

CLINICAL AND ELECTROCARDIOGRAPHIC  
STUDIES ON THE ACTION OF  
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NEW YORK

It is extraordinary that, after continuous use for 130 years, the study of the action of digitalis retains so vital an interest, not only in clinical medicine, but also in experimental pharmacology. This interest has been quickened by the fundamental investigations of James Mackenzie on the mechanism of the heart beat and by the construction by Einthoven of a galvanometer suitable for registering the action currents of the heart.

I mention James Mackenzie especially, because in the bewildering variety of studies which he has stimulated he has, almost alone, kept in view the essential objects of investigation in the domain of cardiovascular disease. These are, first, the study of symptoms suggesting the presence of incipient heart disease, and second, the study of the mechanism of heart failure and its treatment. His study of the disturbed rhythms of the heart was undertaken to ascertain whether they had a vital relation to these subjects, and to learn whether an appreciation of their significance would aid in understanding altered function.

I doubt very much whether the disordered rhythms of the heart, taken by themselves, presented a subject of fundamental interest to Mackenzie, and in that, too, he has differed from his followers. The reader remembers, no doubt, that he called his book "Diseases of the Heart"; but its theme may be said to be the arrhythmias in their relation to heart failure. This view of the arrhythmias gives them a new significance in studying the action of drugs. They can be made to serve as important indicators in estimating the value of therapeutic effects. Mackenzie's work, therefore, provides an important reason for reexamining the action of digitalis. Just as it was important to recognize the arrhythmias and to appreciate their significance, it was necessary to have far more accurate and more satisfactory methods of registering the motions of the heart than arterial and venous tracings, which record only the motions of the vessel walls, and in many instances record them badly or not at all. The string galvanometer, although it is not a substitute for them, has come to replace the older methods by one eminently practical, free from error due to the personal equation and reliable within the limits of its capacity. This instrument has made Mackenzie's work more easily available. Its use, as I hope to show, has made possible the introduction of added criteria for recognizing the action of drugs. Mackenzie's new conceptions and Einthoven's new instrument, reported almost simultaneously, made therapeutic investigation from a new point of view desirable.

I want to discuss the effects of digitalis on heart rate, on conduction, on the electrocardiogram, on blood pressure and on diuresis. But because there is still a very distinct divergence of opinion between practitioners of clinical medicine and pharmacologists, as to how digitalis acts, I must take account of the views of both in presenting the subject. But the matter is not simple, for clinicians differ in the results of their observa-

tions, and pharmacologists on the interpretation of experiments.

The school of Schmiedeberg still maintains that the main action of a digitalis body is on heart muscle; the school of Gottlieb, while it does not deny to digitalis bodies a cardiac action, still maintains the view that it has an important action on the walls of the arteries. Both schools find that the drug increases the excursion of the heart in contraction, both believe that it elevates blood pressure, both believe that it increases the amount of renal secretion.

It is perhaps not an overstatement to say that in a general way clinicians have been too much influenced by these experimental results and have felt obliged to find that the administration of the drug in patients results in parallel phenomena. It requires a very small experience in treating patients suffering from heart disease to find oneself disappointed because the expected results did not occur. And when discrepancies were noticed, the discovery was not often followed by an effort to explain them. The subject was often dismissed by finding fault with the potency of the drug or by discovering an idiosyncrasy in the patient. But even if drugs were always potent and there were no individual idiosyncrasies, it is extremely likely that patients would continue to react in different manners to the drug. And the reason for that must be that individuals, although they suffer from what in a general sense is called heart disease, yet present a great variety of clinical pictures.

If the cardinal symptoms of heart failure alone are considered, rapid pulse, disturbed rhythm, high blood pressure, dyspnea, pain and edema, it becomes clear that patients do not usually present all of these signs at once, that some present one or two of them, or a group. It must be apparent that the pharmacologic experiment does not take this diversity of circumstances into consideration; the experiment is done under artificial conditions, and the doses which are employed bear no relation to those permitted in clinical medicine. There can be no question of the usefulness to therapeutics of these experiments; as guides, they are indispensable, but it must be clear that they neither replace nor parallel the clinical conditions we must treat. That there has consequently been a divergence between the results of pharmacologists and clinicians in a practical sense was inevitable. The responsibility for it is probably shared equally by both. Pharmacologists have dealt usually with simple normal conditions; clinicians with complex pathologic ones.

