was due to a partial paralysis of the medullary centres of the vagi by the fever so that they were no longer easily stimulated by the drug. Hence if digitalis is given in a case of fever, the rate of the pulse is not always a safe guide as to whether the drug has been given in sufficient quantity to affect the cardiac muscle.

The acceleration of the heart which occurs in the later stages of digitalis poisoning was at first attributed to a paralysis of the vagi, for a number of investigators failed to obtain any slowing of the heart by stimulating these nerves during this stage. This explanation has proved insufficient because in some experiments the vagi retain their control over the heart up to the end, and, moreover, digitalis causes an acceleration of the heart after the vagi have been paralyzed by atropine. Attention was called above to the fact that the irritability of cardiac muscle of the frog is increased by digitalis, and, as will be shown later, there is abundant evidence that the same occurs with the mammalian heart. Hence at present it is considered that the acceleration may be due in part to the paralysis of the vagi, but that the increased irritability of the cardiac muscle which renders the heart more difficult of inhibition is a more important factor. Of course, the acceleration may be due in part to a stimulation of the accelerator nerves, but there is no clear proof that this is the case.

The rise of blood pressure caused by digitalis has been a matter of much dispute. Blake (*Edinburgh Med. and Surg. Jour.*, April, 1839) was the first to make blood-pressure experiments with digitalis; he concluded that the rise was due to a contraction of the capillaries and other peripheral vessels. A group of German investigators (among them Schmiedeberg and his pupils) have always maintained that the increased strength of the heart beat is the cause of the rise of blood pressure. They based their view upon experiments upon the frog's heart as well as upon deductions drawn from the behavior of the mammalian heart. There has been much discussion as to whether the vaso-constrictor centre is involved in the rise of pressure; there is no question that a marked rise occurs after section of the spinal cord, but it is not yet settled whether, in the intact animal, stimulation of the vaso-motor centre may not be a factor in the cause of the rise of blood pressure. A large amount of evidence has accumulated which shows that the peripheral vessels are constricted by digitalis. Thus Donaldson and Stevens (*Journal of Physiology*, iv., p. 165, 1883) observed a marked diminution in the outflow from the veins of a terrapin (in which the central nervous system had been destroyed and the heart removed) when digitalis was added to the solutions transfused through the vessels. Similar results have been obtained in transfusion experiments with the kidneys and other "surviving" organs of mammals. On the whole the evidence is very strong that, in a normal animal, the constriction of the arterioles, due to a direct action upon their muscular walls, is a very, perhaps the most, important factor in the rise of blood pressure. Stimulation of the cardiac muscle is another factor, and it is probable that there is also some stimulation of the vaso-constrictor centre. In the case of a man with incompetent valves, the heart action is probably a much more important factor in causing the rise of blood pressure than it is in a normal individual. This point will be discussed later.

The fall of blood pressure and the irregularities of the heart in the late stages of digitalis poisoning are attributed entirely to changes in the heart. It has been shown that there is no dilatation of the arterioles, as was once supposed to be the case, even after very large amounts of the poison.

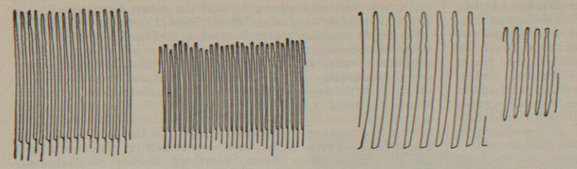
Until comparatively recently very little was known as to the details of the changes produced by digitalis in the mammalian heart; that the strength of the beat is increased was generally inferred from the experiments upon the frog's heart. Moreover, several English physicians in the earlier part of the century (*e.g.*, Beddoes and Kinglake, 1801) had reached the conclusion, from studying the pulse, that while digitalis slows the heart, the strength of the beat is not decreased, but is, on the contrary, increased. The increased energy of the heart's contraction is also evident from a study of the pulse waves in an animal deeply poisoned with chloral. Chloral causes a complete relaxation of the arterioles. If digitalis be administered to an animal in which this has occurred the pulse waves are greatly increased, indicating that the heart is expelling more blood at each contraction. It has been a debatable question whether this increased output of the heart is due to a change in systole or in diastole. Schmiedeberg ("Grundriss der Arzneimittellehre," dritte Auflage, p. 168, 1895) and Williams (*Archiv für exper. Path. und Pharmakol.*, xiii., p. 9, 1880) maintain that there is an increased diastolic extensibility without any change in the contractility. According to these authors, the elastic resistance of the heart is diminished and there is an increased diastole. As the heart contracts to its former volume in systole more blood is expelled and consequently more work accomplished.

