be sustained for considerable periods, but you may not know that the same has been shown for the human heart several hours after death. It is quite within the bounds of possibility that if, in the hands of one accustomed to the method, a heart is taken from one of the patients some while after death, the revival of such a heart may be possible. And it is also probable that in reviving it will return to its former mode of beating—that is to say, the auricle will be seen in fibrillation.

But these are facts which it is for the future to reveal. For the present we must rest content with the proof as I have given it.

Finally, let me refer quite briefly to the results of this conclusion. It explains not only the irregularity as we witness it, but it explains almost all the remaining phenomena which are associated with it as a mechanism—facts which I pointed out in my first communication.

When a healthy dog's auricle passes into fibrillation, the ventricle doubles or trebles its original rate; the gross irregularity of our patients is accompanied by tachycardia. The conclusion explains why digitalis acts so magically in slowing such hearts, for digitalis produces heart-block and heart-block slows the ventricle when the auricle fibrillates. It also explains the spontaneous slowing or original slowness of the ventricular action in some patients, for here disease has affected the conducting tissues and has impeded the rapid and irregular impulses from reaching the ventricle.

In brief, the original rapidity of the pulse and its irregularity, the character of the irregularity, the loss of the auricular wave in the neck, the loss of the P summit in the electro-cardiogram, the loss of presystolic murmurs, the presence of rapid oscillations in the venous curve, the presence of oscillations in the electro-cardiogram, the varying rate of the ventricle in a single patient or from patient to patient, the action of digitalis—each and all are clear once the true explanation of the mechanism is grasped. And this explanation, as I have shown you, is that in such cases we have to deal with fibrillating auricles.

REFERENCE.

¹ BRITISH MEDICAL JOURNAL, November 27th, 1909.

THE EFFECTS UPON THE HEART OF SOLUBLE DIGITOXIN, AN ISOLATED GLUCOSIDE OF THE DIGITALIS GROUP.

BY

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ALTHOUGH digitalis is one of the most valuable of all our cardiac drugs, its therapeutic administration still lies at a stage of development comparable to that of the use of decoctions of cinchona bark before the isolation of quinine.

The physician is still, unfortunately, forced to prescribe an infusion or tincture of digitalis leaves prepared on the same principles as a cup of tea, although the toxicity of the product so administered may vary as much as that of the domestic beverage.

As a matter of fact, when either an infusion or tincture of digitalis leaves is prescribed, not one remedial agent is employed but a blunderbuss of about half a dozen bodies with powerful cardiac action, some undoubtedly favourable for the condition to be combated, others as equally certainly unfavourable in their continued effects upon cardiac muscle.

The reason for this state of affairs in regard to digitalis therapy does not lie so much in a want of knowledge as in a plethora of knowledge, for instead of having in the digitalis leaves one predominatingly important active substance, as in the case of quinine or caffeine, we have, as in the case of the morphine alkaloids, a number of active bodies requiring a great deal of experimental labour and clinical experience to decide between their relative values and uses.

In order to surmount some of these difficulties in the clinical use of digitalis there has been introduced in recent years the process of physiological standardization in order to give some idea of the approximate strength, as a kind

of therapeutic battery, of the complex group of bodies probably present in varying relative amount in any given galenical preparation, such as pharmacopoeial infusion or tincture.

Two methods which have been employed for this standardization are (1) the determination of the minimal amount which will, when injected into a lymph sac, cause complete stoppage of the heart of a frog of average size (20 grams weight) within one hour, and (2) the determination of the minimal concentration in Ringer's solution, which when perfused through the isolated mammalian heart, stops all action of the ventricle within one hour. The amount of a good tincture of digitalis required in the first method should not exceed 0.3 to 0.4 c.cm.; and, in the second method, the digitalis preparation should stop the heart within the hour at a dilution of 1 in 200. A third method of experimentation more recently employed by Waller, with interesting results, is to study the effects of the drug in arresting the contractile power of skeletal muscle immersed in the diluted drug. This method has the merit of greater simplicity, and the results seem to resemble closely those obtained with cardiac muscle itself.

But although those methods of physiological standardization may be safely relied on for giving information as to the genuine digitalis nature of a commercial sample, and also some indication as to the careful preparation from "good" leaves, still, as satisfactory scientific and practical methods of dosage they fail in two important aspects.

In the first place, there is no definite standard such as an isolated glucoside of this class would give, if obtainable and universally agreed upon as a standard; there are many isolated products all differing from one another, some soluble and others insoluble, and all varying in their action upon the heart, and as yet pharmacologists have not been able to select any one of these as a unit.

Secondly, the proposed standardization test is a test of "killing power," and physicians do not want to kill, but cure. Underlying this test of killing within a certain time by ventricular arrest is the tacit assumption that it is the same body which kills and produces the favourable therapeutic effect. On any other hypothesis the so-called physiological standardization is meaningless.

The basis of the whole process is that digitalis in small doses stimulates cardiac muscle, and in large doses paralyzes it, and hence if in the case of a given preparation we determine the larger dose which kills, we can logically infer what is the smaller dose which will just develop the beneficial therapeutic effect. Now, however sound such argumentation might be in the case of a single active body difficult to isolate, and hence standardized by such an indirect method, it loses all application when dealing with at least four bodies so very different in action and toxicity as are the glucosides of digitalis leaves. The test would only hold if there were the same ratio between maximum therapeutic action and minimal lethal dose for each of these bodies, and experience of both pharmacologist and clinician demonstrates that this does not hold true.

This line of thought holds good not only for the standardization of digitalis, but also for the decision as to whether the usual unknown mixture of the *Pharmacopoeia* should be still used, or whether the active glucosides should be isolated and used separately. There is no question that at least one of the glucosides present in the digitalis leaf—namely, digitonin—is injurious in its action, and ought to be eliminated if possible; and amongst the remaining members of the group there can be little doubt that these vary amongst each other in relative toxicity and degree of excitatory action.

It would have been more scientific to separate these active bodies and make use of them according to the clinical indications in varying cases rather than to fire off a blunderbuss of them all in unknown proportions at the patient's heart.

