INVESTIGATIONS
INTO THE
ACTION OF THE DIGITALIS GROUP.

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THE influence of digitalis on the circulation is, of course, the principal feature in the action of this drug. The primary slowing and increased vigour of contraction of the ventricle, the subsequent stage of irregular action as the dose is increased, and the final arrest of the ventricle in full systole are all well-known facts. To these must be added, rise in blood-pressure, an effect occurring uniformly, and which some authors consider of chief importance; certain, at least, of the cardiac effects of digitalis being, according to these, secondary to the increased blood-pressure. In a recent paper on the subject,¹

¹ "Beiträge zur Kenntniss der pharmakologischen Gruppe des Digitalins," 'Archiv f. experimentelle Pathologie u. Pharmakologie,' Bd. xvi, p. 149.

Schmiedeberg thus classes the blood-pressure effects in relation to the cardiac effects :

1. Rise in blood-pressure accompanied, as a rule, but not necessarily, by slowed pulse rate.
2. Continuance of increased blood-pressure, with increased pulse frequency.
3. Continuance of raised blood-pressure with great irregularity in the heart's action.
4. Rapid fall in blood-pressure, stoppage of the heart ; death.

Schmiedeberg attributes the therapeutic value of digitalis alone to this rise in blood-pressure ; the slowing of the pulse, which is usually witnessed, he holds to be secondary to the rise in blood-pressure, a reflex on the heart through the vagi ; the rise in blood-pressure itself, however, he makes dependent on the heart's action, and he further states that it is not attended by diminution in the calibre of the vessels. To a consideration of the relation between the heart's action and blood-pressure rise we shall return later on. What now concerns us rather is the condition of the heart and that of the arterioles. Concerning the former there is no difference of opinion, the ventricle is admittedly arrested in systole ; concerning the latter the balance of evidence certainly appears to show that the arterioles contract under the influence of digitalis,¹ though Schmiedeberg, as above stated, denies this. But, allowing even that digitalis does cause the arterioles to contract, the question still remains, how does it do so ? On the heart the action is generally admitted to be direct, but on the vessels it is held by most to be indirect, by the stimulation, viz. of the vaso-motor centres at the base of the brain. Ackermann almost alone maintaining that the action on the arterioles is direct (Wood, op. cit. p. 139).

The question is clearly one of considerable importance, and it bears directly on the definition of the digitalis action. Schmiedeberg, in the before-mentioned paper, enumerates a long list of bodies resembling digitalis in

¹ 'Consult Wood, 'Treatise on Therapeutics,' 3rd edit., pp. 138-139.

their action, and which he classes as digitalis remedies. The definition of such action being the primarily increased vigour of the ventricular contraction leading up finally to the systolic arrest, together with the blood-pressure rise. The question now, rather, is what is essential in this action, and whether we may not take as such the spasmodic condition of the heart, and accordingly define digitalis action as—the production of continuous spasm of the heart muscle by direct action of the drug on this tissue: this spasm not being of the nature of tetanus, *i. e.* of fusion of adjacent beats, and following on the application of the drug, either to the whole heart or to any limited portion of the ventricle, in the latter case causing a local spasm. Thus defined, Schmiedeberg's already very large group will have to be extended and made to include, among others, the caustic alkalies and barium chloride, acetate and nitrate,¹ and very probably many others.

Taking this as the definition of digitalis action, is it not probable that a drug thus directly acting on the muscular tissue of the heart will likewise affect directly the muscular tissue of the arterioles? Indeed, is one not justified in assuming that the likelihood of similar action of one drug on two or more tissues will be in proportion to the resemblance existing between these, approaching certainty as the tissues increasingly resemble each other, becoming less probable as they diverge? If this be allowed, the inference is not far from the heart to the arterioles, and given a particular action on the one, we should look for similar action on the other, and hence we should expect to find the digitalis (spasmodic) heart accompanied by spasm of the arterioles. This is, of course, on the assumption that the muscular elements of the arterioles may be influenced directly by the fluids bathing them. For the argument in evidence of this we must refer to Gaskell's paper on the tonicity of the heart and blood-vessels.²

¹ Boehm, "Ueber die Wirkungen der Barytsalze auf den Thierkörper," 'Archiv f. Exp. Pathologie und Pharmak,' 1875, iii, pp. 216, *et seq.* Also paper by the writers, 'Brit. Med. Journ.,' Aug. 11, 1883.

Journ. of Physiology,' vol. iii, p. 48.

Whilst bearing in mind the resemblances existing between the muscular elements of the heart and arterioles, it is necessary that we do not lose sight of their differences. These differences are not merely structural, for functionally, whilst the muscular fibres of the heart and arteries resemble each other broadly, in that they are both forms of tissue specialised for the function of contracting, they differ widely in the mode in which they manifest this property. Contractility in the fully-differentiated organism, we find manifested after two modes, viz. after a slow persistent fashion and after a sudden explosive fashion. Non-striated and striated muscular tissues represent structurally the two extremes of this functional difference. The slow persistent contraction above named is closely allied, if not identical, with that condition we name *tonus*, which is specially characteristic of unstriated muscle. In striped muscular tissue, though the sudden contraction is the most striking characteristic, yet the slow persistent form is also present, and we speak of *tonus* for these muscles also. The heart muscle, according to physiologists, is intermediate functionally between the striped and the unstriated tissue; its contractions are more sudden than those of the latter, less sudden than those of the former. At the same time *tonus* is a marked feature of cardiac muscle. Concerning the element rhythm, which is characteristic of plain muscular fibre, and also to a marked degree of the heart, we do not find this intermediate position maintained.