More recent workers have adopted the view that the essential change is one in systole, but that this is combined with the effects of a stimulation of the vagi (Cushny) or of the vagi and accelerators (François-Franck). François-Franck (*Clinique Médicale de la Charité*, Potain, p. 549, 1894) pointed out the resemblance between the action of digitalis upon the heart and the effects of the simultaneous stimulation of the vagi and accelerators; in each case there is a slowing of the pulse but an increase in its force. At the same time the increase in force is due, according to this author, in part to a direct muscular action. In a later paper (*Comptes rendus de la Société de Biologie*, 1897, p. 111) he seems to lean toward the view that the change in the muscle is a more important factor than he at first supposed. Cushny (*Journal of Experimental Medicine*, ii., p. 254, 1897) advanced, independently, a theory for the action of digitalis very similar to that of François-Franck, except that he ascribes those changes which the French writer thought to be due to a stimulation of the accelerators entirely to the muscular action.

As the methods used by Cushny are probably more exact than those of others his results will be given in some detail. Cushny studied the effect of digitalis upon the heart by means of the myocardiograph and the cardiometer of Roy and Adami. The former is an instrument with which the distance between two points on the heart's surface and their movements relative to each other are recorded. The curve made by this instrument is similar to an ordinary muscle curve and shows not only the rate of the heart beat but also its strength and changes in tonicity; *i.e.*, whether the heart tends to assume the position of systole or that of diastole. The cardiometer measures the volume of the heart in its successive phases and therefore records the amount of blood expelled from the heart. The experiments of Cushny were made upon dogs and cats. The action of digitalis may be divided into two stages: the first stage is characterized by a slow pulse due to stimulation of the vagus, while in the second stage the heart is accelerated. In both stages there are very important changes in the cardiac muscle. The first stage may be divided into the "therapeutic stage" and a stage of "excessive inhibition"; the latter stage does not always occur. The early part of the first stage is the one of greatest interest as it is the only one desired in the medicinal use of digitalis.

Within one or two minutes after the intravenous injection of a very small amount of digitalis changes in the heart occur which are characterized by a slowing of the beat and increased excursions of the recording levers toward systole and generally toward diastole. The slowing of the heart, being caused by stimulation of the vagi, is due largely to a prolongation of the diastolic pauses. At the same time the duration of the systole is somewhat increased; but this seems to be due entirely to the slowing of the heart, for there is no evidence that the contraction of the mammalian cardiac muscle is prolonged, as is so markedly the case with the frog's heart. The increased excursion toward systole of the lever fixed

to the ventricle shows that this cavity is emptying itself much more completely than it normally does. It is generally recognized that normally the ventricles do not empty themselves completely so that at the end of systole they contain some blood. Under the influence of digitalis the blood remaining in the ventricle at the end of systole is much less than before. This increased contraction of the ventricle is due to an action of the drug on the cardiac muscle, just as in the frog's heart. The papillary muscles undergo the same change as the rest of the ventricular wall, contracting more strongly and more completely than before the administration of the drug. The intraventricular pressure during systole was found by François-Franck to be much increased. The relaxation of the ventricle during diastole varies considerably in different conditions. As is well known, stimulation of the vagus always tends to increase the relaxation of the ventricle, but in the case of digitalis this action is opposed by the direct effect of the drug upon the heart muscle. The result depends upon these opposing factors, and the effect of these again depends, largely, upon the condition of the heart. If the heart is normal or does not dilate much during diastole, digitalis increases the relaxation (Fig. 1141, *D*). If, however, the heart is weak and dilated digitalis tends to lessen this dilatation so that the relaxation of the ventricle during diastole is less than before the administration of the drug; this is always the case if the vagus terminations have been paralyzed by atropine (see Fig. 1142, *B*).



D′ N′ D N

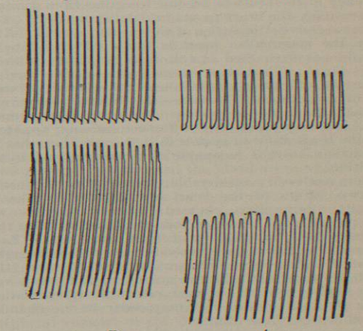
Fig. 1141.—Tracings of the Ventricular Contractions under Digitalis in Experiments on Two Dogs. *N*, *N′*, Normal contractions; *D*, *D′*, contractions under digitalis. The levers move upward during systole. In *D* the rhythm is slower and the movements extend further upward and downward than in *N*, *i.e.*, the contractions are more complete and the dilatation during diastole is greater. In *D′* the rhythm is slower, and the tracing extends further upward than in *N′*, but reaches almost the same point below, *i.e.*, the contraction is stronger, but the dilatation is scarcely changed. (From Cushny.)

In the auricles the same forces are at work as in the ventricle. The direct muscular action tends to cause a more complete contraction in systole while the stimulation of the vagus opposes this action as well as causes a slowing of the beat. As is well known, stimulation of the vagus produces a much greater effect upon the auricle than upon the ventricle, while there is a much smaller amount of muscular tissue upon which the digitalis can act directly. Hence after even a comparatively small dose of digitalis the inhibitory action may at times predominate and thus greatly reduce the extent of the contraction of the auricles and so the volume of blood expelled. With ordinary medicinal doses, however, the effect upon the auricles is very much the same as that upon the ventricles: the heart beat is slowed, but the contraction in systole is increased while the relaxation in diastole is not much influenced.

