ON DYNAMIC EQUILIBRIUM IN THE HEART. By GEORGE RALPH MINES, *Fellow of Sidney Sussex College, Cambridge.*

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CONTENTS.

THE nature of the response of cardiac muscle to stimulation, though independent of the nature or intensity of the stimulus provided it is effective, is intimately dependent upon the conditions under which the muscle is placed. Of the conditions immediately affecting the response of the muscle, those determined by its previous activity are of peculiar interest and importance, since their influence has to be considered in practically every experiment on the spontaneously beating heart. For the beating heart is in a complex dynamic equilibrium. The character of each individual beat depends, *inter alia*, upon the lapse of time between that beat and its predecessors. Therefore, since almost any change in the chemical environment of the heart, or any stimulation of the cardiac nerves is apt to cause alteration in the frequency of the rhythm of the heart, it is necessary to enquire to what extent the

changes observed in the individual beats as a consequence of su
change in chemical environment or nerve stimulation may be due
the alteration in frequency.

On the accuracy of the spontaneous rhythm of the sinus venosus.

Although the regularity of the beat of a heart kept at a stea
temperature and isolated from nervous control is a notion accepted
every physiologist, the idea is derived chiefly from the inspection
tracings on comparatively slowly moving surfaces and on counts of t
number of beats in some selected interval. I do not know of a
work specifically dealing with the question as to the equality
the intervals between a series of consecutive beats of the isolat
heart. The moment at which contraction starts in the auricle
ventricle is not sufficiently definite to allow of very exact determir
tion. The electrocardiogram, on the other hand, gives an exceeding
sharp and clear point in the cardiac cycle in the upstroke of the vent
cular "spike." Measurements of the intervals between successive hea
beats in the intact mammal have often been made from the electr
cardiogram, and they demonstrate in the clearest possible way t
rhythmic variations in the cycle due to nervous influences, in particul
those correlated with the respiratory movements.

I shall give here a few measurements made on various hearts und
conditions comparable with those which obtained in the experiments
be discussed in the later sections of this paper.

Time intervals are expressed in seconds.

Between the points marked * a very loud electric motor-horn was sounded close
the heart.

(1) *Rana temp.*   1·71″: 1·70: 1·70: 1·68: 1·70: 1·71: 1·70: 1·70: 1·70: * 1·
1·70: 1·70: 1·69: 1·70: 1·70: 1·70: 1·71: * 1·70: 1·71: 1·70: 1·70: 1·71: 1·
1·70: 1·71: 1·70.

Rana temp.   1·94″: 1·97: 1·97: 1·98: 1·97: * 1·96: 1·97: 1·96: 1·96: * 1·97: 1·9
2·00: 1·97.

(2) *Torpedo ocellata.*   1·34″: 1·35: 1·35: 1·35: 1·34: 1·34: 1·35: 1·35: 1·34: 1
(3) *Torpedo ocellata.*   1·42″: 1·42: 1·42: 1·42: 1·43: 1·43: 1·43: 1·43: 1·43.
(4) *Emys orbicularis.*   Heart intact.

(a)   2·09″: 2·09: 2·08: 2·09: 2·09: 2·09: 2·09: 2·09: 2·09: 2·07: 2·10: 2·09: 2·0
2·10: 2·09: 2·08: 2·09.

Some time later same heart, auricles excised, lying on glass plate.

(b)   2·70″: 2·69: 2·70: 2·69: 2·72: 2·69: * 2·69: 2·67: 2·70: 2·70: 2·73 * 2·70: 2·
2·71: 2·72: 2·72.

They were made by taking simultaneous records on rather rapid
moving bromide paper, of a series of electrocardiograms and of a tunir

fork signalling ·01" or a vibrating reed. The hearts were exposed and suspended, and electrodes placed on the apex and base. The image of the string was so arranged that the "spike" cut across the time tracing so as to allow of easy measurement.

In certain of the experiments, some of which are quoted below, it was sought to determine whether very intense air vibrations would have any effect in causing premature discharge of the spontaneous beats. Results on this point were negative.

The data show that even under the crude conditions of these experiments, in which the hearts were not perfused nor placed in a thermostat, the rhythm remained constant to within about 1 % over a long series of beats.

I shall now describe another method which I have found useful for the detection of relatively small variations in rhythm of the heart, without the necessity of measuring long photographic tracings. It consists essentially in synchronising with the cardiac cycle a rotating wheel driven by an independent motor, and observing to what extent the synchronism is maintained.