Arguing, then, from this intermediate position of the heart with its affinities manifested in the two directions of the voluntary and involuntary muscles, we would suggest that it may be possible, from action on the heart, to infer in both of these directions; *e.g.* supposing that we find that the stress of action of a drug, applied to the excised heart, show itself mainly as affecting the character of the beat itself, we should then be led to infer that the drug will strongly affect voluntary muscular fibre, whilst, on the other hand, should it powerfully affect the tone of the heart, either in the way of increase or diminution, we should

then conclude that it will similarly affect the arterioles. It is essential to remember here that we are dealing with the excised heart, and hence are inferring from the local action on this tissue to the local action on other tissues.

We have made the above suggestion as to the possibility of inference from the heart to the voluntary muscles; the object, however, which we had principally in view was to establish experimentally the inference from the heart to the arterioles; and, accordingly, taking for our starting point the systolic heart of the digitalis group, we proceeded to examine the direct action of the members of this group on the vessels themselves.

Mode of experimentation.—This was the same as that adopted by Gaskell in his experiments on the direct action of acids and alkalies on the tonicity of the vessels (op. cit.), but here, as in our previous experiments with barium chloride, the tortoise was used instead of the frog. The exact method was as follows:—The animal was pithed, care being taken to destroy as completely as possible the spinal cord, the shell sawn through transversely and the soft parts divided. A cannula was then tied into the abdominal aorta distally, the hinder half of the body alone being used in the experiment. The cannula was fed with the required fluids by simple syphon action, and the flow accordingly was into the abdominal aorta and out through the cut abdominal veins. In order to measure the rate of flow, the preparation was placed on a tilted glass plate from which the escaping fluid drained into a graduated glass measure, by which means we were enabled to read off the amount of outflow for any given interval of time.

The pressure employed varied slightly in the different experiments, averaging about 30 centimetres, but, during each experiment it was maintained constant within 0.5 centimetre by continuous additions to the supply vessel, which was of large capacity, so as to retard changes in level.

The experiments were performed in May, June, and July of 1883. Each experiment lasted some considerable

time, two to three hours or even more, and inasmuch as the circulation of artificial saline fluids continued over lengthened intervals of time tends to produce cedema of the tissues, which cedema may even occasion considerable obstruction to the circulation,¹ it became necessary to try the effect of the circulation of the unpoisoned saline, over periods which would cover the duration of an ordinary experiment. By this means it was possible to see if the amount of *ischæmia* witnessed after the administration of a drug could be accounted for on the grounds of cedema alone.

Another point remained for consideration, viz. the vitality of the tissues. In the case, for instance, of a negative result, i.e. the addition of the drug to the circulating fluid remaining without effect on the rate of flow, the question arose whether the tissues were still vital and the arterioles still capable of contracting; this question was the more important the longer the experiment had lasted. We must here forestall the evidence as to the action of digitalis, and state that this drug acts most unequivocally and most strongly in causing the arterioles to contract, and that the effect comes out so rapidly that it is quite impossible it could be other than a vital effect. Hence, in this drug we had a means of determining the vitality of the tissues, for if at the end of an experiment, and after continued additions of the drug, the flow still remained unobstructed—the addition of digitalis to the circulation would at once determine whether the arterioles were still able to contract and so obstruct the flow. In the case of negative results, accordingly, this plan was adopted.

Two experiments were performed with *simple saline*,²

¹ See experiments by Glax and Klemensiewicz, 'Sitzungsberichte d. Akademie zu Wien,' vol. lxxxiv, Abth. iii, p. 216.

² The saline employed was a solution of 0·6 per cent. of sodium chloride in tap water. It is necessary to make this statement, since the small quantities of salts contained in ordinary tap water appear to exert important effects and make the distinction between such saline and that made with distilled water

we will quote the one showing the greatest variation in the rate of flow.

June 18th.—Temperature of room 17° C.; head of pressure 31 centimetres.

The following numbers were observed : outflow per five minutes in cub. cents. 80, 85, 95, 82, 88, 83, 78, 75, 70, 60, 68, 66, 65, 65, 65, 77, 79, 78, 80, 80, 77, 80, 83, 80, 82, 86, 79, 84, 83, 86, 80, 80, 84, 81, 79, 83,¹ 35, 15.

¹ Digitaline solution, 1 per cent., 1 c.c. added to the 200 c.c. of saline.

The second experiment showed a considerably more uniform rate of flow than that here seen; but the important point to note in the above experiment is that at the end of three hours the rate of flow is undiminished, and that at this time the vitality of the tissues is still maintained, as is manifest by their immediate reaction to digitaline, the flow lessening at once from 83 c.c. to 35 c.c. in the next interval of five minutes, and thence to 15 c.c. Exactly similar results obtained for the second experiment, the rate of flow at the end of three hours was at the highest figure recorded during the experiment, and from this, viz. 48 c.c. it fell, on the addition of digitaline, at once to 25 c.c., and in the five minutes following this to 4 c.c.

