THE REFRACTORY PHASE OF THE HEART UNDER DIGITALIS AND
STROPHANTHUS AND THE INFLUENCE OF DEFICIENT OXYGEN
SUPPLY ON THE HEART.

by

ALEXANDER STEWART GORDON,
M. B. Ch. B.
## CONTENTS

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A. The Question at Issue.</td>
<td>2</td>
</tr>
<tr>
<td>Heart-Block.</td>
<td>2</td>
</tr>
<tr>
<td>The Refractory Phase of the Heart.</td>
<td>5</td>
</tr>
<tr>
<td>B. Technique.</td>
<td>10</td>
</tr>
<tr>
<td>Arrangement of the Apparatus, photograph to face.</td>
<td>14</td>
</tr>
<tr>
<td>C. The Action of Digitalis.</td>
<td>18</td>
</tr>
<tr>
<td>D. The Action of Strophanthus.</td>
<td>19</td>
</tr>
<tr>
<td>Interpretation of Results.</td>
<td>25</td>
</tr>
<tr>
<td>E. Discussion of Results with Strophanthus.</td>
<td>26</td>
</tr>
</tbody>
</table>

Part 2. The Influence of Deficient Oxygen Supply to the Heart. 28.


The work recorded in this thesis was undertaken with the primary object of investigating the behaviour of the refractory phase of the heart while under the influence of Digitalis and Strophanthus.

As is known these drugs may give rise to the condition known as heart-block. Various explanations, including prolongation of the refractory phase, have been offered to account for the heart-block as produced by drugs. There is no unanimity of opinion however, as to the precise way in which Digitalis or Strophanthus cause heart-block. One hoped to throw some light on this part of the subject by the present method of research.

During the investigation my attention was directed to a subsidiary question, namely, the influence of deficient oxygen supply to the heart and a number of experiments were carried out in relation to this subject.

The research was undertaken at the suggestion of Dr. Tait, Physiology Department.
Part 1. THE ACTION OF DIGITALIS AND STROPHANTHUS.

A. The Question at Issue.

HEART - BLOCK.

Heart-block was first described by Gaskell (1). He partially destroyed the conducting mechanism existing between auricle and ventricle by placing a clamp in the auriculo-ventricular groove. According to the tightness of the clamp the ventricle could be made to beat synchronously with the auricles, to respond to every second contraction of the auricles, to respond to every third or fourth contraction, or to remain quiescent.

Erlanger (2) did practically the same thing. His experiments show the effect of gradually compressing the auriculo-ventricular bundle of His in the dog. He found that compression of the tissue in the region of the auriculo-ventricular bundle of His, alone, will block the passage from the auricles to the ventricles, of the impulse which normally causes the heart to beat, and by carefully grading the pressure on /
3.

On this bundle of His, every stage of heart-block may be obtained for example, 2:1, 3:1, &c., rhythms.

It may be pointed out that medullated nerves as well as heart tissue may have their function of conducting interfered with by compression. Thus Bethe (3) found temporary compression of a nerve abolishes conductivity, which returns after compression is removed.

Since the discovery of the Auriculo-ventricular bundle of His in the Mammalian heart, a large number of investigators, Hering (4), Erlanger and Hirschfelder (5) Langendorff (6) -- have found that mechanical compression or destruction of vital continuity in this bundle may give rise to varying degrees of heart-block ranging from slight partial heart-block to complete heart-block.

In partial heart-block the ventricular contractions are less frequent than those of the auricles but there is a constant and definite time relation between the ventricular contractions and those of the auricles, e.g., one ventricular contraction for /
for two auricular or one ventricular contraction for three auricular i.e. a two-to-one rhythm or a three-to-one rhythm.

In complete heart-block the auricles beat rhythmically and likewise the ventricles, but each with an independent rhythm, so that the ventricular systole follows the auricular at varying intervals, sometimes preceding, at others, coinciding with the latter, that is - there is complete auriculo-ventricular dissociation.

