power to contract rhythmically seems to be destroyed by the antimony. That this stoppage of the heart is not due to a stimulation of the vagi is shown by the fact that atropine has no influence upon it.

It is difficult to state exactly the effects of antimony upon the mammalian heart, for in the experiments hitherto recorded the effects upon the heart were not differentiated from those upon the vaso-motor system. It is very probable, however, that after large amounts of antimony the mammalian heart muscle is influenced in a way very similar to that of the frog, but that this action is obscured by the vaso-motor changes. Injected into a vein or an artery of an animal antimony causes an almost immediate acceleration of the pulse. At the same time the blood pressure falls; this fall of blood pressure is gradual but continuous until it reaches zero and the animal dies. When the fall of blood pressure has become very marked (in many cases when it has fallen to about one-half or one-third its previous height) the heart becomes slow and irregular. The diastolic pauses are greatly prolonged, but the changes in the blood pressure following each contraction are very great, indicating that the heart beat is fairly strong and that the vessel walls are much relaxed. This fall of arterial pressure cannot be ascribed to the weakening of the heart, for it precedes this, and there is no constant relation between the condition of the heart and the height of the blood pressure. The cause of the fall of blood pressure seems to be a paralysis of the peripheral vaso-motor system; the blood-vessels, especially those of the splanchnic area, are dilated and the most powerful stimulation of the medulla oblongata is powerless to contract them. It is not known whether the vaso-motor nerves or the muscle of the vessel walls or both are poisoned; the fact, however, that other unstriped muscle (that of the intestines for example) is not paralyzed points to the nerves or their ganglia being the structures acted upon. It is not impossible that the changes in the heart are in reality due to the great fall of arterial pressure, but the fact that antimony has such a poisonous action upon the frog's heart makes it probable that the mammalian heart is similarly affected. The heart finally stops in diastole; just before the final standstill there is frequently a very brief period during which the heart beats with great rapidity, but the contractions are exceedingly weak and the blood pressure remains very low. The cardiac nerves do not seem to be involved in the later stages of the poisoning. Some have stated that the vagus terminations are paralyzed, but this does not seem to be the case. Immediately after death the heart is found to be unirritable to electrical stimulation.

There are a number of other drugs which affect the circulation in ways similar to the above and which might be classified with the cardiac depressants; that they are not so classified is due to the fact that they have never been used to any great extent for their action upon the heart. Among these substances may be mentioned salicylic and carbolic acids, potassium salts, double salts of copper, zinc and some other heavy metals, chloral, saponin, apomorphine, emetine, muscarin, cholin, pilocarpine, hydrocyanic acid, and the various mineral and organic acids. With some of these drugs it is largely a matter of dosage; small amounts may stimulate the heart while larger amounts depress it.

There are also drugs which may at times relieve, in one way or another, the heart and so act as cardiac sedatives. Thus atropine seems to reduce the sensibility of the nervous structures of the heart to increased pressure, and Brunton has found it useful in some cases of palpitation with high blood pressure and in persons suffering from the effects of cardiac strain following violent muscular exertion. Digitalis was at one time called a cardiac sedative from its power to cause a rapid, irregular, irritable heart to beat slowly and regularly; in such cases the action is exerted largely through the inhibitory nerves and so has a certain resemblance to the action of aconite and veratrum viride, although there are other reasons for placing these drugs in entirely different classes.

Some drugs may have the effect of cardiac sedatives by reducing irritation which has caused, reflexly, palpitation of the heart; thus hydrocyanic acid will sometimes relieve the palpitation caused by indigestion. In some cases local irritation will prevent the most powerful of the cardiac depressants from exerting their normal action. An interesting case of this kind is described by Percy (Trans. Amer. Med. Ass'n, 1863, p. 268). Large repeated doses of veratrum viride had no effect upon the pulse of a patient until two large and very active ascarides were removed from the stomach by vomiting; after this had occurred there was an immediate and marked reduction in the pulse. There are certain mechanical means which produce effects analogous to those caused by the cardiac depressants. Thus pressure over the heart—such as that caused by a plaster—removal of blood by venesection, and the application of cold to the cardiac region all reduce the force and frequency of the heart beat and may be used instead of drugs.

It is difficult to form an opinion as to the extent to which the three chief cardiac depressants—aconite, veratrum viride, and tartar emetic—are employed at present, the practice of physicians varying so much. The general indication for their use has been said to be "increased arterial excitement, sthenic fevers, and severe local inflammations." In the first condition they are used simply to reduce the force and frequency of the pulse; in sthenic fevers they are used not only to lessen the force of the heart but to obtain a relaxation of the peripheral vessels, while in local inflammations it is desired to divert, by their use, the blood into other channels. Pneumonia was formerly thought to be pre-eminently a disease in which these drugs were to be used and all three have been employed very extensively in it. At present they are used to a much more limited extent; this is especially true of tartar emetic, and although many use aconite and veratrum viride, some have discarded all three and use the lancet when they think it desirable to depress the circulation. The reader is referred to the articles in this Handbook on the various disturbances of the circulation for a discussion of the use of these remedies, but a few of the cases in which they are employed will be simply mentioned here.