Digitaline.—The digitaline employed was obtained from Morson. The above two experiments both show the effect of digitalis in obstructing the circulation and the rapidity with which this is effected. Of three other experiments, made simply with a view to test the action of digitaline, the results were in each case similar. We will quote only one.

May 24th.—Temperature of room 24° C.; head of pressure 31 centimetres.

Outflow per five minutes in c.c.—90,² 88, 80, 84,³ 48,

² Saline solution, 0.6 per cent. supplied. ³ Digitaline, 1 per cent., 0.5 c.c. added to the 100 c.c. saline.

a very essential one, *vide* Ringer, "On the influence exerted by the Constituents of the Blood on the Contraction of the Ventricle."—'Journal of Physiology,' vols. iii and iv,

28, 12,¹ 6, 9, 17, 24, 31, 34,² 25, 10, 4,³ 2, 2, 2, —, —, 11.

¹ Saline substituted. ² Digitaline saline again supplied. ³ Saline again substituted.

The evidence of the other experiments was precisely to the same effect, and they are omitted simply on account of space. In the above experiment the alternation of effect is to be observed, *e.g.* with the supply of the digitalis saline the rate of flow at once begins to fall rapidly, on resubstituting pure saline it slowly begins to rise.

It is to be noted that the minimum is, in the above, reached after the replacement of the poisoned circulation by saline, this of course simply means that the digitaline had not had full effect and that the process of washing it out was not an immediate one. The blank spaces in the last section simply represent four intervals of five minutes allowed to elapse before again measuring the rate of flow, the last figure shows this to have been slowly increasing.

Barium chloride.—For the details of the experiments with this drug we must refer to our paper in the 'Brit. Med. Journ.' for August 11th, 1883. The method adopted in these experiments was precisely the same and the results equally unequivocal. *Barium chloride acts strongly and directly on the small arterioles, causing these to contract.* It may be remembered that Boehm⁴ had previously demonstrated the digitalis-like action of the salts of this base in the production, *viz.*, of the retarded pulse-rate, the heightened blood-pressure, and the systolic heart.

Strophanthus (the African arrow poison, *Strophanthus kombi*).—Two experiments were made with this drug. A 5 per cent. solution of the crude drug was employed. The results were much less striking than for digitaline, still they were in the same direction as for this latter. We will quote one experiment.

"Ueber die Wirkungen der Barytsalze auf den Thierkörper," 'Archiv für experimentelle Pathologie u. Pharmacologie,' 1875, iii, pp. 216, 251.

May 28th.—Temperature of room 20° C.; pressure 31 centimetres.

Rate of outflow per five minutes in c.c.—42,¹ 39, 41, 41,² 37, 28, 25, 27,³ 23, 24, 22, 18, 16, 10, 10, 11, 11, 12, 15, 16, 18, 20,⁴ 20, 11, 9, 10, 9, 10, 10, 8, 9, 7.

¹ Saline solution, 0·6 per cent. supplied. ² Strophanthus 5 per cent., 0·4 c.c. to 100 c.c. saline. ³ Saline solution replaced. ⁴ Strophanthus 5 per cent., 1 c.c. to 100 c.c. saline.

It is to be noted that in this experiment, though the effect of the strophanthus is much less sudden and much less marked, yet that, following the addition of the strophanthus, there is a steady unbroken fall, continuing it is true long after the replacement by saline, but again re-appearing after the rate of flow had begun to mount, on the readdition of strophanthus.

The second experiment gave a very sudden fall of the rate of flow following the first addition of strophanthus; throughout the remainder of the experiment the rate of flow, during the periods of saline substitution, never rose to within one half the initial rate of flow, and on this lowered rate the subsequent additions of strophanthus gave no decided effect in further reducing it.

*Scillitine.*⁵—Two experiments with a one per-cent. solution were made but the results were not decided, and they scarcely permit of more than the negative conclusion that the action is of the same kind as that of digitalis, comes very far indeed behind it in degree. Large doses were

⁵ We are indebted to Mr. A. W. Gerrard, F.C.S., Lecturer on Pharmacy at University College Hospital, for the following account of his method of preparation of the scillitine employed in our experiments: "Five pounds of squill bulb were exhausted with proof-spirit, and the resulting tincture treated with four times its volume of 84 per cent. alcohol; this caused the precipitation of a viscous, tenacious extract, the spirit retaining in solution the scillitine. The alcohol was removed by distillation and the residue treated a second time with alcohol and the alcohol again distilled off. A pale green extract was thus obtained which was washed with ether to separate the green substance, and further diluted with water to precipitate resin and colouring matter. The clear aqueous solution was now evaporated and gave a pale scaly mass of scillitine, answering to the reactions of a glucoside."

employed, viz. as much as 5 c.c. of the one per-cent. solution to the 100 c.c., and the contrast between the comparatively slight action of this substance and the very striking and sudden effect produced by the digitalis in one fifth the dose, was very marked. The digitalis was tried in the end stages of both of the scillitine experiments, and the rate of flow fell almost at once to a minimum, which practically amounted to complete obstruction.

