

THE INFLUENCE OF DIGITALIS ON THE T WAVE OF THE HUMAN ELECTROCARDIOGRAM.*

By ALFRED E. COHN, M.D., FRANCIS R. FRASER, M.D., AND
ROSS A. JAMIESON, M.D.

(From the Hospital of The Rockefeller Institute for Medical Research.)

PLATES 59 TO 64.

The modifications in the form of the T wave of the electrocardiogram which we report in this communication were observed in the course of detailed studies on the action of digitalis in patients (1). It has been noticed frequently that the time when digitalis takes effect is a matter of uncertainty, so that in a given instance doubt is often entertained as to whether the drug itself is active, and if active, whether it is effective in producing a result. To be certain that the drug is effective, it has been considered necessary to administer it until an alteration in the rhythm of the heart occurs. In our treatment of patients we have, therefore, looked for evidences of altered heart rhythm to indicate that the heart is really digitalized. During the period of treatment, electrocardiograms were made almost daily, and often more than once a day. In examining these records we found the changes in the T wave which we describe in this report.

Other observers have published studies dealing with the effect of a number of agents, including digitalis, on the electrocardiogram. The only investigation dealing with this subject in human beings has been made by Nicolai and Simons (2). Seven ambulatory patients were given powdered digitalis, 0.3 gm. daily, for five days. In two women the treatment was not completed; in one normal man the T wave did not increase in height, but decreased instead (*"verschlechterte sich"*); and in the other four the T wave increased. They limited the taking of records to the first lead (right arm to left arm). Even if the

* A preliminary report was made to the Section on Medicine at the Seventeenth International Congress of Medicine, London, 1913, Section VI, 255-258. Received for publication, April 7, 1915.

dosage had been sufficient, and had been satisfactorily controlled, a comparison of their methods with ours would account for the difference in our results.

A number of experiments on animals have been published in which digitalis bodies, more especially strophanthin, were injected for the purpose of observing possible changes in the electrocardiogram under the influence of the drug. Straub, Selenin, Bickel and Tsvividis, Bickel and Pawlow, and Rothberger and Winterberg have published such reports. In general all observers have detected an increase in size of the T wave under the influence of digitalis, like that described by Nicolai and Simons. Straub (3) described experiments in cats and rabbits, into the veins of which he injected strophanthin (Böhringer). So called therapeutic doses, the exact quantity of which is not given, caused no alterations in their electrocardiograms. When he gave toxic doses, that is to say, 0.3 mg., he obtained an increase in the elevation of the T waves in one experiment, the curve of which he reproduces. He obtained a multiplicity of abnormal ventricular complexes in the late stages of intoxication, but obviously the T waves in these forms cannot be compared with those in the control curves. In a later paper (4) he described experiments on the isolated frog heart, and showed that in the therapeutic stage the T wave increased in size, as in his mammalian experiments, while in the late toxic stages the T wave became negative. The changes in the late toxic stage in frogs are not like those in mammals, because the former do not develop abnormal ventricular complexes.

Selenin (5) found that the T wave increased in size when a digitalis body was given in therapeutic doses to dogs.

Bickel and Tsvividis (6) injected digitalisatum Bürger into the ear veins of rabbits. Small and medium doses (1 c.c. per kg.) increased the size of the waves. Larger doses decreased the size of the waves, including the T wave, but they remained upward in direction.

In a later paper Bickel and Pawlow (7) injected crystalline strophanthin (Thoms) intravenously into dogs, and digistrophin, a combination of digitalis and strophanthin, into dogs and rabbits. They concluded that small doses increased the size of the T wave, whereas large doses decreased the size of all waves. They mention no instance of inversion. They found that the T wave tended to change less than the other waves. Other substances supposedly effectual on the heart, like cardiotoxin, a mixture of convallaria and caffeine sodium benzoate, were quite ineffectual.

Rothberger and Winterberg (8) found that small doses of strophanthin given to dogs had no effect on the shape of the electrocardiogram. When P and T waves were small as the result of the heart's having been isolated from the central nervous system, they report that digitalis restored them to their initial size. When they gave digitalis in progressively larger quantities, aside from alterations in the P, R, and S waves, the T wave became either positive or negative. In the experiments of all these investigators the results depend on the injection of single doses of the drug, the quantities being larger than those which are employed in therapeutics. The change in the electrocardiogram usually obtained is considered to be an increase in the elevation of the T wave. Straub alone seems to have regarded the change in sign in the T wave in his experiments on frogs as unusual and important.

The shape of the T wave has also been changed by the use of other means.

Muscarin, according to Samojloff (9, 10, 11) and Boruttau (12), alters not only its form, but in frogs changes the sign of the wave from positive to negative. After the alteration has taken place, both noticed that the application of atropin restores the initial direction of the wave. Mines (13) believed that spread from the site of application to the ventricular base was responsible for Samojloff's result and that muscarin does not alter the sign of the T wave except on direct application. After alteration has taken place, atropin relieves it. But in his figures 2 and 3 the sign of T changed from negative to positive. Here the heart was perfused with muscarin so that the possibility of local action is excluded. Samojloff and Mines (14, 15) both observed that electrical stimulation alone of the vagus nerve in frogs without the use of drugs produced an inversion of the T wave.

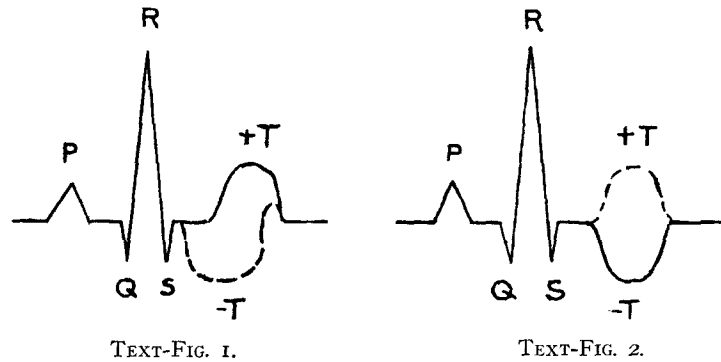
OBSERVATIONS.