Here it should be emphasized that it is not maximum toxicity or brute strength that is to be aimed at. If it were so, strophanthin, which is much more powerful, would in all cases be prescribed; but it is easy enough to stop a heart with any of these drugs given in sufficient dose. The active agent to pick out is that one which possesses what might be described as the greatest factor of safety, that is, the highest ratio between the minimal lethal dose and the dose giving a good therapeutic effect. Some attention ought also to be paid to the possibility of accurate

dosage, and here a body which can be completely isolated holds an advantage because the physician knows exactly how much he has given his patient.

The number of bodies possessing an action closely resembling that of the digitalis group upon the heart is an enormous one, and goes on increasing all the time.

In addition to the older well-known remedies, such as squills and strophanthus, there are the plant principles carpain, helleborein, spartein, and probably all the members of the huge group of the sapo-glucosides, of which commercial saponin from ordinary quillaia bark is the best-known representative. In this laboratory we have recently investigated two isolated glucosides, one named mowrin, from the mowrah bean of India, and the other called hederin, from the leaves of the common ivy. Both of these bodies possess a remarkably stimulating action on the cardiac muscle, and when perfused through the isolated heart show an increased force of beat and a slowing of the rate, and generally give tracings very similar to digitalis. But, unfortunately, they have in the end an injurious effect upon the heart, appearing to render it oedematous; and also they possess a highly injurious action upon red blood corpuscles, causing rapid haemolysis even in dilute solution. In many respects, both chemically and physiologically, these sapo-glucosides possess an interesting and suggestive resemblance to the bile salts, but their haemolytic and certain other properties rule them out as heart tonics.

In crude digitalis such an injurious sapo-glucoside—namely, digitonin—is always present, and in the infusion its presence is even necessary to dissolve the crystalline *digitoxin*, which is quite insoluble in aqueous solution.

In the process of testing various digitalis preparations dissolved or suspended in saline, according to their solubilities, Waller found that the insoluble preparations were without effect upon the muscle preparation; while those three preparations out of the five tested which were active—namely, *Digitonin cryst.* (Merck), *Digitalinum pulverizatum purum Germanicum* (Merck), and *Digitalinum verum* (Schmiedeberg)—all give a soapy froth on shaking. This is the usual physical index of the presence of a saponin or sapo-glucoside.

In the course of the present work, in order to avoid complicating the results by administration of alcohol at the same time and to render intravenous injection possible, I have evaporated off the alcohol from a tincture of digitalis, and then made the residue up as a fine suspension in an equal volume of saline.

Such a suspension I have found entirely inert upon intravenous injection, and it has occurred to me that the uncertain action of tincture of digitalis, when given by the mouth, may be due to its precipitation in insoluble form when largely diluted with water in the stomach.

It is obvious that amongst these many glucosides possessing a marked cardiac action, if one could be found free from the saponin properties of haemolyzing blood and sufficiently soluble in water to be administered without alcohol, and in case of need given intravenously, it would possess a preference as a cardiac tonic.

Such a substance would appear from Waller's work to be a rarity, but Cloetta² claims to have isolated a body with these properties from digitalis leaves in his "*digitoxinum solubile*." The glucoside exists in the leaves, along with the *digitalinum verum* of Schmiedeberg, in smaller quantity. The various other insoluble bodies taken out by alcohol, such as Merck's crystalline digitoxin, are, according to Cloetta, isomeric forms of this soluble glucoside, which become polymerized and insoluble in the manipulations necessary for preparation. The soluble body has half the molecular weight of the insoluble crystalline body.

Soluble digitoxin is manufactured by the Hoffmann-La Roche Chemical Works, and is known commercially as digalen. It is dissolved in dilute glycerine solution, containing in each cubic centimetre 0.3 mg. of the isolated soluble digitoxin; that is to say, the solution is so dilute that it corresponds to only 3 parts of glucoside in 10,000. I have to thank Messrs. Hoffmann-La Roche for supplying me in addition with a corresponding solution, in saline alone, to ensure the absence of any glycerine effect, but as no such effect was found, and the glycerine solution best preserves the activity of the glucoside, the commercial digalen was employed for most of the experiments.

Although experiments with red blood corpuscles clearly demonstrated that digalen satisfied the condition of absence of a saponin-like body, there being not the slightest sign of laking, the first impression obtained in studying the action upon the heart by orthodox methods was disappointing, for it looked as if the substance was very weak, as compared with a standardized tincture of digitalis. So it is, if the ordinary sign of stopping the heart within one hour be taken as the standard of therapeutic activity.

Thus, while a standard digitalis tincture injected into the dorsal lymph sac of a frog in an amount of 0.4 c.cm. stopped the heart within the hour, as much as 1 c.cm. of the digalen solution barely did so, the heart beating feebly and at long intervals up to one hour and fifteen minutes.

Again, while 3 c.cm. of the standard tincture injected intravenously in a medium-sized rabbit killed within a few minutes, it was only a dose of at least 10 c.cm. of digalen which sometimes proved fatal in an hour or more in rabbits of about this weight. Given hourly, or two-hourly, in 1 to 2 c.cm. doses, more than 10 c.cm. can be borne by a 2 kg. rabbit in the course of the twenty-four hours. From the point of view of lethal dose, therefore, digalen solution only possesses one-third to one-fourth of the strength of standardized tincture of digitalis. But the question arises, Does the lethal dose, as determined in this way, fix the therapeutic value of the drug? and in our opinion, the effects upon the heart obtained in the experiments on the intact mammal, and the minimal amounts required to develop a marked therapeutic action in the isolated mammalian heart, negative this proposition, and demonstrate on the other hand that the lessened lethal effect is a distinct advantage.

Equivalent amounts of the digalen solution produce as distinct and marked slowing as the tincture, and on listening to the heart the increased force is obvious in the short, sharp systole. It has the further advantage that it can be given intravenously without pain; the absence of alcohol is here a highly desirable factor, and the safe dose is at least treble that of the tincture.