The apparatus which I have used for this purpose is shown in Fig. 1. It consists of a large Rayleigh motor

Fig. 1.

or phonic wheel driven by the intermittent current from a circuit including a 4-volt accumulator and a tuning fork giving 50 complete vibrations per second. The phonic wheel has thirty teeth and rotates therefore 100 times per minute. This wheel is mounted on ball bearings and bears a brass cone of the form shown in the diagram (Fig. 2).

A massive bracket attached to the base of the apparatus carries a large bearing in which the shaft B slides vertically. The hollow cone in which the lower end of B terminates rests on the male cone of the motor. By means of a fine-pitched screw the relative positions of shafts
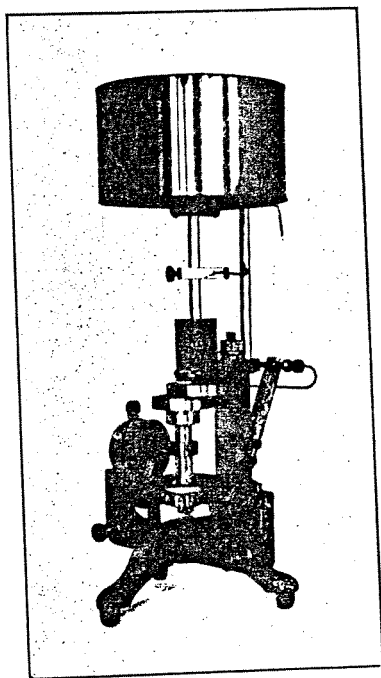
A and B can be adjusted with precision. When B is directly over the shafts turn at the same speed; as B is moved away from A so th the point of contact of the rim of B's cone with A's is nearer and near the apex of the latter, the rate of rotation of B becomes less and les This simple transmission, which was devised by Mr Robinson of Mess W. G. Pye and Co., works over a wide range with sur-prisingly little slip and has proved most valuable in the course of this work. The speed of the shaft B can be adjusted with the greatest ease while the apparatus is working: the uniformity of movement of the motor is assured by the tuning fork. The shaft B carries a recording cylinder for use in certain cases and also projecting arms which can be clamped in any desired position for the purpose of making electric contacts during the revolution.
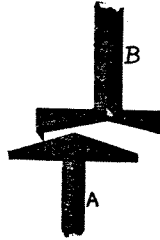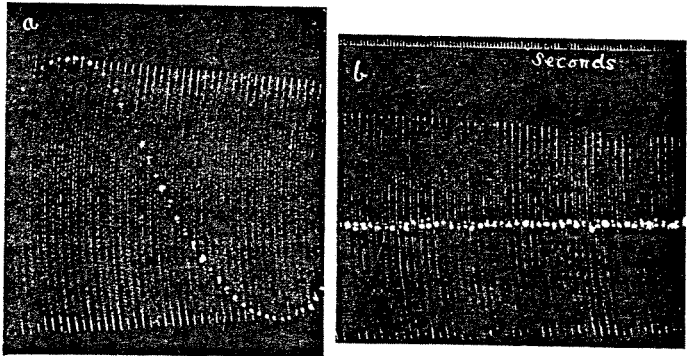

Fig. 2.

Fig. 3.

The apparatus was tested first by comparison with a pendulur A heavy bob attached to a long thread made 27 oscillations per minut This pendulum was made to move a light lever, provided with a Bayli: pointer terminating in a bit of aluminium foil. This was arranged t write on a slowly moving kymograph. Parallel to the drum axis an near, but not touching, the pointer was a stout copper wire connecte with the high tension terminal of an ordinary small ignition coil. Th contacts of the variable rhythm apparatus were placed in the primat circuit of the coil. Fig. 3 shows tracings obtained in this way. In $3a$ th rhythm of the apparatus was rather slower than that of the pendulur while in $3b$ there was almost perfect synchronism. By arranging th

phases of pendulum and rotator so that the sparks are delivered when the lever is moving at its fastest, *i.e.* in the middle of its swing, it is evident that as small a deviation from synchronism can be detected by mere inspection of such a tracing as could be detected by measurement of simultaneous records from the two sources taken on a surface travelling for the whole cycle at the maximum speed. The smoothness of the curve traced out by the sparks in 3*a* and the straightness of the line in 3*b* indicate that the accuracy of the rhythm of the rotator is of a high order.