In the curves of the patients under treatment with digitalis, attention was arrested by the fact that alterations in the T waves of the electrocardiograms occurred in a large number (30 times in 34 patients), and also by the fact that the change was detected before alterations in rhythm or conduction time had occurred and before symptoms referable to the gastro-intestinal tract disturbed the patients, except in five instances. The changes in the T wave consisted in a diminution in the height of the wave, and, finally, in an inversion (figure 1). This diminution in height to an isoelectric line and subsequent inversion of the wave are not the only changes which occurred. If the space from the end of R or S to the end of T is considered, additional alterations become evident. The first part of this interval, from R or S to T, is usually isoelectric or shows a slight upward slope. In place of these conditions may be substituted either an isoelectric period, if it is not isoelectric already, or a downward deflection, directly continuous with the end of R or S. The downward deflection is often carried to a point just short of where in the uninfluenced curve the T wave ends. At this time, then, the inverted wave passes above the base line to form an upward deflection, representing the terminal portion of the original wave. It is indicated in figure 1 D. Text-figure 1 shows this relation. The solid line indicates the outline of the initial curve; the dotted line, the alteration described. Samojloff (11) has drawn a similar diagram.¹ Another alteration which is sometimes seen is shown in text-figure 2. Here the downward deflection occurs, not in the

¹ Samojloff, *loc. cit.* (11), p. 481, figure 2 C.

early portion of the period, but in the later portion. Instead of a diphasic wave in which the upward deflection occupies the last portion, as in text-figure 1, it is in such instances in the first portion.

Other alterations beside those described have been seen when digitalis was administered. One was in a case of complete auriculo-ventricular dissociation. The observation in this patient was especially valuable because he showed, at different times, two quite differ-



TEXT-FIGS. 1 and 2. The unbroken line represents the electrocardiogram, and shows the P, Q, R, S, and T waves. The broken line shows the outline the T wave assumes under the influence of digitalis.

ent electrocardiograms. One indicated an origin for the ventricular beats in the left side of the heart (figure 2); the other, in the right side (figure 3). In figure 2, taken when the ventricular beats were initiated on the left side, inverted T_1^2 became deeper under the influence of digitalis, inverted T_2 moved upward, and so did diphasic T_3 . When the ventricular beats were initiated on the right side (figure 3) diphasic T_1 became isoelectric, inverted T_2 turned upward, and inverted T_3 became shallow, almost isoelectric, and diphasic, while the completely restored curve resembled its control except that T_1 was a monophasic wave, replacing a diphasic wave in the initial curve. That the change was less far reaching in figure 3 than in figure 2 may have been due to the lesser amount of digitalis which had been given, 1.9 instead of 2.6 grams. These curves supply an instance of a change in the sign of T_2 and T_3 from negative to posi-

² T_1 represents the T wave in lead 1; T_2 in lead 2, etc.

tive under the influence of the drug, a change of sign in the reverse direction from that first described.

Still other types of change have been found. In a case, for instance, in which T_1 and T_2 were positive, and T_3 negative (figure 4), T_2 became negative, and T_3 more negative. In pathological hearts, such as these, the redistribution of muscle, resulting from hypertrophy and dilatation, doubtless determines a variety of alterations in the electrocardiogram under the influence of digitalis. We do not at the present time possess a sufficient number of instances of a given class to permit us to reduce the alterations in them to definite order. Originally it appeared to us that T_3 altered earlier than T_2 . Our later observations make us hesitate to state definitely whether the T wave in one lead is influenced earlier than in the others, or whether changes occur simultaneously in all. Recent interpretations of the electrocardiogram by Einthoven, Fahr, and de Waart show that simultaneous alterations may be anticipated, and our later observations indicate that this is so.

The instances so far described relate to cases in which the mechanism of the heart beat was normal. Similar alterations have, however, also been seen when the auricles were fibrillating (figure 5) and also when they fluttered. In curves of this type, recognition of altered T waves may occasionally be difficult, especially if the waves are not large, on account of the greater number of oscillations in the curve, due to the abnormal auricular activity.

We have pointed out that with five exceptions the modifications described were seen at a time when neither a change in rhythm or conduction time nor the onset of gastro-intestinal symptoms had taken place. An alteration in the curve may, therefore, be taken as a sign of the fact that an influence by digitalis is being exerted on the heart. The sign attains the greater importance on account of its appearance early after the beginning of the administration of the drug. We have detected changes in the T waves after an equivalent of 1.2 grams or even less of the dried leaves³ of digitalis has been given, that is to say, on the third day of administration, although

³ We have used digipuratum, a tablet of which represents 0.1 gm. of dried leaves. We usually give 0.4 gm. a day. The dose varies naturally with the patient's requirements. We have not estimated the size of the smallest dose capable of producing a change.

on several occasions we have seen the altered forms after thirty-six to forty-eight hours. On account of certain matters of technique, we have hesitated, in our earlier records, to recognize the onset of the alteration as early as it is quite apparent to us now that it occurs. The sign may, therefore, be looked on as one capable of detection earlier than the others, and as one indicating the fact that the drug is acting. Small changes measured in hundredths of seconds in the auriculoventricular conduction time occasionally occur as early as that noticed in the T wave, and when present may, of course, be employed as corroborating evidence of the fact that the drug is acting. The length of time required before the T wave is restored to its initial state varies. In the patient whose curves are reproduced in figure 6 twenty-two days elapsed before complete restoration occurred. In other cases it required only five days.

The influence of atropin on the T wave, after an alteration in it has become established, was tested more than forty times. Atropin sulphate was given either subcutaneously or intravenously in doses ranging from 0.9 to 1.8 milligrams, the size of the dose depending on the age of the patient and the method of administration. In every instance, the alteration which had taken place persisted after the drug was given. In several instances, when no change had been observed before atropin was injected, the characteristic modification appeared under the influence of the drug. Those alterations which atropin brought on or intensified almost always disappeared promptly; that is to say, before the next curve was taken, twenty-four hours later. Atropin alone, when no digitalis had been given, did not produce changes in the T wave. We have, however, an instance in which atropin lowered the isoelectric line between R and T slightly. Another modification in the outline of the digitalis curve occurs during the activity of atropin. The acceleration in rate which atropin causes is accompanied by a reduction in the time which elapses from the beginning of R (Q) to the end of T (figures 1 and 6 and text-figures 1 and 2). As a result of acceleration, the various elements which make up the ventricular electrocardiogram contract, but the essentials of the change which digitalis has brought about in the curve remain quite unaffected.