On perfusion through the isolated mammalian ventricle a marked therapeutic effect is obtained with as little as 2 c.cm. in a litre (see Fig. 2), and in the later full physiological effect there is a marked increase in the tonicity of the heart muscle, as shown by the elevation of the base line.

The results appear to indicate that in the use of ordinary pharmacopoeial preparations of digitalis the tonic effects and toxic effects are produced in varying degree by the different glucosides, and that soluble digitoxin is one which possesses more valuable therapeutic properties, with a large factor of safety, than the mixture as extracted in the tincture.

EFFECTS ON THE HEART IN THE INTACT MAMMAL.

Rabbits were employed throughout for the experiments, on account of the ease of intravenous injection into the marginal vein of the ear, and for the purpose of comparison with the results of perfusion of the drug in solution in Ringer's saline in the same animal, as shown in the next section of this paper.

It requires some training of the ear to count the rate of heart-beat accurately in the rabbit, on account of the speed of the beat, but the heart-beat, although so rapid, is steady and regular, and with a little practice can be counted quite well.

In addition to the slowing in the rhythm recorded in the experiments below, the ear, after a little training to the work, soon detects and appreciates what the numbers do not show, and that is a sharpening in pitch of the systolic heart-sound, which gives the impression of a sharper blow. This is very characteristic, and corresponds doubtless to the therapeutic stage marked by the increased stroke in the earlier part of each tracing of the effect on the perfused isolated heart, as shown in the next section.

One very striking result, resembling that obtained by Sherrington and Sowton³ when studying the comparative concentration of chloroform in saline and in serum which acted upon the heart, is seen on comparing the results of this section with the succeeding section, in which the drugs dissolved in saline acted upon the isolated heart. This result is a very beautiful one, and the physico-chemical explanation of it is most interesting and of important practical application in therapeutics, showing

that the dosage of a drug depends on its relative chemical affinities for saline, serum, and cell substance.

When the solution of the digalen is injected intravenously in a 2-kilogram rabbit, it takes about 3 c.cm. to produce a full therapeutic effect with recovery to normal in about two days' time, and even as much as 10 c.cm. can be given without producing a lethal result. Now, if we make the assumption—to be on the safe side—that the blood of the rabbit represents one-tenth of the weight, the amount of fluid in which the 3 c.cm. injected is distributed is about 200 c.cm.* This gives a solution of the digalen solution of about 1 in 70 for the therapeutic dose, and 1 in 20 or less for the lethal dose. If this be now contrasted with the concentration of the drug in saline which acts upon the isolated heart, it is found that even 1 in 500 rapidly gives a large therapeutic effect, and even with this dilution the heart muscle does not remain in equilibrium, but goes on taking up the drug continuously from the saline until it poisons itself, and in about another hour and a half to two hours the heart-beat is enormously reduced, and, in fact, almost stopped, while its muscular tonicity has increased enormously (see Fig. 2); with a concentration of 1 in 200 the rapidity of the whole process is increased, but the picture as a whole is the same (see Fig. 1). The whole thing is a beautiful example of the application of physical chemistry in bio-chemistry and medicine. Even with the five-hundredfold diluted solution there is no equilibrium at any point at which the heart can go on functioning, and the muscle is finally poisoned just as with the 1 in 200 concentration, but the absorption is slower and the system—*cardiac muscle, saline, and drug*—moves more slowly towards equilibrium. Contrasted with this, even so high a concentration as 1 in 70 does not poison when serum is the circulating medium instead of saline, but instead the system—*cardiac muscle, serum and drug*—comes into equilibrium at the stage of therapeutic effect, and remains there steadily for days until the drug becomes changed or excreted. The drug has to distribute itself between saline and cardiac tissue in the one case and between serum and cardiac tissue in the other.

In the former case the *Coefficient of Distribution* is a high one and practically all the drug goes on passing over into the heart. If the saline is perfused long enough the heart will be overcome, even with a high dilution in the saline.

In the case of the serum, the *Coefficient of Distribution* of the drug between cardiac muscle and serum is a comparatively low one, and even at a much higher concentration of the drug in the blood an equilibrium point will soon be reached at which no more drug will leave the blood and pass into the heart muscle. The amount in the blood will then act as a fly-wheel regulating the amount kept up in the heart. If the amount in the blood diminishes, some will slowly diffuse out from the heart till a lower equilibrium-point is reached with the heart less under the digitalis control. Proceed now in the opposite direction and increase the concentration of the drug in the blood, and the concentration of the drug in the heart muscle will go up accordingly to a higher equilibrium-point. So, corresponding to each concentration in the blood there will be a concentration in the heart tissue. As the concentration in the heart tissue is heaped up that organ comes more and more under the influence of the drug, and, finally, after passing through the therapeutic stage, there is a level or range at which it becomes embarrassed and finally stops beating.

It is interesting here to compare the difference between chloroform and digitalis in action upon the heart in the light of this result. Chloroform is a readily diffusible body, easily got rid of by lungs and kidney. If the administration is stopped for a few minutes the concentration of the chloroform in the blood rapidly falls, and the heart recovers and again beats more rapidly. But digitalis is a slowly diffusing substance, not rapidly got rid of from the blood nor quickly moving from blood to heart, or vice versa, even when injected directly into the blood stream. As shown in most of the experiments recorded below, except where the dose is a very huge one, it is some hours before any effect is seen. It is well known to

physicians that when the drug is given by the mouth little effect is seen for a day, or even till the second day. Naturally, in the disappearance of the effect of the drug there is the same slowness in the inverse order, the drug slowly coming out of its interlocking position in the cardiac muscle as the concentration of the drug in the blood slowly diminishes.

This is the chemico-physical basis which really underlies the phenomenon usually described as the cumulative action of digitalis, and teaches a twofold lesson—first, as to the proper administration of digitalis; and, secondly, as to which among the digitalis group of glucosides should be chosen to reduce this undesirable result to a minimum. In the first place, the drug should be pushed by a physician having large experience of such cardiac cases until the full therapeutic advantage is developed, and then the dosage should be largely depressed, just to compensate, and no more, for the amount of drug destroyed or slowly excreted. There should be no attempt made by pushing afterwards to attain the impossible, as that will only result, on the chemico-physical basis above outlined, in driving the heart on into the full physiological stage, where the output is diminished and the heart embarrassed and stopped (see later parts of Tracings 1 to 3).