In therapeutics, divergent accounts of the action of the digitalis bodies are also found. For instance, they are sometimes said to reduce the heart rate, and to act almost as specifics; others deny such an action. In the presence of fever their use is discouraged by some as valueless. In the domain of valvular defects a variety of indications and contradictions for giving the drug prevails; some regard these as unimportant. Until recently, some avoided it in cases of high systolic arterial pressure, because it was reputed to elevate this to dangerous limits. Some, again, have detected a striking effect in a short time (Marvin), while others have recently reported that it has no effect on pressure at all. Its effect on diuresis has, on the whole, been commonly held and has been gained on account of the disappearance of edema, when this sign of heart failure is present.

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\* Read before the Section on General Medicine, College of Physicians, Philadelphia, Dec. 14, 1914.

A drug having apparently such very powerful actions as digitalis must be extremely valuable and must gain in usefulness if its modes of action are carefully studied and precisely recorded. It has been no easy task to reconcile the divergent views drawn from experimental experience, and equally difficult to understand the contradictions expressed by reliable clinicians. We have therefore been engaged in the Hospital of the Rockefeller Institute in the attempt to understand and to reconcile these differences, in order to make more available the data of experimental pharmacology, and to ascertain whether the indications for the use of digitalis could be simplified if patients were grouped with a view of delimiting the conditions in which uniform results might be expected. For these purposes it has been deemed wise to study digitalis in the human subject, because in the first place it is about its action in patients that information is wanted, because, in the second, that information can, in practically all respects, under present conditions be satisfactorily obtained, and because, in the third place, the study can be made not only without any prejudice to the patient, but, indeed to his advantage.

It is apparent, if the cardinal symptoms of heart disease during heart failure are considered, rapid pulse, disturbed rhythm, high blood pressure, dyspnea, pain and edema, that not all patients present all of these complaints, and that each patient suffers from only a selection of them; of these symptoms the most obvious

#### CLASSIFICATION OF PATIENTS

A. Normal rhythm.	a. Without edema.	1. With normal blood pressure
	b. With edema	2. With high blood pressure
B. Auricular fibrillation	a. Without edema	3. With normal blood pressure
	b. With edema	4. With high blood pressure
	a. Without edema	5. With normal blood pressure
	b. With edema	6. With high blood pressure
	a. Without edema	7. With normal blood pressure
	b. With edema	8. With high blood pressure

basis for the arrangement of patients into groups for the purposes of treatment, especially at the present time, is rhythm. Rhythm, it will be remembered, was the subject with which Mackenzie started. The basis has, in point of fact, been found extremely serviceable, for in a general way it has been said that the drug acts on cases of auricular fibrillation very successfully, and has even been called, erroneously of course, a specific; while in cases presenting a sinus rhythm it has been said to fail. We have therefore divided patients primarily into fibrillators and nonfibrillators. On the question of rhythm, pulse rate also depends, and we regard these two factors together, but not, of course, as the same. The second basis on which patients can be divided is the question of edema and the retention of water, involving the question of salt metabolism, and these two symptoms may also be regarded as phases of a similar disturbance. The third basis on which we have found it useful to study patients has been on the basis of the height of blood pressure. We do not, of course, pretend that a classification such as this presents all the points of view from which either heart failure or the treatment of heart failure can be viewed; it omits important symptoms such as dyspnea and pain. Often these are cardinal, often they are secondary signs. But, after much consideration, we have adopted it as a useful working plan for testing the effect of drugs. The classification then, is as in the accompanying tabulation.

The group of patients which presents the simplest form of disease is the first one, in which the rhythm

of the heart is normal, there is no edema and the blood pressure is not elevated. This is the state found in a patient who, if he presents himself for treatment at all, is in an early stage. It is naturally understood that an early stage of heart failure does not by any means suppose an early stage in heart disease. It is, on the whole, the simplest kind of heart failure which one is called on to treat. The general physiology of such a patient presents the nearest approach to the normal. It is the effect of giving digitalis to him to which we have confined our attention and with which this report principally deals. It is clear that often he requires no drugs; if digitalis is given him it is important to determine what effects are to be expected, and also how the expected effects are to be recognized. This is the method of experimental pharmacology, and the results obtained in this way can be most nearly compared with experimental conclusions. They can be made also to serve as a basis for considering the effects on the more complicated groups.