DISCUSSION.

In view of the fact that for human beings the form of the electrocardiogram is constant, and varies only because of distinct cause, the changes in it which have just been described must be looked upon as changes of significance. That they result from the action of digitalis must be concluded from the fact that they occur almost invariably when the drug is administered, and disappear more or less promptly when administration of the drug is discontinued. If the drug is given again to the same patient, after an interval during which the initial form of the electrocardiogram is restored, the same changes take place.

The interpretation of the changes in the T wave which have been described as occurring under the influence of digitalis presents difficulties, based on the interpretation of the formation of the electrocardiogram itself. If we adopt the current view, held by the earlier writers, Burdon-Sanderson and Page, Bayliss and Starling, and most of the later investigators, Einthoven, Samojloff, Garten, Boruttau, and Mines, that the cardiac action currents depend on electrical changes as an expression of muscular activity, then the changes in the T wave must be attributed to an alteration in muscular state under the influence of the drug. The fact that the T wave becomes negative indicates that the preponderance of electrical activity persists in the region near the apex of the heart longer than it does at the base; or, conversely, shorter at the base than at the apex. This is substantially the explanation that Samojloff and Boruttau adopt in explaining the action of vagus excitation and of muscarin. It opposes the view that persistence of electrical activity depends on a specific action directed toward a given part of the heart muscle, as Selenin supposed.⁴ Greater electrical activity near the apex, therefore, accounts for apex negativity, and the consequent inversion of the T wave. The variations in the alteration of the terminal part of the wave already described depend on the exact site of longer electrical activity. If electrical activity at the base outlasts that at the apex, a diphasic wave results, the first portion of which is directed downward, corresponding to greater activity at the apex, and the second phase ends in a short upward deflection, corresponding to

⁴ Selenin, *loc. cit.*, p. 154.

greater persistence of activity at the base (text-figure 1). Occasionally activity lasts longer, in the terminal phase of ventricular systole, at the apex, and this is shown by a diphasic wave, the direction of which in its first portion is upward, if the activity at the base is the greater, and in the latter portion downward (text-figure 2).

The observations of numerous pharmacologists on the action of digitalis bodies on the frog's and on mammalian hearts have demonstrated a diminished diastolic relaxation of the apical regions of the ventricles. In the later toxic stages of the action of the drug a systolic standstill of the apical regions is seen, while the base is still relaxing in diastole.⁵ The changes we have observed in the T wave during the action of digitalis on the human heart may be evidence of a similar condition of the apical portion of the ventricles.

A fact to which we have called attention in these observations necessitates a possible modification in the view that the effect of digitalis is, so far as its influence on the T wave is concerned, wholly muscular. We refer to the fact that, on occasion, when a heart is subjected to the influence of digitalis, no change or only a slight one, takes place in the outline of the T wave. If atropin is injected under these circumstances, the alteration in the T wave, which was expected but failed to appear, becomes manifest immediately; the T wave either becomes inverted or becomes more negative than it was. When the influence of atropin terminates, the T wave returns to the state before injection. The view taken that atropin acts on the terminals of the inhibitory nerves implies, in this connection, that these exert an influence on the alteration in the wave, besides that attributable to the action of digitalis on heart muscle. Their influence, stimulated perhaps by the action of digitalis, is exerted against the full expression of increased electrical activity on the part of a given muscle area. When atropin is given, the inhibitor power is removed, and the full influence of digitalis on the muscle is manifest.

⁵ This phenomenon is recorded by Cushny, A. R., *A Textbook of Pharmacology and Therapeutics, or the Action of Drugs in Health and Disease*, 4th edition, Philadelphia, 1906, 439. Asynchronous contractions of the frog's ventricle, due to strophanthus, are also described by Fraser, T. R., *On the Kombé Arrow-Poison (Strophanthus cuspidus, D.C.) of Africa*, *Jour. Anat. and Physiol.*, 1873, vii, 139.

These observations have yielded two-fold evidence bearing on the nature of the mechanism of digitalis action, considered from the point of view of whether this is muscular or nervous. We recall, in the first place, the difference between the effect of atropin on the T wave during digitalis, and during muscarin action. It has been shown that both drugs are capable of producing modifications in the T wave. The injection of atropin in the case of muscarin abolishes these, according to Samojloff and Boruttau, while in the case of digitalis the change persists or is intensified. The difference brought out between the two by the injection of atropin appears to depend on a difference in the site of their respective actions. The site of the action of muscarin on the cardiac inhibitors is well established;⁶ its effect is consequently abolished when atropin, which acts on the nerve terminals, is given. It follows from this that if the inversion of the T wave under the influence of digitalis is not relieved by the injection of atropin, that influence is exerted at a site distal to the nerve endings; that is to say, on the heart muscle. We have shown that the inhibitors can prevent the formation or the full development of inversion in the T wave because it sometimes does not appear until after atropin is given. This curious phenomenon is exerted in opposition to the obvious muscular digitalis effect, and represents what appears to be a new phase of the function of the nerves. The second observation relating to the mechanism of the action of digitalis to which we have referred shows that it has two separate and distinct effects on the heart. The first consists in an alteration in the mechanism of the heart beat, a function which has been abundantly proved, and the second in the alteration of the T wave we are describing. The effect of the injection of atropin indicates that these two alterations depend on two activities of digitalis, quite distinct from each other, for the altered mechanism is abolished, while the altered T wave either persists or is intensified (figure 6). We attribute the altered heart rhythm which atropin is able to relieve to the action of digitalis on the inhibitory mechanism. The altered T wave which atropin fails to restore to its initial

⁶ Recently the site of the action of muscarin has been reconsidered in papers by Straub, Samojloff, and Mines. Inasmuch as all agree that atropin has the effect mentioned, the argument advanced is considered valid.

state we attribute, as we have just shown, to the muscular action of digitalis. We assume for the purpose of this discussion that the effect of atropin is uniform; but we shall show in another place that this is true only within certain limits.