Aconite seems to give the best results in inflammations of limited extent, especially in tonsillitis, quinsy, and acute sore throat. Much of the relief in these cases seems to be due to the perspiration which follows the depression of the circulation. By diverting the blood away from the inflamed tissues these become less painful and the swelling subsides. Aconite is often serviceable in severe colds, in otitis, and in certain forms of asthma. It is sometimes used in nervous palpitation of the heart and in that occurring in excessive hypertrophy of the heart—although here it may become a very dangerous remedy. Occasionally it will relieve restlessness and give the patient refreshing sleep.

Veratrum viride seems to be used as a cardiac depressant to a more limited degree than aconite; it is probably used more extensively in pneumonia and puerperal fever than in the numerous other conditions for which it has been recommended.

Tartar emetic is probably used still less for its action upon the circulation, although it is praised very highly in typhus and other fevers when there is much excitement and wild delirium. It is used much more extensively as a diaphoretic, although its action as such may depend to some extent upon its power to depress the circulation.

II. Cardiac Stimulants.

There are a great many drugs which can increase, in one way or another, or under certain circumstances, the force of the circulation; to a few of these which are used largely by physicians for this purpose the name "cardiac stimulants" is applied. Aside from their action on the circulation, these drugs have little in common in either their chemical or their physiological properties. Their

action upon the circulation is, moreover, brought about in the most diverse ways, and is often determined to a considerable extent by the previous condition of the circulation. Some act chiefly upon the blood-vessels, others upon the heart; some act reflexly, others directly; while some may cause one kind of change reflexly and just the opposite when absorbed; some slow, others accelerate, the heart. The action of some is very rapid while that of others is slowly developed and long continued. The last-named difference has served as a basis for the only classification of these drugs it seems possible to make. Those which act rapidly are called "cardiac stimulants proper" or simply "cardiac stimulants," those with a slower action "cardiac tonics."

Cardiac stimulants, used in the narrower sense, bring about their effects largely reflexly and are used to prevent or counteract sudden failure of the heart's action. They are used especially in fainting fits or syncope due to sudden emotion, physical injury, poisoning by cardiac depressants, or when the heart fails suddenly in fevers, after snake-bites, etc. The action of most of them is primarily upon the blood-vessels, and the heart is usually influenced only secondarily. They may be administered by inhalation (as is the case with ammonia in smelling salts), by the stomach or subcutaneously or intravenously. When applied to a mucous membrane they exert their influence largely through their local irritating action; some have little action after absorption while others (such as alcohol and ether) are essentially cardiac depressants when they once get into the circulation. These drugs are seldom used when there are organic changes in the heart.

The most important members of this group are alcohol and the various liquids containing it in concentrated form, ether and chloroform—these three only when brought into contact with a mucous membrane or injected subcutaneously—the various preparations of ammonia, camphor, and the volatile oils.

One of the most powerful of all cardiac stimulants is heat applied to the cardiac region. In addition to the above there are many drugs which, under certain circumstances, may act as cardiac stimulants but which are not ordinarily included under that heading.

Alcohol.—Dr. J. J. Abel, who has given considerable attention to the subject of alcohol, has prepared the following summary of its action upon the circulation. (For a more complete account see Dr. Abel's paper in the report of the "Committee of Fifty.")

It has long been a matter of discussion how best to define the action of ethyl alcohol and of alcoholic fluids on the circulatory apparatus. The term "circulatory stimulant," as applied to alcoholics of all kinds, is firmly fixed in medical literature, but it has become impossible, in view of modern analyses, to retain this term in its original significance. The appearances of so-called stimulation are manifest especially in those individuals who are unaccustomed to the use of alcohol, and who possess an excitable vascular apparatus. In such the eyes become more brilliant, a sensation of warmth is experienced in the stomach and on the surface of the body, the sweat glands, the salivary and gastric glands are stimulated, the pulse is fuller and faster, gestures and muscular movements in general are more frequent and more pronounced, and the respiration responds by an increase in rate and depth. The environment often supplements the action of the wine or other beverage in its emotional or intellectual effect. In view of these phenomena it is not strange that mankind speaks of alcohol as a cerebral, circulatory, or respiratory stimulant.

When it comes to the action of alcoholics on the circulatory apparatus, numerous difficulties are encountered; secondary or reflex must be separated from primary actions. But nowhere has modern analysis given us a clearer idea of the true action of a substance than in that of alcohol on the various parts of the circulatory apparatus. What is to follow holds, strictly speaking, for pure ethyl alcohol only. Yet it will be found to hold also for wines, spirits, and other forms of alcoholics which mankind has accepted after long and frequent empirical trials. It must be borne in mind that esters, aldehydes, the small quantities of higher alcohols, the salts, etc., in short the sum of the by-products of alcoholic fermentation, are quantitatively insignificant in comparison with the ethyl alcohol contained in all alcoholics. This becomes strikingly evident when they are studied in the light of toxicology. Thus, 1 litre of brandy will kill 64.9 kgm. of living animals (dogs, rabbits, etc.), while the ethyl alcohol alone of this litre of brandy will kill 64.3 kgm. It is not denied that these by-products have a very important action on the sense of taste and that of smell, and on the functions of the digestive tract, nor that they noticeably enlarge the effects about to be described. It is especially the esters of wines and spirits which are to be thought of in this connection as slightly increasing the action of the ethyl alcohol, as their action is similar to that of alcohol, though more intense, quantity for quantity.