It is clear that the output of the ventricle at each beat must be increased by digitalis, for the ventricle usually contains more blood at the beginning and less at the end of systole than normally. If the rate of the heart remained the same, it is evident that the output per unit of time would also be increased. But the slowing of the heart tends to reduce the total output; hence only cardiometer records can show which of these opposing factors prevail. As a matter of fact, Cushny found that the output of the heart per unit of time (*e.g.*, in a minute) was uniformly increased by small doses of digitalis: this increase amounted at times to fifty per cent. With somewhat larger doses the inhibitory action may become extreme and now the output is diminished. The output is increased again when the heart becomes more rapid.

During all the early part of the first stage the rhythm of the heart is normal; each beat of the auricles is followed by one of the ventricles, and the two sides of the heart beat together. If the drug is pushed the slowing becomes extreme and, as always happens when the vagus is strongly stimulated, the rhythm is disturbed. The muscular action may be entirely concealed by the inhibitory action so that the systoles become weaker and less blood is expelled; as a rule, however, the output per beat is still greater than normal while that per unit of time is less owing to the slow rate of the heart. The auriculo-ventricular beat may be more or less dissociated and the two chambers beat at different rhythms. Sometimes this is due to the excessive inhibition preventing the impulses from the auricle reaching the ventricle, a "block" being formed between the two chambers. At the same time the irritability of the ventricular muscle may be so increased that the ventricle assumes a rhythm entirely independent of the auricle; this "idio-ventricular" rhythm may be more rapid or slower than that of the auricle (see Fig. 1143). These changes in the rhythm of the heart always indicate a grave condition of poisoning and are not met with in the therapeutic use of digitalis.

During the second stage of the action of digitalis the muscular prevails over the inhibitory action. The pulse becomes very rapid, the inhibitory nerves no longer being able to keep the heart in check. The auricles are often later in being accelerated than the ventricles because the inhibitory nerves have a greater influence over them. The difference in rhythm of the two divisions leads to very characteristic variations in the strength of the contractions of both auricles and ventricles. Numerous other forms of irregularities occur which it is impossible



B A

Fig. 1142.—Tracings of the Movements of the Ventricle (Lower) and Auricle (Upper) under Digitalis. During systole the levers make an up-stroke. In this experiment the inhibitory terminations had been paralyzed, so that only the muscular action is developed. *A*, Normal; *B*, after digitalis. The rhythm of the heart is slightly accelerated in *B*, and the levers extend further upward, indicating a more perfect systole in both auricle and ventricle. The ventricular lever does not reach so far downward in *B*, *i.e.*, the ventricular diastole is less complete. (From Cushny.)

to describe in a few words. They have many points of resemblance to those described under aconitine and can all be traced to the increased irritability of the cardiac muscle and to the interference of the (independent) auricular and ventricular rhythms. (For detailed accounts of these irregularities, which are of toxicological rather than of pharmacological interest, see the elaborate descriptions of Cushny, Knoll [*Sitzb. der Wiener Akad.*, xcix., Abth. iii., p. 31, 1890, and ciii., Sitz. November 8th, 1894], and François-Franck.) Many of the forms of irregularity can be imitated in the normal animal by electrical stimulation of different parts of the heart (see Cushny, *Journal of Physiology*, xxv., p. 49, 1899). Stimulation of the accelerators or of the vagi will often cause the most irregular heart to become regular again,

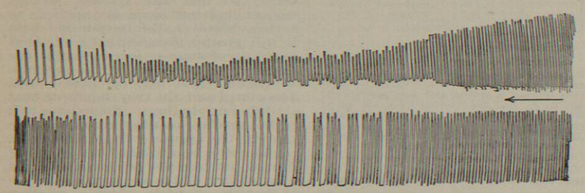


FIG. 1143.—Tracing of the Auricular (Upper) and Ventricular Movements (Lower) under Digitalis, as the First Stage Passes into the Second. During systole the levers move upward, during diastole downward. The rhythm of the two chambers is at first the same, but soon changes, the auricle maintaining its rapid beat, while the ventricle becomes slow and irregular. At the end of the tracing the ventricle again becomes rapid, while the auricles become slow. The strength of the contractions and the extent of relaxation of the ventricular muscle remain little altered, while the auricle rapidly weakens in strength, but improves again at the end of the tracing. (From Cushny.)

and there is some evidence that the tonic activity of the accelerators is an important factor in counteracting the tendency of the heart to become irregular from digitalis.