Secondly, we see in the case of the saline experiments that where the *Coefficient of Distribution* between heart and circulation fluid is a high one, it is almost impossible to get the concentration of drug in the circulation fluid so low that an equilibrium is obtainable at the therapeutic stage. Now such an evil result would be accentuated if the drug had a stronger affinity for cardiac muscle, and had to be given in still lower concentration. Hence a stronger drug—such as strophanthus—is not so safe, even in correspondingly less dose, than a digitalis glucoside, because it cannot be regulated so nicely. It possesses more tendency to go into the heart, stay there, and become cumulative for succeeding doses. A drug with less specific affinity and more readily diffusible in or out, will also have a larger range and *factor of safety* between its therapeutic and its lethal dose, than a more specific one entering into firmer union with the cardiac tissue at lower concentration. Accordingly, in treating ordinary heart conditions of failing compensation, it is distinctly the weaker drug that is indicated and not the stronger one, and also the more readily soluble and diffusible one, so that accumulation may be avoided.

What constituent is it in the blood which confers upon it this power of retaining such a drug as digitoxin and balancing against the pull of the heart for it? It is probably in part the protein of the blood, and in part the fatty constituents, as in the case of ordinary anaesthetics, and an exhaustive investigation is required as to whether it is cardiac proteins or cardiac lipoids which absorb and hold these glucosides that act so powerfully on the heart. In any case, some organic constituent in the blood is pitted against another organic constituent in the heart muscle for the possession of the dose of cardiac glucoside, and the ratio of distribution varies for each glucoside and determines the specific power of that glucoside.

EXPERIMENTS.

As it was found that subcutaneous injection in mammals caused a certain amount of inflammation and oedema, the drug was in most cases given by intravenous injection followed by a small amount of normal saline. By this method the drug can be introduced almost painlessly and very effectually; the smallest trace of phlebitis or other evil result has never been observed, and in those clinical cases where the condition of the stomach contraindicates administration by the mouth intravenous injection of digalen can be recommended. There is the added advantage of increased rapidity of action over the ordinary oral administration of digitalis, although even with intravenous injection a full effect is not obtained until the expiration of three or four hours. (See experiments.) The reason for this is to be found in the chemico-physical explanation of the action of the drug given above.

EXPERIMENT I.—Continued Administration of Digalen in Medium Doses.

Rabbit of 2,090 grams. Initial rate of heart, 43 in 10 seconds. First Day. At 11.45 a.m., rate 43 in 10 seconds. At 11.52 a.m., injected intravenously 3 c.cm. of digalen; at 11.53 a.m., rate 46 in 10 seconds; at 11.56 a.m., rate 38 in 10 seconds; at 11.57 a.m.,

* According to recent determinations by Boycott, *Proc. Physiol. Soc.*, November, 1911, the blood volume in the rabbit is only one-twentieth of the body weight,

rate 40 in 10 seconds; at 12.2 p.m., rate 42 in 10 seconds; at 12.16 p.m., rate 46 in 10 seconds; at 12.53 p.m., rate 45 in 10 seconds. At 2.56 p.m., injected intravenously 3 c.cm. of digalen; at 3.4 p.m., rate 45 in 10 seconds. At 4.3 p.m., injected intravenously 3 c.cm. of digalen; at 4.36 p.m., rate 47 in 10 seconds. Total amount administered in first day, 9 c.cm.

Second Day. At 11.12 a.m., rate 35 in 10 seconds. No digalen given.

Third Day. At 11.15 a.m., rate 28 to 35, and varying rhythmically in rate, fast and slow alternately.

Fourth Day. At 1.30 p.m., rate 34 to 36 in 10 seconds.

Fifth Day. At 11.30 a.m., rate 40 in 10 seconds.

Seventh Day. At 11.23 a.m., rate 39 in 10 seconds, regular. At 11.45 a.m., injected intravenously 6 c.cm. of digalen; at 11.52 a.m., rate 46 in 10 seconds; at 2.50 p.m., rate 49 in 10 seconds.

Eighth Day. At 11.15 a.m., rate 33 in 10 seconds.

Ninth Day. At 11.0 a.m., rate 41 to 43 in 10 seconds. Note that there is remarkable slowing of the heart on the day succeeding administration, and that this slowing is prolonged in duration; note also the low toxicity of the digalen.

EXPERIMENT II.—Continued Administration of Digalen in Smaller Doses.

Rabbit of 1,630 grams. Initial rate of heart, 50 in 10 seconds.

First Day. At 3.54 p.m. rate 50 in 10 seconds. At 3.57 p.m., injected intravenously 2 c.cm. of digalen; at 4 p.m., rate 48 in 10 seconds; at 4.38 p.m., rate 45 in 10 seconds. At 5.2 p.m., injected intravenously 2 c.cm. of digalen; at 5.4 p.m., rate 44 in 10 seconds; at 6.3 p.m., rate 45 in 10 seconds. At 6.5 p.m., injected intravenously 2 c.cm. of digalen; at 6.7 p.m., rate 47 in 10 seconds; at 6.30 p.m., rate 46 in 10 seconds; at 7 p.m., rate 45 in 10 seconds. At 7.5 p.m., injected intravenously 2 c.cm. of digalen; at 7.6 p.m., rate 46 in 10 seconds. Total amount administered during first day, 8 c.cm.

