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Thesis for the M.D. Degree

by

FRANCIS RICHARD FRASER

M.B., Ch.B.

"OBSERVATIONS ON THE ACTION OF DIGITALIS IN MAN".

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In recent years evidence has been produced that makes clearer certain points that have been observed by clinicians during the administration of digitalis for therapeutic purposes, that helps to indicate with more certainty the effect that can be expected in a particular case, and that enables the drug to be administered with greater efficiency.

The author of this thesis has worked in collaboration with others in producing some of this evidence, and some of the results have already been published as follows:-

1. Certain Effects of Digitalis on the Heart.
Cohn and Fraser.
International Congress of Medicine.
London, 1913.

2. The Influence of Digitalis on the T wave of
the Human Electrocardiogram.
Cohn, Fraser and Jamieson.
Journal of Experimental Medicine.
Vol. XXI, June, 1915.

The Author of this thesis had clinical charge of the cases employed in the investigations. The electrocardiographic records were made and analysed by him under the direction of Dr. A. E. Cohn, but for the analysis and discussion here presented the author is entirely responsible. The preparation of this thesis was commenced in 1914 but was interrupted by the war.

In a field of this nature, where so many observers have been engaged, it is necessary to indicate the work of others, whether previous or contemporary, to such an extent that the sequence

of thought may be maintained, but it is impossible to refer to much work of importance that has helped to build up the present knowledge of the actions of the digitalis bodies.

The observations will be recorded in so far as they apply to our knowledge of the action of digitalis in human beings on :-

- (I) the normal pace-maker of the heart,
- (II) the auriculo-ventricular conducting mechanism,
- (III) the ventricular muscle.

Material.

Cases were selected for study that had a normal cardiac mechanism: that is to say, in which the heart beat was initiated in the sino-auricular node, and in which auricle and ventricle contracted in the usual sequence and at time intervals within the normal limits. The material available consisted of nine patients (Nos. I to IX) who had some slight valve lesions that had been recognised by their medical attendants, and for which advice was sought at the Hospital of the Rockefeller Institute, New York, but who gave no evidence of heart failure when at rest, or when living a quiet life as hospital patients walking about the wards freely. They were without subjective or objective signs of circulatory insufficiency and had no oedema, dyspnoea, precordial pain, increased heart rate, etc.

For the purpose of studying the effect on the pace-maker, a case of complete heart block (No.X) was included in which the auricular rate could be

studied, independently of any effect on conduction or on the ventricle.

Three cases (Nos. XI, XII, XIII), which were in hospital for conditions other than circulatory and that showed no evidence of circulatory disability, were also available. Two of these (Nos. XI, XII) were under treatment for cerebro-spinal syphilis, and the third (No. XIII) was a case of slight dwarfism in which the metabolism was being studied.

In addition to these, a number of cases with heart failure were studied under headings I and II, while for the purposes of heading III, thirty-four patients of various types and conditions were utilised. For the purposes of this last group of observations, the details of the cases are not important and will not be given.

Methods.

The digitalis was administered in the form of the Tincture, in doses of $\frac{1}{2}$ dr. to 1dr. daily according to the age of the patient, or the equivalent amount of the leaves in the form of tablets of Digipuratum.

To ensure that the full effect of the drug was obtained, the administration was continued until toxic symptoms appeared.

The observations were carried out by means of electrocardiographic records which were usually made daily, and sometimes more often. The records were made on rolls of films so that longer

records were obtained for measurements of rate than would be possible by means of plates. The curves were then analysed with calipers, and the results recorded in the form of charts, photographs of which are reproduced for the cases employed under the headings I and II. Under heading III, printed copies of illustrative electrocardiographic records are included. These printed copies were prepared for the publication in the Journal of Experimental Medicine referred to above. The original charts, clinical records and electrocardiograms are in the Hospital of the Rockefeller Institute in New York.

I. For many years it has been shown by means of animal experiments and clinical observations, that in the mammalian heart, digitalis and other bodies with a similar action slow the rate of the whole heart. Cushny(1) maintains that this action is brought about by two distinct mechanisms: (a) in animals with the heart in situ and normal rhythm, through stimulation of the inhibitory mechanism and therefore removed by atropine: (b) in excised perfused and exhausted hearts with normal rhythm, by direct action ofⁿ the cardiac structures and therefore not removed by atropine.

It has been considered that this action is an essential action of digitalis, and slowing of the rate of the heart has been looked for as an indication of the action of the drug, and an absence of slowing as an indication of the failure of the drug. It has long been recognised that digitalis is pecu-

liarily ineffective in slowing the rapid heart in acute infections and in exophthalmic goitre, but no explanation has been offered, and suspicion is sometimes thrown on the efficiency of the preparation used to account for this failure.

Results.

Of the thirteen cases (see Charts Nos.I to XIII) with no evidence of heart failure, six (Nos. V,VI,VII,IX,XI,XII) showed slowing of the pace-maker, and in five (Nos.V.VI,VII,XI,XII) of these, the slowing occurred only after signs of intoxication were present, and in four (Nos.V,VI,XI,XII) of them this slowing was accompanied by disturbances of mechanism, either ventricular extrasystoles or heart block. In the sixth case (No.IX), the slowing occurred before signs of intoxication and was not accompanied by any disturbance of mechanism, but the patient showed considerable variations in rate before the administration of the digitalis. In the remaining seven cases, no slowing was produced. Of the thirteen cases, therefore, twelve showed no slowing with therapeutic doses.

When, however, cases (Nos.XIV to XX) with normal mechanism but showing rapid heart rates with other signs of heart failure, such as oedema or dyspnoea when at rest, were treated and observed in the same manner, slowing was produced with beneficial effect to the patient before signs of intoxication were produced.

It would appear, therefore, that slowing

Case (No.I).

Rate of Heart -

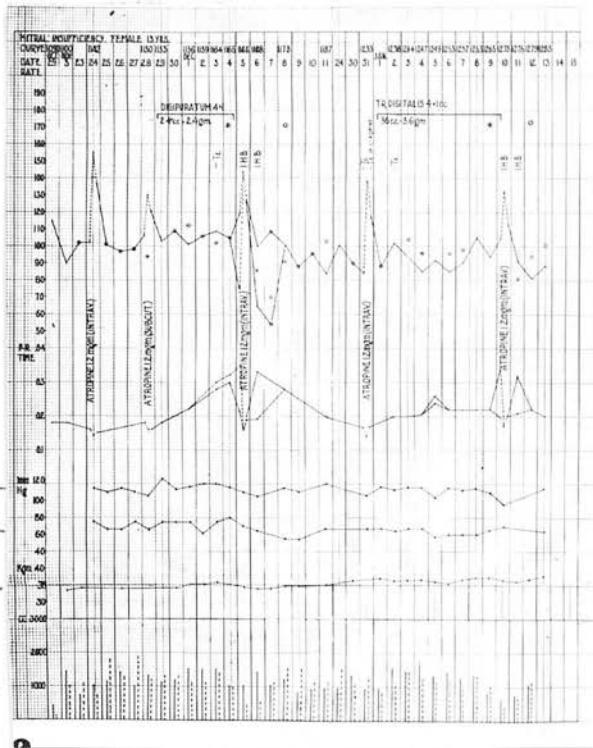
P-R time -

Blood Pressure } systolic
Diastolic

Body Weight -

Fluid Intake
(continuous line)

Fluid Output
(broken line)



* = Onset of toxic symptoms
o = Cessation of toxic symptoms

IHB = Incomplete Heart Block

When the average heart rate as recorded by the 4 hourly pulse records made by the nurses differed markedly from that calculated from the electrocardiogram, it is entered on the Chart as a ringed dot.

Case (No.I).

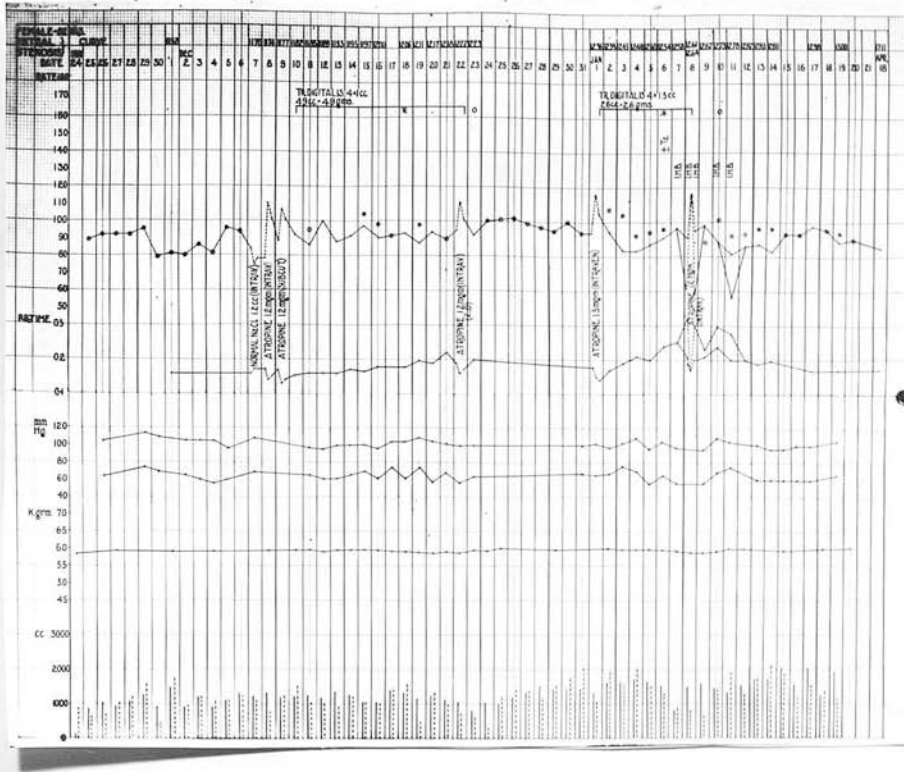
Female aged 13 years.

History of indefinite "rheumatic" pains.

Presence of loud mitral systolic murmur.

No evidence of heart failure obtained.

Case (No. II).



Case (No. II).

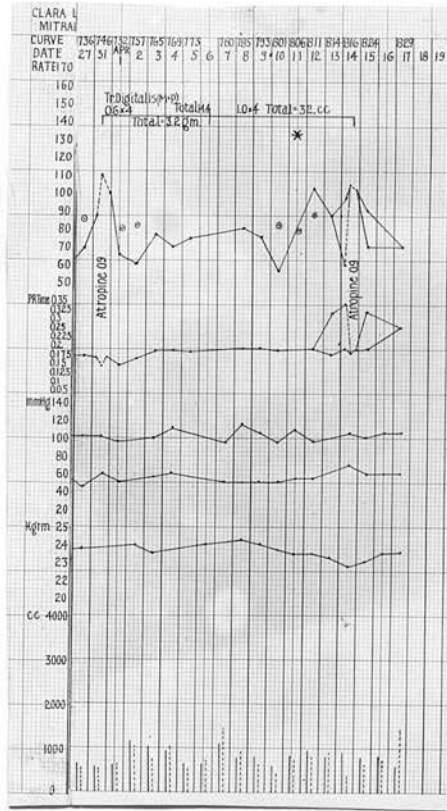
Female aged 22 years.