Eventually the heart passes into delirium cordis owing to the excessive stimulation of the cardiac muscle. After death the mammalian heart is found widely dilated in diastole, not contracted in systole as is the case with the frog's heart. Thus there seems to be a difference between the effects of digitalis upon the hearts of warm and of cold blooded animals—the former stopping in diastole, the latter in systole. François-Franck maintains, however, that this difference is only apparent; that the heart stops in systole in both cases, but that the mammalian heart is incapable of remaining long in this condition.

There has been considerable discussion as to whether the two halves of the heart are influenced alike by digitalis. Some have claimed that one ventricle was more powerfully stimulated than the other and that they at times beat at entirely different rhythms. Later writers, using more exact methods, have failed altogether to confirm these results. The auriculo-ventricular rhythm may be disturbed but the two aruricles and the two ventricles always beat at the same rate, although variations in the strength of the beat may occur in one chamber independently of the other.

Experiments upon the isolated mammalian heart give results in entire accord with those obtained by Cushny upon the heart in connection with the nervous and vascular systems. Tschistowitsch (*Centralbl. für Physiol.*, i., p. 133, 1887) showed, several years ago, that helleborein stimulates the isolated heart and increases its output per unit of time. Recently Hedbom (*Skand. Archiv für Physiol.*, viii., p. 185, 1898) has described in detail the action of digitalin upon the isolated rabbit heart. Immediately after the drug reached the heart there was a slight acceleration, just as we have seen to be the case when digitalin is applied to the frog heart. This primary acceleration was followed by a long-continued slowing during which, however, the amplitude of the beats was much increased. If the heart had from any cause become irregular, small doses of digitalin caused it to become more regular as well as more powerful. If the amount of digitalin was increased, the heart beat became rapid and the various kinds of irregularities described by Cushny were produced; then there was a sudden shortening of the ventricle (amounting in some cases to fourteen per cent. of its length) and the heart soon stood still. Bock (*Archiv für exper. Path. und Pharmakol.*, xli., p. 175, 1898) studied the action of helleborein upon the isolated mammalian heart, using a method differing in some respects from that of Hedbom; the results were, however, essentially the same. Bock emphasizes especially the rise of pressure which occurred in the tubes by which the peripheral vessels were replaced in his experiments and which resulted from the increased output of the heart. In one experiment in which the heart had been beating feebly, helleborein caused the pressure to rise from 29 mm. to 80 mm. of mercury—a striking example of the power of the drug to stimulate the cardiac muscle.

To sum up the results of these experiments upon the heart, digitalis in small doses slows the heart, but its chief action is to increase the contraction in systole. This increased contraction leads to a more complete emptying of the ventricle and so to a greater output of the heart and a rise of blood pressure. In the normal animal, with perfect valves, and in which there is no dilatation of the heart, constriction of the arterioles caused by the direct action of the drug upon their walls is probably as important a factor in the rise of blood pressure as is the increased output of the heart. But experiments upon animals have shown that the increased output of the heart is especially marked when there is even a slight dilatation of the heart; and the experiments of Bock show what a marked rise of pressure may be produced by the cardiac action alone. When it comes to certain cases of chronic valvular lesions in man in which the dilatation is far in excess of anything we ever have in experiments upon animals, we are justified in concluding that the cardiac action of the drug is by far the most important factor in the rise of blood pressure which undoubtedly occurs. The heart action of digitalis also has a different effect upon the pressure in the veins in cases of valvular insufficiency from its effect in normal animals. In the latter mere increase in the output of the heart is powerless to lower the venous pressure and so relieve venous congestion; only a constriction of the arterioles can bring this about. With incompetent valves, however, the greater contraction of the cardiac muscle caused by digitalis will lessen the regurgitation and so the backward pressure in the veins; this leads to a fall of venous pressure and so to a lessening of venous congestion. The constriction of the arterioles caused by digitalis will add to this result, but the cardiac action alone is often sufficient.

Too much emphasis is sometimes laid upon what are, after all, but minor features of the action of digitalis—the slowing of the heart and the constriction of the arterioles. Both of these actions are undoubtedly important in many, perhaps in most cases, but they are entirely subordinate to the action upon the cardiac muscle. Aconitine or veratrum viride will cause as great a slowing of the heart as will digitalis; strychnine or the extract of the suprarenal glands will constrict the vessels even more strongly, but none of these drugs or any combination of them can replace digitalis.