Dyak poison.—This is an arrow poison used by the inhabitants of Borneo, concerning the origin of which nothing certain is known, but it contains in all probability the juice of *Antiaris toxicaria* as a chief constituent.¹ It is a heart poison and acts in this respect like digitalis. Two experiments were made with this substance, we will quote one of these which, in addition to illustrating the influence of the dyak poison, shows well the relative action of digitaline. The solution strength was a one per-cent. of the crude drug.

June 15th.—Temperature of room 19° C.; head of pressure 31 centimetres.

Rate of outflow per five minutes in c.c.—72,² 74, 76, 71,³ 70, 63, 55, 48, 39, 37, 37, 36, 32, 36, 36,⁴ 36, 42, 40, 44, 46, 46, 46, 48,⁵ 47, 47, 47, 46, 45, 45, 47, 48, 44,⁶ 48, 43, 40, 40, 36, 36,⁷ 24, 4.

² Saline solution, 0·6 per cent. supplied. ³ Dyak poison 1 per cent.; 0·6 c.c. to 100 c.c. saline. ⁴ Saline solution resubstituted. ⁵ Dyak poison 1 per cent.; 1 c.c. to 100 c.c. saline. ⁶ Dyak poison 1 per cent.; 4 c.c. to 100 c.c. saline. ⁷ Digitaline 1 per cent.; 1 c.c. to 100 c.c. saline.

This experiment shows in the first instance a decided fall on the administration of the poison, from this fall the recovery with the saline is but slight, but the further addition of the poison remains practically without effect, though in the last instance the dosage is increased considerably. The last two figures show well the powerful relative effect of digitaline and they further demonstrate the persistence of vitality in the tissues after over three

See Husemann, 'Vergiftungen,' p. 482 (Maschka's 'Handbuch d. Gerichtlichen Medicin,' vol. ii).

hours of artificial circulation. The second experiment gave results more decided in favour of the dyak poison, both the first and the second additions of the poison reducing the rate of flow by one half; still it places this poison far behind digitaline in its direct action on the vessels.

Convallamarin.—This is a glucoside obtained from *Convallaria majalis* and is classed among digitalis remedies¹. But one experiment was made with this substance; we quote it as follows:

June 21st.—Temperature 17·5°; head of pressure 31 centimetres.

Rate of outflow per five minutes in c.c.—22,² 22, 24, 29, 33,³ 23, 22, 24, 19, 16, 16, 18,⁴ 18, 22, 25, 26, 29, 30, 33,⁵ 29, 24, 20, 17, 16, 15, 17,⁶ 15, 17, 17, 16, 16, 16,⁷ 16, 3, 1.

² Saline solution, 0·6 per cent. supplied. ³ Convallamarin 1 per cent.; 0·4 c.c. to 100 c.c. saline. ⁴ Saline solution replaced. ⁵ Convallamarin 1 per cent.; 0·8 c.c. to 100 cc. saline. ⁶ Saline solution replaced. ⁷ Digitaline 1 per cent.; 1 c.c. to 100 c.c. saline.

The results are not very striking, but it will be observed that the first addition of convallamarin reduced the rate by almost one half, viz. from 33 c.c. to 18 c.c.; that saline replacement brings back the previous rate of flow 33, and that convallamarin again reduces this rate by one half; the subsequent addition of saline does not show recovery. The last three figures show the immediate and marked effect of digitaline.

It will be remembered that Gaskell (op. cit.) demonstrated the effect of alkalies on the arterioles of the frog,

¹ Mr. Gerrard kindly prepared this substance for us and as follows: "The plant was exhausted with rectified spirit and the spirit distilled off; the residual extract was dissolved in water and evaporated to a thick fluid, then treated with ten times its volume of alcohol, filtered, and evaporated. The residue was now treated with tannin in excess, to form tannate of convallamarin, which after purifying by washing with alcohol was rubbed up with a little water and lead oxide—tannate of lead and free convallamarin being the result; the latter was removed by alcohol and obtained as a straw-coloured scale on evaporation."

this effect being constriction even to the extent of complete obstruction in some cases. The reverse obtained for acids, *i.e.* the vessels dilating under the influence of the acid. Dr. Gaskell employed solutions of sodium hydrate and of lactic acid to demonstrate these effects. We have repeated these experiments on the tortoise for the following alkaline salts; potassium hydrate, carbonate and bicarbonate, sodium carbonate and bicarbonate. The potassium salts gave us like results as also did the sodium carbonate; in all cases the vessels became constricted. With the sodium bicarbonate, however, we did not get this result, the flow instead of diminishing in rate appeared, if anything, to actually increase. This result, moreover, was obtained although the sodium bicarbonate was employed in such doses as to produce a deeper blue with test-paper than did the sodium carbonate. What this may mean exactly it is difficult to say, but if the ability to turn red litmus paper blue be accepted as the definition of alkalinity then an exception must be made in favour of sodium bicarbonate in respect of the statement that alkaline salts increase vascular tone. The power of a salt to saturate an acid obviously cannot be taken as a measure of its alkalinity since a molecule of sodium hydrate and of sodium bicarbonate would for all the stronger acids show an equal capacity in this respect, yet the latter is a comparatively saturated salt as contrasted with the former. We have laid the greater stress on this point because Gaskell has drawn attention to the acid and alkaline effects as rather fundamental differences and has suggested that all bodies may show a general division into acid-, and alkali-like actions; thus he suggests that antiarin and digitaline would come under the latter heading, muscarin under the former. However, with this exception of sodium bicarbonate the results obtained on the tortoise with the remaining alkaline salts confirm those obtained by Gaskell on the frog.