We wish finally to indicate the bearing that these observations have on the phenomenon of persistence of digitalis action. If alteration of the T wave depends on the action of digitalis, the time which elapses between the end of its administration and the return of the T wave to its initial state must be considered the measure of time during which digitalis is an active agent. The length of time required for restoration to the initial state has been seen to vary. In one observation it has been seen to take as little as five days; it has been observed to require as long as twenty-two days. The latter, if it is a common example of the duration of action, is a longer period for the drug to be active than is commonly supposed. Persistence of action may be compared with the duration of digitalis effect on rate in auricular fibrillation. In at least one such patient we have several times seen fourteen days elapse, after the administration of digitalis was stopped, before the ventricular rate began to rise. The statement (16) sometimes made that a second course of treatment with digitalis requires less of the drug to produce a given effect than the first is probably explained by our observation. For it is clear that if a second course is begun, before the first is completely terminated, a greater amount, equal to the residual quantity of the drug, must be present in the heart than had been expected.

SUMMARY.

It has been shown in this investigation that digitalis, administered orally to patients, can modify the T wave in the electrocardiogram. When the T wave in the initial curve is directed upward, the first change noticed is a lowering, and the final change is an inversion of the wave. It is not only the wave itself, but that portion of the curve between the end of R and the end of T which is involved. Instances in which the initial T waves have other than upright forms are described and their behavior under the influence of digitalis has been indicated. This influence of digitalis on the T wave may be

detected in thirty-six to forty-eight hours after the administration of digitalis has commenced; it may persist as long as twenty-two days after the administration has been stopped. Instances where it persisted only five days have been encountered. The unexpected length of duration of the sign probably explains why a second treatment with digitalis requires a smaller amount of the drug to produce the same effect, than the first.

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EXPLANATION OF PLATES.

In all figures divisions of the abscissæ equal 0.04 of a second; divisions of the ordinates equal 10^{-4} millivolts.

PLATE 59.

FIG. 1. A to H. The curves were taken from a patient who had a moderate grade of arteriosclerosis. A is the control. B, C, D, and E were made under the influence of digitalis; a few minutes before E atropin was injected. F and G show the gradual return to the form of the control. H substantially reproduces the control, A. The date to the left of each curve indicates when the curve was taken. The three usual leads (Einthoven) arranged in columns were obtained on each occasion. During the atropin test only lead 2 was made. The total amount of digitalis taken at the time each curve was made is given at the right.

PLATE 60.

FIG. 2. A to C. The curves were taken from a patient who had complete auriculoventricular dissociation. The three leads are arranged from above down. A is the control. B was taken after digitalis, 2.6 gm., was given. C substantially reproduces the control. The date on which each set of three curves was made is placed below, likewise the rate of the ventricles.

PLATE 61.

FIG. 3. A to D. These curves were taken from the same patient as those in figure 2. A is the control; B was taken under the influence of digitalis; C shows partial recovery; D substantially reproduces the form of the control curve.

PLATE 62.

FIG. 4. A to L. These curves were taken from a patient who had mitral stenosis. The leads are arranged in columns. The date when each curve was taken is given at the left. A is the control. B, C, and D were taken under the influence of digitalis; the amount taken when the curve was made is given at the right. E to K shows the gradual return to the control. J, a single instance, breaks the gradation. L substantially reproduces the control curve.

PLATE 63.

FIG. 5. A to C. These curves were taken from a patient whose auricles were fibrillating. The leads are arranged as in figure 2. A was taken after digitalis, 3.2 gm., had been given. B is the control. C was taken after digitalis, 3.6 gm., had been given.

PLATE 64.

FIG. 6. A to C. These curves were taken from a patient who has mitral stenosis. The leads are arranged as in figure 2. A is the control. B was taken after digitalis, 2.5 gm., was given. The altered cardiac mechanism is described in the text. B₁ was made shortly after B, when atropin, 1.0 mg., had been injected. C substantially reproduces the control curve.