I have mentioned earlier the topics I mean to discuss, but it is well to dwell for a moment at this point on another. Aside from changes in the physical signs which some clinicians believe themselves capable of appreciating, we have no means whatever of estimating alterations in the functional efficiency of the heart, referable to the heart itself. If it were possible, an accurate estimation of contractile force would be the most important single measure to take, but for this we have no satisfactory criteria. Observations on blood flow, blood pressure, estimations of volume output, electrocardiography, have all been equally disappointing. Those effects reported earlier, of changes in the magnitude of ventricular contractions gained in experiments, are more recently admitted (Joseph) to have been obtained by doses far too great. The much smaller doses now used are still much larger than are permitted in therapeutics, but even these fail to show marked changes in the extent of the excursion of the ventricular wall which were formerly held to indicate the nature of effective digitalization. The methods employed in pharmacology are not superior to those now available in clinical medicine. Both are on a par in respect to obtaining objective records of this phase of digitalis action. We must believe, therefore, that if digitalis increases the ability of the ventricles to pump blood, it does so by means of a change which is more subtle than can be distinguished by our methods.

The most important alteration we look for traditionally is in the pulse, or better, the heart rate. This is the first subject we have investigated. For the present we omit fibrillators from consideration. The reduction in the rate of the heart is an effect of digitalis on which we have been taught to rely, both by pharmacologists and clinicians. It is, unfortunately, an effect which we have not found constant in the type of case we are considering. We know also that it fails to reduce rate in the tachycardias of a paroxysmal nature, in those of exophthalmic goiter, and in those of fever. That the pharmacologist could report such an effect depended, no doubt, on the size of his dose. That the clinician believed it to occur depended until recently on his not distinguishing between fibrillators and nonfibrillators. The brilliant reduction in rate was found in the former. It was also found in the sinus rhythm when edema was present; but neither group of patients is at present under discussion. In

the absence of edema, a reduction in rate may be said to occur principally in the hypodynamic and unstable heart, in the heart which for unknown reasons undergoes spontaneous alterations in rate. In hearts of this nature, a natural tendency to reduction is accentuated by administering digitalis. Aside from these, the majority of individuals do not respond to therapeutic doses of digitalis by a fall in heart rate. When amounts equal to 0.4 gm. of leaves a day are given for five to seven days, ventricular slowing does occur, but it occurs as the result of the blocking of the auricular impulses. The latter continue at an unreduced speed and do, as a matter of fact, usually exceed their initial rate. In view of the continued initial, or, in most cases, accelerated auricular rate, it is doubtful whether one may speak of a digitalis slowing of the heart as a primary phenomenon. It depends obviously on the disturbance of a function other than that of stimulus production. We have been led to conclude from our observations, therefore, that digitalis slows the sinus rhythm only in the group of hypodynamic hearts, and that to produce slowing is not a primary function of digitalis in therapeutic doses.

Mention has been made of the blocking of auricular impulses after a sufficiency of digitalis has been given. It is a phase of its action to which Mackenzie drew attention clinically and von Tabora in experiments. Mackenzie, and more especially Lewis, believed it to be produced only when the conducting fibers between auricles and ventricles were previously damaged, more especially by rheumatic inflammation, as evidenced by the fact that the auriculoventricular interval was unduly lengthened. We have been able to show that an action on conduction can invariably be observed in patients, varying from simple lengthening to block. An effect on conduction may therefore be set down as a usual effect of giving the drug, apart from specific preexisting injury. An evidence of delayed conduction can be observed very early after the administration of the drug has been started. We have noticed it within forty-eight hours. In many instances, the auriculoventricular interval gradually lengthened during the succeeding three to five days until partial heart block occurred. We have believed it possible to maintain conduction time at any length we have thought suitable, by controlling electrocardiographically the amounts of digitalis requisite to produce the effect desired. Not all cases, however, show the gradual lengthening in conduction which I have described; block then occurs with extreme abruptness within a few hours. After the administration of digitalis has been terminated, alterations in conduction usually continue about two days. In the exceptional case, it may persist for two weeks. If gastro-intestinal symptoms have occurred, they do not persist beyond two or three days.