Simultaneously with these experiments on the vessels others were made on the excised frog-heart. In these an

artificial saline solution was circulated through the heart tied on to the perfusion cannula of a Roy apparatus by a ligature placed in the auriculo-ventricular groove. To this solution was then added the particular drug under experiment. The results were as follows:—Digitaline, strophanthus, dyak, scillitine, convallamarin, all caused persistent spasm of the ventricle, in varying degree however, digitaline being by far the most active in this respect. The experiments on barium chloride have already been given elsewhere ('Brit. Med. Journ.' Aug. 11th, 1883); they too showed persistent spasm as the result of direct action of the drug on the heart. Similarly experiments made in 1882 with the hydrates and carbonates of potassium and sodium,¹ showed persistent spasm to result from direct action on the excised ventricle, with the notable exception, however, of sodium bicarbonate which is there recorded as not producing persistent spasm. This exception then would accord with the results obtained for the vessels.

In the last-mentioned experiments it was noted that the bicarbonate of potassium caused much less persistent spasm of the ventricle than did either the carbonate or hydrate. These experiments were repeated now with like results. It was, however, observed in addition that the adding of sodium bicarbonate to a saline solution not containing a potassium salt (in physiological dose) did cause persistent spasm. This at first led us astray, showing as it appeared to do a difference in the action of the sodium bicarbonate on heart and vessels. When, however, we made the experiments exactly comparable by adding a physiological quantity of a potassium salt to the pure saline, or instead of this employed saline made with tap water in place of distilled water (the former containing the necessary trace of potassium salt), when this was done the discrepancy disappeared, and the heart behaved just as the vessels had done. It must be remembered that the saline fluid employed to circulate through the vessels was made with tap water.

¹ Vide 'Practitioner,' Aug., 1883, "On the individuality of action of the component parts of a drug."

We did not mention aconitia among the foregoing experiments on the tortoise; this drug, however, was tried with the result of apparently causing dilatation of the vessels. When, however, tested on the excised frog's heart an opposite result obtained, viz., spasm of the heart muscle. We suggest that the following may possibly explain this seeming contradiction; the heart possesses the property of rhythmic contractility, and we have elsewhere shown that, where there is a tendency to persistent spasm of the ventricle, the rhythmic contractions accentuate their spasm or appear to develop it. In the present experiments on the heart with aconitia the spasm was in connection with rhythmic contractions, and when these were prevented as by ligaturing the ventricle through its upper third, the spasm did not develop. Should this explanation be the true one, this second discrepancy would be apparent only.

Thus far we have seen the direct action on the vessels to be similar to that on the heart; there yet remains for determination the question as to whether any of the effect on the vessels is to be attributed to nervous agency, *i.e.*, whether in addition to direct action on the vessels, these may be influenced reflexly through the nervous system. The following experiment was designed to answer this:—The cerebral and optic lobes were destroyed, care being taken to ensure there being the entire thickness of the cerebellum between the surface of section and the fourth ventricle. We may thus take it that the vaso-motor centre was uninjured. From the brainless tortoise the whole abdominal shell wall was then removed, and the peritoneum carefully separated up from the shell wall; it was then opened longitudinally, the descending aorta exposed, ligatured proximally and a cannula tied in distally. The large vein running up in front of the lung to the liver was then exposed and ligatured proximally; the same was done for the two large veins in the anterior abdominal wall. All three veins were then opened distally, and the saline solution started as for the previous experiments.

By the means adopted a free outlet from the veins was provided for the inflowing saline, and the escaping fluid could be caught and measured as in the foregoing experiments. In addition to this the vessels through which the saline was flowing were under central nervous control, since the spinal cord, including the medulla with its vaso-motor centre, was intact. The poison was then injected into the muscles of the back of the neck.

Two experiments were made with digitaline ; of these the first gave purely negative results, just as occurred in two out of the three experiments made after the same method with barium chloride. The digitaline when injected into the muscles remained without effect on the saline circulation, and even when added to the saline solution itself it failed to produce any very definite effect. The second experiment gave similarly a negative result for the injection of the poison into the anterior circulation, but on adding the drug to the saline circulation the tissues at once reacted. We record the details of this experiment.

June 27th.—Temperature 18° ; head of pressure 30 centimetres, maintained constant within 0.5 centimetre.

Rate of outflow per five minutes in c.c.—29,¹ 29, 26, 29, 30, 32,² 33, 33, 37, 42, 43, 48,³ 46, 52, 50, 46, 55, 53,⁴ 43, 12, 2.

¹ Simple saline solution (made with tap water), 0.6 per cent. ² Digitaline, 1 per cent. 1 c.c. injected into muscles of neck in 0.5 c.c. doses. The ventricular contractions seemed to increase in vigour, but the diastoles remained good, or even more complete. Rhythm somewhat irregular. ³ Digitaline, 1 c.c. injected in 0.5 c.c. doses, as above. Both diastole and systole remained good. ⁴ Digitaline, 1 c.c. added to the saline circulation.