History of rheumatic fever.

Signs of mitral stenosis.

No symptoms of heart failure when in hospital,
but a history of palpitations and shortness
of breath on exertion.

Case (No. III).



Case (No. III).

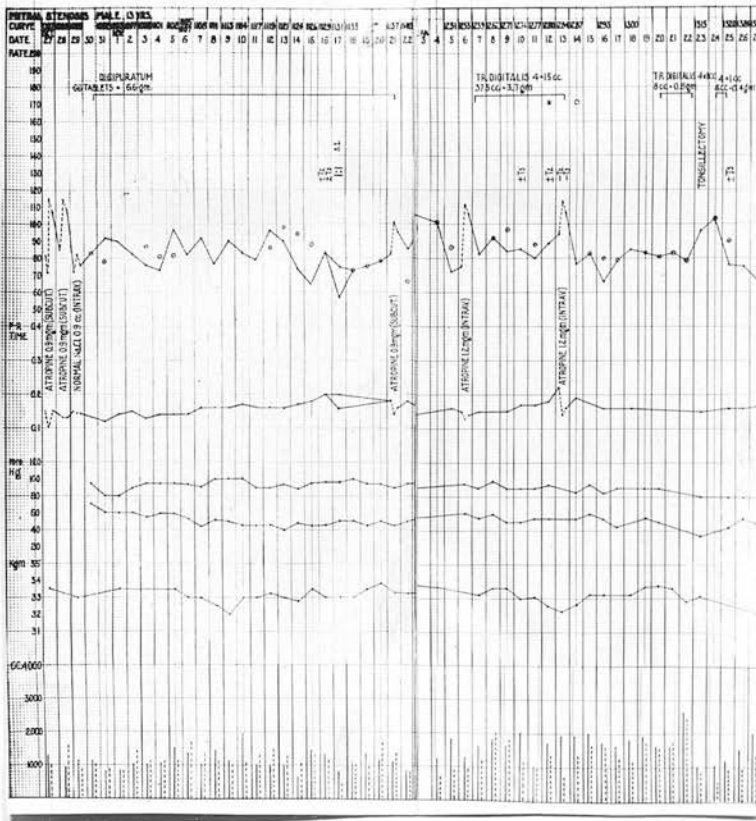
Female aged 9 years.

History of repeated attacks of tonsillitis.

Signs of aortic and mitral incompetence.

No signs or symptoms of heart failure when in hospital, but said to be lazy and not to play as other children.

Case (No. IV)



Case (No. IV).

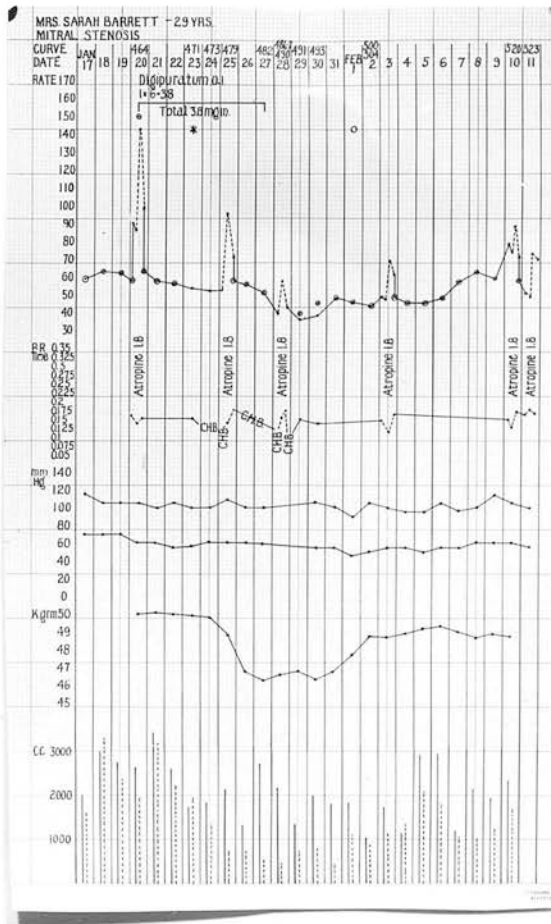
Male aged 13 years.

History of rheumatic fever.

Signs of mitral stenosis.

Shortness of breath and palpitations when running, but no evidence of heart failure when in hospital.

Case (No.V).



C.H.B. =
 Complete Heart
 Block.

Case (No.V).

Female aged 29 years.

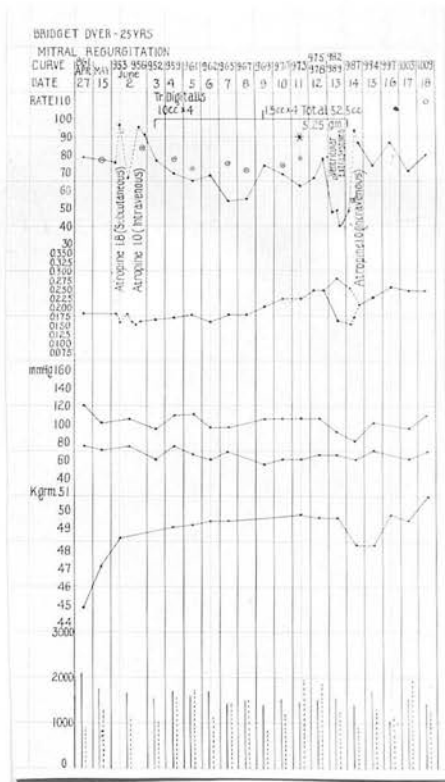
History of rheumatic fever.

Signs of mitral stenosis.

Symptoms of heart failure when at work,
 but no evidence while in hospital.

Slowing after toxic symptoms appeared.

Case (No.VI).



Case (No.VI).

Female aged 25 years.

History of "rheumatism".

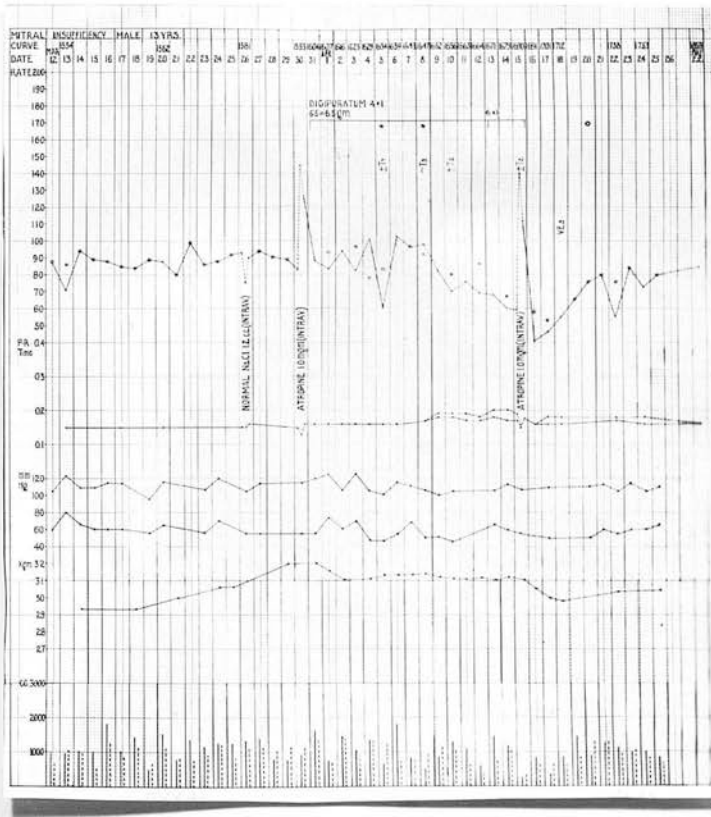
Signs of mitral regurgitation.

No evidence of heart failure in hospital,
but shortness of breath on exertion.

Marked slowing after toxic symptoms
appeared.

Rate from electrocardiograms slower than
average from Ward readings of pulse.

Case (No.VII).



VEs = Ventricula extrasystole

Case (No.VII).

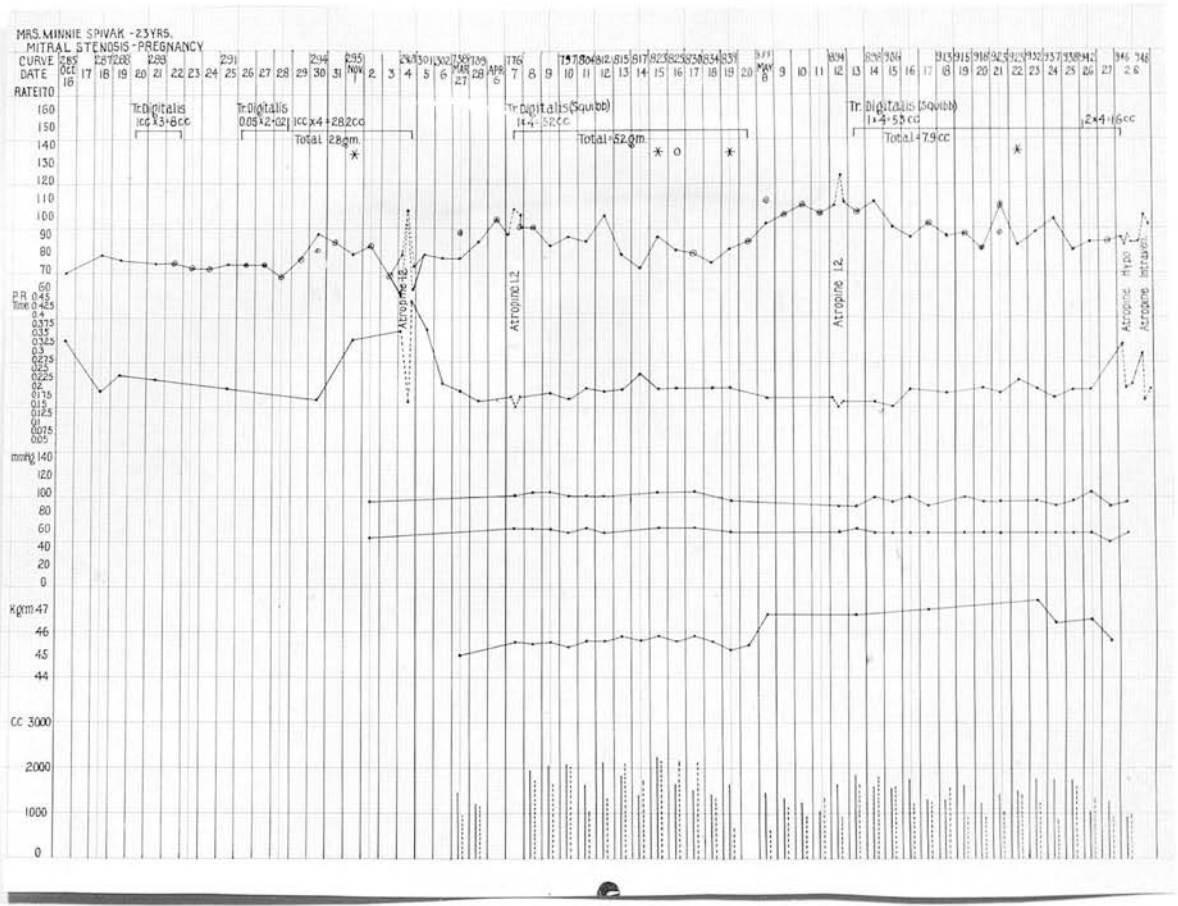
Male aged 13 years.