When we inquire into the direct action of alcohol on each of the several parts of the vascular apparatus taken by itself, we reach the following conclusions.

I. *Action of Alcohol on the Isolated Heart.*—Alcohol in small and moderate quantities, that is, in such amounts as are to be found in the blood in any condition far short of intoxication, does not have a direct stimulating action upon the isolated heart of either warm- or cold-blooded animals; indeed, moderate quantities show no appreciable action either in the way of stimulation or depression. The experiments of Martin and Stevens, Hemmeter, Ringer and Sainsbury, Dreser, Diaballa, Bock and others, furnish incontrovertible proof of this statement. But such a statement does not refer to the long-continued daily administration of small and moderate quantities of alcohol, but solely to its administration during brief periods, as in physiological experiments.

In very large doses, such, for example, as result in helpless and perhaps fatal intoxication, alcohol is seen to be a direct and powerful depressant of the heart, weakening first the auricular, later the ventricular systole, causing more or less distention of both cavities, marked slowing of its movements and great diminution of its output of blood. As we shall see later, these positive statements do not stand in contradiction of the fact that alcohol is of frequent and beneficial use in conditions of great depression of the heart or central nervous system. In experiments like those from which the above conclusions were deduced, the heart was severed from all vital connection with the rest of the body.

II. *Direct Action on the Walls of the Arteries and Veins, that is, the Blood-Vessels Removed from all Central Nervous Control.*—Small and moderate quantities of alcohol have no direct action on the walls of the blood-vessels. Very large amounts no doubt have a direct dilating action on the vessels, like that shown for the heart itself. The flushing of the face and other parts of the body so frequently observed after moderate quantities of alcohol is brought about by an action on the central nervous mechanism which controls the calibre of the vessels.

III. *Influence on the Arterial Blood Pressure.*—Here we are dealing with a resultant effect of the work of the heart, and of the peripheral resistance offered by the smallest blood-vessels. These interdependent variables are affected through controlling nerves, and it is evident that here is an opportunity for indirect influences of various kinds.

It must be admitted that blood-pressure measurements are of minor importance to the clinician. It is well known that minor fluctuations in the arterial pressure are of frequent occurrence, and Hensen even affirms that daily changes of 40 to 60 mm. Hg are not uncommon in individuals lying in bed. Arterial pressure, as usually measured, gives us only the lateral pressure on the walls of the larger arteries, and without additional data it gives us no information on that important question, the intensity of the blood flow—in other words, the amount of blood which passes in the unit of time through a given capillary area. Whether an organ will receive its re-

quired amount of oxygen and other necessary material must all depend on this. Now the state of constriction of the peripheral arterioles is a factor of the greatest importance in determining the value of this resultant as well as of the arterial pressure. As Krehl, Hensen, and others have pointed out, even during periods of little or no variation in the aortic pressure, considerable variations are possible in the unit quantity of blood passing through the aorta. In other words, variation in the peripheral resistance may be offset in such a way by responsive variations in the action of the heart that a change occurs, either in the way of an increase or decrease in the amount of blood passing through the organs of the body, although aortic pressure remains practically unchanged. As a rule, however, an increase in arterial pressure means an increase in the intensity of the peripheral circulation. Being an important item in the study of the hæmodynamics, blood-pressure determinations cannot be neglected; yet it is necessary to point out, as Hensen has well said, that what we most need to know is not the arterial blood pressure, but rather the relation of the quantitative blood flow in any given organ to the actual needs of that organ, a relation which at present it is impossible to determine.

In regard to the action of alcohol on the arterial pressure, we may say that, given in moderate quantities and in such a dilution as to avoid the consequences of *local irritation*, it has no appreciable effect on it. When so large a quantity is given that a change in the pressure becomes apparent, it is always in the direction of a fall and not of a rise. In the early stages of its action it usually causes some degree of flushing of the skin and brain, and later, when very large quantities have been taken, dilatation of the abdominal vessels occurs. A marked fall of blood pressure due to such large quantities is a toxic phenomenon, and is never met with under ordinary circumstances. It is due to a sedative or depressant action of the alcohol on the vaso-motor centres, and also in part to its action in weakening the heart.