Second Day. At 11.37 a.m., rate 42 in 10 seconds. At 11.40 a.m., injected intravenously 2 c.cm. of digalen; at 11.42 a.m., rate 42 in 10 seconds; at 12.10 p.m., rate 33 in 10 seconds; at 12.50 p.m., rate 32 in 10 seconds. At 12.56 p.m. injected intravenously 2 c.cm. of digalen; at 12.58 p.m., rate 36 in 10 seconds; at 2.10 p.m., rate 36 in 10 seconds. At 2.18 p.m., injected intravenously 2 c.cm. of digalen; at 2.20 p.m., rate 39 in 10 seconds; at 3.2 p.m., rate 31 in 10 seconds. At 3.10 p.m., injected intravenously 2 c.cm. of digalen; at 3.14 p.m., rate 35 in 10 seconds; at 3.40 p.m., rate 30 in 10 seconds. At 3.45 p.m., injected intravenously 2 c.cm. of digalen; at 3.55 p.m., rate 34 in 10 seconds. Total amount administered in second day, 10 c.cm., making 18 c.cm. in first and second days. The heart-rate has been reduced from 50 in 10 seconds to 30-34 in 10 seconds.

Third Day. At 1.45 p.m., rate 33 in 10 seconds. No digalen administered this day.

Fourth Day. At 3.35 p.m., rate is 31 in 10 seconds. No digalen administered.

Fifth Day. At 12.55 p.m., rate is 44 in 10 seconds; at 5.40 p.m., rate 36 in 10 seconds.

Twelfth Day. At 4.40 p.m., rate steady at 40 in 10 seconds.

EXPERIMENT III.—Effects of Large Dose of Digalen Injected Intravenously.

This experiment was really carried out to determine the minimal lethal dose, but the glucoside was so much less toxic than was expected that the animal did not die from the amount injected.

This amount was, however, so considerable that paralysis of the vagus with increased heart-rate was obtained as with large doses of digitalis.

Rabbit of 2,290 grams. Initial rate of heart-beat before drugs, 36 in 10 seconds.

First Day. Heart-rate at 3 p.m., 36 in 10 seconds. At 3.5 p.m., injected 5 c.cm. of digalen into marginal vein; at 3.15 p.m., heart-rate 30 in 10 seconds; at 4.50 p.m., 32 in 10 seconds; at 5.47 p.m., 32 in 10 seconds.

Second Day. Heart-rate at 12 noon, 42 in 10 seconds; at 5.30 p.m., 40 to 42 in 10 seconds. No drug given this day as heart so much above normal.

Third Day. Heart-rate at 11.55 a.m., 40 in 10 seconds. Injected 5 c.cm. of digalen intravenously at 12.7 p.m.; at 12.9 p.m., heart-rate 36 in 10 seconds; at 12.12 p.m., 37 in 10 seconds; at 1.44 p.m., 40 in 10 seconds; at 6.25 p.m., 38 in 10 seconds.

Fourth Day. At 11.15 a.m., heart beating almost too fast to count and irregularly; rate about 54 in 10 seconds; at 5.30 p.m., 44 in 10 seconds.

Fifth Day. At 11.40 a.m., beat 40 to 42 in 10 seconds. At 11.55 a.m., injected 5 c.cm. of digalen intravenously; at 11.58 a.m., 36 to 38 in 10 seconds.

Sixth Day. At 11 a.m. rate almost uncountable at about 54 in 10 seconds. The rate remained high for about three days, and then fell to about normal again. The animal, which had received about 15 c.cm. of the digalen solution within four days, completely recovered, a demonstration of the exceedingly low toxicity of the drug, although the action on the heart was pushed past the slowing stage into the rapid stage accompanying vagal paralysis.

EXPERIMENT IV.—Still Larger Doses of Digalen.

Rabbit of 2,250 grams. Initial rate of heart beat before drugs 42 in 10 seconds.

First Day. At 4.20 p.m., rate 42 in 10 seconds; injected 8 c.cm. of digalen intravenously; at 4.30 p.m., rate 37 in 10 seconds; at 1.55 p.m., 34 in 10 seconds; at 5.45 p.m., 32 in 10 seconds.

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Second Day. At 12.5 p.m., 48 in 10 seconds; at 5.35 p.m., 44 in 10 seconds.

Third Day. At 12.25 p.m., 45 in 10 seconds. At 1 p.m. injected 10 c.cm. of digalen intravenously; rate immediately after 47 in 10 seconds; at 1.5 p.m., 42 in 10 seconds; at 1.50 p.m., 40 in 10 seconds; at 5.30 p.m., 39 in 10 seconds.

Fourth Day. At 11.55 a.m., rate 43 in 10 seconds; at 5.30 p.m., 46 in 10 seconds.

Fifth Day. At 12 noon, 38 in 10 seconds.

Sixth Day. At 11 a.m., 35 in 10 seconds.

Seventh Day. At 5 p.m., 42 in 10 seconds; a return to the normal rate.

This animal survived and remained quite well, although it received a dose of 8 c.cm. of the drug, followed within two days by another dose of 10 c.cm., making 18 c.cm. in all. Except for a very short period after the injection when there is slowing, the rate of the heart is increased with such large doses. The most striking effect is the low toxicity accompanying a marked cardiac action.

EXPERIMENT V.—Minimal Lethal Dose of Digalen.

Rabbit of 2,130 grams. Initial rate of heart, 44 in 10 seconds.

At 3.28 p.m., rate 44 in 10 seconds, very regular; at 3.37 p.m. injected intravenously 10 c.cm. of digalen; at 3.40 p.m., rate 37 in 10 seconds; at 3.41 p.m., rate 38 in 10 seconds; at 3.43 p.m., 37 in 10 seconds. At 4.20 p.m., rabbit dead; heart found *post mortem* in diastole.

EXPERIMENT VI.—High Toxicity of Tincture of Digitalis (Standardized).

Rabbit of 1,880 grams. Initial rate of heart, 39 in 10 seconds.

At 12.5 p.m., rate 38 to 40 in 10 seconds.

At 12.10 p.m., injected intravenously 2 c.cm. of standardized tincture of digitalis.

At 12.10 p.m. animal dead.

EXPERIMENT VII.—Toxicity of Small Dose of Tincture of Digitalis (Standardized).

Rabbit of 1,790 grams. Initial rate of heart, 46 in 10 seconds.

At 12.19 p.m., rate 46 in 10 seconds.

At 12.21 p.m., injected 2 c.cm. of a tincture intravenously.

At 12.22 p.m., rate 37 in 10 seconds; at 4.10 p.m., animal lying on side, rate 56 to 60 in 10 seconds; at 4.20 p.m., heart becomes blocked and irregular, fast and slow alternately, and finally stops.