Signs of mitral regurgitation.

No evidence of heart failure in hospital, but "did not play like other boys".

Marked slowing after toxic symptoms developed.

Case (No.VIII).



Case (No.VIII).

Female aged 25 years.

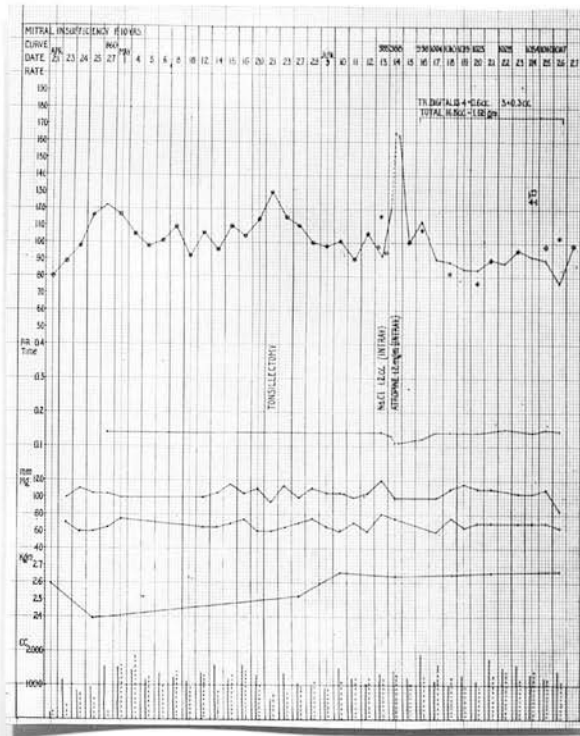
Signs of mitral stenosis.

No evidence of heart failure until four months later during pregnancy.

An abnormal conduction time was noted before digitalis was administered.

During pregnancy signs of heart failure developed with rapid pulse, and digitalis then caused slowing.

Case (No.IX).



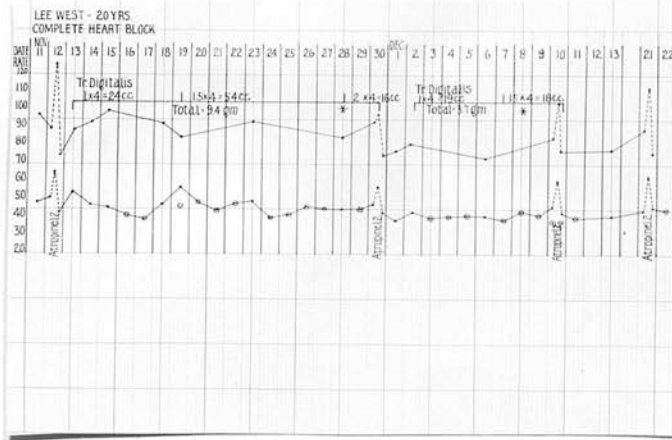
Case (No.IX).

Female aged 10 years.

No evidence of heart failure,
but signs of mitral regurgitation
and a very variable heart rate.

Case (No.X).

Auricular
Rate -
Ventricular
Rate -



Case (No.X).

Male aged 20 years.

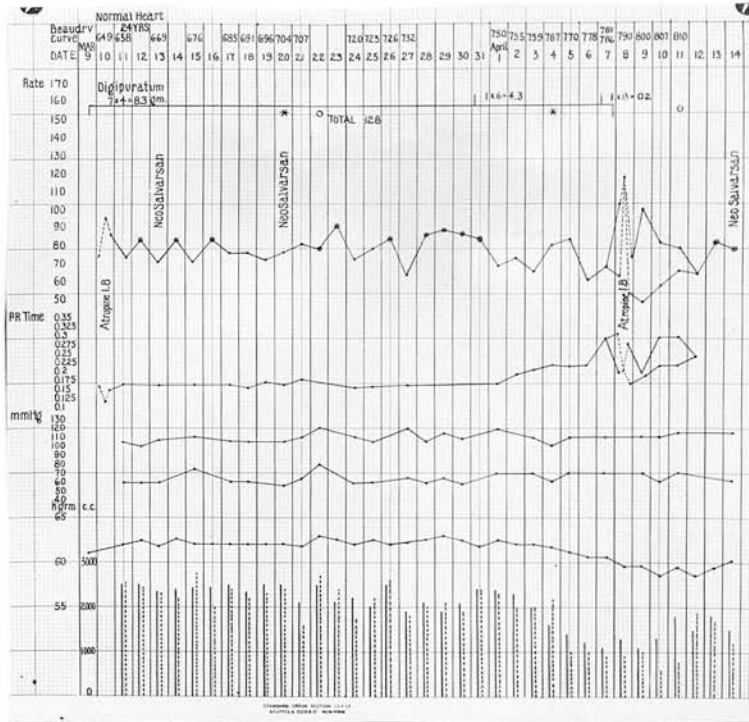
Complete Heart Block.

No evidence of heart failure
when at light work.

No slowing of auricular rate
during courses of digitalis.

Slowing followed atropine
injection and persisted.

Case (No.XI).



Case (No.XI).

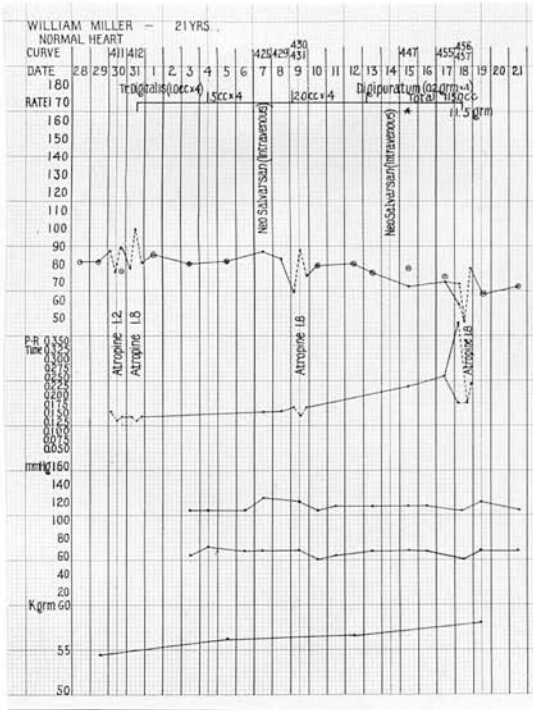
Male aged 24 years.

Under treatment for cerebro-spinal syphilis.

No ascertainable evidence of circulatory disorder.

Slowing of heart rate after toxic symptoms developed.

Case (No.XII).



Case (No.XII).

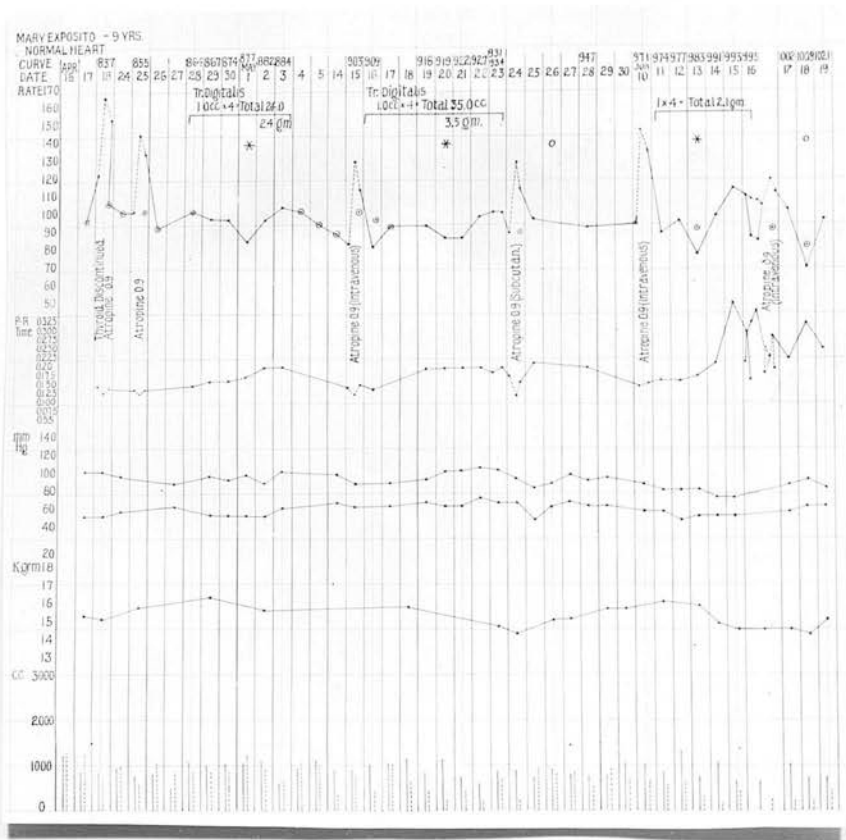
Male aged 21 years.

Under treatment for cerebro-spinal syphilis.

No ascertainable evidence of circulatory disorder.

Slowing occurred after toxic symptoms developed.

Case (No.XIII).