IV. *Action of Alcohol on the Pulse Rate.*—When alcohol or beverages containing alcohol are administered to *healthy* persons in small doses, or even in such doses as will produce transient psychical changes, no alteration of the *pulse rate* is usually observed, provided that local irritation in the mouth and stomach is avoided, and the indirect effects of the mental action of the alcohol, such as bodily movements, are not allowed to influence the experiment. It is not improbable that in some excitable individuals the cerebral effects of the alcohol and the circumstances of its administration may combine to induce such mental effects that slight changes in the pulse rate occur.

As a rule, when the quantity of alcohol administered is not too small, the *character* of the pulse wave undergoes a slight change, the pulse becomes fuller and softer in consequence of a dilatation of superficial arteries. The heart is not weakened at this time, and the fuller pulse may give a false impression and lead to the belief that the arterial tension has been raised. The pulse tracings of Marvaud, Parkes, von Jaksch, Jaquet, and others, show that moderate quantities of alcohol influence the form of the pulse wave in like manner with chloral and other hypnotics, though less markedly from a quantitative point of view. The slight dilatation of the superficial arteries is due to the sedative action of the alcohol on the vaso-constrictor centre of the medulla, and is not sufficient to lower the arterial tension as measured in the carotid.

By virtue of its local action on mucous membranes, and also by virtue of its cerebral effects, alcohol is capable of influencing the several parts of the vascular apparatus in a number of ways often directly opposed to those mentioned above. Such indirect effects are common to its pharmacological congeners, and are familiar in the use of alcohol in daily life and in medical practice. Of these none is more often observed than a quickening of the pulse rate. Such indirect effects must not be allowed to obscure its true inherent action, which is always depressant in kind. When once in the blood and tissues, it must be classed with the anæsthetics and narcotics.

It is not to be inferred that the above statements forbid a reasonable and prudent use of alcohol in therapeutics. The records of clinical medicine show that alcohol, by virtue of its numerous indirect as well as direct influences, often serves the purpose of a "circulatory stimulant." In conditions of shock the weak pulse may become fuller and stronger, the feeble heart may beat more vigorously. Again, a quick pulse may become slower as the rapidly beating, fluttering heart is induced to slow down to a regular rhythm. Other examples need not be cited. The day is happily past when the therapeutist plied his patient with a number of bottles of wine a day in the belief that he could stimulate the heart, lower the temperature, supply nutriment, and effect other good ends, without detriment of any kind, by giving these large quantities. Certainly its administration in excessive doses can only do harm.

Though the pharmacologist cannot admit that this agent is capable of stimulating the isolated mammalian heart, it would be rash to assert that it cannot serve as a cardiac stimulant in the human system. Gutnikow, who accepts it as a proved fact that alcohol can only lower the arterial pressure, when once it has reached the circulating blood, has made it the object of his researches to harmonize this with the equally well-known fact that it is often used in medical practice as an analeptic, as an agent that "strengthens and fortifies the heart." According to this author the sum total of the action of alcohol on the circulation is to the effect that, although there is a condition of lowered arterial tension, yet the mutual relations of the pressures in the cavities of the heart and in the arteries and veins are such that *the heart works as if it were strengthened.* It now has an easier task to keep all the minute arteries and veins and the capillaries well filled; under the new conditions its propelling power is not injured but rather improved. It may well be the case in certain clinical conditions, in the light of the remarks made in a previous paragraph on the relations existing between aortic pressure and the volume of the peripheral circulation, that alcohol will give cause for a better peripheral circulation, although the aortic pressure is slightly lowered.

Whatever may be the future theories in regard to its clinical uses, the old position of alcohol as a blood-pressure-raising agent and heart stimulant can no longer be defended, and it remains for the practitioner to use this agent with care and great discretion.

Ammonia.—The preparations of ammonia which are used for their effect upon the circulation are solutions of the gas in water or in alcohol and the carbonate; the latter is a rather complex mixture of the carbonates and carbamates of ammonia, which give off ammonia on exposure and hence has an action similar to but less powerful than that of the solutions of ammonia.

Ammonia has a very powerful local action as well as an action upon the nerve centres when it reaches the circulation and it is important to distinguish between these. When ammonia reaches the circulation it is converted into urea very rapidly; hence unless considerable quantities are injected at once into the circulation no symptoms are produced. While ammonia is absorbed with considerable rapidity from the stomach, it is doubtful whether after the use of medicinal doses it reaches the circulation in sufficient concentration to have any appreciable effect. Hence the effects of ammonia (and of ammonium carbonate) when given by the stomach are due largely, if not entirely, to the reflexes caused by its local action; the effects of the intravenous injection of considerable quantities will be discussed later.

The effects of ammonia can be elicited by applying it to either the respiratory or the digestive tract or subcutaneously, and consist of a powerful reflex stimulation of the vaso-motor and respiratory centres. The result is a rise of arterial pressure and an improvement in the pulse; the latter is probably dependent upon the rise of blood

pressure, for the heart, so far as it is affected reflexly at all, seems to be slowed by a stimulation of the vagus centre. The rise of blood pressure will rouse the patient from a fainting spell, from a condition of sudden collapse, from failure of the circulation during anæsthesia and from similar conditions. The effect is very transitory, but is often sufficient to carry a person through a dangerous period. Both the physiological action and practical experience point to the conclusion that ammonia is of little service when the failure of the circulation is dependent upon some slow and persistent cause. If ammonia is applied to the nostrils for too long a period or in too concentrated a form it may produce inflammation of the respiratory passages; also when it is swallowed in large quantities some of the vapor may reach the respiratory passages and cause death by œdema of the larynx.