The occurrence of delayed conduction has been dwelt on for the purpose of showing that in certain cases, probably in a large number, the fact that digitalis is

acting on the heart can be ascertained early in the administration. When the sign is obtained, it is definite. The problem which arises for decision is whether or not it is a sign which indicates a beneficial action on the heart. For a definite answer on the basis of this sign alone, more experience is required. A greater degree of digitalization can be obtained; but we may learn that on obtaining this effect, the maximum which is desirable has been reached.

When full doses of digitalis have been given, sufficient to cause delayed conduction, abnormal heart rhythms are commonly seen. They have been much described and occur as exaggerations of the normal sinus arrhythmia, extrasystoles, partial heart block, and rarely auricular fibrillation. We shall omit further mention of these. One arrhythmia which is still practically unknown as the result of giving digitalis may be described here. In this form none of the auricular beats is blocked; auricles and ventricles both continue to beat and do so almost at the same rate (Fig. 1). But there is incomplete coordination between them, so that a fixed relation ceases to exist. They

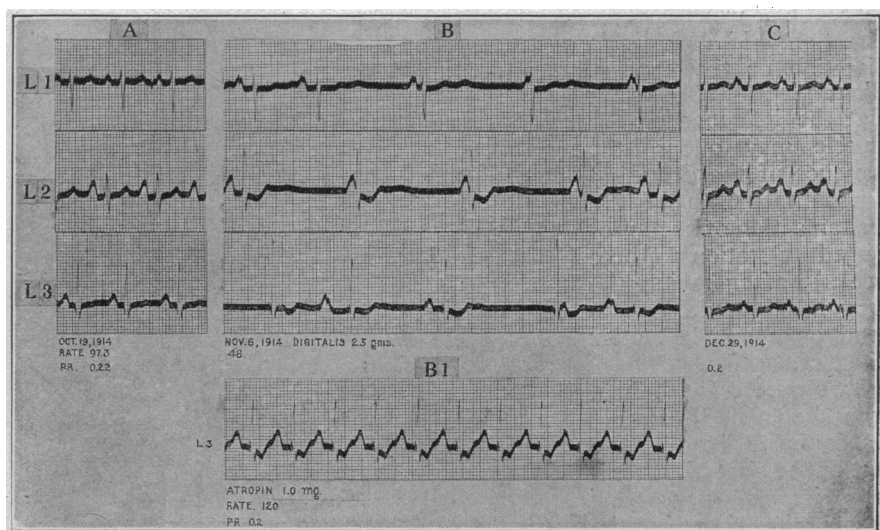


Fig. 1.—Divisions of the ordinates equal 0.1 millivolt; divisions of the abscissae equal 0.04 second. *A*, before digitalis was given; three leads (Einthoven) are shown. *B*, after 2.5 gm. of digitalis had been given; inversion of the *T* wave is shown in Leads 2 and 3; the curves in Leads 1 and 2 show a type of nodal rhythm described in the text. *B 1* was taken a few minutes after *B*; atropine, 1.0 mg. was injected; it shows that the rhythm of the heart returned to normal; the inverted *T* wave persisted; Lead 3 is shown. *C* shows the three leads; the curves were taken when digitalis had been completely eliminated and the curve had returned to the outline of the control, *A*.

must, however, be closely related. The conclusion cannot be escaped that they have an origin in common, or two related origins. If it is a common origin, the lack of exact coordination must depend on a shifting of the site of stimulus production, similar to one we have described in the ventricles, possibly complicated by changes in conduction; if it depends on two competing stimulus-producing foci, they must be actuated by a common factor. It is a matter of interest that we have found arrhythmias of this form associated only with various forms of intoxicants, notably digitalis. Robinson and Auer have seen it also in the presence of anaphylactic shock.