In Fig. 4 the lever was moved by a frog's heart, suspended and beating spontaneously. In 4*a* the approximate synchronism of the rotator had been adjusted; at the beginning of the tracing the sudden rise in the position of the spark was produced by altering the relative
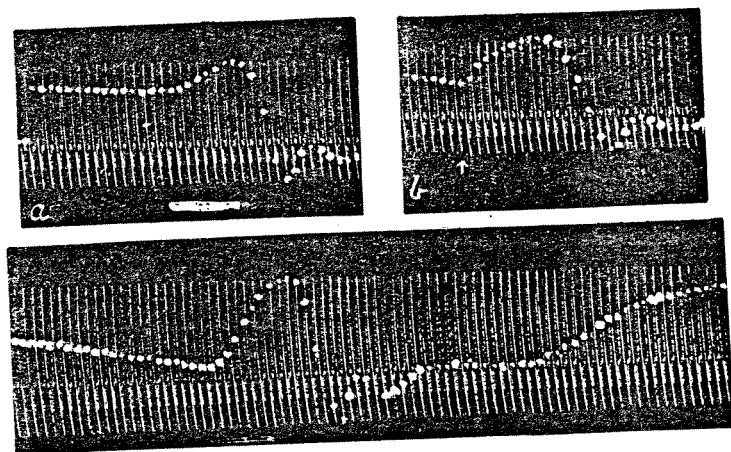
Figs. 4 and 5.

phases of rotator and heart, the spindle of the rotator being lifted for an instant by hand. This can be done without affecting the adjustment of the transmission. As is seen in the record, the approximate synchronism was maintained during the next 16 beats. The period of the rotator was very slightly less than that of the heart cycle. During the period marked by a white line on the tracing the beam from a small Leitz arc lamp with condenser at a distance of several metres was allowed to fall on the heart. The quickening, due to the slight warming, is immediately apparent in the altered position of the sparks. Similarly, Fig. 4*b* shows the effect of breathing once very lightly on the heart, at the point marked by an arrow in the tracing. It is evident that the position of the spark on the tracing would be altered either by a change in the

rhythm of the beats or by a change in the velocity of contraction of the ventricle. But if the latter changed to a greater value the effect would be displacement of the spark which would then retain a steady position in successive beats. If the rhythm is altered there is a corresponding displacement in successive cycles even though the new heart rhythm is maintained without any acceleration, positive or negative. Fig. 5 shows the prolonged effect of a very slight degree of warming. Even at the end of the tracing the rhythm has not quite returned to its normal value.

Such observations throw into relief the regularity of the spontaneous rhythm of the heart when left to itself.

Some relations between duration of cycle and height of contraction.

The regularity of height generally observed in a series of ventricular contractions depends largely though not wholly on their being evenly spaced. A change in rhythm usually involves a change in the height of contraction of each beat. The nature of the relations varies in
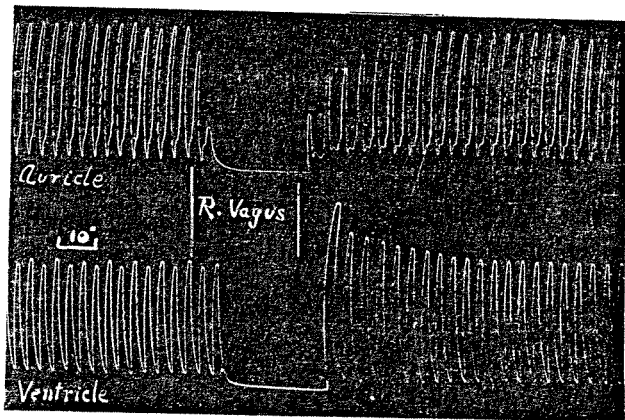
Fig. 6.

different cases; a quickened rhythm may lead to larger or to smaller contractions.

In the tortoise heart beating spontaneously at a temperature of about 15° C., if the rhythm of the excitations of the ventricle is slowed without other external change, provided this slowing is not excessive, there is a well-marked increase in the amplitude of the ventricular contractions. This is very well seen in Gaskell's experiments on the stimulation of the vagus. Gaskell (1880) showed that the vagus has

no direct action whatever upon the ventricle of the tortoise ; his figures show again and again that only when there is arrest of the auricle is the ventricle stopped. After such arrest the ventricular beats are at first greater. A repetition of this experiment is given in Fig. 6 for comparison with the other cases which follow. Here it is seen that the rhythm of the auricle after the arrest was a little slower than before, and so the ventricular contractions were a little higher.