This experiment illustrates the high toxicity of the mixed glucosides in digitalis tincture as contrasted with digalen, and taken with Experiment VI, shows that digitalis in tincture cannot be used intravenously, while digalen can be so used with safety.

EXPERIMENT VIII.—Determination of Lethal Dose of a Standard Tincture of Digitalis.

Rabbit of 2,140 grams. Initial rate of heart, 40 in 10 seconds. Injected intravenously 5 c.cm. of a "good" physiologically standardized tincture of digitalis. The animal died almost immediately. Heart found after death in diastole.

EXPERIMENT IX.—Lethal Dose of Tincture of Digitalis.

Rabbit of 1,490 grams. Initial rate of heart, 38 in 10 seconds.

First Day. At 3.13 p.m. injected intravenously 2 c.cm. of standardized tincture of digitalis; at 3.15 p.m., rate 28 in 10 seconds; at 3.17 p.m., 32 in 10 seconds; at 3.20 p.m., 34 in 10 seconds.

Second Day. At 3.5 p.m., rate about 50 in 10 seconds, very rapid with faint sounds. At 3.25 p.m. injected intravenously 3 c.cm. of standardized tincture of digitalis; rate just after injection 42 in 10 seconds; one minute later, rate 37 in 10 seconds; at 3.28 p.m., 23 in 10 seconds, and heart very irregular; at 4.30 p.m. the animal is dead; heart found on examination after death in diastole.

EXPERIMENT X.—Lethal Dose of Tincture of Digitalis.

Rabbit of 1,850 grams. Initial rate of heart, 37 in 10 seconds. At 5.10 p.m. injected very slowly 4 c.cm. of tincture of digitalis; the animal died almost instantly. The heart was found *post mortem* in diastole.

EXPERIMENT XI.—Continued Administration of Standardized Tincture of Digitalis.

Rabbit of 1,600 grams. Initial rate of heart, 44 in 10 seconds.

First Day. At 2.31 p.m., rate 44 in 10 seconds. At 2.33 p.m. injected intravenously 2 c.cm. of a standard tincture; at 2.36 p.m., rate 40 in 10 seconds; at 3.15 p.m., rate 40 in 10 seconds. At 3.19 p.m. injected intravenously 2 c.cm. of standard tincture; at 3.22 p.m., rate 40 in 10 seconds; at 3.50 p.m., rate 40 in 10 seconds. At 3.52 p.m. injected intravenously 2 c.cm. of standard tincture; at 3.56 p.m., rate 40 in 10 seconds. Total amount injected on first day, 6 c.cm. of standard tincture.

Second Day. At 1.47 p.m., rate 41 in 10 seconds. No digitalis given.

Third Day. At 3.55 p.m., rate 36 in 10 seconds. At 4 p.m. injected intravenously 2 c.cm. of standard tincture; at 4.3 p.m., rate 36 in 10 seconds; at 4.7 p.m., 37 in 10 seconds; at 4.55 p.m., 46 in 10 seconds.

Fourth Day. At 12.57 p.m., 54 in 10 seconds; at 5.41 p.m., 42 in 10 seconds.

EXPERIMENT XII.—*Absence of all Activity when an Active Standardized Tincture of Digitalis is Evaporated to Dryness and made up to an Emulsion of Equal Volume in Saline.*

Rabbit of 1,220 grams. Initial rate of beat, 55 in 10 seconds.
First Day. At 2.5 p.m., rate 55 in 10 seconds. At 2.59 p.m. injected 3 c.cm. of saline suspension of digitalis; at 3 p.m., 56 in 10 seconds. At 3.45 p.m. injected 4 c.cm. of saline suspension of digitalis; at 3.50 p.m., rate 56 in 10 seconds; at 4 p.m., 54 in 10 seconds.

Second Day.—At 2.7 p.m., rate 51 in 10 seconds; at 5.30 p.m., 51 in 10 seconds.

This animal showed no signs of any effect from an amount of a saline emulsion corresponding to 7 c.cm. of this tincture, which was the same as killed in the previous three experiments, and also killed a frog, heart in systole, within one hour, and perfused through the isolated rabbit heart at a dilution of 1 in 200 in Ringer's solution arrested the heart in systole within 30 minutes.

EFFECTS OF PERFUSION OF THE DRUG IN SALINE THROUGH THE ISOLATED MAMMALIAN HEART.

The hearts used in these experiments were taken from medium sized rabbits, so that the results can be strictly compared with those obtained in the previous section on intravenous injection.

The perfusion was made through the coronary arteries from the aorta, Ringer's saline saturated with oxygen in the usual way being used. The drug was added, in the amounts stated under each tracing, to 1 litre of the Ringer's saline. After the tracing of the heart-beat had become steady, as shown in the first section of each tracing, the connexion with the warmed saline containing the drug was established and the variations in heart-beat recorded. For comparison, portions of this record belonging to the time intervals noted under each portion have been brought together. The lowest trace shows time in seconds, the line above is the injection signal, and the upper trace is that of the heart apex, the heart being suspended freely by the cannula fixed in the aorta.

The three experiments illustrated by the tracings are samples showing concordant results with those obtained in other experiments. In each case there is a pure digitalis effect shown of: (1) Increase in force, shown by the increased amplitude of beat; (2) slowing of the heart; (3) increased slowing of the heart accompanied by decrease of force; (4) arrest in systole, or nearly so, with marked increase in tonus, shown by the elevation of the base line.

The experiment in Fig. 1 is with the digalen solution diluted two hundred times with saline. As the digalen solution only contains 0.3 mg. of the amorphous digitoxin in 1 c.cm., this represents a concentration of 3 in 10,000, and it follows that the concentration being perfused in this case is 3 in 10,000 $\times$ 200, or 3 in 2,000,000 parts.

In the second experiment, illustrated by Fig. 2, the concentration is 2 ampoules of 1 c.cm. per litre, corresponding in actual strength of drug to 3 parts in 5 millions. Yet even at this exceedingly low concentration, when saline is the perfusing medium, there is no equilibrium, but the heart goes on absorbing from the saline until it has taken up enough to stop its beating. With such a concentration as this in blood there would be no apparent effect, for the reasons given in the preceding section.