Aside from the lengthening in auriculoventricular conduction which, as has been said, begins in many cases soon after digitalis treatment is initiated and can be taken as an indication that an effect on the heart is being obtained, even though no change in rate has occurred, another new sign in the electrocardio-

gram appears to be one of great importance. This sign is an alteration in the size, shape, and direction in the *T* wave (Fig. 2, *A* and *B*). If digitalis is given to a patient whose electrocardiogram contains a *T* wave pointing in the usual upward direction, the first change noticed is usually a diminution of the height of this wave, usually in the third lead first, and later in the second. The first lead may also show changes, but relatively speaking, less frequently. The change may be noticed as early as twenty-four hours to consist in a diminution in the height of the wave, but at the end of forty-eight hours this change is more distinct and the wave may by this time have become iso-electric. At this time or, more often, later, it becomes inverted. Instead of becoming iso-electric or inverted, it may become diphasic, and in a number of cases of this sort it is easy to distinguish *T* waves consisting of two parts, a first portion which becomes inverted and then returns quickly to a second portion which represents the end of the original wave. The diagram (Fig. 2 *A*) explains this relation. The dotted line represents the altered portion of the curve. There are, of course, many electrocardiograms in which, for pathologic reasons, the *T* wave is originally pointed in a downward direction. If digitalis is given to such patients, the direction of the *T* wave is altered, and during the taken place. It is clear that the influence on the muscle may outlast the presence of the drug, but it is difficult to believe that an action of such prolonged duration (three weeks), after giving the drug has ceased, can depend on a simple matter of concentration.

Two criteria have, then, been shown in electrocardiograms to indicate surely the fact that digitalis is acting on the heart: the first in the slight but definite lengthening in conduction, the second the very curious certain of the change, we have repeated the observation a number of times in the same individual, and to be certain, also, that it is not dependent on a pathologic heart, we have shown it to exist in persons whose hearts are quite normal. It is a sign, then, that the heart is digitalized, and it is a sign which appears early. It appears at a time when no change in conduction need have occurred. It appears in the absence of any alteration in rate. The factors on which the change in the *T* wave depend, we cannot explain precisely at the present time. That it is an evidence of an alteration in the contractile substance of the heart is an inference which is naturally drawn from the circumstance that at the present time the electrocardiogram is generally regarded as the expression of changes in the electric state of the muscle. Whether, in a clinical sense, the change in the *T* wave is to be taken as an indication of beneficial or not beneficial action, it is impossible to say, though there seems little reason to question the fact that it is.

Many matters for consideration arise in relation to the sign. It is a matter of discussion just now, for

instance, whether the effect of digitalis on heart muscle depends on an intimate combination of the drug with the muscle (*Speicherung*) in which digitalis is destroyed or consumed, or whether it acts merely by virtue of its concentration in the circulating fluid. In the latter case, the signs of its effect disappear promptly with the withdrawal of the drug, with the diminution in its concentration. The drug is not consumed and, if the solution is recovered, may be used with equal efficiency in a succeeding heart. The essential point of difference is as to whether or not the drug is actually consumed when it is given. In both cases it must, of course, be excreted. If the drug acts merely by virtue of its concentration, a rapid excretion may be expected, and its composition may, of course, be altered; it need not necessarily reappear as the original substance. In the case of its being consumed, its composition on excretion would naturally be altered, but one would expect the rate of its excretion to be much delayed.

In view of what has been said of the change in the *T* wave, under the influence of digitalis, and more especially of the dependence of the change on alteration in the heart muscle, it is difficult to escape the conclusion that a degree of great intimacy in the combination between the drug and the muscle must have

action of the drug may be directed upward (Fig. 2 *B*). An especially beautiful example of this variety we have found in a case of complete heart block. Usually the negative *T* wave becomes deeper, especially in the third lead. That the change is due to digitalis is proved by the fact that when the drug is stopped, the *T* wave returns to its original size and shape. The length of time required for it to return to its initial condition varies between five and twenty-two days. To be