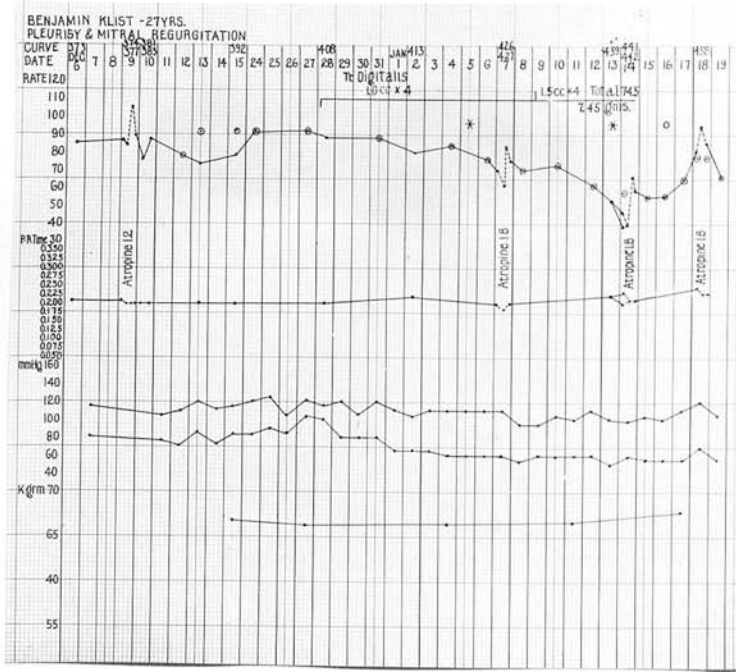
Case (No.XIII).

Female aged 9 years.

Moderate " Dwarfism " of
 unknown origin.

No evidence of circulatory
 disturbance.

Case (No.XIV).



Case (No.XIV).

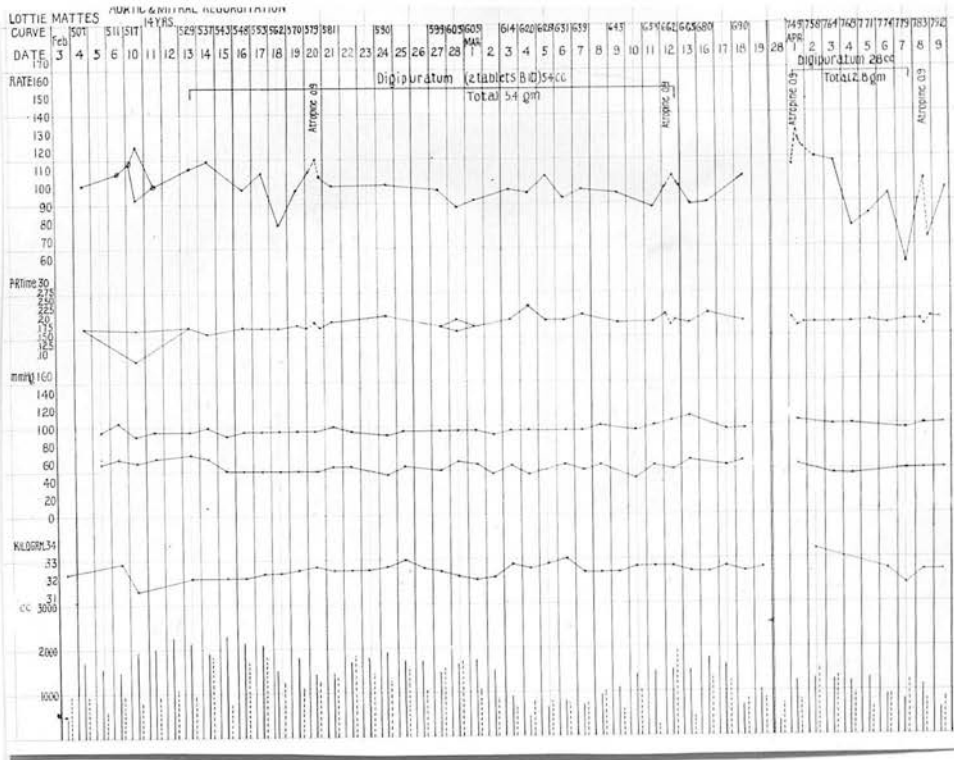
Male aged 27 years.

Admitted with pleurisy with effusion probably tuberculous.

Signs also of heart failure and mitral regurgitation.

Oedema of ankles, enlargement of liver, area of cardiac dulness increased.

Case (No.XV).



Case (No.XV).

Female aged 14 years.

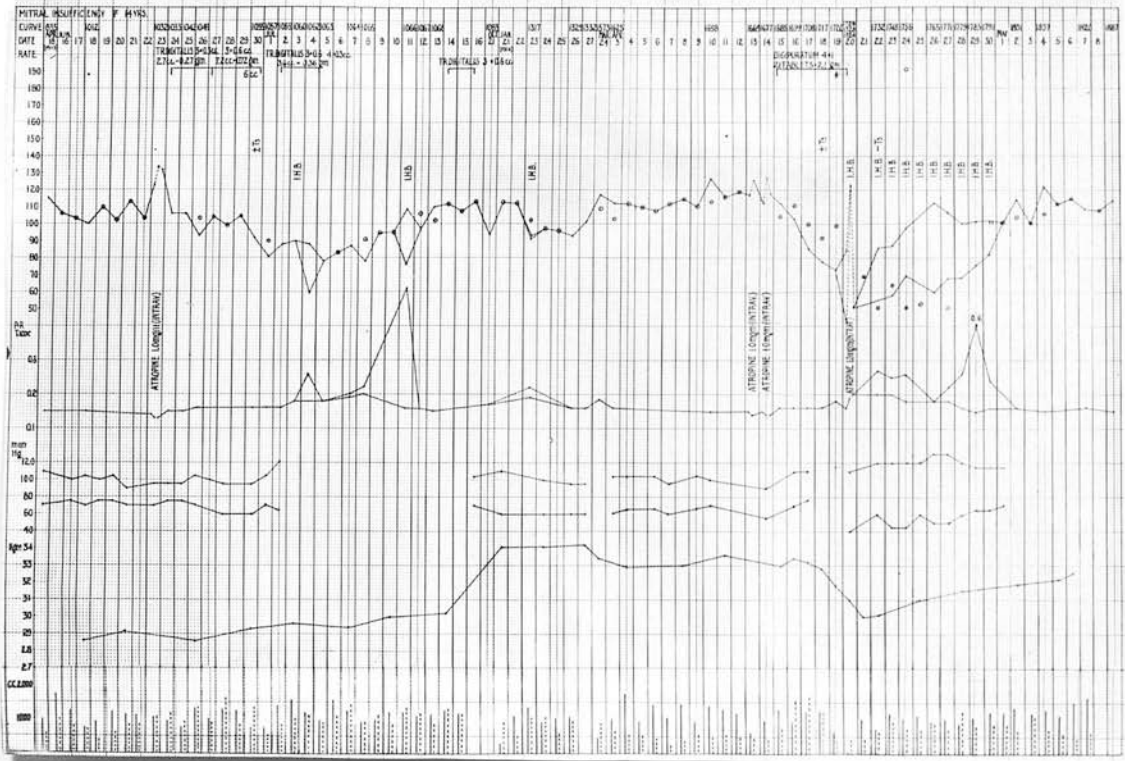
History of repeated attacks of rheumatic fever.

Signs of severe aortic and mitral disease.

Oedema of ankles, enlargement of liver, cyanosis and dyspnoea.

Incomplete heart block was noted previous to any digitalis administration.

Case (No.XVI).



Case (No.XVI).

Female aged 14 years.

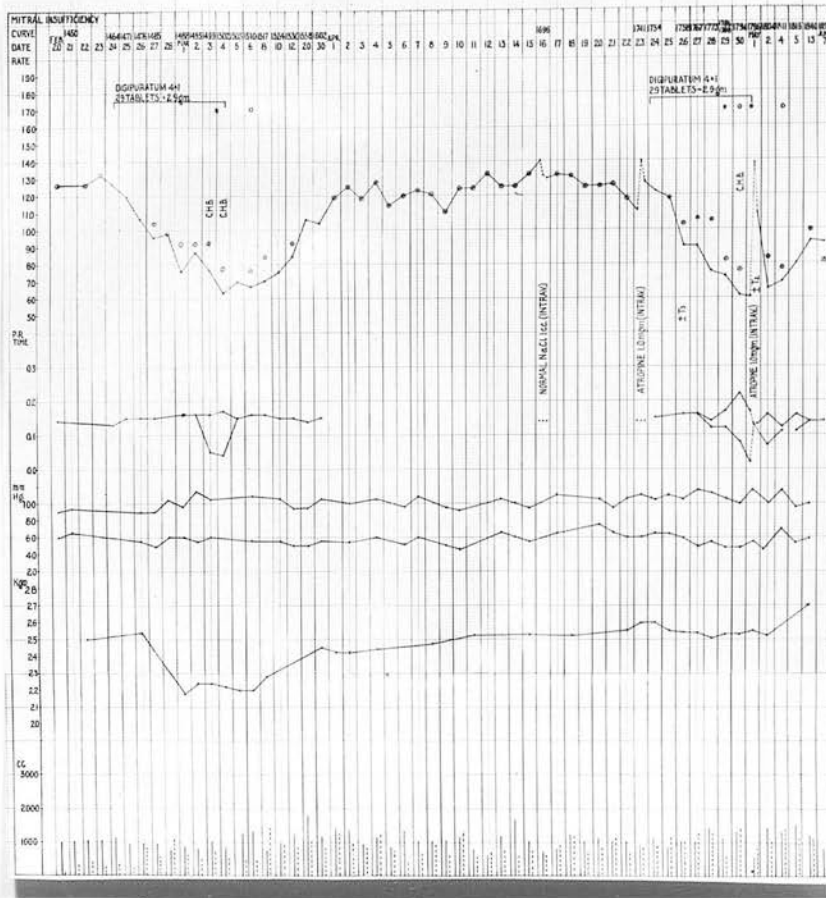
Signs of mitral incompetence and heart failure.

Oedema of ankles and of bases of lungs.

Slight cyanosis and marked dyspnoea when at rest.

Heart enlarged.

Case (No. XVIII).