A number of clinical cases in man have likewise been described by Mackenzie (7), Wenckebach (8), Nagayo (9), Lewis (10), Monckeberg (11), Beck and Stokes (12), Gibson and Ritchie (13) Webster (14), Gerhardt (15) and others. Post-mortem examination has, in certain cases, shown varying degrees of lesion of the auriculo-ventricular bundle of His, and the accepted explanation of heart-block is that it is due to an interference with conductivity between auricle and ventricle.

Now Straub (16) in 1901 put forward an alternative explanation of partial heart-block, and that is, that it is due not so much to an interference with conductivity /
5. conductivity as to a prolongation of the refractory phase of the ventricle. This view, however, needs some further explanation.

THE REFRACTORY PHASE OF THE HEART:

The refractory phase of the heart may be defined as a condition of greatly reduced excitability induced by activity. It has been found that the ventricle is, during a certain stage of the cardiac cycle, inexcitable to stimuli however strong. Immediately succeeding this stage of total inexcitability there follows a stage of diminished excitability where the ventricle will respond to stimuli. The excitability becomes gradually increased till a maximum stage is reached. Immediately succeeding the absolute refractory phase strong stimuli are necessary to elicit an extra contraction, but, as irritability is gradually restored during diastole, comparatively weak stimuli are sufficient towards the end of relaxation. This return to a condition of greater excitability is at first, fairly rapid and then more gradual. During this stage a recuperative process is presumably going on in the heart muscle. A stimulus applied during the /.
6.

the absolutely refractory phase has no effect on the development of contractile energy during the following diastole.

The ventricle has thus an absolute refractory phase, and a phase which is relatively refractory. In regard to the absolutely refractory phase it begins at the commencement of systole, and ends at a point just short of its completion. The duration of this absolute refractory phase bears a constant relation or ratio to the period of systole. This has been found never to vary. On the other hand the ratio of the relatively refractory phase to the period of diastole is not constant.

A stimulus applied during the absolutely refractory phase has no effect on the development of contractile energy during the following systole.

Schultz (17) found that chemical agents do not affect the duration of the absolutely refractory phase.

The view of Straub, who, however, makes no clear/
9.

clear distinction between the absolute refractory phase and the relatively refractory phase, is that the whole refractory period may be abnormally prolonged by, say, a drug, and seeks in accordance with this suggestion to account for heart-block. This explanation is ingenious and it is easy to see how it might account for the phenomena of heart-block.

The auricular stimuli are conducted as before in a presumably perfect way to the ventricle. This chamber of the heart, however, takes a longer time to recover its normal excitability, and one or more of the conducted auricular stimuli may be ineffective. This explanation, it will be seen, throws the whole onus of the existence of heart-block on the ventricle itself and not on the conducting mechanism that exists between auricle and ventricle.

It may be pointed out, however, that on this view alone, it is impossible to account for those clinical cases in which the heart-block vacillates between a complete and a partial.
Tait (18) has lately sought to reconcile the view of Straub with the older view that heart-block is due to an interference with conductivity alone, on the hypothesis that one and the same mechanism in the heart is responsible for both its conductivity and its excitability.

Tait's view is based partially on experimental results obtained with the drug Yohimbin and partly on an analogy drawn from the case of nerve.

In nerve we know that conductivity and excitability are essentially the same property - if one is depressed the other is -, also, and to an exactly corresponding degree. He found the action of Yohimbin on the heart to be readily explicable on the assumption, that conductivity and excitability in the heart are one and the same property.

The phenomenon of the refractory period is one which primarily involves the excitability of the heart and any prolongation of it is found to coexist with certain phenomena pointing to depressed conductivity.

As mentioned above both Digitalis and Strophanthus /
9.