The tracing shown in Fig. 3 is that obtained by adding 2.5 c.cm. of a saline solution containing 0.9 mg. in 1 c.cm. to 1 litre of saline—that is to say, 2½ parts in 1,000,000. This is the strongest of the three solutions shown, as the tracing likewise demonstrates.

CONCLUSIONS.

1. Present methods of standardization of such drugs as digitalis rest on an erroneous basis, which presupposes a direct linear relationship between therapeutic dose and lethal dose, whereas in a varying mixture of active substances in a galenical preparation no such relationship need exist.

2. The ratio of lethal dose to therapeutic dose may be defined as the factor of safety of a drug.

3. In picking out from a mixture of active principles that one which is most advantageous therapeutically, the substance should be chosen which possesses the highest factor of safety, and not that one with the highest toxic action, and hence producing an effect in smallest quantities. For example, the experiments above recorded show that soluble, or amorphous, digitoxin has a higher factor of safety than the mixed glucosides of standardized tincture of digitalis; and, again, tincture of digitalis is safer than strophanthus, or mowrin, or hederin.

4. The physico-chemical basis determining the toxicity of such a cardiac drug, as also the factor of safety, is the relative adsorption, or combining powers for the drug, of

Fig. 1.—Rabbit's heart perfused with Ringer's solution. Effect of digalen at 1 in 200 dilution (5 ampoules of 1 c.cm. to 1 litre of Ringer's solution). Tracing reads from left to right. Observe increase of force of beat and slowing of heart and final tonicity.

Fig. 2.—Rabbit's heart perfused with Ringer's solution. Effects of digalen at 1 in 500 (2 ampoules of 1 c.cm. in 1 litre). The increase in tonic is well shown, as also increased force and diminished frequency at the earlier stages.

Fig. 3.—Rabbit's heart perfused with Ringer's solution. Effects of digalen at $7\frac{1}{2}$ per 1,000 in saline solution. This is the strongest concentration tested on the isolated heart. Note the strong tonic effect produced as shown by elevation of lever at end above highest point of systole of normal beat.

the blood on the one hand and the cardiac tissue on the other. The ratio of cardiac tissue adsorption to blood adsorption fixes the value of the Coefficient of Distribution, and on this the effect of the drug depends. Although the Coefficient of Distribution is nearly constant, it varies somewhat at different concentrations of the drug, and if the Coefficient of Distribution decreases with increasing concentrations, this will lead to a higher factor of safety. In comparing different drugs with one another, a high Coefficient of Distribution means high toxicity, and usually a low factor of safety and a rapid cumulative action.

5. Soluble digitoxin, on account of its solubility in water, can be used for intravenous injection. This solubility prevents any pain or local inflammation, such as is occasioned by injection of alcoholic solutions, and the low toxicity as compared with that of the mixed glucosides in tincture of digitalis renders intravenous administration safe (compare Experiments IV and V with VI, VII, VIII, and IX). At the same time, a full therapeutic effect, which is very persistent, is obtained on the heart.

6. In administering soluble digitoxin (digalen) a full therapeutic effect should be aimed at, and thereafter the

drug should not be pushed farther, but just enough given to maintain the advantage by keeping pace with the elimination of the drug.

7. The heart tracings show that a pure digitalis effect is obtained on perfusing digalen, the therapeutic effect being marked, and the tonus at the end very considerable.

8. The tracings also demonstrate the much higher Coefficient of Distribution of the drug in saline solution than in the blood so resembling the chloroform action. Even at the lowest concentration tested no therapeutic equilibrium is established, but the heart goes on taking up the drug from the saline till the death point is reached. This does not occur with a much heavier dosage in the intact animal where the drug is dissolved in the blood.

9. Soluble digitoxin shows none of that haemolytic action in destroying red blood corpuscles which is possessed by those sapo-glucosides which act on the heart, as, for example, the digitonin present in ordinary tincture of digitalis.

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A CASE OF CARDIAC FAILURE TREATED BY CANE SUGAR.

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THE following notes of a case of cardiac failure treated by cane sugar show how remarkably an apparently hopeless case was benefited by its use.

The patient, a plumber, aged 28, first consulted me on December 4th, 1910, complaining of great shortness of breath and swelling of his abdomen, which had commenced in July, 1910, and gradually grew worse; he had, however, continued his occupation. He had previously always been healthy and temperate. In March he was helping to pull a heavily-laden hand-cart up a stiff hill, when he suddenly felt giddy and faint, great difficulty in getting his breath, and had to sit down for a time. After a short rest he was able to continue his work, and thought no more about this incident.

State on Examination.

The patient looked ill, dusky complexion, anxious expression, marked dyspnoea, had to gasp between his sentences whilst talking to me. *Heart*: Faint apex beat, little to left of left nipple line, diffused. No definite bruit heard at apex, but a galloping, tumbling kind of rhythm, very irregular and intermittent. *Aorta*: No bruit heard, but second sound accentuated. *Pulse* 100, feeble, small, irregular and intermittent. *Lungs* normal. *Respirations* 35. *Abdomen* much enlarged and definite signs of dropsy. Slight oedema of skin over lower part. Girth measurement at level of umbilicus 35½ in. *Liver* not enlarged to any extent. *Appetite* only fairly good. *Tongue* fairly clean. *Urine*: No albumen, high-coloured urates.

Diagnosis.

I considered his condition of failing heart most serious, and that the cause was probably due to damage of mitral valve at the time he was helping to pull a hand-cart the previous March. I ordered him to bed, to lie absolutely quiet, put him on light nourishing diet and tinct. digitalis $\mathfrak{m}$ v, tinct. nucis vom. $\mathfrak{m}$ v, every four hours; large doses of mag. sulph. mornings.

Progress.

December 7th, 1910. Condition much the same; head and shoulders well propped up with pillows. Taking nourishment fairly well. Passed three pints of urine in twenty-four hours. Increased tinct. digitalis to $\mathfrak{m}$ x doses every three hours.