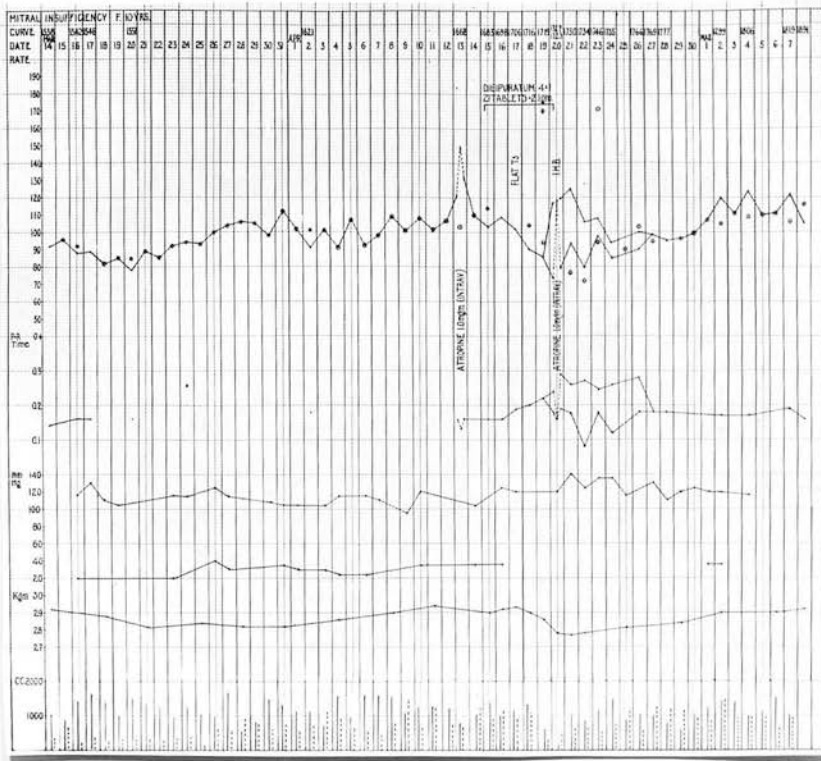
Case (No. XVIII).

Male aged 7 years.

Signs of mitral incompetence.

Slight cyanosis, oedema of ankles, marked
dyspnoea when at rest.

Case (No.XIX).



Case (No.XIX).

Female aged 10 years.

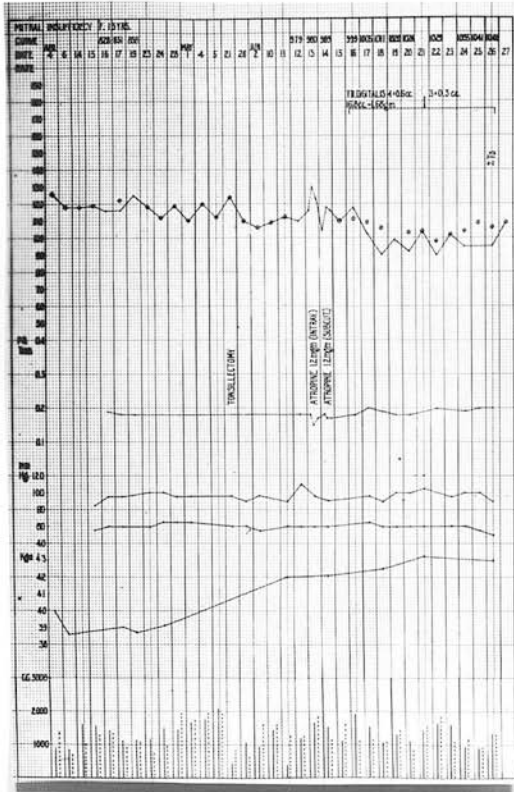
Signs of mitral regurgitation.

Greatly enlarged heart.

Dyspnoea, slight cyanosis and

oedema of ankles.

Case (No. XX).



Case (No. XX)

Female aged 13 years.

Signs of mitral regurgitation.

Heart not enlarged. Slight cyanosis
and rapid heart rate when at rest.

of the whole heart or of the pace-maker is not an essential action of digitalis on the human heart, but that this action is seen in the rapid rate accompanying heart failure. It was also seen in one case (No.IX) where considerable variations in rate occurred from time to time, independently of digitalis or of signs of circulatory insufficiency.

Atropine was given before the course of digitalis was commenced, and again at the height of the digitalis effect. Doses varying between 0.9 millegrammes and 1.8 millegrammes were given either subcutaneously or intravenously. The latter method was always used in the later cases, but for each patient one dose and method of administration were employed. Frequent electrocardiographic records were made to determine the maximum release from inhibition. Of eleven cases with normal mechanism, two observations were made in four cases (Nos.I,II,IV,XIII), and of the fifteen observations, eight (Nos.I,III,IV,V,VIII,XII,XIII) showed a diminished release, and seven (Nos.II,IV,VI,VII,XI,XIII) showed as great a release when a maximum digitalis effect was present than before the administration was commenced. Of five observations in cases (Nos.XIV,XV,XVI,XVIII,XIX) with heart failure and slowing, a full release was obtained in two (Nos.XVI,XVIII), and a diminished release in three (Nos.XIV,XV,XIX).

From these results it would appear that in addition to the inhibitory effect of digitalis through the vagus, there is a direct effect on the

cardiac structures and that this direct effect is more pronounced in some cases than in others. It cannot be concluded that it is more pronounced in cases showing signs of heart failure, for by the time the maximum digitalis effect was produced the circulation had so improved that there was probably an improvement in the condition of the heart muscle and other structures, thereby another condition was altered making the two atropine observations not strictly comparable.

II. Cushny(1) and others (2) showed by animal experimentation and by clinical observation, that the auriculo-ventricular block produced by digitalis is partly due to vagus inhibition and partly to a direct effect, but that in cases of auricular fibrillation the effect on conduction by which the ventricular rate is slowed is due to a direct effect. Lewis(3) argued that digitalis only produces block when the conducting structures are damaged, and that the fact that auricular fibrillation cases respond so well to treatment with it, is the result of the fact that as a rule auricular fibrillation occurs in cases of mitral stenosis due to rheumatic disease in which there is frequently a bundle lesion.

Results.

The effect on auriculo-ventricular mechanism was studied by the measurements of the P-R interval in the electrocardiograms. In eleven normal cases in which the drug was continued until intoxication resulted, this interval lengthened in each. In nine (Nos. I, II, III, IV, V, VIII, XI, XII, XIII,) complete or in-

complete heart block resulted, and in one (No.VII), numerous extrasystoles developed, In ten, the lengthening was gradual: in the eleventh (No.V), complete heart block developed without any gradual lengthening of the P-R interval. Three of the cases (Nos.XI,XII,XIII) that showed gradual lengthening to a condition of heart block were those that showed no lesion of the circulatory system and were in hospital for other conditions. In all cases the P-R interval, before digitalis was commenced, was either below 0.15 sec. or but little over it.

Of six cases with heart failure (Nos.XIV - XIX) lengthening of the conduction time occurred in five (Nos.XIV,XVI,XVII,XVIII,XIX). In three (Nos.XIV, XVI,XIX), it occurred gradually and block occurred in all of them, and in one (No.XVIII) block occurred suddenly with but little previous lengthening. In the sixth case (No.XV) no lengthening or block occurred during the administration of digitalis, though block had occurred previously, independently of any drug action.

In no case did sufficient lengthening to cause block occur until the patient showed other signs of intoxication.

It would appear, therefore, that lengthening of the conduction time is a remarkably constant effect of digitalis, and that it occurs before any signs of intoxication.

Of the fifteen times in which the effect of atropine was ascertained in the normal cases the

release of inhibition was as great under digitalis as before in six (Nos. IV, V, VI, VII, VIII, XIII), while in the remaining nine the release was only partial. Of the three cases (Nos. XI, XII, XIII) in which there were no signs of circulatory disease, the release was complete in one only (No. XIII). Of five cases with heart failure the release was as great under digitalis as before in two (Nos. XV, XVIII), and in the remaining three (Nos. XIV, XVI, XIX) was partial only.

These results show that the lengthening of the conduction time is partially due to vagus inhibition and partially to a direct effect on the cardiac structures, whether in cases with heart failure or in normal hearts.

Since these observations were made, Cushny(1) has suggested that where there is malnutrition of the cardiac structures the inhibition of conduction is mainly a direct effect, but that in normal hearts the effect is mainly vagal. Our observations do not entirely confirm this view, evidence of a direct effect being obtained in a large proportion of cases where there was no evidence of circulatory inefficiency.

III. While pharmacologists have insisted on an increased ventricular systole under digitalis, it is not susceptible of direct demonstration in the heart of man under therapeutic doses. The recognition of the importance of the effect on auriculo-

ventricular conduction in the treatment of heart failure with auricular fibrillation, and the relative inefficiency in other forms of heart failure have given rise to doubts whether a direct effect on ventricular systole enters into the therapeutic effect of digitalis in man.

From time to time, cases of heart failure are met with that improve clinically under digitalis without any ventricular slowing and cases of auricular fibrillation where more pulsations become palpable at the radial artery in the wrist before any striking slowing of ventricular rate occurs. Such cases have been considered as indicative of a direct effect on ventricular contraction.

Results.

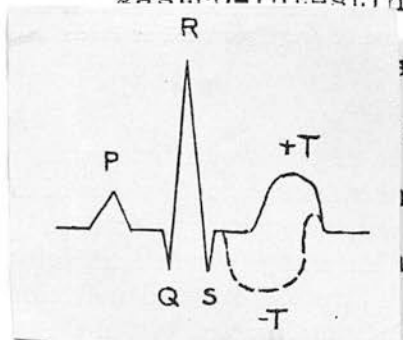
In studying the electrocardiographic curves from patients under digitalis certain remarkably constant changes are seen in the T - wave. This occurred thirty times in thirty-four patients, and except in five instances was detected before any lengthening of conduction time and before any gastro-intestinal disturbances of intoxication. In general this change consisted of a flattening, and eventually an inversion of the wave. The process might be more advanced in the first part of the wave and involve the part of the electrocardiogram between S and T, so that a diphasic wave resulted, the new form being identical with the original wave in the last part of the T deflection

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Results.

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This change consisted of a flattening, an inversion of the wave. The process more advanced in the first part of involve the part of the electrocardiogram S and T, so that a diphasic wave resulted, the new form being identical with the original wave in the last part of the T deflection

(see Fig.1.D). In other cases the later part of the T deflection became flattened and inverted earlier than the part near to the S wave, and so produced a diphasic wave of a different type. These changes are more noticeable in lead II and lead III than in lead I, but careful examination of the curves show that they occur simultaneously in all.

In pathological conditions where the form of the electrocardiogram in the three leads shows departures from the physiological, the changes in the T waves under digitalis are less simple.

For example, Fig.2 shows the changes occurring in a case of complete auriculo-ventricular dissociation. Here the original curve shows that the ventricular contraction was initiated in the left ventricle and a negative T1 becomes more negative, a negative T2 becomes positive, and a diphasic T3 becomes positive.

Fig.3 shows curves from the same patient in which the form before digitalis was given indicates a contraction initiated in the right ventricle. Here a diphasic T1 becomes flattened, a negative T2 becomes positive, and a negative T3 becomes positive.

Fig.4 illustrates the changes in a case of mitral stenosis in which a positive T1 becomes diphasic, a positive T2 becomes negative, and a diphasic T3 becomes negative.

In cases of auricular fibrillation it

Figure I.