Strophanthus are known to produce heart-block. They are also known to interfere with conductivity, prolonging the A. s - V. s. interval. The question then comes to be, do they likewise either prolong the refractory period or depress the general irritability or excitability of the heart. If it should be found that they depress the excitability at the same time as they depress the conductivity, it is clear that it would be still further evidence in support of Tait's view.
The experiments were carried out in the Physiology Department of the University during January, February, March and part of April 1910. Rana esculenta was the species of frog used, the male giving usually better results than the female. The heart with the interauricular septum divided, was attached to a gilded cannula, - gilded to minimise the possibility of electrolysis and polarisation taking place when using strong electrical stimuli. Otherwise, it is possible that these might be sufficient in intensity and duration to cause an excitation at the return of excitability. The heart was fixed to the cannula by a ligature passed round close to the auriculo-ventricular junction so that a small part of the auricles was left free along with the ventricle. A Schäfer heart plethysmograph was used for recording the contractions of the heart. The lower half of the plethysmograph was filled with Rusch's modification of Ringer's fluid.

Sodium chloride \(0.6 \text{ gm.}\)
Potassium chloride \(0.042 \text{ gm.}\)
Calcium chloride \(0.024 \text{ gm.}\)
Sodium bicarbonate \(0.01 \text{ gm.}\)
Distilled water \(100 \text{ c.c.}\)
The upper half including the horizontal arms was filled with pure liquid paraffin.

When the heart, attached to the cannula, was inserted in the plethysmograph, only the apex, both in systole and in diastole, dipped into the Ringer solution, - the remaining part of the heart being surrounded with the paraffin. A platinum wire, fused through the bottom of the plethysmograph, passed in a small coil a short way into the Ringer, - the other end communicated with the exterior. It was possible in this way to send an electrical stimulus from this wire through the Ringer to the heart and so to the cannula.

The "break" induction shocks of a Kronecker coil attached to an accumulator of 4½ volts kept fully charged, were used to stimulate the heart. The "make" shocks were short circuited. The current for the signalling coil was, by means of a special key, kept separate from that for the stimulating coil. This is the arrangement as used by Tait in his recent research on the action of Yohimbin on the heart and in his publication is thus described:-

"The special key used for the purpose of "simultaneously breaking two contacts consisted of an "iron /
"iron rod or shaft fixed horizontally in bushes, so that it could be rotated about its long axis by means of a crank and handle at the end.

"Excentrically attached to this shaft and some little distance from each other, were two circular vulcanite cams. Pressing against the upper surface of each cam was a straight steel spring, one end of which was clamped in such a way that the spring stood out more or less horizontally above, and at right angles to the direction of the underlying shaft. Thus the springs moved up and down with each revolution of the shaft, their free platinum tipped ends dipping each into a separate pool of mercury, over which in each case a constant stream of water flowed. By proper adjustment it was easy to arrange that the springs should dip into and rise out of the mercury at practically the same time. At the opposite end of the shaft from that carrying the handle was a revolving contact key which on each revolution short-circuited the "make" shock of the stimulating coil.

The shocks on the tracings are indicated by dots which were produced by sparks passing through the paper between the drum and the writing point.

"Connection with the spark coil through the attached /
"attached vibrator was made in such a way that closure "of the spark-coil circuit occurred just for a short "period at the moment of break of the stimulating "circuit. In this way a rapid but short-lasting "succession of sparks passed between the writing-point "and the drum, and thus one ensured that the moment "of stimulation should be well marked".

At the beginning of every experiment the heart was first perfused with Rusch's solution for about twenty minutes and then with fresh defibrinated ox blood diluted with Rusch's fluid in the proportion of one part blood to two parts Rusch's. This dilution was always filtered and then well oxygenated in the usual way. The perfusion with blood had usually a marked effect in making a previously irregular heart beat quite regularly. The experiments with Digitalis and Strophanthus were not started until the heart had been perfused for an hour or more with fresh blood. These two drugs were freshly prepared for every experiment, - made up in solutions in Rusch's fluid in a concentrated form (usually 1 in 1000) and these solutions were added in varying quantities to the fresh blood.