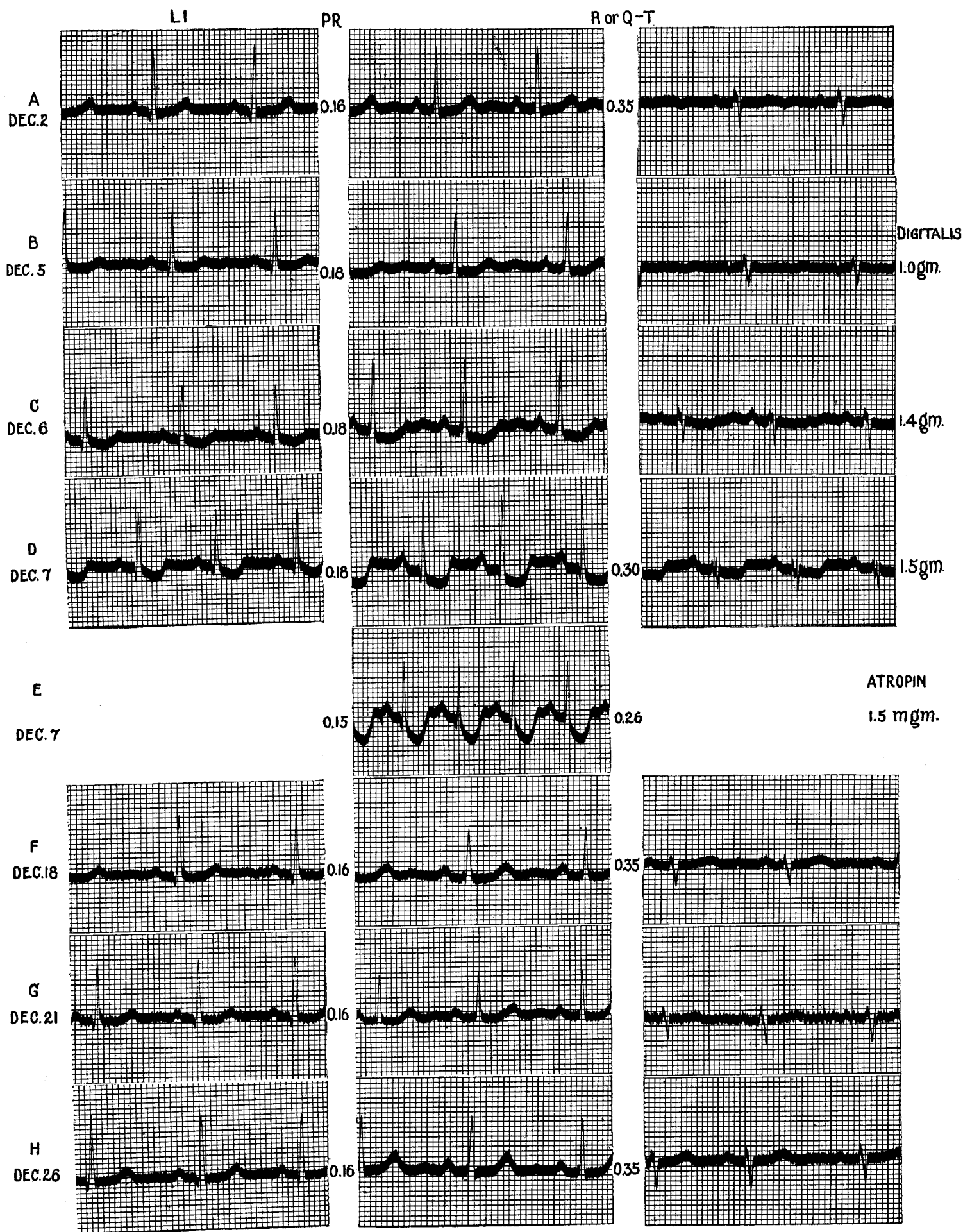


FIG. 1.
(Cohn, Fraser, and Jamieson: Influence of Digitalis on Human Electrocardiogram.)

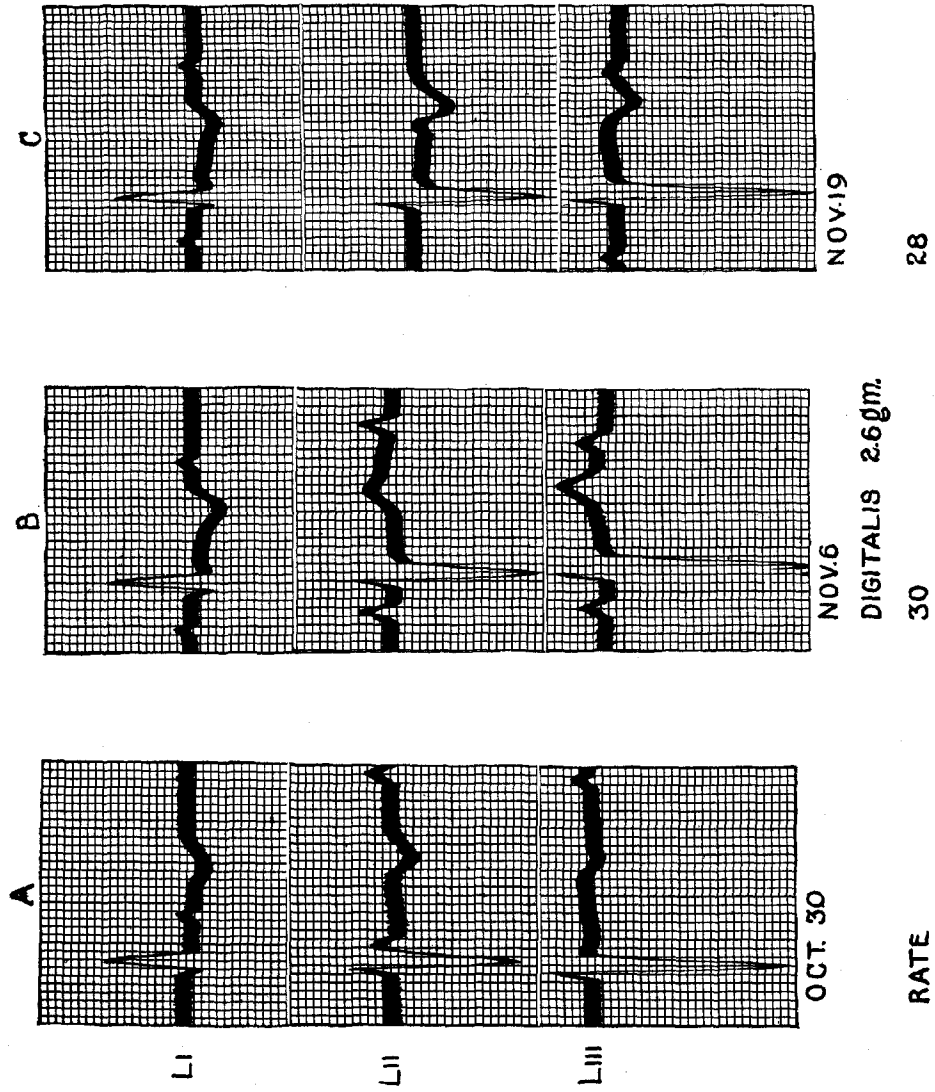


FIG. 2.
(Cohn, Fraser, and Jamieson: Influence of Digitalis on Human Electrocardiogram.)