When ammonia or one of its neutral salts is injected directly into the circulation of a mammal the effects are those observed whenever a powerful stimulant to the medulla or spinal cord is injected—increase of respiration, convulsions, tetanus, and a rise of blood pressure. These effects are probably due to the irritating action of the ammonia upon the nerve cells rather than to any specific stimulation of them, as is the case with such an alkaloid as strychnine for example. Very similar effects follow the subcutaneous application of ammonia or of its salts, although here the effect is complicated by changes brought about reflexly. The results are the same whatever the salt used, provided the acid in combination has not, of itself, a poisonous action; this shows that the results are due to the ammonium ion.

A considerable amount of a salt of ammonia may be injected into the circulation of an animal without producing any toxic symptoms, provided the injection be made very slowly. Thus Marfori (*Archiv für exp. Path. und Pharmakol.*, xxxiii., p. 71, 1893) showed that .03 gm. of ammonia (in the form of the carbonate) per kilogram could be injected per hour into a dog without causing any symptoms. The explanation of this is that the ammonia is rapidly converted into urea.

The effects of ammonia and its salts when injected rapidly into the circulation or subcutaneously into an animal have been investigated by Blake (*Edin. Med. and Surg. Jour.*, lvi., p. 1, 1841), Lange (*Archiv für exp. Path. und Pharmakol.*, ii., p. 375, 1874), Funke and Dealna (*Archiv für die ges. Physiol.*, ix., p. 416, 1874), and Formanek (*Archives internat. de Pharmacodynamie et de Therapie*, vii., p. 229, 1900). The first effect is usually a slowing of the heart and a slight fall of blood pressure; then there is a marked rise of blood pressure, the heart sometimes remaining slowed, sometimes being accelerated. The slowing of the heart and the first fall of blood pressure are due almost entirely to a stimulation of the centre of the cardio-inhibitory nerves, for they usually disappear immediately upon section of the vagi. There may sometimes be a slight, unimportant slowing of the heart after section of the vagi; this is probably due to a slight stimulation of the vagus endings in the heart, for these are stimulated by a great many of the drugs which stimulate the medullary centres of the vagus. If a very large amount of ammonia is injected into a vein the heart may be poisoned directly and may either beat very slowly or be arrested at once in diastole.

The rise of blood pressure has been attributed by some to a stimulation of the heart, by others to a stimulation of the vaso-motor system; it is due to both of these, but probably more to the latter than to the former. The action of the salts of ammonia when directly applied to the frog's heart has been studied by Ringer and Sainsbury. These results are of especial value because no similar experiments have been made upon the mammalian heart. Briefly stated, Ringer finds that ammonium salts added to the nutrient fluid circulating through the isolated frog's heart increase, in small doses, the strength of the ventricular contractions, but that larger doses destroy muscular contractility; spontaneous action, however, continued until contractility was lost; in the end stage there was no response even when the ventricle was strongly stimulated electrically. Ringer also finds that ammonia lessens dilatation of the ventricle and arrests it in systole. If the heart has been weakened by chloroform or other anæsthetics, the beat is strengthened by ammonia, and a heart stopped in diastole by chloroform passes into the condition of systole under the influence of ammonia. Since these experiments were made upon the ventricle of the frog's heart we are justified in concluding that ammonia stimulates the cardiac muscle directly. It is not known to what extent ammonia has a similar action upon the mammalian heart. An acceleration and strengthening of the heart beat sometimes follows its injection, but this stimulation is usually of short duration and does not always occur. Some think that the improvement in the heart beat is to be attributed to the rise of blood pressure rather than to a direct effect upon the heart, while Formanek thinks it is due in part to a stimulation of the accelerator nerves.

The great rise of blood pressure following the injection of ammonia is usually attributed to a stimulation of the vaso-motor centre, and this view is made very probable by the fact that the other medullary centres are so powerfully stimulated by this substance. Funke and Deahna found that in frogs section of the cord or of the sciatic plexus greatly diminished or abolished altogether the constriction of the blood-vessels following the subcutaneous injection of ammonia. On the other hand, there is considerable experimental evidence that the peripheral vaso-motor system (the nerves or the muscles of the vessels) is stimulated directly. Thus Lange obtained a marked rise of pressure after division of the cord, *i.e.*, after the vaso-motor centre had been separated from the arterioles. Beyer (*Medical News*, 1886) transfused the vessels of terrapins (from which the heart had been removed) with Ringer's solution to which salts of ammonia had been added. There was first an increased then a diminished outflow from the veins, *i.e.*, a dilatation followed by a constriction of the blood-vessels. We are probably justified in concluding that the rise of blood pressure caused by ammonia is due partly to a stimulation of the vaso-motor centre and partly to a direct action upon the arteries; it is very probable that direct stimulation of the heart also is a factor, especially if this organ has been previously weakened by anæsthetics, etc. Binz (*Centralbl. für klin. Med.*, ix., p. 26, 1888) found that if the arterial pressure of an animal was made very low by the administration of chloral hydrate, ammonia would cause it to rise; the improvement was, however, temporary and when the ammonia was pushed convulsions followed.