Mariotte's bottles were used to keep the pressure constant.
Fig. 1. SHOWS THE ARRANGEMENT OF THE APPARATUS.

Description of Fig. 1

1. Sandstrom variable-rate drum.
2. Schafer's heart plethysmograph arranged to permit of electrical stimulation of the heart.
3. Mariotte's bottles to contain perfusion solution
4. Double "make" and "break" key for electrical stimulation of the heart by means of induction coil (5) and for signalling by means of spark coil (7).
5. Kronecker induction coil for heart stimulation.
6. 4½ volt accumulator for induction coil.
7. Spark coil for signalling, supplied by an accumulator not shown in photograph.
8. Reservoir of water used for washing surfaces of mercury contacts.
15.

In testing the excitability to induced shocks two methods were employed:—

1. Method of single stimuli applied during any phase of the heart’s activity.

   As is known, stimulation applied to the heart during the phase of systole fails to excite. During diastole on the other hand, adequate stimuli are capable of exciting, and the strength of stimulus necessary to excite the heart at any one phase of diastole can be readily determined by a few trials. Practically it is found that a stronger stimulation is necessary to excite in early diastole than in late diastole, thus, while 200 Kronecker units may be necessary just to excite at the end of systole, 40 or 50 such units may excite at a later stage.

2. The method of slow (rhythmical) stimulation.

   In this method a definite strength of stimulus is fixed on, and this is applied repeatedly and regularly. If it is not sufficient to excite the heart at the end of systole, that is, at the beginning of the relatively refractory period, it may still excite the heart during some part of the phase of diastole. A description of an actual experiment /
experiment will best illustrate the use of this method, see Fig. 2. The heart used for this experiment happened to be showing a Luciani groups with intervening periods of inactivity - (see later). When the heart is regularly and fairly rapidly, (say 3 - 4 per second), stimulated with a strength of 60 Kronecker units it responds by a kind of incomplete "tetanus", that is to say, it does not fully relax between the individual beats. On the other hand when it is stimulated with 200 Kronecker units it shows a nearly complete "tetanus". The explanation is the following:— 60 Kronecker units suffices to excite the heart when diastole is about one-third advanced. On the other hand 200 Kronecker units is sufficiently strong to excite it at the end of systole.

![Fig. 2.](image)

After every experiment the plethysmograph, bottles, and rubber tubes were thoroughly cleaned.
Experiments with Strophanthus and Digitalis.

Strophanthus and Digitalis cause a better systolic contraction of the heart with more complete emptying of the ventricular chamber. Now a current which is applied to the apex of the heart has two routes by which to reach the metal cannula, first, along the wall of the heart itself, and second, during part of its course at least through the blood contained in the ventricle. It follows that the less blood there is in the ventricle, in other words, the more complete the systole, the more of this current will be conveyed by heart tissue, so that for purely physical reasons an induction shock applied to the heart when in systole has, ceteris paribus, more chance of exciting than the same current applied during diastole. In the same way an induction shock applied during the more complete systole produced by Strophanthus and Digitalis will, other things being equal, tend to excite the heart more than in an ordinary systole.
The first experiments were carried out with Merck's Digitalin (German pure) in various concentrations from 1 in 50000 to 1 in 1000 and perfused through the frog's heart for at least three or four hours. In none of the experiments was heart-block produced. With a fairly strong concentration 1 in 5000 or 1 in 3000 the heart was invariably arrested in systole. Merck's preparation of Digitalin is therefore ill-adapted for showing the phenomenon of heart-block on the frog's heart.

I did not continue experiments with other preparations of Digitalis but proceeded to investigate the action of Strophanthus.
Numerous experiments were carried out with Extract of Strophanthus B.P. 1898 - Duncan, Flockhart & Co., and with an extract of Strophanthus specially prepared for me by the same firm, i.e., 100 parts of seeds = 15 parts of extract.