The frequency of excitation of the ventricle in the spontaneously beating heart may also be altered by Gaskell's method of slitting up the auricle so as to obtain partial block. Fig. 7 illustrates the point well. When the condition of half block is reached, it is seen that the ventricular contractions are distinctly higher; the condition lasted only for two ventricular beats in this particular instance. A longer pause
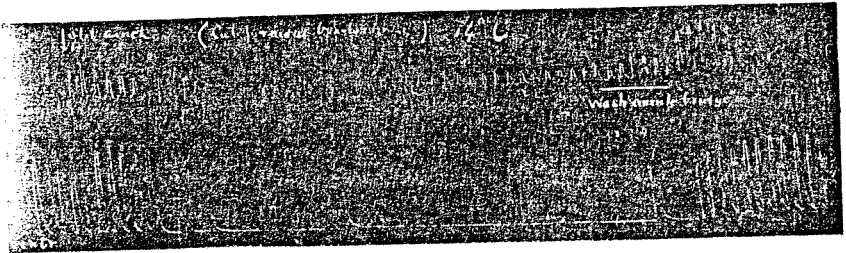

Fig. 7.

follows and then a beat gets over. The contraction is of just about the same height as those at the beginning of the tracing. A still longer pause follows; the application of a slightly alkaline Ringer's solution to the auricle bridge removes the block and it is then seen that the contraction which appears in the ventricle is much smaller than any before. Further, the recovery of the original rhythm is accompanied by marked increase in the height of the successive responses. We recognise, in fact, an ordinary "Treppe."

For a particular ventricle, under a given set of external conditions, there exists therefore an "optimal" rhythm at which the amplitude of the contractions will be greatest[1]. Too fast a rhythm or too slow a rhythm involves smaller contractions.

[1] Since writing this paper I have become acquainted with the admirable work of Bornstein (*Archiv f. (Anat. u.) Physiol.* 1906, p. 343; *Ibid.* 1907, p. 383; *Ibid.* 1909, p. 100). Bornstein has developed the conception of an optimal rhythm as regards height of contraction in heart muscle and he has shown that this optimal rhythm is increased by a rise in temperature and markedly altered by a number of drugs.

The spontaneous rhythm of the heart may be on either side of the optimum.

At a temperature of 12° or 15° C. the rhythm of the sinus of the tortoise heart is on the " quick " side of the " optimum " rate for the ventricular contractions. Thus, provided the whole musculature reacts on each occasion, in the tortoise heart under the conditions mentioned an extra systole of the ventricle will be of smaller amplitude than the ordinary contractions while a missed beat will be followed by a contraction greater than those preceding it. Such are indeed the experimental facts.

The condition in which the spontaneous rhythm of the sinus is on the " slow " side of the " optimal " rate for the ventricular contraction, I observed repeatedly in experiments on the excised hearts of the elasmobranchs *Torpedo ocellata* and *Scyllium canicula* at temperatures ranging from 20° to 25° C. In many cases the effect of slowing the
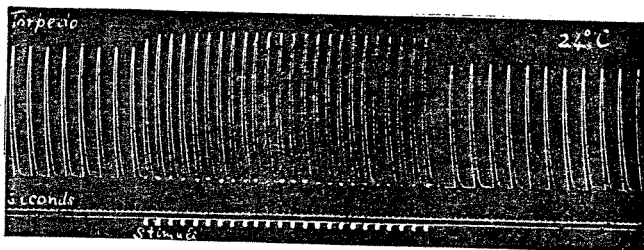

Fig. 8.

rhythm was to diminish the height of contraction, while quickening the rhythm increased the height of contraction. An instance is given in Fig. 8. At the beginning and at the end of this tracing the ventricle was beating in response to excitations arising in the sinus; during the middle portion rhythmic stimuli at a greater rate were sent in. This tracing resembles some of those obtained by Cushny (1912) from the isolated ventricle of the cat, beating spontaneously and therefore at a rate slower than the ordinary sinus rhythm. Yet Cushny's results do not appear capable of such simple expression as mine, for in some of his figures, it is seen that either a shortening or a lengthening of the normal pause results in an increased contraction. This applies however only to particular beats; it is not shown that there exists a " pessimal " rhythm somewhere in the middle of the observed range. There remains the possibility that in such cases there was sometimes contraction of a portion of the musculature which at other times was in abeyance, just as in Fig. 7 the various sizes of the auricular contractions do not

denote difference in the strength of contraction of the contracting muscle but merely differences in the amount of muscle which contracted.