So far we have spoken of the action of "digitalis," ignoring the fact that several active principles are contained in the usual preparations. Our knowledge of the

active principles is, however, so unsatisfactory and the isolation of some of them is attended with such difficulty and expense that they are not used very extensively in medicine. Schmiedeberg (*Archiv für exper. Path. und Pharmakol.*, iii., p. 19, 1874) described three active principles in digitalis and named them digitalin, digitalein, and digitoxin. Kiliani (*Archiv der Pharmacie*, 1892–99) has published a series of papers in the earlier of which he stated that the digitalein of Schmiedeberg was probably a mixture of digitalin and some inert substance; he also described a new glucoside occurring in the leaves which he named digitophyllin. According to these earlier investigations of Kiliani the leaves, from which the pharmacopœial preparations are made, contain three glucosides, digitoxin, digitophyllin, and a body resembling digitalin; digitalin itself is probably absent. All of these glucosides have a similar action, but digitoxin seemed to be the most abundant and was found to be by far the most active. In fact digitoxin is one of the most toxic substances known. From these investigations of Kiliani it seemed that the pharmacopœial preparations owed their activity largely to digitoxin, although the almost complete insolubility of this body in water and its extremely irritating properties made it difficult for some to accept this view. Very recently Kiliani (*Archiv der Pharmacie*, ccxxxviii., p. 464, 1899) has confirmed the old statement of Schmiedeberg that there is a distinct body, digitalein, easily soluble in water and which occurs in both the seeds and leaves. Böhm (quoted by Kiliani, *loc. cit.*) believes that the activity of the infusion is due very largely to this digitalein. This work is so recent that no experiments seem to have been made to determine to what extent digitalein can be used instead of the galenic preparations. Experiments had already indicated that neither digitalin nor digitoxin could entirely replace the tincture and infusion in therapeutics.

A very large number of other plants contain substances with a physiological action very like that of digitalis. A few of these are used in medicine, while others are of interest chiefly because they have been used as arrow or ordeal poisons. It is known that there are minor differences between the action of some of these substances and that of digitalis; some, for example, have a greater effect upon the heart and a less effect upon the blood-vessels, others stimulate the vagus centre very powerfully, etc. Few comparative studies have been made, however, although they are extremely desirable.

Some of the other members of this series will be mentioned, and the points in which their action differs from that of digitalis noted when this is known. Strophanthus hispidus and S. Kombé contain a body, strophanthin, which is usually considered to be a glucoside. Strophanthin acts as powerfully upon the heart as does digitalis but has less effect in constricting the vessels; it does not cause as great a rise of pressure in the pulmonary artery as does digitalis. Erythrophlœin (a glucosidal alkaloid, derived from Erythrophlœum, sassy or casca bark) seems to act less upon the cardiac muscle and more upon the vagus centre than the others. Squills contains a glucoside, scillain, about which very little is known. Preparations of squills act upon the heart like digitalis, but they are used less for this action than for their action as expectorants and diuretics; it is very probable, however, that their cardiac action is an important factor in bringing about the changes in the respiratory mucous membrane and in the kidneys, for the circulation through these parts is improved by the drug. Helleborein (the glucoside found in Helleborus niger) and convallamarin (derived from the lily of the valley) are both very soluble in water, and it was hoped that they might prove valuable remedies when it was desired to use pure substances. Extended observations have shown them to be unreliable, and when they are used at all it is in the form of the galenic preparations. Euonymin (from Euonymus atropurpureus, wahoo) is used as a purgative rather than as a cardiac stimulant.

Some of the other substances belonging to this series are apocynein (from Apocynum cannabinum, Canadian hemp), adonidin (from Adonis vernalis, pheasant's eye), antiarin (from Antiaris toxicaria, the upas tree), one of the most powerful substances of the series; neriin and neriodorin (to which the poisonous properties of nerium or the oleander are partly due), thevetin and cerberin (from thevetia), coronillin (from coronilla) and tanghinin (from Tanghinia venenifera). The arrow poisons quabain and echujin also belong to this series.

The skins of certain toads were formerly used as remedies for dropsy. Modern investigations have shown them to contain a poison, phrynin, which has an action upon the heart very similar to that of digitalis. Epinephrin, the active principle of the suprarenal glands, also resembles digitalis in some of its physiological properties. The salts of barium have an action upon the heart and blood-vessels similar in many respects to that of the digitalis series.

For a discussion of the use of these drugs in therapeutics the reader is referred to the articles on *Heart Diseases*; only a few of the more general indications for their use can be given here. It has been shown that the circulation is influenced in three principal ways by medicinal doses of digitalis: the pulse is slowed, the heart contracts more completly in systole so that the pulse volume is increased, and the peripheral arterioles are constricted. Of these the second action is by far the most important in therapeutics. The action of digitalis in slowing the heart is taken advantage of in treating some cases of palpitation, of "irritable heart," and in a number of other cases, as in certain stages of valvular diseases, acute febrile conditions, etc., in which the heart is beating feebly, but rapidly and irregularly. On the other hand, the slowing of the heart is in some cases an undesirable feature of the action of digitalis, for, as has been already shown, it is due to a stimulation of the inhibitory nerves, and the latter has an effect just the opposite of the action of the drug upon the cardiac muscle. It is the inhibitory action which often prevents an increase in the contraction of the auricle; in fact, a diminution of the force of the auricular contraction is often observed. The same effect is produced upon the ventricle, but here the muscular action is able to overcome the inhibitory action to such an extent that the latter is not usually a disturbing element. A drug in which the muscular action of digitalis was well marked while the inhibitory action was minimal, would doubtless be much more valuable in many cases than digitalis. In erythrophlœin the inhibitory action is well developed while the muscular action is but little marked; unfortunately no drug is at present known in which the opposite is the case.