Intravenous and hypodermic injections of ammonia are sometimes made in cases of sudden and dangerous collapse, as in failure of the heart during anæsthesia, in cholera, after injuries, etc. It has been used extensively in cases of poisoning from snake bite but the improvement in these cases seems to be temporary. When ammonia is administered by the mouth or by the respiratory tract the only effect upon the circulation is the reflex stimulation of the vaso-motor centre; by its intravenous use the peripheral vaso-motor system as well as the medullary centre is stimulated and there is further probably some direct action upon the heart. When ammonia is given intravenously in very large amounts there is danger of causing convulsions; animals, however, usually recover quickly from such convulsions.

Camphor.—Camphor has long been used, especially in Germany, as a cardiac stimulant in cases of collapse and cardiac weakness from fevers and other causes; the pulse becomes fuller and stronger under its influence. Statements as to the action of camphor upon the heart are incomplete and in some cases contradictory; moreover, its cardiac action is undoubtedly much obscured by its action on the central nervous system, the respiration, and the vaso-motor centre. The beneficial effects in collapse, etc., are probably due quite as much to these effects as to the effects upon the heart. Camphor has, moreover, a well-marked local action and it is not easy to distin-

guish between the effects produced reflexly and those produced after its absorption.

Some of the rather fragmentary statements as to the action of camphor will be given. Lewin (*Archiv für exper. Path. und Pharmakol.*, xxvii., p. 229, 1890) found that camphor administered to rabbits in which the blood pressure was extremely low as a result of large doses of chloral hydrate caused a marked rise of pressure; frequently it was doubled. The rise of blood pressure was longer continued when the camphor was given by the stomach than when it was injected into a vein. Lewin argues that since the vaso-motor centre was paralyzed by the chloral the rise of blood pressure must have been due largely to a stimulation of the heart (for camphor has, so far as is known, no direct stimulating action upon the peripheral vessels). If the chloral anæsthesia was not so very deep then the vaso-motor centre was stimulated, as was shown by the fact that it became sensitive to the effects of asphyxia.

It is a significant fact, however, that Wiedemann (*Archiv für exper. Path. und Pharmakol.*, vi., p. 228, 1876) failed to obtain any rise of blood pressure from the administration of camphor after section of the spinal cord—as would be expected if Lewin's conclusions are correct. It is very probable that there was some source of error in the experiments of one or the other investigator. Their results could, however, be brought into accord if we suppose the medullary centres of the accelerator nerves to be stimulated by the camphor. There is, however, no experimental basis for the latter supposition.

Small doses (five to ten grains) administered to a healthy man usually cause an acceleration of the pulse, although sometimes they have little effect or may even cause slowing. Larger doses (twenty grains or more) slow and weaken the pulse; after toxic doses the pulse may be accelerated again.

When from any of a number of causes the pulse is very weak or almost imperceptible, camphor will make it fuller and stronger. Binz and Baum found that in animals in which fever had been induced by the injection of putrid matter, camphor increased the strength of the heart beat and caused it to continue longer after death than in the case of control animals.

Heubner (*Archiv für Heilkunde*, xi., p. 334, 1870) and Harnack and Witkowski (*Archiv für exper. Path. und Pharmakol.*, v., p. 427, 1876) state that camphor causes the frog's heart to beat more slowly but more powerfully; this is due, according to these authors, to a direct action upon the heart, for the latter can be made to beat again after it has been brought to a standstill by muscarine, and, on the other hand, neither muscarine nor stimulation of the vagus can stop the heart poisoned with camphor. Lewin (*loc. cit.*) found the frog's heart to be slowed by a prolongation of the systole; the diastole was less complete and so the output was diminished. Thus the effect of camphor upon the frog's heart is similar in some respects to that of digitaline.

The blood-pressure in mammals is usually considerably increased by camphor; this seems to be due in part to an action upon the heart, in part to a stimulation of the vaso-motor centre. Whether the latter is stimulated directly or reflexly is not known. In some cases rhythmical variations of the blood pressure appear; these are especially marked if convulsions occur, but they are also seen when convulsions are prevented by curare (Wiedemann, *loc. cit.*). It has been suggested that these rhythmical variations are due to a direct action upon the vaso-motor centre, just as the convulsions are due to a direct action upon the cerebral cortex; or the cerebral cortex may send rhythmical impulses to the vaso-motor centre independently of those causing the convulsions.