The brain cavity after completion of the experiment was more completely opened and the brain found to have been destroyed at the level of the posterior part of the optic lobes ; cerebellum apparently intact.

Assuming the poison to have been absorbed then it must have been pumped by the heart to the vaso-motor centre, yet it appears to have been unable to influence the calibre of the vessels of the hinder extremities, which

latter the final addition of digitaline to the saline circulation itself proves to have been ready to respond.

The very free vascular anastomosis which obtains in the tortoise may at first sight appear to invalidate the experiment, since it scarcely allows of complete isolation of the two circulations. This objection would certainly hold had we obtained a positive result, *i.e.* had the injection of the poison into the anterior circulation caused contraction of the vessels of the posterior circulation, since the poison might have entered the latter through the anastomoses; it can, however, scarcely stand for a negative result.

Finally, there remains for us to record some experiments made on warm-blooded animals with digitaline.¹ This drug alone was selected as typical of the group, and the warm-blooded animals were experimented on in order to complete the series and bring our results a step nearer to human physiology.

The apparatus we employed was very similar to that used by Glax and Klemensiewicz in their experiments on artificial circulation.² A large air-chamber in connection with a force-pump allowed us to get up pressure. The efferent tube from the air chamber was put in connection with two three-necked Woolf bottles by a T tube, both arms of the T tube being provided with clamps. Into each of the Woolf bottles a mercury manometer was inserted, and, finally, from the third neck of each bottle an efferent tube was brought into connection by means of a T tube with the cannula for the aorta. Each afferent tube was provided with a clamp. Each Woolf bottle was of large capacity and was filled with the saline fluid for circulation. Both stood in a large water-bath, which was maintained at a constant temperature of 39° to 40° C. The use of the two bottles was to allow of the filling of the spent bottle without stopping the flow or altering the pressure. And

¹ We are indebted to Professor Schäfer for having kindly performed these experiments for us.

² 'Beiträge zur Lehre von der Entzündung. Sitzungsberichte der Wiener Akademie,' Bd. lxxxiv, Abth. iii, p. 216.

this was readily managed by simply clamping off the tube leading from the pressure bottle to the spent Woolf bottle and opening the tube leading to the other, and similarly opening the efferent tube from the latter and closing that from the spent bottle. By keeping a large stock supply of the artificial circulating fluid also immersed in the bath we were able to replenish the bottles whilst maintaining the temperature of this fluid nearly constant. We will first of all give an experiment in which the fluid was not poisoned, the saline circulation being maintained right through. This gave us our control experiment and showed us the limits of variation independent of drug action.

July 13th.—Temperature of room 23° C.; experiment on a cat.

Temperature of bath 39°—40° C.; artificial circulating fluid = simple tap water saline 0·6 per cent. + a physiological trace of potassium chloride, viz. 0·7 c.c. of a one per-cent. solution to the 100 c.c. saline. Pressure 100 mm. Hg. The animal was chloroformed, the abdomen opened by an incision in the linea alba, the inferior cava and descending aorta exposed and both vessels ligatured proximally. Into the descending aorta the afferent cannula was then inserted distally and tied in; into the inferior cava the efferent cannula was likewise inserted distally and tied in. The experiment was then started.

During the whole experiment up to the death of the animal narcosis was maintained so that the experiment was painless.

Rate of outflow per five minutes in c.c.—300, 240, 310, 380,¹ 415, 380, 335, 320,² 265, 155, 170,³ 170, 190, 180, 200,⁴ 175, 175, 150,⁵ 130, 130, 120,⁶ 115, 100, 85,⁷ 75, 65,⁸ 100,⁹ 120, 110.

¹ No œdema so far. ² Animal dying. Doubtfully slight œdema of tissues.

³ Animal dead. Distinct œdema. ⁴ Œdema marked. ⁵ Leakage from the tissues exposed in the wound, especially from the surface of the intestines. The leakage is due to simple sweating through the tissues. ⁶ Skin of legs quite tense from the œdema. ⁷ Skin very tense. ⁸ Free incision through skin and subcutaneous tissue of one leg. ⁹ Free incision into other leg.

The experiment teaches several things; in the first place the rather considerable variations in the rate of flow in the early stages before the change was in any particular direction. Then with oncoming œdema the steady and somewhat rapid fall in the rate of flow till from a rate of flow of from 300 c.c. to 400 c.c. per five minutes it has fallen to 65 c.c. in the five minutes. That this effect was largely the result of the œdema, we learn not only from the advance of the two *pari passu*, but also from the effect of the free incisions, which lessening tension at once allowed a freer circulation.

The figures representing the rates of flow subsequent to the incisions are certainly lower than they should be, and probably decidedly lower since from the large surface of the incision considerable oozing took place which in part would represent escape through some of the smaller cut vessels, and by this quantity the above numbers would be deficient.

To contrast with this we give the following experiment.

July 9th.—Temperature of room 20° C.; experiment on rabbit.

The same apparatus was employed, but the stock supply of saline was not so large as in the previous experiment, and the through flow was so rapid that, though the bath was maintained at a constant temperature of about 40° C., the saline supply must have been below this temperature, therefore the temperature conditions were less satisfactory. The saline was of the same composition as in the previous experiment, the pressure in the manometer was 50 mm. Hg.

The animal was kept under chloroform throughout the experiment.