The constriction of the arterioles by digitalis is in many cases a desirable feature of its action, for by it the general blood pressure is raised and the blood accumulates in the arteries and excessive venous pressure is relieved. The constriction of the arterioles seems to be a factor in the production of diuresis; at least strophanthin which does not have so marked an effect upon the arterioles causes much less diuresis than does digitalis. In many cases, on the other hand, it has been found desirable to counteract the effect of digitalis upon the arteries while retaining its action upon the heart. This result is obtained by combining the digitalis with some drug (usually a member of the nitrite group) which causes a dilatation of the peripheral vessels; or the difficulty may be got around by the use of strophanthin, which does not constrict the vessels very greatly.

It is in virtue of its action upon the cardiac muscle that digitalis is chiefly used in medicine and by which it is enabled to play a rôle which can be filled by no other substance. Dilatation of the heart from almost any cause, provided that extensive degeneration of the cardiac muscle is not present, is the indication for its use. In such a case the action is very simple and is almost specific. In dilatation the heart is not only abnormally relaxed in diastole, but the amount of blood remaining at the end of systole is greatly increased. Digitalis causes a more complete emptying of the ventricle, *i.e.*, the pulse volume is increased; this and the constriction of the arterioles lead to

a higher blood pressure and a more uniform flow through the capillaries. Venous congestion is relieved and the nutrition of the various organs, including the heart, is improved. At the same time the relaxation in diastole is usually lessened so that the heart assumes more nearly its normal form. It is especially in dilatation in cases of valvular disease that digitalis is used; in such cases in addition to the above action the drug causes a contraction of the ring of muscle surrounding the diseased valve, and this tends to limit the regurgitation. As a result of the increased work of the heart and its better nutrition the condition of the muscular tissue is improved to such an extent that after a time the drug can often be dispensed with for longer or shorter periods.

The question is often debated whether digitalis should be used in aortic insufficiency; the theoretical objection has been made that the prolonged diastole might allow time for sufficient blood to regurgitate to lead to syncope. Physicians seem to hold now that digitalis is just as serviceable in the dilatation accompanying aortic insufficiency as in other cases, provided it is given with care. A little experiment of Dreser's (*Archiv für exper. Path. und Pharmakol.*, xxiv., p. 238, 1888) may be mentioned in this connection. The valves of the ventricle of a frog's heart were destroyed, the ventricle was tied to a perfusion cannula on one limb of which was an outflow tube. This arrangement represented roughly the condition in aortic insufficiency; the pressure of the liquid in the upright tube represented the aortic pressure, while the side tube, from which the blood was collected, represented the peripheral circulation. Blood was led to the heart and the amount expelled from the side tube measured. Digitalis (or helleborein) was now added to the blood; the heart was slowed so that there was a greater opportunity for the blood to drain back through the broken valves into the ventricle, and if the above theory were correct the outflow from the side tube (*i.e.*, the peripheral circulation) should be diminished. Dreser found, on the contrary, the outflow to be uniformly much increased; the increased output of the ventricle and the prolonged systole had more than counteracted the effect of the prolonged diastole. This little experiment is of interest as it shows that the only experimental evidence we have agrees with the clinical evidence that digitalis is useful in aortic insufficiency.

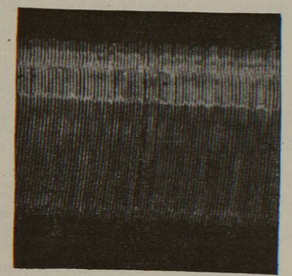


FIG. 1144.

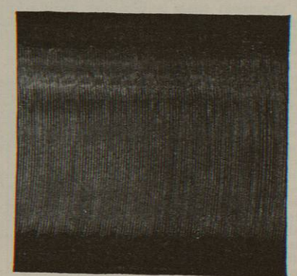


FIG. 1145.

FIGS. 1144 AND 1145.—Tracing of the Ventricle of the Dog's Heart; 1144, Normal; 1145, After Caffeine. The lever moves upward during systole, downward during diastole. The only alteration caused by caffeine is acceleration. The slightly larger excursion in diastole in 1145 is mechanical. (Contrast tracings under digitalis: Figs. 1141 and 1142.) (From Cushny.)