Thus, as far as we are able to judge from the available data, camphor has an action upon the circulation similar to that of ammonia, and it seems to be of use in similar conditions. Like that of ammonia the action of camphor is very transitory. Van der Helm ("Versuche über einige arzneiliche Erregungsmittel," Dissert., Bonn, 1887, p. 28) says that the action of camphor upon the blood pressure, as well as upon the respiration, is longer continued than is that of ammonia. Attention was called above to the fact that the effect of camphor is more lasting when it is given by the stomach than when injected intravenously; the explanation of this is probably that in the latter case the camphor is very rapidly destroyed in the organism. Moreover, when the drug is given by the stomach, the reflex as well as the direct effects of its action are obtained. The slight solubility of camphor in water and the consequent great irregularity of its rate of absorption from the digestive tract are two of the chief drawbacks to its employment in therapeutics. A number of the other members of the camphor group have been studied, but as yet no good substitute for camphor has been discovered. Camphorol, amido-camphor, and camphoric acid resemble camphor in their physiological action but are less powerful.

Musk has also been used as a cardiac stimulant in conditions similar to those for which camphor has been prescribed; it has been especially recommended in certain cases of advanced typhoid fever. Almost nothing is known as to its physiological action, but it seems to strengthen the heart beat; it has a more decided action upon the respiration.

Most of the volatile oils when taken into the stomach act as mild cardiac stimulants. Their action is entirely a reflex one, for when injected into a vein they depress the vaso-motor centre and, in large doses, the heart.

Cardiac Tonics.—Those drugs which are employed to produce a more lasting effect upon the heart are called cardiac tonics. They act chiefly upon the cardiac muscle; to a less extent upon the cardiac nerves and the vaso-motor apparatus. Their action is usually slow; frequently no change in the circulation can be made out for many hours, sometimes not for days, after their administration has been begun. It is chiefly in diseases of the heart, especially those associated with valvular lesions in which dilatation has occurred, that these drugs are used. Among them are some of the most valuable remedies known to medicine.

The most important members of this group are those belonging to the "digitalis series," including digitalis itself, strophanthus, scilla, convallaria, adonis, erythrophlœum, helleborus niger, etc. Caffeine and strychnine, as far as their action upon the heart is concerned, also belong to the group of cardiac tonics.

The Digitalis Series.—The "digitalis series" embraces a number of substances derived from various families of the vegetable kingdom and having little in common as regards their chemical composition; some substances found in the animal and even in the mineral kingdoms may be included in this series. The bond that unites these various substances is a peculiar and specific influence upon the heart; the action of any one member is almost identical with that of all the others and different from almost all other substances. So great is this similarity of action that pharmacologists do not hesitate to apply the discoveries made concerning one member to all the others and speak of the action of "digitalis," although the experiments in questions were made with some other member.

The three drugs of this series which are most used are digitalis, strophanthus, and scilla, and most of the physiological experiments have been made with these, especially with the first two.

Few drugs in the Pharmacopœia have been the subject of so much discussion as digitalis, and even yet writers are not in accord as to some of its physiological actions. Clinicians formerly classed it with the cardiac sedatives, although now it is placed first in the list of cardiac stimulants or tonics. Different experimenters have credited it with having nearly every action upon the vascular mechanism which it is possible for a drug to have. These discordant results are all the more remarkable as they are not due to the workers having used different preparations; almost any preparation of these drugs, provided it is active at all, will produce the effects typical of the

series. The real source of trouble has been that the pharmacologists and physicians have failed, until very recently, to make use of the advances in methods of work and of the facts discovered by modern physiology.

Very little knowledge of the action of digitalis upon the circulation can be obtained by its administration to healthy men beyond the fact that the pulse first becomes very slow and later intermittent and irregular. The apex beat is stronger and the arteries feel more tense. At the same time the irritability of the heart seems to become abnormally great; slight exertion may cause it to assume a rate of 120 to 130.

Experiments upon the frog's heart have played a very important part in the history of the study of the physiological action of digitalis; the greatest service such experiments have rendered is the proof that the action of digitalis is primarily upon the cardiac muscle. The changes brought about in the frog's heart are readily observed by exposing the heart and injecting the drug into a lymph space. The heart soon becomes slowed, but the essential feature is that the ventricular systole becomes more complete. The blood is more completely expelled from the heart, and during each systole the ventricle becomes almost white; it also remains contracted for a longer period. The diastole becomes shorter and then less complete; the time relations between systole and diastole become almost reversed. Instead of a short, sudden systole and a long-continued diastole, as normally, the systole becomes very long while the diastole is a sudden, imperfect relaxation of very short duration which merely interrupts for an instant the prolonged contraction. Finally the ventricle stops in systole; it is firmly contracted and white, while the auricles are distended with blood and may contract feebly for a short time. Before the ventricle is finally arrested certain irregularities usually appear. One part of the ventricle, usually the apex, does not relax during diastole and the blood is thrown against the relaxed walls of the other parts causing little bulgings. Or the ventricle may assume a mottled appearance from there being numerous small areas of muscle which remain contracted. The blood may be thrown from one side of the ventricle to the other, the heart undergoing the "peristaltic contractions" so often mentioned by German writers.