As in the case of Digitalis a fresh solution of the extract of Strophanthus in Ringer was prepared for each experiment. This solution of the extract was added to the fresh diluted ox blood. The B.P. extract was used in concentrations varying from 1 in 50,000 to 1 in 5000, but usually from 1 in 12,000 to 1 in 7000.

The special extract was used in concentrations of 1 in 150,000 to 1 in 50,000.

Experiment, 8th February, 1910.

The heart was first perfused with fresh blood mixture for an hour. (See Fig. 3).

Fig. 3.
Fig. 3, shows the heart to be beating regularly.

Fig. 4, shows that stimulation with 100 Kronecker units (4½ volts in primary circuit) is not sufficient at the apex of systole to cause an extra contraction but stimulation at the same point with 200 Kronecker units elicits an extra contraction.

By the method/repeated stimulation (about 4 per second) with 100 Kronecker units there is no visible effect on the heart but with 200 units the heart only partially relaxes - this is shown in Fig. 5.

Fig. 6. By the same method but with 300 Kronecker units /.
units, the heart is kept in a condition of almost complete systole - very little relaxation being apparent. Thus at the beginning of the experiment the excitation of the heart at the end of systole lies between 200 and 300 Kronecker units.

Fig. 6.

After an hour's perfusion with fresh blood, extract of Strophanthus, B.P. 1898, 1 in 10,000 in fresh blood mixture was perfused. After thirty minutes perfusion with this Strophanthus solution, stimulation is exactly the same way as described and shown in Figs. Nos: 4 to 6, was applied with no appreciable difference in the effect on the heart.

After an hour's perfusion with Strophanthus the response to electrical stimuli was again tried - the results are shown in Figs. Nos: 7 and 8.
In Fig. 7 stimulation at the apex of systole with 200 units and with 300 units now fails to elicit an extra contraction but with 400 units an extra contraction is produced.

Fig. 8. By the second method. - Stimulation (4 per second) with 200 units and also with 300 units does not prevent the heart from relaxing. The effect of 400 units and 500 units is shown in the same tracing.

After two hours' perfusion with Strophanthus, the effect of electrical stimuli was again tried. Fig. 9 shows that stimulation with 200, 300, 400, 500, and 600 units, at the apex of systole, is not sufficient to evoke an extra contraction. With 1000 units a late response is got. With 2000 units an extra contraction is elicited.
Fig. 10 shows the effect of stimulation (4 per second) with 500, 800 and 1000 units.

After two and a half hours' perfusion with Strophanthus partial heart-block was visible through the plethysmograph with a 2:1 rhythm.

Stimulation now with 1000 units at the apex of systole fails to produce an extra contraction. This is seen in Fig. 11. To 2000 units however the heart responds.

Fresh blood was now perfused through the heart for an hour and at the end of that time the excitability was again tried. Fig. 12 shows that the heart has recovered to a certain extent from the effects of Strophanthus. Heart-block is no longer visible and at the apex of systole it is more excitable as 500 units now produce an extra contraction.
After two hours' perfusion with fresh blood the heart has apparently regained its normal condition of excitability. This is shown in Fig. 13.

Similar experiments with the special (concentrated) extract of Strophanthus gave precisely the same result. A tracing of one such experiment is shown in Fig. 13a.
it is clear that 50 Kronecker units excites at the end of systole, whereas 40 such units fails to do so. After two hours' perfusion with a 1 × 10⁻⁶ solution of the concentrated extract - by means of which a considerable amount of systolic contraction was produced 50 and even 70 units fails to excite just at the end of systole. — Fig. 13b.

This depression of excitability is present in spite of the fact (see page 17) that a large systolic contraction of the heart should, for physical reasons, make it apparently more excitable.

Fig. 13b.

Time Tracing: 2.67 mm per 10 seconds.
INTERPRETATION OF RESULTS.