Members of the digitalis series are used for other purposes than as cardiac tonics, although the heart action probably plays a more important part here than is always recognized. Thus the good results following the use of squills as an expectorant are almost certainly due in part to an improvement of the pulmonary circulation. Several of the series are used extensively as diuretics; the fact that as a rule they produce marked diuresis only when there is a diseased condition of the heart points to the effect upon the kidney being secondary to changes in the circulation. On the other hand some of these drugs produce diuresis in normal rabbits, and occasionally in healthy dogs and man, when there is no evidence that the renal circulation is altered; this indicates that some of the series, especially squills and digitalis, have a direct action upon the renal epithelium, but comparatively little satisfactory work has been done upon this subject. There can be little doubt that the extraordinary diuresis produced by digitalis in cases of cardiac dropsy is due largely to an improvement in the renal circulation; the blood is removed from the veins and collected into the arteries, the congestion of the kidney relieved and a more uniform and active circulation established—a condition favorable for the secretion of the urine.

Sparteine, the alkaloid of broom (Cytisus scoparius), has been included by some in the class of cardiac stimulants. It has been said to have an action similar to that of digitalis; recent work (Cushny and Matthews, *Archiv für exper. Path. und Pharmakol.*, xxxv., p. 129, 1895) has shown this resemblance to be entirely superficial and that the drugs have little in common. Broom is used to some extent as a diuretic in cardiac diseases; it is also said to make the heart beat more regularly.

Cactus grandiflorus (cereus) has been warmly recommended by some clinicians as a cardiac stimulant. Very little is known about the chemistry of this drug or its physiological action; there is certainly no evidence that it belongs to the digitalis series, as has been claimed by some. It is said to accelerate the heart and to cause a rise of blood pressure; the latter seems to be due in part to a stimulation of the vaso-motor centre. It is sometimes combined with digitalis, but is said to be especially useful in certain cases in which digitalis is contraindicated. It is said to be valuable in cardiac weakness due to tea, coffee, alcohol, tobacco, etc.

Caffeine.—Caffeine has a very characteristic action upon cardiac muscle which makes it a cardiac stimulant of great value in some cases; it has also a stimulating action upon the vaso-motor and other medullary centres. The changes in the cardiac muscle have been most carefully studied in the frog's heart. When blood containing minute quantities of caffeine is perfused through a frog's heart placed in a William's heart apparatus, the rate of the heart is slightly accelerated and the amount of blood expelled at each beat slightly increased, but the most marked change is an increase in the force of the beat (Dreser, *Archiv für exper. Path. und Pharmakol.*, xxiv., p. 233, 1888). The heart is able to contract against a much greater aortic pressure than normally—that is, the "absolute power" of the cardiac muscle is increased. Dreser compares this action of caffeine to an increase in the cross section of the muscle fibres while their length remains the same. Caffeine has thus an action entirely different from that of digitalis; the effect of the latter is the same as lengthening the muscle fibres while the cross area remains the same; the extent of the contraction under digitalis is increased, while the absolute force is scarcely altered.

After larger quantities of the drug the heart becomes slower and its volume smaller; then the apex ceases to relax with the rest of the ventricle, but remains white and contracted, and eventually the whole heart passes into a

condition of rigor. In all these respects the action of caffeine upon the cardiac muscle is very similar to the remarkable effects the drug is known to have upon ordinary skeletal muscle.

Upon the mammalian heart the chief effect of caffeine which has been described is an acceleration of the rate: this acceleration occurs when the heart is entirely isolated from the central nervous system (Bock, *Archiv für exper. Path. und Pharmakol.*, xliii., p. 367, 1900), and must therefore be attributed to a stimulation of the cardiac muscle. No observations seem to have been made upon the effect of caffeine on the absolute power of the mammalian heart; that the extent of the contractions, and so the pulse volume, is not increased is shown by the accompanying myocardiograms (Figs. 1144 and 1145).

When caffeine is administered to a normal animal the effects upon the heart are somewhat obscured by the simultaneous action upon certain nerve centres. As a rule the heart is accelerated, but at times it is slightly slowed by a stimulation of the centre of the cardio-inhibitory nerves. On the other hand, stimulation of the vagi is usually less effective in slowing the heart after caffeine owing to the increased irritability of the cardiac muscle. That the cardiac acceleration is not due to a paralysis of the terminations of the vagi is shown by the fact that it occurs after these have been paralyzed by atropine; the acceleration must be attributed to a direct stimulation of the heart muscle. After larger doses the heart becomes weak, irregular, and arhythmic, resembling the condition seen in digitalis poisoning. The vaso-constrictor centre is stimulated by caffeine: this and the increased output of the heart due to the acceleration cause a rise of blood pressure. The most marked effects upon the circulation are seen in animals in which this has been depressed by such a drug as alcohol. Thus Binz found that the blood pressure of a dog deeply under the influence of alcohol rose from 84 to 120 mm. in ten minutes after the subcutaneous injection of caffeine; the pulse rate was doubled. The respiration was also greatly improved.

Administered to a healthy man a moderate dose of caffeine causes the pulse to become full and hard; it is also moderately accelerated. Occasionally there is a slowing due to stimulation of the vagi.

Theobromine has an action upon the heart very similar to that of caffeine; the peripheral vessels are not constricted, however, and so the rise of blood pressure is much less marked.