Rate of outflow per five minutes in c.c.—178, 188, 174, 270, 310,¹ 102, 80, 16, 14,² 8, 8, 9, 10, 11, 13,³ 13, 14, 14, 16, 16, 16, 19, 20, 16, 19,⁴ 17,⁵ 17, 14.

¹ Digitaline 1 per cent., 1 c.c. to 100 c.c. saline. ² Unpoisoned saline re-substituted. ³ Animal dead. ⁴ Marked œdema. ⁵ Incision into subcutaneous tissue to try and free the vessels.

Making all allowance in this experiment for the temperature not being quite constant, the results are yet too striking to admit of any other interpretation than that the digitaline did act directly and powerfully on the vessels. If the numbers be compared with those in the previous experiment this will be at once apparent. It will be observed that the resubstitution of saline did not appreciably improve the circulation; with reference to this, however, it must be remembered that the rate of flow at the time of resubstitution was exceedingly slow, and hence it would naturally take a long time to wash through the vessels; further, that in the later stages the increasing œdema was an obstacle to improvement, and finally, that the tissues of warm-blooded animals are much more delicate, and hence less likely to recover from damage done. That the incision into the tissues should be without effect will be comprehensible on similar grounds.

Another experiment on a cat was made in which, after establishing a saline flow, digitaline was injected into the subcutaneous tissue, of the anterior or heart circulation. The results obtained were negative, but the apparatus employed was rather less convenient than the above described, and various sources of fallacy crept in.

Confining our attention, however, to the two experiments just described, we find the results in keeping with those already obtained with cold-blooded animals, and we think the present series of experiments establishes tolerably definitely the direct action of digitalis and the group of bodies of which it is the type on the vessels.

To complete the argument which we stated at the commencement of the paper, experiments were made to ascertain the degree of poisonous action of these drugs on the skeletal muscles. Definite quantities of the drugs were injected beneath the skin of the back in frogs, and subsequently to systemic death, or in some cases even before, the muscles tested electrically as to their excitability.

The following were the results obtained :

Digitaline. 1 per cent. solution.

Weight of frog.	Quantity injected.	Condition of muscular irritability.
34 gms. ...	0.3 c.c.	... Systemic death in 3½ h.; muscular irritability gone in 6 h.
18.5 „ ...	0.2 c.c.	... Muscular irritability gone in 5 h. 30 m.
31.5 „ ...	0.2 c.c.	... Frog quite well after 19 h.
16.5 „ ...	0.2 c.c.	... Muscular irritability gone in 4 h. 45 m.
11 „ ...	0.2 c.c.	... Muscular irritability gone in 3 h. 25 m.
? „ ...	0.4 c.c.	... Systemic death in 1 h. 20 m.; muscular irritability fair after 3 h. 25 m.

Strophanthus. The crude drug.

25.5 gms. ...	0.2 c.c. (2.5 %)	... Lost in 2 h. 20 m.
25.75 „ ...	0.2 c.c. (1 %)	... Lost in 2 h. 40 m.
14.75 „ ...	0.2 c.c.	... Lost in 2 h. 30 m.
10.75 „ ...	0.2 c.c.	... Lost in 2 h. 40 m.
32 „ ...	0.2 c.c. (5 %)	... Lost in 1 h. 10 m.
12 „ ...	0.2 c.c.	... Nearly gone in 1 h. 30 m.
10.5 „ ...	0.2 c.c.	... Nearly gone in 1 h. 30 m.
? „ ...	0.4 c.c.	... Quite gone in 2 h. 45 m.

Dyak. The crude drug; but one experiment.

22 gms. ...	0.2 c.c. (1 %)	... Lost in 1 h. 20 m. (Systemic death in 50 m.)
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Scillitine.

31 gms. ...	0.2 c.c. (1 %)	... No effect; frog normal.
38 „ ...	0.3 c.c. „	... No effect; frog normal.
45 „ ...	0.5 c.c. „	... Muscular irritability lost in 6 h. Systemic death in 2 h.
18.5 „ ...	0.2 c.c. „	... Muscular irritability nearly gone after 20 h.

Barium chloride.

23 gms. ...	0.5 c.c. (10 % solution)	... Lost in 3 h. 15 m.
19.75 „ ...	0.3 c.c. „	... Lost in 3 h. 15 m.
20.75 „ ...	0.2 c.c. „	... Lost in 3 h. 15 m.
20.75 „ ...	0.3 c.c. „	... Still slight persistence after 3 hours 15 minutes.

Weight of frog.	Quantity injected.	Condition of muscular irritability.
23.75 „ ... 1 c.c. (1 % solution)		The frogs developed within the first few hours peculiar stiff movements and the cry-reflex described by Boehm; from this state they for the most part recovered, and at the end of 24 hours were fairly normal.
24.75 „ ... 0.5 c.c. „		
27.5 „ ... 0.5 c.c. „		
? ... 0.2 c.c. „		... No effect.