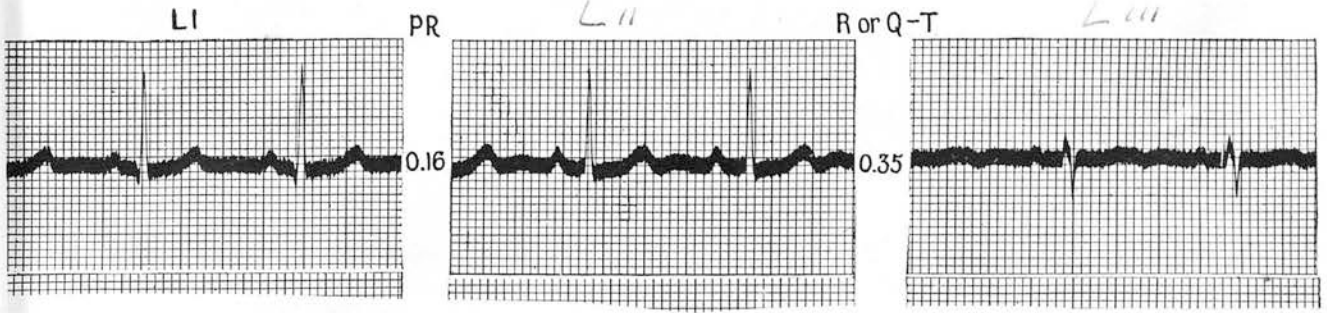


Figure I.

A is the control curve.

B. C. D. during digitalis administration. The amount administered to the time the curve was made is indicated on the right.

E a few minutes after the injection of atropine.

F.G.H. digitalis effect passing off.

L I L II L III = Leads I. II. III.

Figure I.

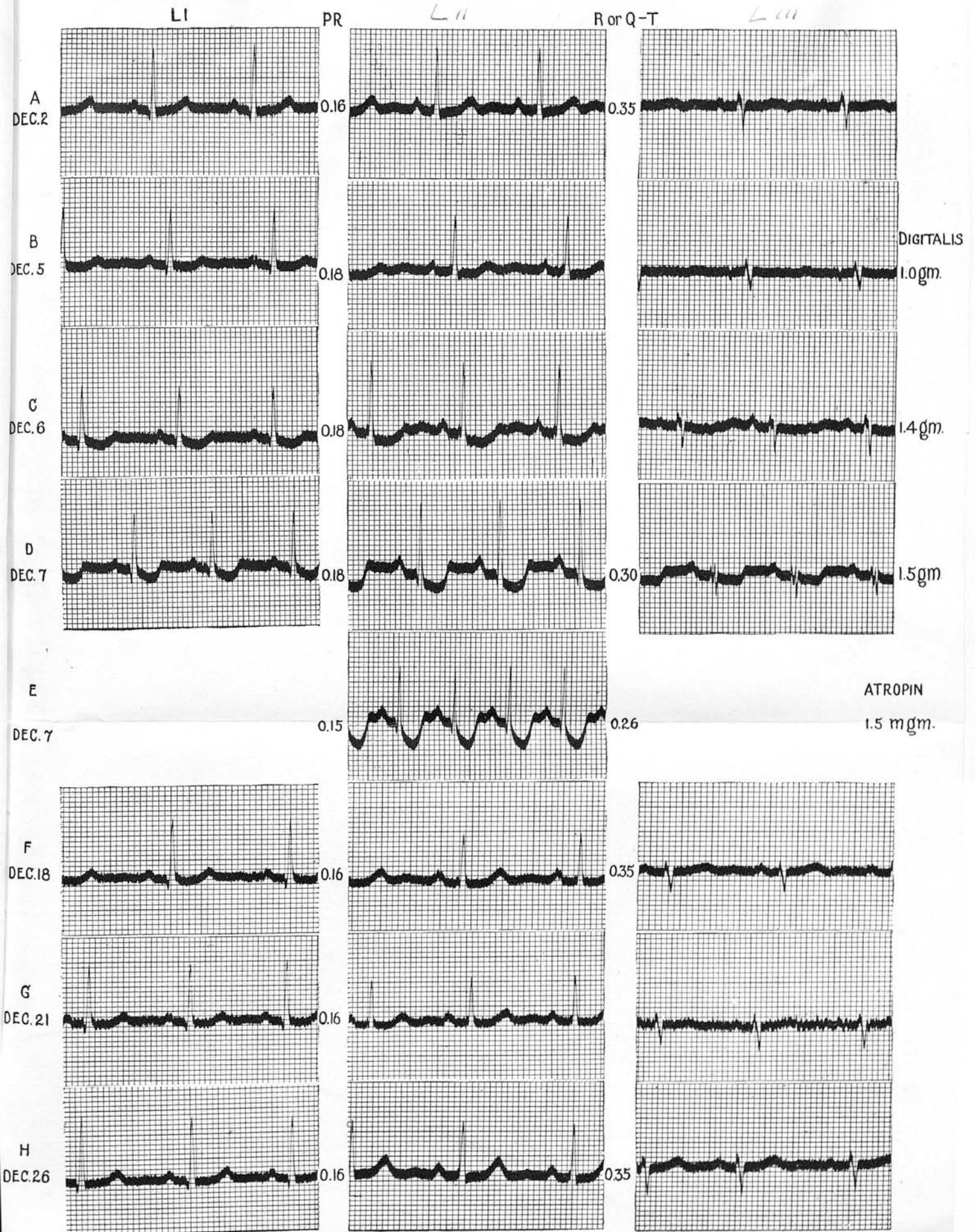


Figure III.

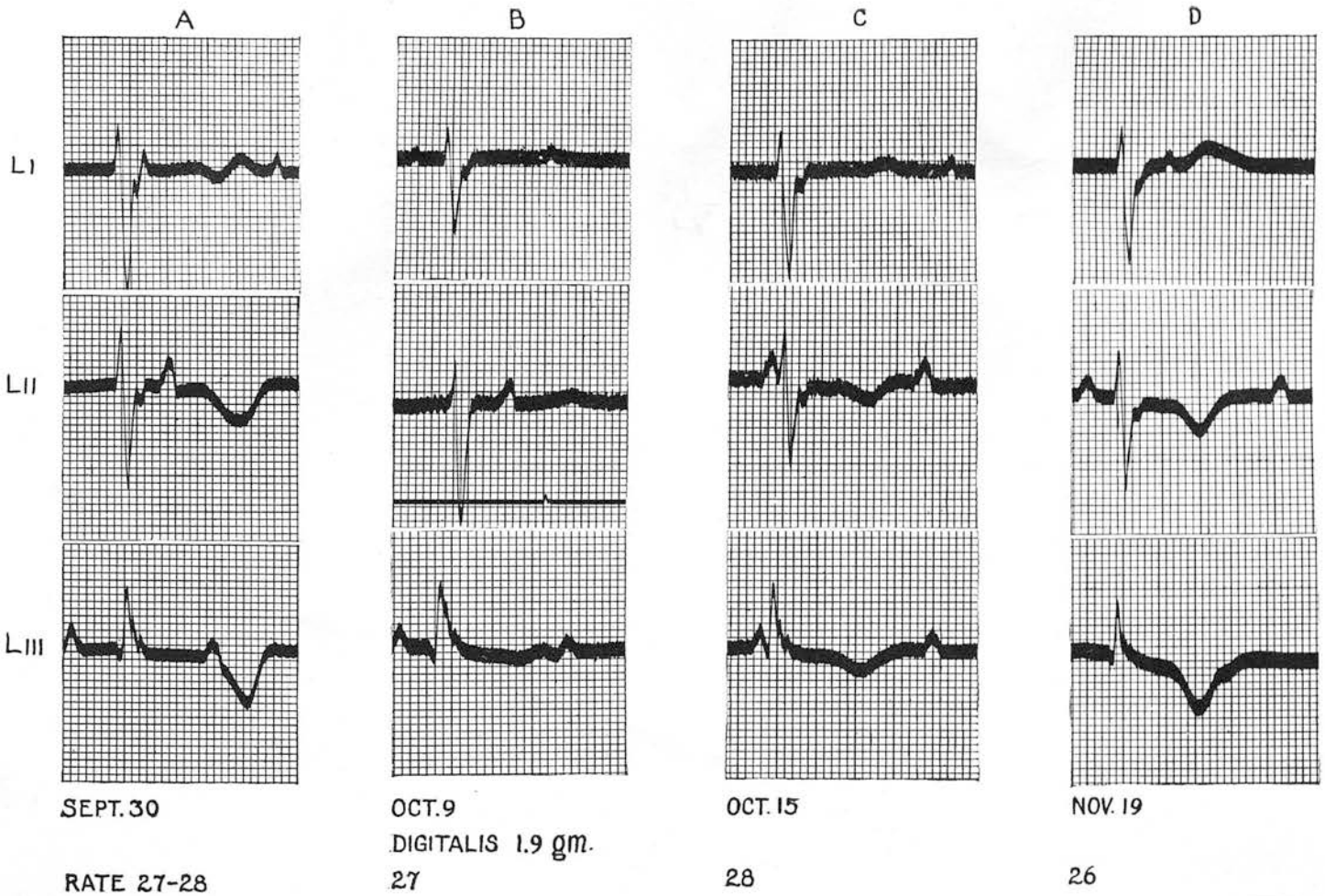


Figure III.

From the same case as Figure II.

A control

B under digitalis

C and D digitalis effect passing off.

Figure IV.

