notice that Dr. Sansom, in his article on *Disease of the Mitral Valve*, in Clifford Allbutt's System of Medicine, recommends tincture of digitalis in doses of 5-30 minims, and tincture of strophanthus in doses of 2-10 minims, every 4 hours. He says 'there are some probabilities that it (strophanthus) may lead to sudden death in the course of its administration for heart disease (Gottlieb) I cannot doubt that the protracted injudicious administration of digitalis and strophanthus has often been productive of dangerous and fatal results.'

SUMMARY OF RESULTS

1. When standard tinctures of the three drugs, digitalis, squill, and strophanthus, are freshly prepared strictly according to the British Pharmacopoeia, then, supposing the toxicity of digitalis to be represented by one, squill will also represent one, but strophanthus nine or ten.

2. It is essential that these drugs should be standardized. The only way by which this can be done effectually at the present time is the bio-chemical method.

3. Digitalis, squill, and strophanthus all have a specific action on the heart, which can be divided into two stages; a first stage characterized by stimulation of the cardiac muscle and of the vagal nerve endings; and a second, in which the tonus is much increased, and the rate accelerated by the extension of the action on the muscle to the excito-motor area of the heart.

4. Tincture of squill differs from the other drugs in its action upon the heart in the following ways:—

- (a) In therapeutical doses it increases the force of contraction to a considerably greater extent than either digitalis or strophanthus. Not only is systole more complete and prolonged but diastole also.

(b) It slows the heart-beat more than digitalis, and, considering its relative toxicity, more than strophanthus. This, however, is its effect only so far as the peripheral vagal mechanism is concerned.

(c) It produces more vaso-constriction of the coronary vessels than either digitalis or strophanthus.

5. Tincture of digitalis is less efficient as a cardiac stimulant (that is a drug which increases the cardiac output per beat) than squill, in that it has not the same effect in increasing the energy of contraction of the heart. Moreover, it is not possible by altering the relative dosage of digitalis to produce a stimulant effect in any way comparable to that of squill. Digitalis has less peripheral effect on the vagal mechanism than squill.

6. Tincture of strophanthus being eight to ten times more toxic than the other two drugs, it is hardly fair to compare it with equal quantities of them. Such comparisons, however, serve to confirm the experiments made on frogs, showing the greater activity of this drug. With regard to its effect on the force of the heart-beat, strophanthus occupies a position considerably below squill and rather less than digitalis. It slows the heart more than either of the other two tinctures in equal doses. In contra-distinction to digitalis and squill, strophanthus has practically no action on the coronary vessels. At first it slightly increases the outflow from the coronary veins the result of metabolites set free by the increased work of the heart. This drug is very apt to cause sudden death of the heart without previous excitation of the excito-motor area.

7. After previously atropinizing the excised heart, perfusion of these drugs causes very little decrease in the heart-rate. Their local action on the peripheral vagal mechanism is a large factor in the production of the usual slowing seen during their exhibition to patients.

8. To mucous membranes digitalis is the most irritant, then comes squill, while strophanthus has very little irritant action.

9. In any case in which it is desirable to raise the blood pressure and stimulate the heart, squill should be used in preference to the other two drugs.

FIG. 6.—Rabbit's heart: perfusion with Ringer's solution. At 11.55, a piece of normal tracing is shown; at 12, 1 in 2,500 Tr. Digitalis was substituted, and tracings of the heart-beat are shown at various subsequent times. Death here occurs in diastole, which is very exceptional. Upstroke = systole. Time = secs.

FIG. 7.—Rabbit's heart : perfusion with Ringer's solution. At 3.45, a piece of normal tracing is shown ; at 4.0, 1 in 2,500 Tr. Strophanthi has been substituted for 15 mins. ; at 4.15 and 4.30, later effects are shown.

FIG. 10.—Rabbit's heart : perfusion with Ringer's solution. At 3.15, gm. 0.0025 atropine sulphate was added ; at 3.25 a tracing of the atropinized heart-beat is shewn ; then 1 in 2,500 Tr. Strophanthi was substituted.

FIG. 8.—Rabbit's heart : perfusion with Ringer's solution. A piece of normal tracing at 11.55 is shown ; at 12.0, 1 in 2,500 Tr. Scillae was substituted—the subsequent tracings show the effects on the heart-beat.

FIG. 9.—Rabbit's heart : perfusion with Ringer's solution. At 12.35, gm. 0.0025 atropine sulphate was added ; at 1.10, a tracing of the atropinized heart-beat is shown ; at 1.15, 1 in 2,500 Tr. Digitalis was substituted, and the effects are shown at various intervals.

FIG. 11.—Rabbit's heart: perfusion with Ringer's solution. At 3.0, gm. 0.0025 atropine sulphate was added, and a tracing is shown at 3.15 of the beat of the atropinized heart; at 3.20, 1 in 2,500 Tr. Scilla was substituted.