December 12th, 1910. Feeling better, breathing more comfortably, and sleeping better. Better colour. Pulse a little steadier, 88. Heart sounds much the same. Appetite improving. Increased tinct. digitalis to $\mathfrak{m}$ xij every four hours; added liq. strychninae $\mathfrak{m}$ iij. Girth measurement of abdomen less 32 in.

December 17th, 1910. Substituted strophanthus for digitalis. Condition much the same.

December 22nd, 1910. Much the same. Returned to digitalis and strychnine. Calomel gr. v at night occasionally.

December 26th, 1910. Rather worse. Increased amount of fluid in abdomen. Pulse 88, respirations 40. Slight oedema at bases of both lungs. Passing less urine. Heart sounds much the same.

December 31st, 1910. Same galloping sounds heard at apex, with a faint systolic bruit as well. Continuing digitalis and strychnine, also mag. sulph. mornings and calomel at night. Had a consultation with Dr. Wood, who gave a very bad prognosis.

January 2nd, 1911. Discontinued digitalis for a while and gave pot. iod. instead.

January 4th, 1911. Slightly better; breathing more comfortable. Passing more urine, 2 quarts. Amount of dropsy much the same.

February 1st, 1911. Considerably worse; more fluid in abdomen; signs of fluid in left pleura; also some pleuritic frictions in left axilla causing pain. No rise of temperature. Heart sounds the same; bruit still heard at apex.

March 3rd, 1911. More comfortable, and is now lifted out on couch and wheeled out of doors when fine. Appetite better; sleeping better. Certainly improved by being in open air. Still taking cardiac drugs.

April 30th, 1911. Condition of heart much the same. More comfortable on the whole. Amount of fluid in abdomen much the same, though fluid in left pleura less marked. Taking nourishment fairly well.

May 5th, 1911. Not so well; not well enough to go out of doors last few days. Abdomen increasing in size; oedema of skin of abdomen more marked. Breathing more distressed. Respirations 40; pulse feebler, 100. Heart sounds at apex very irregular and bruit distinct. Appetite bad. Colour dusky.

May 7th, 1911. Very ill, condition appears hopeless. Taking very little nourishment and vomiting at times. Fluid in both pleurae at bases; tapped abdomen, and drew off 22 pints.

May 8th, 1911. Much relieved by tapping, better colour, and able to take more nourishment. Pulse 80. Respirations 30. Heart sounds much the same.

May 10th, 1911. Able to be wheeled out of doors again, and seems to be improving slightly. Still taking digitalis, which seems to do more good than any other drugs.

June 2nd, 1911. Breathing becoming difficult again, unable to lie down, not well enough to go out of doors for some days. Fluid reaccumulating in abdomen. Pulse 94, weaker. Heart's action weaker, sounds of same character.

June 11th, 1911. Much worse. Abdomen filled up again. Breathing very bad. Pulse very feeble, 100. Oedema of bases of both lungs, and fluid in left pleura. Abdomen tapped, and 16 pints drawn off.

June 12th, 1911. More comfortable since fluid of abdomen removed. Condition of heart much the same. Commenced sugar treatment. Taking 5 oz. Glebe's granulated cane sugar a day. Continuing small doses of digitalis as well.

June 16th, 1911. Discontinued all medicines with the exception of occasional doses of mag. sulph. and calomel. Persevering with the sugar, taking the full 5 oz. most days. Occasional feeling of nausea. Able to be wheeled out in bath chair.

June 20th, 1911. Says he feels decidedly better, much more comfortable, and able to lie down at night now. Better colour. Breathing much better. Pulse a little stronger, but still very irregular and intermittent. Heart sounds much the same. Some fluid in abdomen, but no marked increase. Fluid left side of chest less. Oedema at bases of lungs less. Taking the 5 oz. of sugar regularly. Appetite good.

July 2nd, 1911. Decided improvement in general condition, able to go out in bath chair and remain out all day. Much better colour. Appetite good. Taking the full 5 oz. of sugar without any inconvenience. No increase of fluid in abdomen. No signs of fluid in left pleura. Diminished breath sounds at left base behind, due to thickened pleura. No oedema of lungs.

August 30th, 1911. Still improving, every day in bath chair, and able to sit upright in chair. Taking the 5 oz. of sugar regularly. Appetite good. Sleeps well. Seems much better in every way. Scarcely any fluid can be detected in abdomen and none in chest. Heart sounds more regular. Pulse stronger. Passing normal quantity of urine.

September 12th, 1911. Wonderfully better; still out of doors every day in chair. Says he would like to walk, but I advised him not. No appreciable quantity of fluid in abdomen. No oedema of skin. Good colour. Heart sounds less irregular. Bruit not always heard. Pulse stronger.

He continued to improve up to October 9th, 1911, when he had a severe shock on being told that a friend and neighbour of his had been run over by a train and had lost a leg. He experienced difficulty in breathing again, not eating or sleeping well. Pulse weaker. I ordered him to bed for about a week, and gave him digitalis for a few days. He soon improved with the rest, and was able to go out in his bath chair again on October 16th.

October 20th, 1911. Condition much improved, and is now as well as he was before October 9th.

November 29th, 1911. Has been going out every day in chair, in which he sits up quite comfortably. Says he feels quite well. Appetite good, sleeps well, able always to lie down at night; passing good quantity of urine; no shortness of breath. Has not walked yet, but is very anxious to; is able to stand by himself. Still taking the 5 oz. of sugar. Heart: Apex beat in normal position; no bruit heard; still the continuing irregular rhythm at apex; heart's action considerably stronger. Pulse 80, small, irregular, and intermittent, but much stronger. Lungs normal, with exception of diminished breath sounds at left base. No oedema or fluid in abdomen.

REMARKS.

This is evidently a case of failing heart which dates from March 1910, and due to his damaging his mitral valve by overexertion.

From the time he first came under my care he was treated with all the various cardiac drugs, in variable doses, with absolute rest and suitable diet. He at times showed signs of improvement, but it was never lasting, and