The picture of the frog's heart under digitalis is an extremely characteristic one, and such an experiment as the above is of much more value as a means of identifying one of this series in toxicological examinations than are most of the chemical tests.

If, after the ventricle has stopped, the intracardiac pressure be increased, the heart will commence beating again, showing that the cardiac muscle is not in a condition of rigor. If apomorphine, or some other drug which tends to paralyze the heart muscle, be applied to the contracted ventricle, the latter will relax and commence beating again. These facts led Schmiedeberg to the view, which has been widely accepted, that the essential action of digitalis upon the cardiac muscle is a change in its elasticity. There are certain facts which make it difficult to accept this view of Schmiedeberg's, and the only statement we can safely make is that digitalis tends to increase and prolong the contraction of the heart and to diminish and shorten diastole. The absolute power of the heart muscle—*i.e.*, the pressure against which the heart is able to contract—does not seem to be increased by digitalis. Since the extent of the contraction is increased, the effect of digitalis has been compared to an increase in the length of the muscle fibres while their cross section (which determines the absolute power) remains the same. That this action of digitalis is upon the cardiac muscle itself, and not upon nervous structures contained in the heart, is shown by the fact that entirely similar changes are produced in the apex of the frog's ventricle and in the hearts of certain invertebrates which are free of nerve cells. So specific is the action of digitalis upon the heart that this organ may be completely stopped in systole and yet the frog jump about very much as if it were normal, *i.e.*, the central nervous system and skeletal muscles are very little affected when the action upon the heart is at its maximum.

These effects of digitalis upon the cardiac muscle are sometimes obscured by the results of a stimulation of the vagus caused by the drug. In some cases after the application of digitalis the systole is incomplete while the diastole is much prolonged and the relaxation during it very great; the heart may even stop temporarily in diastole. Section of the vagi or the paralysis of their endings by atropine causes this picture to change instantly and the results are now as those described above.

One other action of digitalis upon the frog's heart is to be noticed, viz., an increase in its irritability. That the irritability of the muscle is increased is shown by the fact that a preparation of the apex of the ventricle which has been exhausted by the transfusion of normal saline solution through it and which has ceased to beat will commence again when digitalis is applied to it. Sometimes there is a slight acceleration of the heart immediately after the injection of digitalis; this is doubtless due to an increase in the irritability of the muscle.

The study of the effects of digitalis upon the frog's heart is of importance because the changes produced by it in the mammalian heart can be traced back to the same two factors—an alteration of the cardiac muscle combined with a stimulation of the cardio-inhibitory nerves.

The action of digitalis upon the circulation of mammals is usually divided into four stages (Schmiedeberg. *Archiv für exper. Path. und Pharmakol.*, xvi., p. 175, 1882).

1. Rise of arterial pressure accompanied as a rule by slowing of the heart.
2. Continued rise of blood pressure with increase in the pulse rate.
3. Continued high pressure with great irregularity of the heart.
4. Rapid sinking of the blood pressure, failure of the heart, standstill, and death.

Such a division of the action into stages serves a useful purpose in so far as it emphasizes some of the salient points; but as a matter of fact these stages merge into each other and frequently some of the features of one appear in the others. Some of the chief points to be considered, then, are (1) the slowing of the heart, (2) the rise of blood pressure, (3) the secondary acceleration of the heart, and (4) the cause of the irregularity and death of the heart.

The slowing of the heart was observed in man by Withering, by whom digitalis was introduced into medicine ("An Account of the Foxglove and Some of its Medical Uses; with Practical Remarks on Dropsy and Other Diseases," Birmingham, 1785). Withering was chiefly interested in the diuresis produced by digitalis and paid but little attention to its action upon the heart, although he remarked "that it has a power over the motion of the heart to a degree yet unobserved in any other medicine and that this power may be converted to salutary ends." John Ferriar wrote an essay in 1799 on the action of digitalis in which he states that the chief action is to slow the heart. The first efforts to discover the cause of this slowing of the heart seem to have been made by Traube in 1851. Traube found that the slowing was removed by section of the vagi, and he therefore ascribed it to a stimulation of the cardio-inhibitory centre in the medulla—an explanation which has received abundant confirmation. Occasionally digitalis causes a slight slowing of the heart after section of the vagi; this has been shown to be due to a stimulation of the vagus endings in the heart. The irritability of the vagi is increased by digitalis, for a stimulation of these nerves which was inefficient before, will slow the heart after, its administration. An attempt was made to show that the stimulation of the vagus centre was not a direct effect of the digitalis but a secondary effect due to the rise of blood pressure; this is disproved by the fact that the heart is often slowed although there is no rise of blood pressure.

Thomas observed that digitalis sometimes failed to slow the heart in pneumonia; Brunton and Cash investigated the cause of this and reached the conclusion that it