It is observed that when a steady new rhythm is started, whether by natural or artificial excitations, the attainment of an apparent equilibrium as regards height of ventricular contraction is generally complete within half a dozen beats. In Fig. 9 I have plotted the heights of contraction in such equilibria against the frequency of stimulation in an experiment on the excised heart of *Torpedo ocellata* at about 24° C. The optimal rate was in this instance so high that, owing to the slowness of relaxation of the muscle it could not be satisfactorily determined.
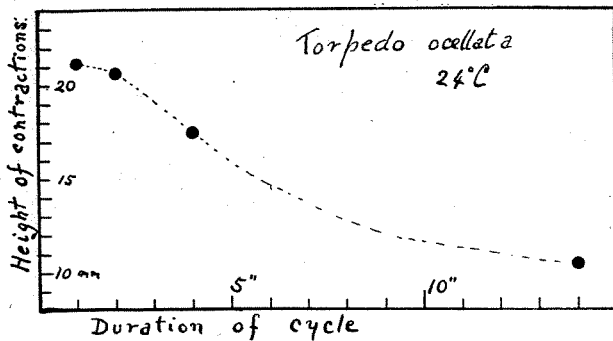
Fig. 9.
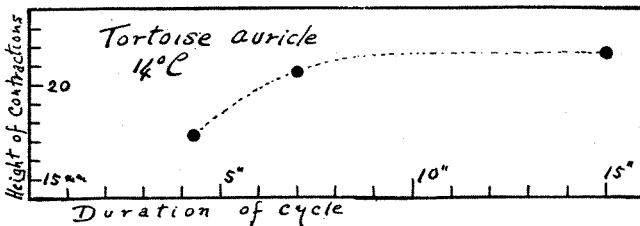
Fig. 10.

In the tortoise heart, the auricles, when uninjured, may show definite relations between the strength of contraction and the rhythm of excitation, similar to those described for the tortoise ventricle. I have plotted three observations on conditions of equilibrium from an experiment on the isolated tortoise auricle in Fig. 10 on the same scale as Fig. 9. It represents the opposite extreme, where the "optimal" rhythm is of extreme slowness.

G. R. MINES.

Relations between duration of cycle and certain features of the electrocardiogram.

In the following experiments I attempted to gain some informatio as to the effects of alteration of frequency of excitation on the characte of the individual electrical responses of the heart. I have discussed elsewhere (1913) the principal significant features of the experimenta electrocardiogram. The methods of derivation were those described in my former paper.
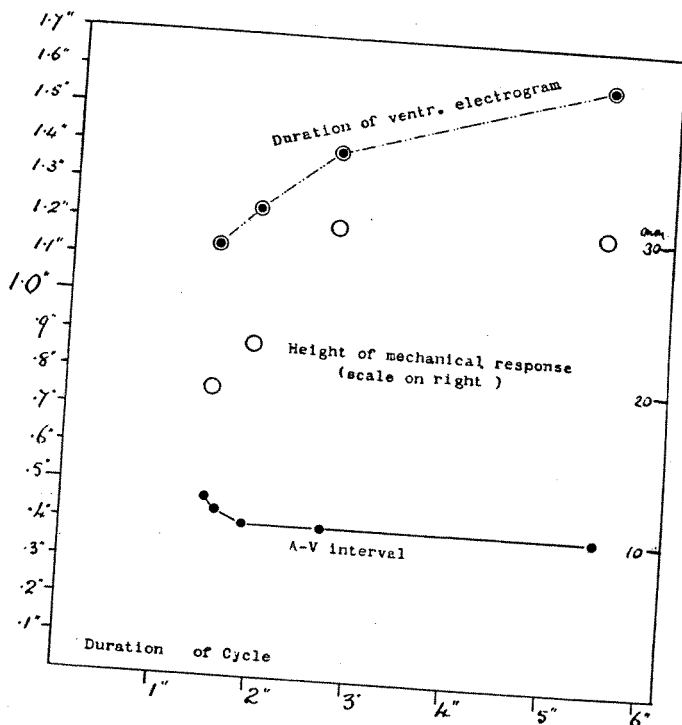
Fig. 11.