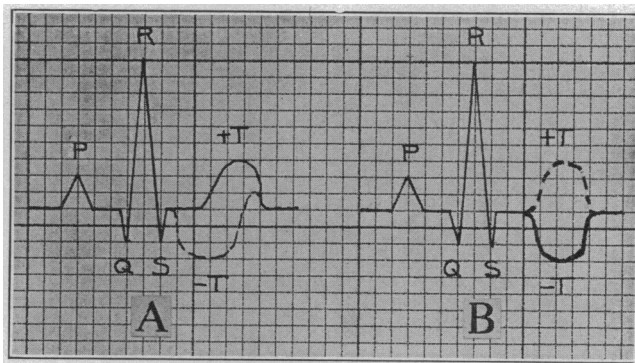


Fig. 2.—*A*. The solid line represents the normal outline of the electrocardiogram. The *T* wave is directed upward. The dotted line shows the change which occurs in the *T* wave under the influence of digitalis. *B*, in a similar way, shows the change in certain cases when the *T* wave is initially directed downward. Under the influence of digitalis it turns upward.

and very constant alteration in the *T* wave. Even if no slowing whatever of the heart occurs, we may be certain, by virtue of finding one or both these phenomena in electrocardiograms, that definite digitalis action on the heart has taken place. Rate, the criterion for which we looked and on which we relied, fails us, but in its place we have these other and surer ones. If these statements prove to be correct, they necessitate an alteration in the indications for the use of digitalis. It is not a drug, at least in the cases we are considering, which alters the rate of the heart—it is a drug which, by virtue of its combination with heart muscle, has a bearing on contraction, an effect which is evidenced by its effect on the *T* wave. It appears, then, that the groups of cases in which the drug was supposed to be of value have decreased in number, that is to say, those in which an effect on rate was expected, while groups in which new indications for the use of the drug may be found in the light of muscular and conduction effects we may hope will increase. In consequence, many patients with heart disease from whom digitalis has been withheld may,

with new criteria, be drawn into groups for whom it is indicated.

In contrast with the action of digitalis in nonfebrile patients, it is worth referring to the well-known and often mentioned failure of the action of digitalis in cases of fever. Its general failure has been dwelt on by Mackenzie, whose opinions have recently suggested an investigation of the problem to Gunn in Cushny's laboratory. Its failure in pneumonia, in particular, has been dwelt on by G. A. Gibson of Edinburgh. Similar views in regard to the reputed impotence of the drug are no doubt held in this country. Elsewhere, as in Krehl's clinic, it is usually given and thought to be beneficial. It is not exactly clear what is meant by a failure of digitalis to act in the presence of fever. As an antiphlogistic it need not be considered. What is usually wanted in fever is an agent either to slow the pulse or to increase its strength. It is no doubt a general experience that digitalis does not slow the pulse in fever, and its failure to do so is the complaint most often made. That failure in this respect is not unexpected is clear from our experience in nonfebrile cases. Whether it strengthens the pulse or, in other words, increases the force of ventricular contractions, is an effect which has also been much discussed. Satisfactory objective measures of this are not available, but there is much clinical, that is to say, subjective evidence on the part of observers favoring the idea that it exists. In the absence of evidence bearing on contraction, electrocardiographic evidence can be supplied to show that digitalis has an action during fever of a nature precisely similar to that already described in nonfebrile patients. This evidence consists, as in the nonfebrile, in its influence on the auriculoventricular interval and on the *T* wave. Here, as in the nonfebrile cases, the changes begin within from twenty-four to thirty-six hours and persist for days after defervescence and after the giving of the drug has been stopped. Whatever its nature, it is clear that the same sort of support can be given the heart by digitalis during fever as in its absence. That this is the sort of support that the heart demands may be open to question. It is an error, therefore, to regard its action as a failure until its efficiency from actual, rather than from incorrect points of view, shall have been examined. Possibly as an aid to contraction, much may be gained from its use; but the expectation of obtaining an action on heart rate must be abandoned.