The great diuretic power of caffeine has been attributed to the changes in the circulation, and it is probable that these do exert a favorable influence when the blood pressure is very low. Under ordinary circumstances, however, the constriction of the blood-vessels antagonizes the diuretic action, and the latter can often be obtained only when the caffeine is combined with such drugs as chloral hydrate or paraldehyde which dilate the vessels. It is now generally held that caffeine and theobromine produce diuresis by a direct action upon the renal epithelium, and entirely independent of their action upon the circulation.

The experiments upon animals indicate the class of cases in which caffeine might be expected to give good results in therapeutics. It is chiefly in cases in which the heart is simply weak and in which there is no dilatation that caffeine is indicated; it causes the output of the heart to be increased and the blood pressure to rise. It is especially useful in cases of alcoholic and opium poisoning, for not only is the cardiac muscle stimulated in these, but the vaso-motor and respiratory centres are also thrown into increased activity. Caffeine cannot be considered a substitute for digitalis, for it has almost no effect upon dilatation of the heart in valvular lesions; it is often used in such cases, either alone or combined with digitalis, but the beneficial results seem to be due much more to its diuretic than to its cardiac action.

Strychnine.—Strychnine has come into somewhat extensive use in recent years as a cardiac stimulant; the good results following its use are probably to be attributed to its action upon certain parts of the central nervous system (especially the vaso-motor centre) and the nutrition generally, rather than to any special action upon the heart. At the same time there is some evidence that the frog's heart is directly stimulated by small quantities of strychnine while larger amounts weaken and slow it. In the mammal strychnine causes a slight slowing of the heart due to stimulation of the vagus centre. If convulsions occur, the heart becomes accelerated just as it does in struggling from any cause. Few drugs have such a powerful action upon the vaso-constrictor centre as has strychnine. Whether convulsions occur or not the arterioles are constricted to an extreme degree and the blood pressure rises enormously. The irritability of the subsidiary vaso-motor centres in the spinal cord is increased, so that a reflex rise of blood pressure may follow stimulation of a sensory nerve after the influence of the chief vaso-constrictor centre has been removed by section of the cervical cord.

Strychnine, like iron, seems to be used rather as an adjuvant to digitalis in the treatment of heart diseases; at the same time it is frequently recommended in those cases in which digitalis is contraindicated. It is also used in cardiac failure during typhoid and other fevers, shock, etc.; in these cases the action is probably mainly upon the vaso-motor centre.

Reid Hunt.

CARDIOGRAPHY. See *Heart*.

CARLSBAD (Karlsbad) is one of the most important thermal stations of Europe; indeed, its reputation is world-wide. It is charmingly situated in the northwestern corner of Bohemia, some 70 miles from Prague, at an altitude of about 1,160 feet, lying in the narrow valley of the Tepel River among the pine- and fir-clad hills traversed by paths in all directions. There are many beautiful walks and drives in the woods covering the slopes of the valley, and attractive excursions in the environs. "The valley in which it lies is shielded from the south and east winds by the mountains, but is exposed to the winds from the north and west, and the climate is consequently somewhat trying and subject to sudden changes in temperature" (Stedman). The native population is about 12,000, and upward of 30,000 people visit the springs annually.

These thermal waters are said to have been discovered in 1347, by the Emperor Charles IV., while hunting, but Carlsbad was known as a health resort a century earlier (Baedeker). "The springs issue from apertures in the rocky shell upon which most of the town is built, and are sixteen in number, all similar in their ingredients, which are principally sulphate of sodium, carbonate of sodium, and common salt. They are chiefly taken internally. They vary in temperature, the hottest having the least amount of carbonic acid gas. Some of the principal springs are the following (with their temperatures, Fahrenheit scale):

"Sprudel, 162.5°—a steaming fountain leaping up at short intervals, and having a capacity of four hundred and fifty gallons per minute; Felsenquelle, 138°; Schlossbrunnen, 127°; Mühlbrunnen, 124.5°; Theresienbrunnen, 122°; Marktbrunnen, 118°. These waters are classed among the sulphated alkaline waters." The following is the composition of the Sprudel water, according to the analysis of Ragsky, as given by Stedman. "Each litre (1.76 pint) contains:

	Grams.	Grains.
Sulphate of sodium	2.372	= 35.58
Sulphate of calcium	.163	= 2.44
Chloride of sodium	1.030	= 15.45
Carbonate of sodium	1.361	= 20.41
Carbonate of calcium	.297	= 4.45
Carbonate of magnesium	.124	= 1.86
Carbonate of strontium	.0008	= .012
Protoxide of iron	.002	= .03
Protoxide of manganese	.0006	= .009
Fluoride of calcium	.003	= .045
Phosphate of calcium	.0002	= .003
Silica	.0072	= .108

Carbonic acid in one litre 210.59 c.c." (Stedman).