From the records on quickly moving paper measurements may be made most satisfactorily of the duration of the cycle, of the A–V interval and of the total duration of the ventricular complex—i.e. the duration of the excited state in the ventricle. In order to control the frequency of the excitations I employed the apparatus described in a previous section, and arranged two knock down keys with springs, one in the primary and the other across the terminals of the secondary coil of an inductorium, so that the arrangement would deliver a single break shock for each

revolution. Using the heart of the frog it was found that the application of induction shocks to auricle or ventricle often caused reduction in size of the spontaneous beats, even when the stimuli fell within the refractory period; the effect was evidently due to the stimulation of the intracardiac inhibitory apparatus. I therefore injected the frogs, after pithing the brains and some hours before the experiment, with a dose of atropine (1 c.c. of a 1% solution of the sulphate (Merck), subcutaneously) sufficient to paralyse the inhibitory endings. To remove the natural sinus excitations I tied a Stannius ligature. Mechanical records of one auricle and ventricle were taken at the same time as the electro-cardiogram. The stimulating electrodes were placed upon the auricles, or in some cases on the ventricle. These experiments were carried out at a temperature of 13° to 15° C. The results may be stated in a very
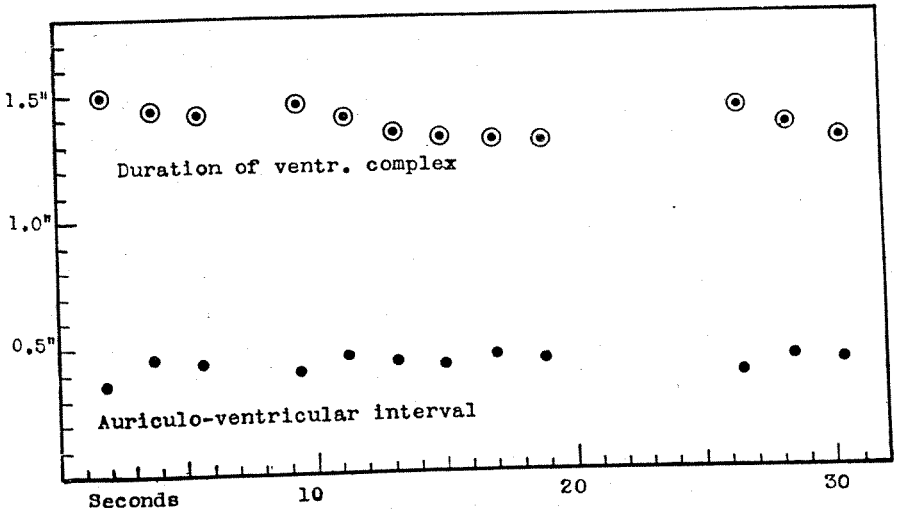
Fig. 12. Atropinised Stannius preparation, frog. Induction shocks applied to auricle. The points show duration of the periods indicated in single heart beats. Effect of missing stimuli.

few words. It was found that over a wide range of excitation frequencies, the electrocardiograms attained a constant form after a small number of beats at the new rhythm. As a rule records were taken of two or three beats at some particular rhythm, after the heart had performed about ten beats at this rhythm. Comparing a series of such tracings it was noted that as the frequency of the excitations was increased, provided the heart was able to respond to each, the duration of the electrical response in the ventricle diminished, while the duration

of the A–V interval increased. I have already published an example of the curves obtained by plotting such an experiment (*Proc. Phys. Soc.* May, 17, 1913). Another example is given in Fig. 11. Intermission of one or more excitations in such a rhythmic series was[*]always followed by an increase in the duration of the electric response in the next beat and a decrease in the A–V interval (Fig. 12). Precisely similar relations were found to occur if the stimuli were applied to the ventricle. The duration of the V–A interval was found to be subject to the same modifications as the A-V interval (see Fig. 13).
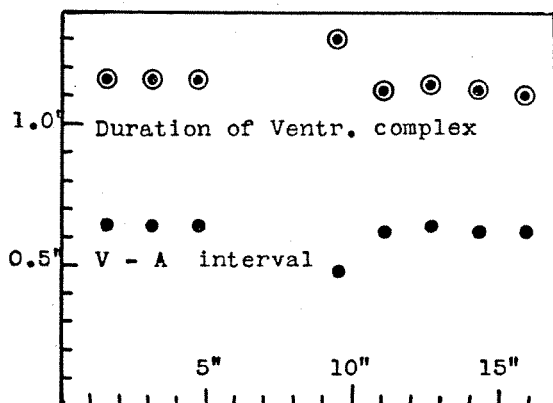
Fig. 13. Same as Fig. 12, but stimuli applied to ventricle, at rather higher frequency.