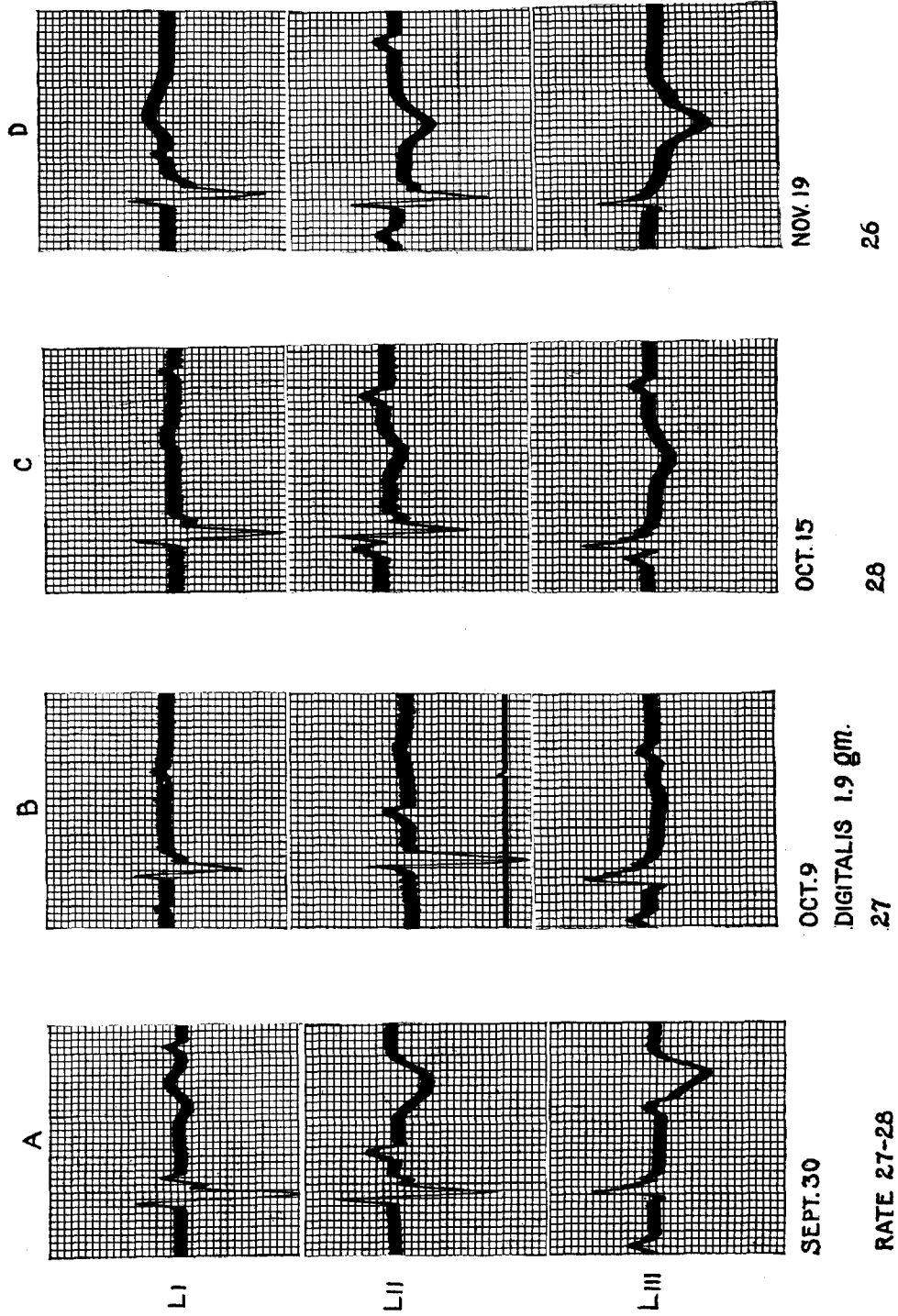


FIG. 3.
(Cohn, Fraser, and Jamieson: Influence of Digitalis on Human Electrocardiogram.)

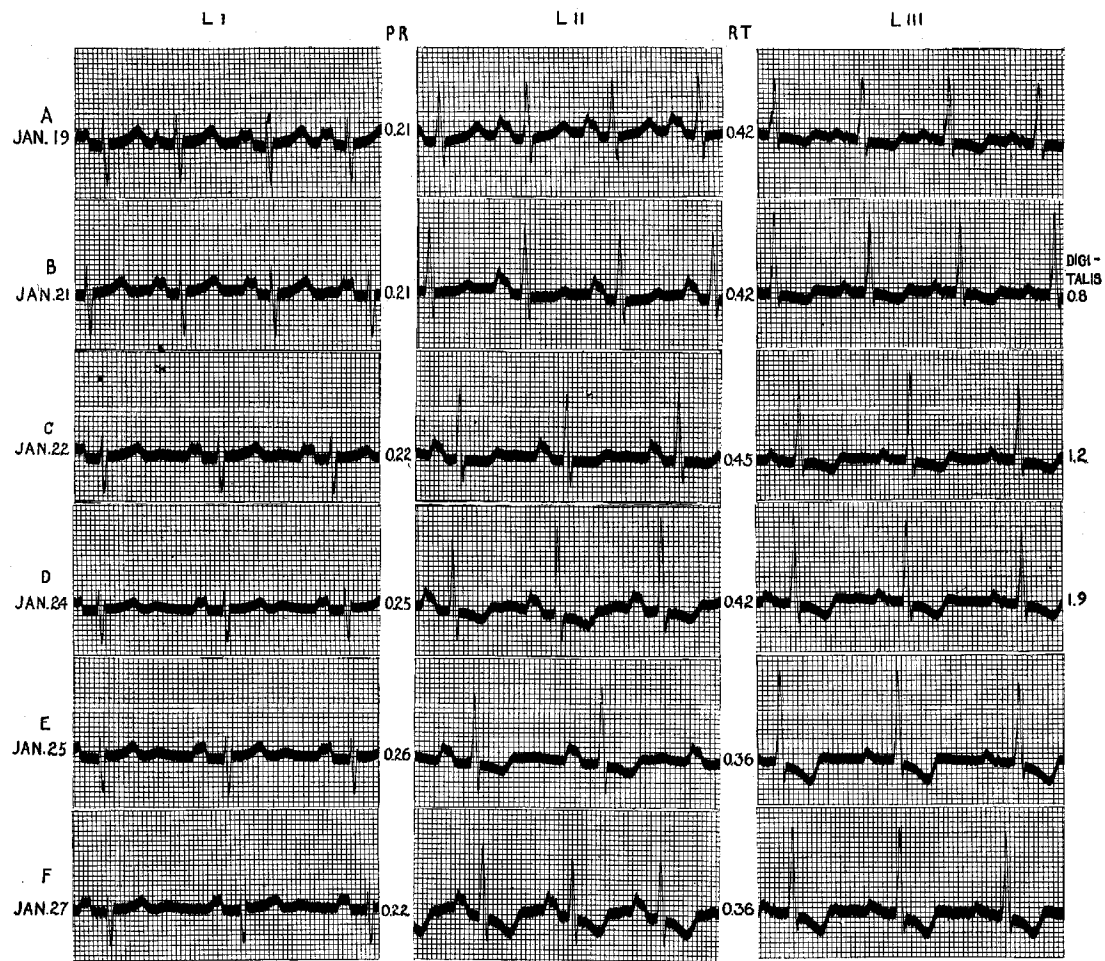


FIG. 4.