There is, however, a group of febrile cases in which digitalis acts efficiently on rate. In our experience these have not been patients exhibiting the normal sinus rhythm, but patients showing auricular fibrillation or auricular flutter. These rhythms appear spontaneously during attacks of fever and disappear spontaneously afterward. Occasionally the ventricular rate in such cases is inordinately high, the high rate itself being a predisposing factor toward heart failure. The most desirable thing to accomplish in these instances is a reduction in rate. By the use of intravenous doses of strophanthin, one might expect to block the greater number of auricular impulses which cause the acceleration of the pulse and to reduce the ventricular rate to reasonable limits. In several patients in whom the abnormal rhythms were found, strophanthin was injected and has acted in the described way. Under these circumstances this method of treatment has seemed to us a life-saving remedy. It may be mentioned that, except for its greater speed in action, strophanthin is not necessary and that

exactly similar results in cases of flutter have been obtained by the use of digitalis by mouth. The effect on rate which digitalis has on auricular fibrillation and flutter, when these occur in fever, is precisely the same as in the nonfebrile state, and the results obtained are precisely the same. We are led to believe, therefore, although we have reached no definite conclusion, that there is no difference in principle between the way digitalis acts in fever and in nonfebrile conditions. One might venture the suggestion that, from the point of view of heart rate, and from the point of view of an emergency, the possession, in certain cases, of a heart beating after the manner of auricular fibrillation or flutter may, in fever, be a valuable asset, for it is in these rhythms that digitalis, by blocking auricular impulses, is able to slow the pulse rate. It may be mentioned, incidentally, that fever patients having auricular fibrillation initially are not necessarily prejudiced in the outcome of the disease by the abnormal rhythm.

Another topic long a subject of conflict is the relation of digitalis action to blood pressure. Clinicians have often withheld the drug from patients having high pressure in the fear of producing unpleasant consequences, as, for instance, cerebral apoplexy. One of the most recent contributions to this phase of the action of digitalis has been Marvin's. His investigations with a single dose of the tincture in normal medical students led him to conclude that, after five hours, an elevation of from 10 to 15 mm. Hg occurred in systolic pressure, and that the effect of this persisted for fifty hours, when the curve resumed its initial height. Many exact studies have been made in recent years, notably by Mackenzie, Price, and Lawrence. These and other investigators have failed, on the whole, to find pressure changes resulting from the administration of the drug. The form of this statement demands a certain modification. The clinical reports bear the defects mentioned earlier—that they are based on cases indiscriminately selected, or not grouped at all. They include cases with high pressure and cases with low. The heart mechanism, in itself an important factor, is, especially in the German reports, not considered. The estimation and interpretation of pressures in auricular fibrillation, as will be shown in another place, present problems much more intricate than those in the sinus rhythm, and the results of investigations indicate a different response to digitalis.

In the group of patients under consideration, those with sinus rhythm, without edema, and with a moderate or low systolic pressure, we have seen no substantial alteration in the level of either the systolic or the diastolic curve. Our conclusions are like those of other more recent observers. The few opportunities we have taken to verify the observations made by Marvin have failed in establishing results similar to his. In the cases we have studied, then, no alteration in pressure was found. In so far as the older fears are concerned, it is apparent that digitalis must be considered a safe drug to use.

Vascular effects, however, aside from changes in pressure, may be produced, and the untoward or beneficial nature of these requires consideration. A specific vascular action, not dependent on heart action or on pressure effects, has been advanced and held by the school of Gottlieb. Gottlieb, while admitting a cardiac action of digitalis, nevertheless maintains that the peripheral action of the drug is the one by virtue of



which its prime effects are produced. More recently clinicians, employing optical methods of registration devised by Frank, have again taken up these aspects of digitalis action, and reports are now being published of alterations in reaction of the blood vessels, notably in the tension of the vessel walls, when they are under the action of the drug. It is the results of these investigations, far from satisfying as yet, which demand further study in order to establish the assurance that the vessels of the body, and more especially of the brain and meninges, do not become subject to injury as the result of giving digitalis.