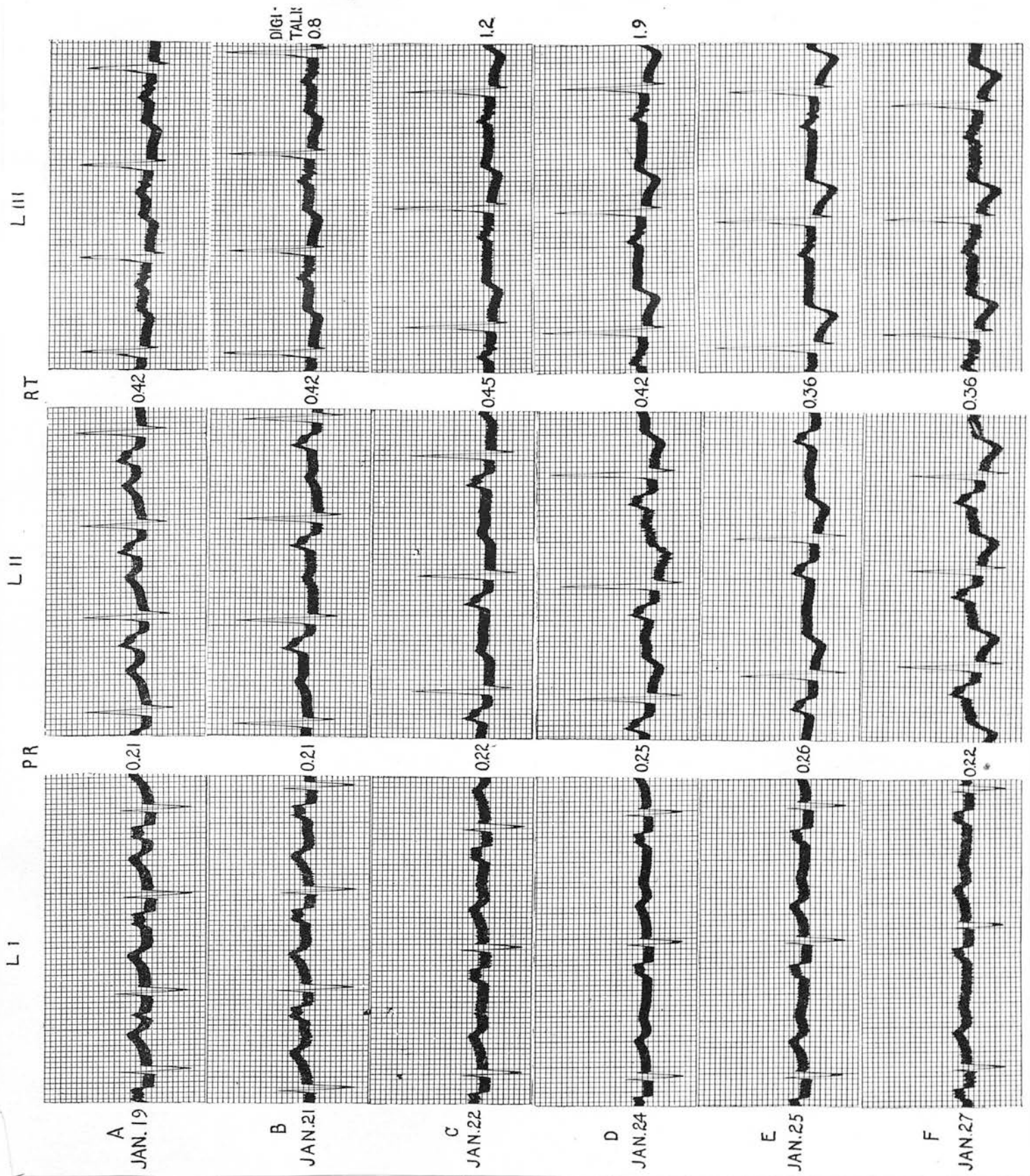


Figure IV.

Case of Mitral Stenosis.

A control. B. C. D during digitalis administration.

E.F. effect still increasing.

is often difficult to ascertain the changes in the T wave because of the irregular undulations due to the disturbed auricular state, but in Fig.5 the changes can be seen. In this case, a negative T1 becomes flatter, while T2 and T3 originally negative, become flattened or even positive. In Fig.6 are reproduced the curves from a case that showed an unusual type of irregular mechanism under digitalis and the changes in the T wave are seen in addition.

These changes can be detected very early in the administration of the drug, and we have noted them definitely within thirty-six and forty-eight hours after the administration has been commenced, when the rate of administration has been equivalent to 15 minims of the Tincture four times a day at intervals of four hours.

After ceasing the administration on the appearance of early toxic symptoms, it takes five days or more before the changes in the T waves disappear. In one case which is illustrated in Fig.4 the initial form of the wave was not restored until the twenty-second day after the administration was stopped.

In all cases where more than one course of digitalis was given, the changes described above occurred on each occasion.

The effect of atropine on these changes in the T wave was studied on forty occasions in the

Figure V.

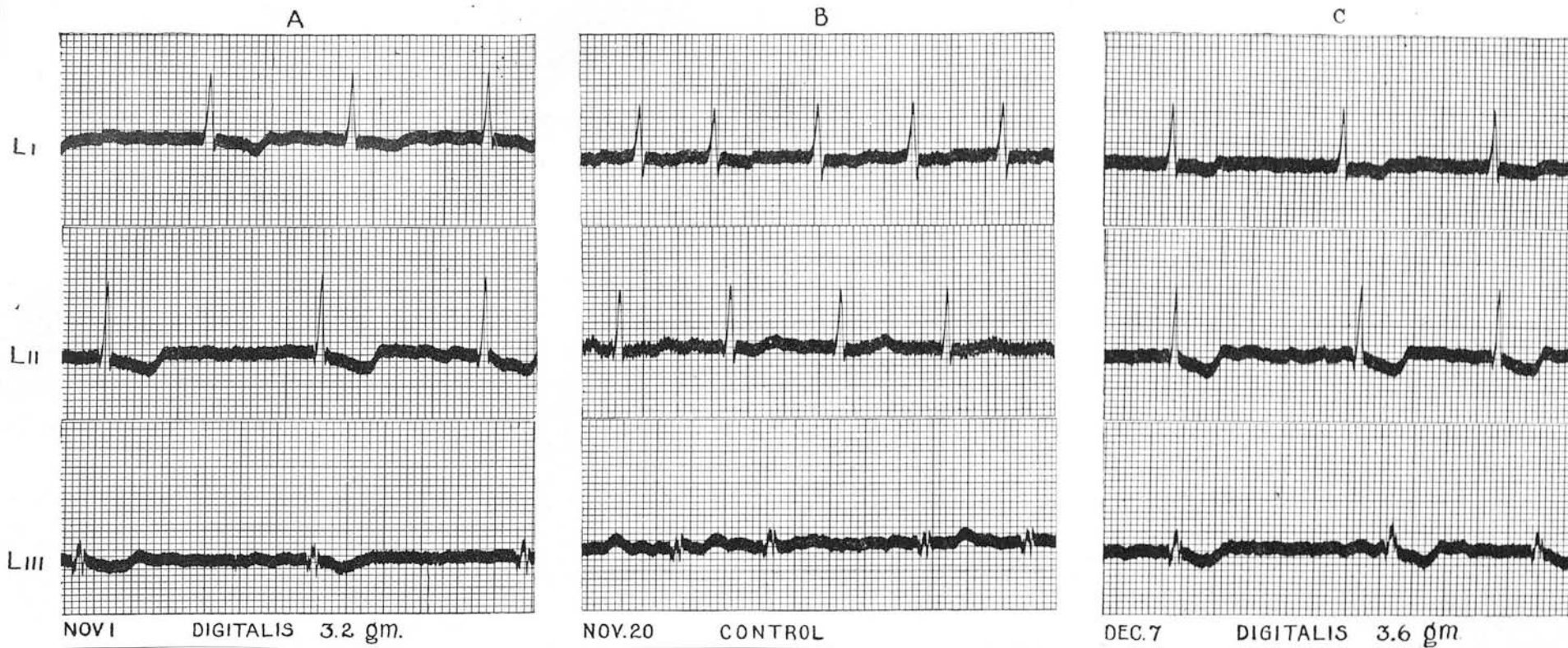


Figure V.

From a case of Auricular Fibrillation.

B is the control

A. C. digitalis effect on two administrations.

One before and one after B was taken.

Figure VI.

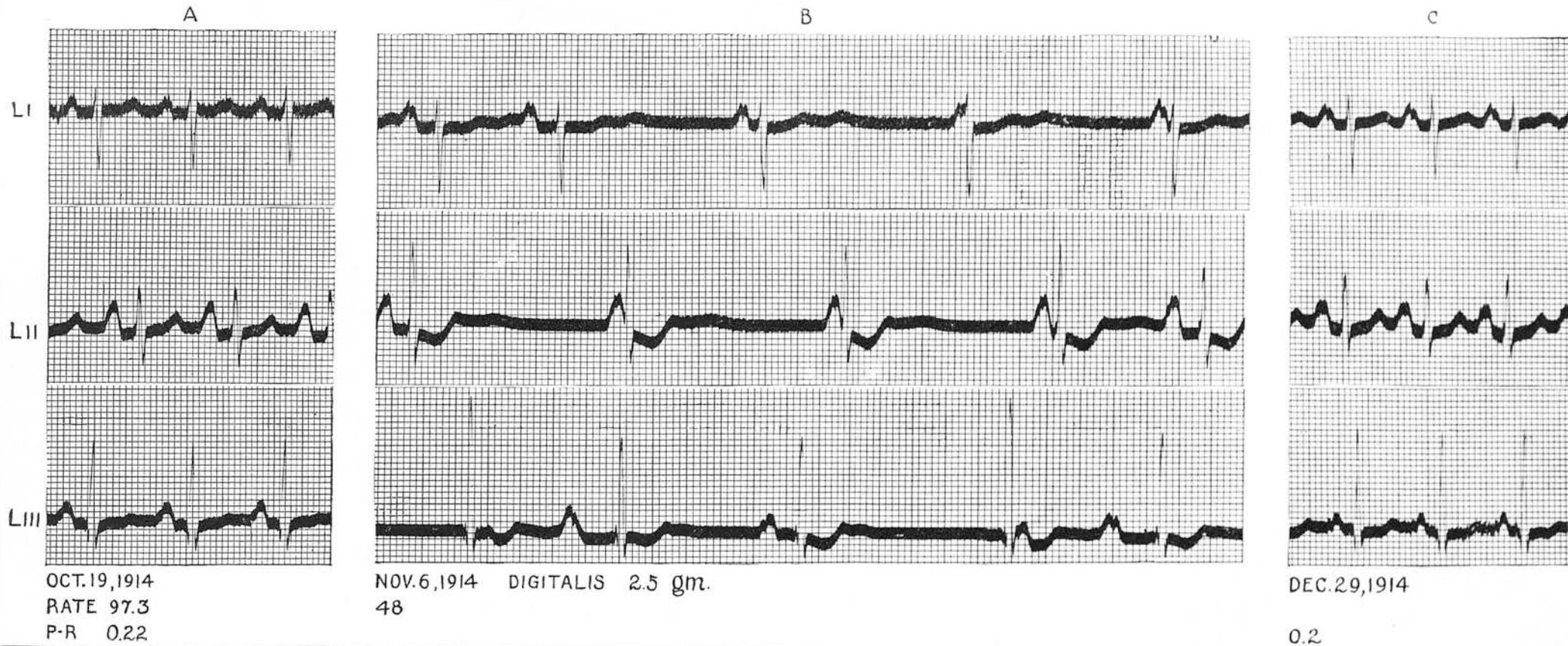


Figure VI.

Case of Mitral Stenosis.

A control

B shows effect of digitalis

C digitalis effect passed off

in the thirty-four patients, doses of 0.9 to 1.8 millegrammes being used subcutaneously and intravenously, the dose and method of administration depending on the age and size of the patient. In no case did the changes that appeared under digitalis disappear under atropine. In some cases the change that had occurred became accentuated: and in one case, where no marked change had been noted, it became obvious after atropine. Injections of atropine before a course of digitalis in no case produced the changes, and any alteration produced by atropine in the changes always disappeared within twenty-four hours after the atropine injection.