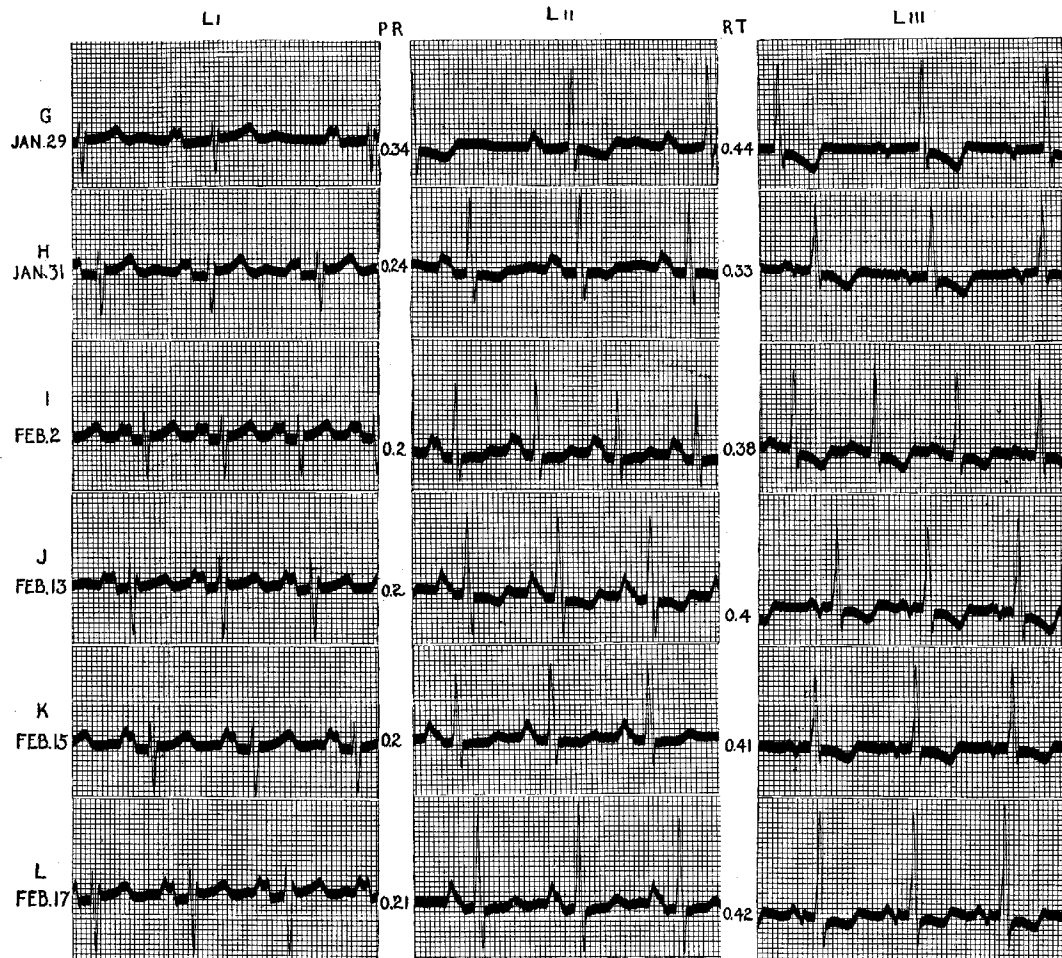


FIG. 4A.

(Cohn, Fraser, and Jamieson: Influence of Digitalis on Human Electrocardiogram.)

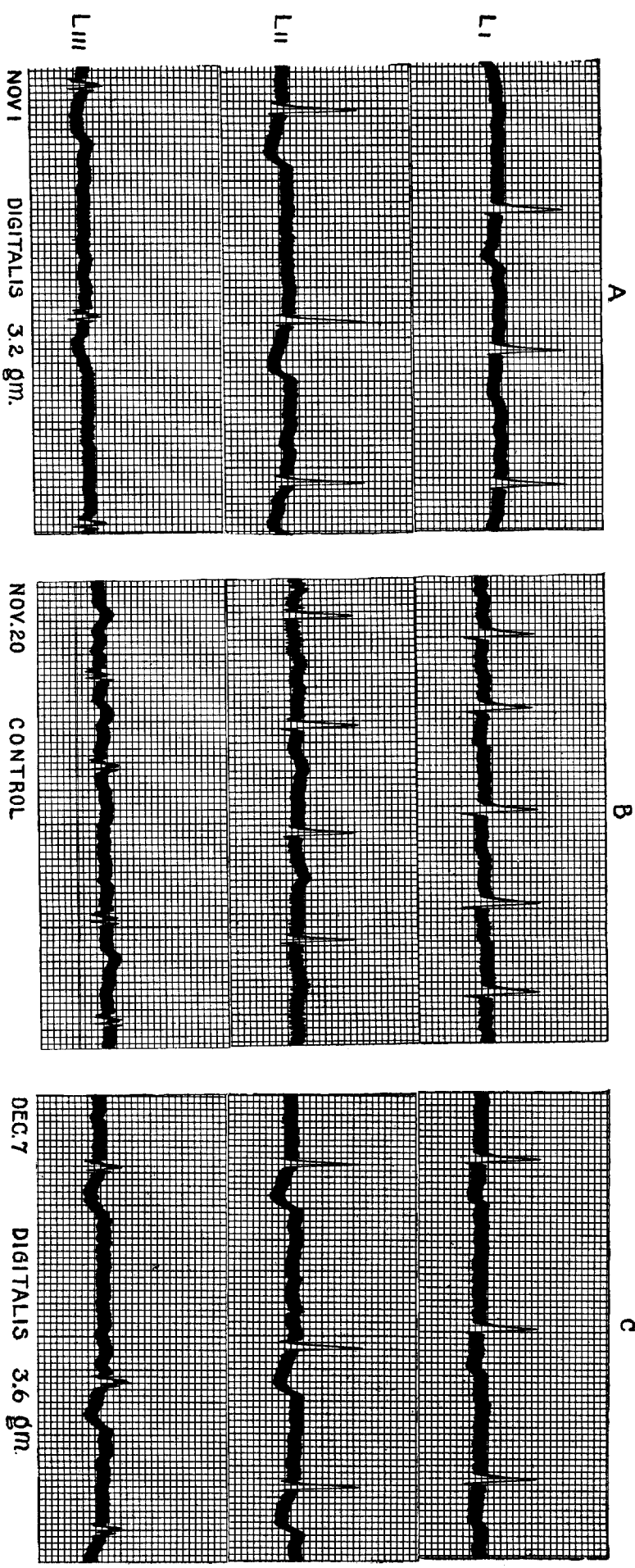
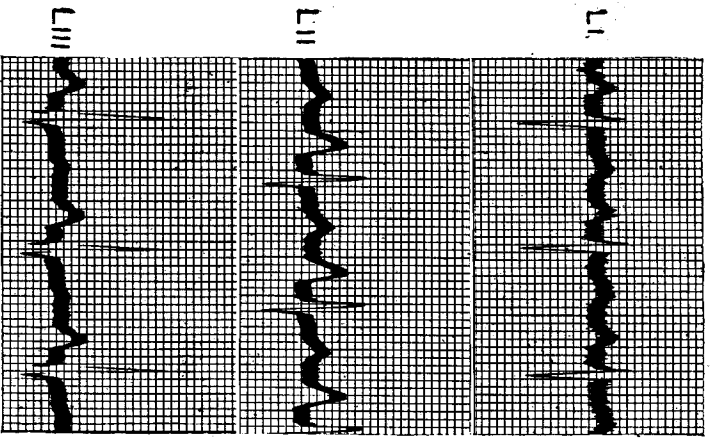