The last phase of the action of digitalis which I wish to discuss is the relation of the drug to the excretion of urine. The foxglove obtained its initial reputation because diuresis was so enormously increased when it was administered. For almost a hundred years it was supposed that this was the one and most striking of its effects; but now the situation in regard to this phase of the problem is less simple. The questions now being discussed relate first to when digitalis does, and when it does not, increase the amount of urine, and, second, when it does, by virtue of what mechanism this result is brought about. The first problem, whether or not the amount of urine is increased, is a clinical problem and can be definitely solved. In the patients in the group under consideration, it may be stated definitely that no increase in diuresis takes place. It is, of course, remembered that these patients have no edema. The problem as it relates to patients having edema is naturally different, and involves other factors; but in the simplest form of case, no increase in the amount of urine takes place. So far, digitalis cannot be considered a specific diuretic. In experiments the situation is different, because there, although obviously edema is likewise absent, it is almost universally maintained that increased urinary flow takes place. But the clinical and the experimental conditions are not quite parallel, because in the latter, doses which have usually been employed are much larger than normal, that is to say, from three to fifty and more times the lethal dose for man; and because the method is an acute method, for the drug is given intravenously, or under the skin, and the effect is observed under the conditions of surgical operation. But, although the clinical and experimental conditions present results so divergent, it may be interesting to enumerate the theories which are given in explanation of the occurrences observed in experiments, the more in that they discuss factors which must be considered in the diuresis which occurs when digitalis is given in edema. As may have been supposed, three possible explanations have been urged, first that the experimental diuresis depends on a local vascular action in the renal vessels; second, that it depends on the general elevation in vascular blood pressure, and third, that it depends on the increased force of the heart's action. It will be noticed that none of these explanations refers to an action on renal epithelium. But this phase of the discussion of digitalis action scarcely bears on the problem now being considered, and may consequently be dismissed.

We return to considering the effect of digitalis in patients of our group. Diuresis, as has been said, does not occur in any stage of the treatment. When the cardiac effects are clearly discerned, as in the auriculo-ventricular interval and in the state of the *T* wave, no alteration in output is found. Intake is, of course, maintained level. But later, when dissociation occurs,

and gastro-intestinal symptoms have taken place, the output actually diminishes. On account of loss of appetite, and, in some cases, of nausea and vomiting, the fluid intake naturally falls and accounts satisfactorily for urinary decrease. In view of these considerations, the conclusion is justified that a specific effect on urinary output does not occur as the result of giving digitalis to the class of patients under discussion. This, in itself, is not a significant contribution to an understanding of the pharmacology of the drug, but in another place it will be shown that it has an important bearing on the drug's action in edema.

No consideration of the action of digitalis on the various functions of the heart, on rate, on conduction, on contraction, and on circulation, is complete without a reference to the nature of this action. For many years a war of words, the two most prominent of which were "myogenic" and "neurogenic," was fought. This fight was waged on the question of the conduction of impulses in the heart. The battle became a drawn battle; no decision could be reached. Anatomic studies showed that both nerve and muscle elements were inextricably associated in the heart in general, and in the special muscular systems as well. The effort to distinguish the functions of one tissue from those of another became impossible, and the struggle was abandoned.

The same words, "neurogenic" and "myogenic," have in a similar way formed centers around which another battle has been fought, the battle to elucidate the mechanism of the action of digitalis. Fortunately, these battles have been less violent, and the lesser violence was probably due to the fact that it was always more than half suspected that neither one side nor the other was altogether wrong, and, in fact, that both sides were partially right. Our studies, it seems to us, indicate that this is so. So far as atropin may be taken to be a drug acting especially on the ends of the vagi, a release of the heart from a phase of digitalis action by its use indicates a nerve action of digitalis (Fig. 1 *B*). So far as digitalis has other effects, which atropin does not release, it may be inferred that it has an action directed more especially to muscle. Both effects can be observed at the same time, as we have seen, and by virtue of them another struggle, one may hope, has been terminated.

Our studies have, then, led us to draw a number of definite conclusions in regard to the way digitalis acts, and to find new criteria in the *T* wave and in the effect on conduction for detecting when the drug is acting. It seems important to emphasize the fact that it is essential to distinguish differences which patients suffering from heart disease present, and to study them in groups, with these differences in mind. Rhythm certainly offers a prime basis. The effect of digitalis on rate and on a number of other capacities varies with the nature of the disturbed function. In the use of the drug in pneumonia we have found it to have an action essentially similar to that found in the nonfebrile. In the absence of edema, we have not observed a diuretic effect. Evidence has been found which indicates persistence of action, longer than can be accounted for if the drug acts only by virtue of its concentration. We have shown that digitalis has a twofold action on the heart, nervous and muscular. We believe that clearness of indications will result only if the exact mechanism of the action of the drug is ascertained; for only when these are clearly met, can rational treatment be instituted.