In spite of the gradual contracture produced by Strophanthus it is quite evident from the above tracings that under the influence of Strophanthus:—

(1) the absolutely refractory phase is not prolonged.

Before Strophanthus is perfused a stimulus of 200 Kronecker units at the apex of systole is sufficient to cause an extra contraction. After Strophanthus has been perfused, — although 200 units fail to produce any visible effect, with 400 units an extra contraction is got. Later in the experiment it has been shown that while stimulation with 200, 300, 400, 500 and 600 units, gives negative results — stimulation with 2000 units shows that the heart is still excitable at the apex of systole because an extra contraction is produced.

(2) With regard to the relatively refractory period the tracings show that, under the influence of Strophanthus at the beginning of diastole the excitability of the heart to induced currents is very markedly diminished. At the same time the experiment has shown that heart-block was present. Coincident with the heart-block there is, therefore, an alteration of the relatively refractory phase. Strophanthus therefore reduces the excitability of the heart to induced electrical currents, and prolongs the relatively refractory phase.
E. DISCUSSION OF RESULTS WITH STROPHANTHUS.

1. We thus see that while drugs of the Strophanthus group cause an increased contraction of the heart, at the same time, make it less excitable. Engelmann (19) institutes a sharp distinction between the contractility of the heart on the one hand, and the excitability on the other. The foregoing experiments support this distinction.

2. At the same time as Engelmann distinguishes between contractility and excitability, he also distinguishes between excitability and conductivity. Tait’s view, however, as we have seen, is, that conductivity and excitability are aspects of one and the same essential property depending on one and the same mechanism, - excit-conducting mechanism. Now, previous observers have shown that Strophanthus depresses the conductivity between auricle and ventricle e.g., the A. s. - V. s. interval is prolonged. The work described in the preceding pages shows that Strophanthus depresses the excitability which is one more piece of evidence in support of Tait’s view.

3. We have further shown that while Strophanthus interferes /
interferes with the relatively refractory phase of the heart, prolonging it to a considerable extent, it has no influence whatsoever on the duration of the absolutely refractory phase. This, again, supports the statement of Schultz that chemical agents have no effect on the absolutely refractory phase, and is a further piece of evidence in favour of the view, now being held, that the whole refractory phase of the heart is made up of two fundamentally distinct components - the one pointing to katabolism, the other to anabolism. Strophanthus allows of perfect katabolism - it has a slight tendency to delay - not to diminish - the anabolic change which succeeds upon activity.
Part 2. THE INFLUENCE OF DEFICIENT OXYGEN SUPPLY ON THE HEART.

The phenomenon whereby an excised frog's heart is subject to spells of heightened activity - separated by periods of rest has again and again attracted the attention of observers. Luciani first accurately described the phenomenon, since when it has been commonly known as Luciani groups. Its cause, however, still remains obscure.

These groups remind one strongly of the phenomenon known as Cheyne-Stokes respiration in which the respirations, slow and weak at first, increase in rate and depth to die away gradually again. It is quite probable that in a Luciani group an activity occurs in the heart which is exactly analogous with the activity occurring in the respiratory centre during Cheyne-Stokes breathing. Each heart beat is due, as we know, not to a continuous stimulation but to individual "explosions" which arise from time to time within its tissue. In a Luciani group we can satisfy ourselves from a glance at a tracing that the "explosions" occur at first slowly, increase in rate, and slow down again. At the same time, however, it is highly probable that not merely the rate of the "explosions"
"explosions" increases but that the vigour or extent of each individual explosion gains in amount and dies down again. For a tracing such as that shown in Fig. 14 indicates that about the middle of its activity each "explosion" is of sufficient strength to excite the heart in mid diastole, that is when its excitability is relatively low. The individual explosions therefore, must, at this time, be stronger than normal. Once we have grasped this fact, the resemblance to the Cheyne-Stokes phenomenon is seen to be very close. In all probability we are dealing with an essentially similar phenomenon. The stimuli produced in the heart are at first weak, and of small amount, they rapidly increase in rate and in strength till a maximum is attained after which the process occurs in the reverse order.