Examining these results we observe in the first place that the above drugs from the digitalis group are all *notable poisons to the skeletal muscles*. And we observe, further, that strophanthus and dyak poisons act most powerfully in this respect. It is true that some of the experiments with strophanthus were with 2.5 per cent. and 5 per cent. solutions as against 1 per cent. of digitaline, but then we must bear in mind that of the former we were employing the crude drug as against the active principle itself in the latter case. Hence it is clear that both of these drugs, strophanthus and dyak, affect more powerfully the voluntary muscles than does digitaline. If, now, we refer back to their action on the heart we shall find that whereas the chief feature in the digitaline action is the contracture excited, which may be almost complete with scarcely any weakening of the heart's action, in the case both of strophanthus and dyak we find that though contracture is well-marked it is less so than with digitaline, whilst at the same time there is more decided weakening of the individual beats. For scillitine the results are less decided; in its action on the skeletal muscles, it scarcely exceeded digitaline in power, whilst on the heart it caused less marked contracture, but decided weakening of the individual beats.

With these results in view we are able to speak less positively as to the possibility of inferring from the action of these cardiac drugs on the heart contractions to action on the skeletal muscles themselves. To determine this point a more extended range of experiments will be needful.

We may now briefly re-state the steps of the argument and sum up the results obtained.

1. Starting from the systolic digitalis heart, which is admittedly a result of direct action on the cardiac muscle, we have found :

2. That for the other members of the digitalis group here examined a like direct action obtains.

3. We have suggested that this local action on the heart, which may affect either the whole heart or a limited portion, according as the drug comes in contact with the whole heart or a limited portion of the heart, that this action may serve as the definition of *digitalis action*, and that such definition would necessarily enlarge Schmiedeberg's already large group.

4. Taking this as the definition we have argued therefrom to local action on the vessels, and have found experimentally such to hold—the digitalis group causing persistent spasm of the arterioles.

5. We have endeavoured to ascertain if the calibre of the vessels may be influenced by these drugs *indirectly* through the nervous system, and, so far as our experiments go, have been answered in the negative.

6. Finally, we have found by experiment that the drugs digitaline, strophanthus, dyak, scillitine, and barium chloride, are markedly poisonous to the skeletal muscles.

The results require some criticism. In the first place, we note that the definition adopted admits into the group such bodies as the caustic alkalies, barium salts, &c. The former certainly do not rank with us clinically as digitalis-like drugs. But it is obvious that clinical use is practical use. And that it must very extensively weed this large scientific group, for it is at once clear that it is practically impossible for us to give alkalies to the extent of alkalinising the system to the degree requisite to bring out the digitalis-like action. Hence the alkalies would be excluded from the clinical group. It is very possible that for similar reasons the barium salt may prove impracticable, and that the gastro-intestinal irritation (vomiting

and purging) excited by the drug, may not allow of its being given in dose sufficient to bring out the cardiac and vascular effects. This point, however, will have to be determined by experience. The like may obtain for many other drugs yet to be included in the digitalis group as above defined, for clinical value is a question of fitness, and results from the fact that the body is an assemblage of organs, and that the action of a drug in many cases is simultaneously on several of these; hence whilst its action on one organ would qualify it for clinical use, by its action on another organ it disqualifies itself.

One other point we would wish to touch upon, viz. the question of the rise of pressure and its dependence on cardiac action. According to Schmiedeberg the blood-pressure rise is due solely to increased cardiac action. "It has been shown," says Schmiedeberg, "to be not attended by diminution in the calibre of the vessels."¹ In view of our own experiments and also of those by Donaldson and Stevens, the results of which have been recently published² (subsequently, however, to the completion of our own experiments both on barium chloride and on the digitalis group), we can hardly accept this statement and hold that part at any rate of the pressure rise must be attributed to narrowing of the calibre of the arterioles. This interpretation indeed appears to us much more in consonance with the data which Schmiedeberg himself furnishes us with, for in the above paper he gives rise of blood-pressure as continuing through the first stage in which there is as a rule slowed pulse-rate, through the second stage in which there is increased pulse frequency, and through the third stage in which there is great irregularity in the heart's action; in the fourth stage, however, with systolic arrest there is rapid fall in blood-pressure. Here we see increased blood-pressure obtaining with most varied heart action, and we can scarcely imagine that in the third stage the cardiac action can be effective in main-

¹ *Op. cit.*

² 'Journal of Physiology,' vol. iv, pp. 165, *et seq.*

taining the increased tension. Arguing from this we should rather be tempted to exclude the heart and refer all to the vessels ; a conclusion, however, which we think would necessarily be faulty, for is not the question one of action and reaction—the heart acts on the arterioles which again react on the heart ? It is quite clear that without a peripheral resistance you could never whip up blood-pressure just as clearly as that with no matter how great a peripheral resistance (provided there were still means of out-flow, *i.e.* that the obstruction were not complete) raised blood-pressure could never be maintained with a failing heart. Donaldson and Stevens more especially deal with the question of the work of the heart, though they also take up the question of the condition of the blood-vessels ; these latter results being similar to our own. As to the work of the heart they find it diminished. We would, however, suggest that it is possible this resulted from their having pushed the drug too far, for in their experiments on the terrapin, where they record lowered work and also the condition of the heart, we note of this latter that it is very markedly affected ; thus, the ventricle is either distinctly shrunken, or there is marked irregularity in its action, or dicrotism, or many auricular beats to one ventricular. In this stage we should scarcely look for increased work of the heart, but should feel rather that we were bordering on stage 4 of Schmiedeberg with fall in blood-pressure.