In addition to any changes in the T waves that resulted from the atropine injection, other alterations in the electrocardiogram were noted. These consisted of a shortening of the time between the end of R and the end of T, as well as in an acceleration of the pace-maker. The result of this is to make the waves between the end of R and the end of T sharper and steeper.

The electrocardiogram is an indication of the electrical changes accompanying the excitation and contraction of the heart muscle. The T wave accompanies ventricular contraction. Changes in the T wave must, therefore, be due either to changes in the distribution of the ventricular muscle, or to changes in the time or

direction of the spread of the contraction. That the changes occur in the course of a few days make it improbable that changes in the distribution of the muscle can account for them, and therefore they can be considered as indicative of changes in the contraction of the ventricular muscle. That they are not abolished by atropine is indicative of their being due to a direct effect on the muscle.

These changes reported in the T wave are evidence, therefore, of an early and constant effect of digitalis on the contraction of the ventricular muscle.

In view of the pharmacological proof of improved systole and the clinical evidence of improved output of the heart, independent of ventricular slowing, it is probable that these changes are evidence of more complete ventricular systole under therapeutic doses of digitalis in man.

Discussion.

1. That the pace-maker should be slowed in the rapid action of heart failure and not when the rate is normal, and there are no signs of heart failure, is surprising only because of the generally unquestioned acceptance of the pharmacological evidence that slowing of the pace-maker is one of the fundamental actions of digitalis. That it is so when the drug is pushed till toxic symptoms develop, there can be no doubt: but in full therapeutic doses this

slowing occurred in one case only out of thirteen. The fact could be accounted for if digitalis has a more powerful action on tissues that are in a condition of poor nutrition due to heart failure and general circulatory insufficiency than on healthy tissues. Cushny has argued that there is direct action on the tissues when these are in a poor state of nutrition, and that on healthy conduction tissues the action is largely through vagus stimulation. Our observations on the atropine release showed, however, that both in the group of normal rates that were not slowed and in the rapid rates that were slowed, some of the cases gave full release after digitalisation, while others did not. A direct action on the tissues in the one group and not in the other cannot, therefore, be maintained. Similarly vagus stimulation in the one group and not in the other cannot be demonstrated. Four at least of the cases (Nos.V,VII,XI,XII) in the group that showed no slowing under therapeutic doses showed distinct slowing after toxic symptoms developed: and of those cases, Nos.V and XII alone showed a diminished atropine release, suggesting that even in them the action may be a vagal one. It is impossible, therefore, to consider that when slowing does occur it is due to a more powerful direct tissue action consequent on malnutrition. It is possible, of course, that the slowing due to direct tissue action after the

administration of toxic amounts is the result of malnutrition due to the toxicity of the drug itself.

It is suggested that the slowing is an indirect consequence of some other action of the drug. We have shown that there are two extremely constant actions: one, a lengthening of the auriculo-ventricular conduction time, and the other, a direct action on the ventricular muscle. It is inconceivable that a lengthened auriculo-ventricular conduction time could affect the pace-maker, but it is conceivable that the pace-maker should be slowed reflexly by a direct action on the ventricular muscle causing improved ventricular systole. In an efficiently contracting ventricle an improved systole cannot increase the output, but in a dilated ventricle with incomplete systole an improvement in the contraction of the ventricular muscle would result in an increased output. It has been shown by Bainbridge(4) that the pace-maker of the heart in dogs is influenced by the variations in the output of the heart and the supply of blood to the heart under the influence of respiratory movements. The mechanism necessary to affect this would cause the changes in output and supply resulting from heart failure to affect the pace-maker, and may account for the rapid heart in cases of heart failure with normal mechanism. Improved ventricular output in such cases as a

result of digitalis would then cause slowing of the pace-maker.

Since the rapid hearts with normal mechanism in heart failure are slowed, and the rapid hearts with normal mechanism in febrile conditions and in Grave's disease are not slowed, it is probable that the rapid action in these cases is of a different nature. If the rapid hearts in febrile conditions and in Grave's disease were the result of a disturbance, primarily, of the pace-maker, it would be easy to understand why in such cases slowing should not be produced. That signs of heart failure are seen in febrile conditions and in Grave's disease is undoubted, but such signs are not observed for some time after the establishment of the tachycardia, and when such signs do develop digitalis is recognised as being of value. In the febrile conditions, toxins resulting from the particular infection present and in exophthalmic goitre toxic action resulting from the disturbed thyroid secretion acting on the pace-maker, either directly or through a nervous mechanism, may be the causes of the tachycardia. If this were so, it would be clear that digitalis could not be expected to slow such hearts, whatever other action on them it might have. That it does act on such hearts is seen in the fact that lengthening of conduction time and changes in the T wave

occur in animals with pneumonia just as in normal animals(5).

Whatever the explanation may be, it is certain that the beneficial action of digitalis in heart failure cannot be due to a primary action on the pace-maker to produce slowing, and that a beneficial effect may be expected from the action of digitalis without any slowing of the pace-maker necessarily taking place.

II. The remarkable constancy with which lengthening of the auriculo-ventricular conduction time occurred, excites suspicion that there was more severe damage to the cardiac structures present than had been ascertained by clinical or electrocardiographic methods. This is the more important in view of Lewis's contention that digitalis only causes such lengthening when the conduction mechanism is diseased. The cases studied were all selected because they showed no signs of severe cardiac damage, and because they had no subjective evidence of heart failure when leading quiet sedentary lives. If these cases had the conduction apparatus damaged by disease, then it may be concluded that the conduction apparatus is damaged in all cases of cardiac disease sufficient to cause symptoms on severe exertion. Of the three cases included who had no evidence, subjective or objective, of circulatory disturbance, two were under treatment for cerebro-spinal

syphilis, and it is possible that they had disease of the cardiac structures without any ascertainable evidence: but the third was a case of slight dwarfism of unknown origin whose metabolism was being investigated and in which there was no reason to suspect cardiac damage. It must be concluded that the cases selected were examples of conditions of normal cardiac mechanism without evidence of damaged conduction apparatus. It may then be deducted that a lengthening of the P-R time is a constant action of therapeutic doses of digitalis in man.

This action is not one that can be of benefit in cases with normal mechanism, but it should be of benefit in cases of auricular disturbance, such as flutter and fibrillation where the ventricle is disturbed and rendered less efficient by the abnormal activity conveyed to it from the auricles, for by means of it the ventricle can be protected from the auricles and its rate of contraction regulated.

The constancy of this action must further be considered as indicating that care must be taken not to produce deleterious effects because of it. In normal hearts, the milder grades of auriculo-ventricular dissociation result only when other toxic phenomena are so pronounced as to point to the limits of beneficial action, but in cases with already damaged conduction apparatus this action of digi-

talis may set a limit to the administration before the full benefit of the drug is obtained. It is a constant action that may be beneficial or may be deleterious, and it must always be considered in the therapeutic use of digitalis.

In the majority of our cases, the lengthening of the P-R time was seen before toxic phenomena appeared, and this can be of value in estimating to what extent a patient is already digitalised in considering the treatment of a case of heart failure when a drug of this group has previously been administered.

III. The importance of a direct effect on ventricular muscle contraction cannot be overestimated. It is possible that the effect does not always act to the benefit of the circulation, as for example it may be the cause of the premature ectopic ventricular contractions that sometimes appear, and we have much to learn of this effect before the indications for producing it are clear. That there is such a constant effect independent of any slowing is, however, indicative that other indications than slowing of the heart rate must be looked for as proof of a digitalis action. The lengthening of the P-R time and the change in the T wave are not proofs of beneficial action, and at present we have no indication of such, other than the disappearance or lessening of the general signs of circulatory failure. A slow ventricular rate or a long con-

duction time would not necessarily be a contra-indication to digitalis if heart failure is present, and it may be possible to avoid conduction effects or other slowing effects, and yet retain the direct muscle action by combining digitalis with a drug with an atropine action, with improvement in the general circulation.

The indication for the use of digitalis is heart failure.

It is probable that the condition of the heart muscle is frequently such that because of acute or chronic degenerative changes, it is impossible to obtain more efficient work from it. If, as is usually the case, however, it is not working at maximum efficiency because of stretching of fibres from the presence of residual blood, incomplete systole, etc., then digitalis can improve the efficiency of output.

It should therefore be tried in all cases of heart failure before it can be concluded that no benefit can be obtained.

In pathological conditions in which one only of the constant digitalis actions is of benefit, the therapeutic effects should not be so striking as in those conditions where both actions are of benefit. This is well seen in the striking benefits obtained from digitalis in auricular fibrillation where conduction effects, as well as direct ventricular muscle effects, can operate. The action in heart failure with normal cardiac mech-

anism is striking, but not so rapid or dramatic as in auricular fibrillation, and in such cases the conduction effects can be of no value and only the direct ventricular muscle action can operate beneficially.

SUMMARY.

Observations by means of electrocardiographic records on human beings under the action of digitalis are described. In some of the subjects there were signs of heart failure: in others, no signs or indications of heart failure could be ascertained. The following conclusions are made, and their significance discussed:-

- (1) Slowing of the pace-maker of the heart is not an essential action of digitalis in therapeutic doses in man.
- (2) Slowing of the pace-maker is seen in cases with rapid hearts and signs of heart failure.
- (3) Lengthening of the auriculo-ventricular conduction time is a nearly constant action of digitalis in therapeutic doses, both in cases with and without heart failure or signs of cardiac damage.
- (4) The effects noted under (2) and (3) are not constantly removed by atropine in either group of cases.
- (5) Change in the form of the T wave is a nearly constant effect, and is an early

effect of therapeutic doses.

It is not removed by atropine and is indicative of a direct effect on the contraction of the ventricular muscle.

The following deductions are made:-

Since digitalis in therapeutic doses in man exerts a direct effect on the contraction of the ventricular muscle, it is indicated in all cases of heart failure.

The effect on the conduction time is a further indication for the use of digitalis in cases of auricular fibrillation, but must be considered as a deleterious effect in certain cases with normal cardiac mechanism and damaged conduction apparatus.

Absence of slowing of the heart rate must not be considered as evidence of failure to obtain a beneficial effect with digitalis.

BIBLIOGRAPHY.

1. CUSHNY. Journal of Pharmacology and Experimental Therapeutics.
(Vol.XI. P.103. 1918).
2. CUSHNY, MARRIS, SILBERBERG.
Heart. (Vol.IV. P.33. 1912).
3. LEWIS. British Medical Journal.
(Page 1670. 1910).
4. BAINBRIDGE. Journal of Physiology.
(Vol.LIV. No.3. P.192. 1920).
5. JAMIESON. Journal of Experimental Medicine.
(Vol.XXII. P.629. 1915).