Fig. 14.

In two recent communications by Douglas and Haldane (20) (21) it has been conclusively shown that, at least, one of the causes of Cheyne-Stokes breathing is deficient oxygen supply to the respiratory centre.
Are the Luciani groups due to a similar cause? At first sight it would seem that they cannot be due to this cause for they occur in a heart perfused with well oxygenated blood. Nevertheless I have found that they may be produced in a regularly beating heart by the simple device of replacing the oxygen in the blood with CO gas, so as to form carbon monoxide blood.

Contrary-wise the addition of a few drops of hydrogen peroxide to the blood used for the perfusion of a heart in which Luciani groups are temporarily present, suffices to abolish the phenomenon for the time being.
EXPERIMENT, 17th March, 1910.

Fig. 15 shows a normally beating heart—perfused with the usual oxygenated blood mixture (one part blood to two parts Rusch's). After an interval of one hour, CO blood, prepared by saturating blood mixture with coal gas, was perfused. After perfusing for twenty to thirty minutes with the CO blood the effect on the heart became manifest as is shown in Fig. 16. It shows a gradual transition to a rhythmic irregularity. The Luciani groups are well marked.

The object of using CO blood instead of ordinary venous blood was to get as far as possible a pure effect due to absence of oxygen rather than mere asphyxia with CO₂.

Experiments in which venous blood has been perfused through the heart—Öhrwall (22) failed to produce this.
this phenomenon. It is, therefore, one due simply to absence of oxygen, and not to excess of CO₂. Apart from its specific action on haemoglobin we know that CO gas is an absolutely neutral gas in regard to the tissues of the body generally. Thus it has been shown that it has exactly the same influence on muscle and on nerve as nitrogen and we can hardly imagine that it would have any specific action on any constituent of the heart tissue.

To account for the fact that Luciani groups may occur in a heart perfused with oxygenated blood, we must suppose that, although a sufficiently rich store of oxygen stands at the disposal of the heart, there is some intervening mechanism which hands on the oxygen from the blood to the "exploding" mechanism and that this mechanism has gone out of gear.

EXPERIMENT, 17th March, 1910.
-----------------------------

The frog's heart used in this experiment and perfused with oxygenated blood mixture, showed that it was from the beginning beating with a rhythmical irregularity./ Fig. 17 shows, well marked Luciani groups.
33.

After an interval, five minims of pure hydrogen peroxide were added to the perfused blood. Fig. 18 shows the gradual abolition of the Luciani groups. In fifteen minutes the heart was beating normally and regularly as shown in the tracing.

We here see that it is possible, partially at least, to abolish the Luciani phenomenon by providing excess of oxygen supply. Hydrogen peroxide, as we know, dissociates readily in contact with living tissue - its application to a clean wound or to the tongue proves this. It is probably also dissociated in the blood for if we add more than a few drops to well oxygenated blood frothing is produced. It is therefore impossible to charge the blood with great excess of oxygen by this means. At the same time by the addition of hydrogen peroxide to the blood one can insure that it is oxygenated to the very fullest capacity.

Experiments on the excised spinal cord of the frog by Baglioni (23) have shown that the addition of hydrogen peroxide /.
peroxide to ordinary Ringer's solution suffices to keep the excised spinal cord alive for days on end. It is consequently non-toxic when used in small amounts.

By means of this substance therefore, one may supply to the heart, blood which is absolutely saturated with oxygen presumably without interfering with its CO₂ content. The fact that it tends to abolish the Luciani groups shows once more that they are due to some defect in the ability to consume oxygen apart from any change in the CO₂ content. That hydrogen peroxide does not completely abolish the occurrence of Luciani groups may be attributed either to the fact that it is impossible to supersaturate the blood with oxygen by means of it, or that the oxygen in the blood is not in direct contact with the "exploding" mechanism in the heart, but is separated from it by means of a "middleman" which hands on the oxygen (the pathological process being present in this intervening "middleman" and not actually in the "exploding" mechanism.