FIG. 5.

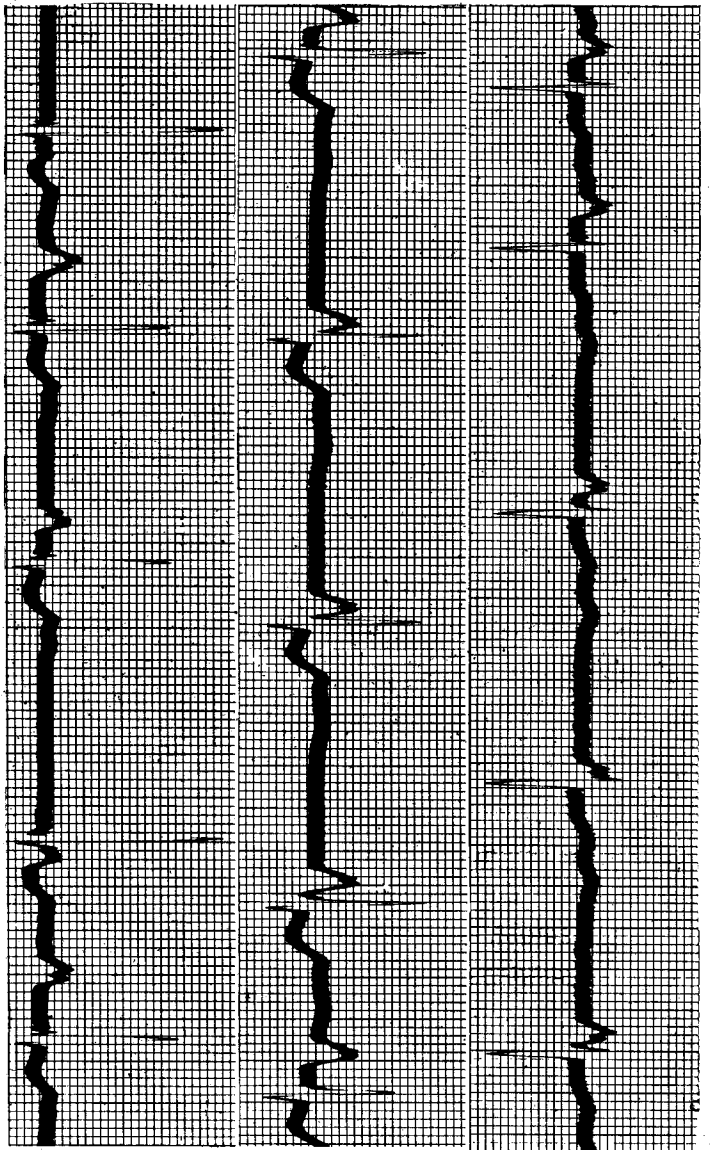
(Cohn, Fraser, and Jamieson: Influence of Digitalis on Human Electrocardiogram.)

A



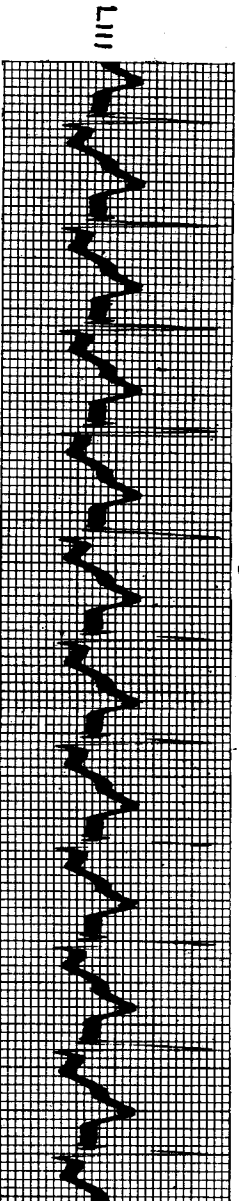
OCT.19,1914
RATE 97.3
P-R 0.22

B



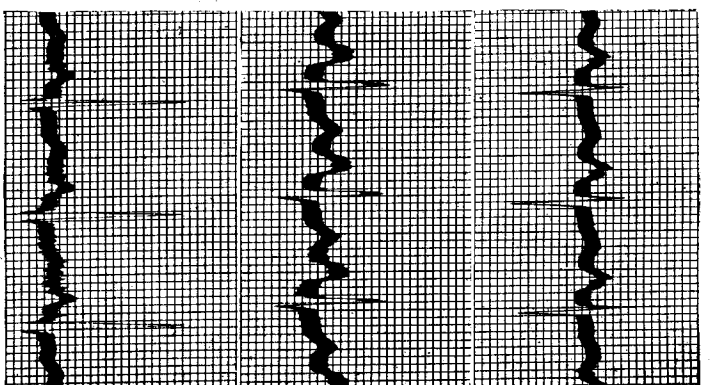
NOV.6,1914 DIGITALIS 2.5 gm.
48

B1



ATROPINE 1.0 mgm.
RATE 120
P-R 0.2

C



DEC.29,1914
0.2

FIG. 6.

(Cohn, Fraser, and Jamieson: Influence of Digitalis on Human Electrocardiogram.)