I likewise attempted, by altering the chemical reaction of the blood, by the addition of small quantities of sodium hydrogen carbonate, and of organic (lactic) acids to produce the Luciani phenomenon in a normally beating heart, but without success. The phenomenon is one which depends on
35.
on deficient oxygenation (or deficient oxygen supply) and on that alone.
There is thus a complete analogy between this rhythmic irregularity in the heart and the rhythmic irregularity in the respiratory centre, which we known by the name of Cheyne-Stokes respiration.

The facts just discussed may come to have an important bearing on the question of stimulus production in the heart. As is well known there exists at the present time two competing views with regard to the source of origin of the rhythmical stimulus which normally excites the heart. According to the older view the successive stimuli arise in the nerve cells situated in the heart wall (neurogenic theory). According to a more recent view (myogenic theory) the stimuli are produced within the actual heart muscle. Now, the respiratory centre is composed entirely of nerve cells, and when we find a mechanism in the heart whose function in detail is similar to that of a nerve cell mechanism, we have a certain amount of presumptive evidence that the stimuli rhythmically produced in the heart likewise arise in the nerve cells.
In any case, it may be taken as proved that, whether this mechanism resides in muscle or in nerve tissue, the /
the ultimate basis on which its function depends, is the same as that in the respiratory centre, and we may talk of a Cheyne-Stokes action of the heart just as we may talk of a Cheyne-Stokes action of the respiratory centre in the full assurance that the two things are identical phenomena and depend on an essentially similar internal mechanism.
SUMMARY of CONCLUSIONS.

1. Digitalin (Merck's German pure) does not produce the phenomenon of heart-block.
2. Extract of Strophanthus may produce heart-block.
3. Strophanthus in any concentration and after any duration of perfusion, does not affect the absolutely refractory phase of the heart.
4. On the other hand it deepens and prolongs the relatively refractory phase. It thus may be said to depress the excitability of the heart.
5. The fact that it depresses excitability at the same time as it increases its contractility is evidence in favour of Engelmann's view that the property of excitability is distinct from that of conductivity.
6. The fact that conductivity is also depressed by Strophanthus is evidence in favour of Tait's view as opposed to the view of Engelmann that excitability is merely another aspect of the property of conductivity - the two things depending on the same mechanism - the excito-conducting mechanism.
7. The heart-block produced by Strophanthus is due not merely to prolonged refractory phase, but to a general depression of Tait's "excito-conducting mechanism."
8. The rhythmic irregularity of the heart known by the name of Luciani groups is due to the deficient oxygen supply. This is proved (1) by the fact that Luniani groups may be produced in a regularly beating heart by substituting CO gas for the oxygen present in the blood used for perfusion, (2) by the fact that the Luciani groups when present may be abolished by the addition of hydrogen peroxide to the blood.

9. The phenomenon of Luciani groups is exactly analogous to the Cheyne-Stokes effects on the respiratory centre which Douglas and Haldane have similarly shown to be due to deficient oxygen supply.

10. The essential mechanism responsible for stimulus production in the heart is in consequence closely allied to the rhythmically functioning mechanism present in the respiratory centre.

In conclusion I wish to express my sincere thanks to Professor Schafer for the facilities for research granted me in his laboratory and to Dr. Tait for much kind advice and criticism during the progress of my work.

-----000-----000-----
BIBLIOGRAPHY.

8. Wenkebach: Die Arhythmie, 1903.
40.

14. Webster: Glasgow Hospital Reports, 1900, Ill, p 413.
21. Douglas and Haldane: Regulation of Normal Breathing,
22. Öhrwall: Skan. Archiv f. Physiol Vol VIII.