It was found that the time occupied in the rise of the ventricular spike also increased when the frequency of excitations was raised. Burdon-Sanderson (1884) first pointed out that the rate of rise of the spike gave information as to the rate of propagation of the excited state in the ventricle. Since the rate of propagation is reduced with greater frequency of excitation, it follows that under this condition the total duration of the excited state in the ventricle is greater than it would be if the rate of propagation were unaffected. The shortening of the electric response is more marked if the curves are measured from the downstroke of the spike (which is always very sudden in the uninjured heart) than if measured from the upstroke.

In Fig. 14 are given measurements from tracings taken with the heart in equilibrium at different rhythms, illustrating this point. A little reflection will show that the total duration of the ventricular complex represents the time during which there is any electrical disturbance in any part of the muscle between the two electrodes

The downstroke of the ventricular spike represents the instant of arrival of the wave at the distal electrode while the interval between this point and the end of the final variation represents (in those cases, at any rate, where propagation has been slow) the duration of the excited state under the distal electrode.

From these experiments, then, the inference is justified that in the muscle excited frequently each wave of excitation is propagated more slowly and yet lasts a shorter time at any one point in the muscle. In the experiments so far described, the shortening of the wave has been such as to exceed the slowing and thus the total duration of the excited state in the ventricle as a whole has been reduced. Obviously, if the length of tissue between the electrodes were sufficiently increased, the same amount of slowing or shortening of the wave of excitation, which in these cases has resulted in a reduction, would produce either no change or else an actual increase in the total duration of the excited state in the tissue as a whole. Similarly exaggeration of the slowing would yield the same results. Fig. 15 shows a case in point. This experiment
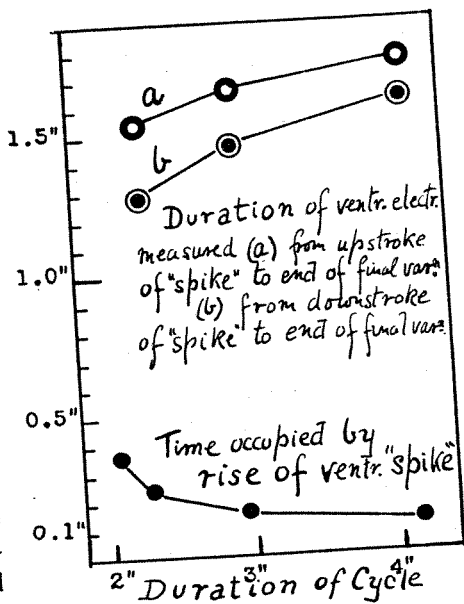
Fig. 14.

also brings out an important fact regarding the differentiation of the musculature responsible for the A–V transmission and the ventricular musculature. It is seen that the curve expressing the time of conduction of the electrical disturbance through the ventricular muscle does not begin to rise until a frequency of excitation is reached considerably higher than that at which the A–V interval is perceptibly lengthened.

Heart block. By gradual increase in the frequency of the stimuli applied to the auricles a rhythm could be reached at which every fourth or fifth beat failed to be transmitted to the ventricle. Again, with a slight quickening of the rhythm, every third beat would fail to pass, and again, with a slightly quicker rhythm there would be established a

condition of "half-block," every alternate beat being transmitted to the ventricle. The condition of half-block is easily maintained for prolonged series of beats : the other conditions of partial block are less stable, but may often be kept up with regularity for very many cycles. Their mechanism becomes clear from a consideration of the electrical records. On repeated excitation at a rhythm faster than that maintained before, the A–V interval tends to increase to a new equilibrium length. But equilibrium is not as a rule attained until several of the beats at the new rhythm have taken place. Thus in the early part of such a series the A–V interval becomes a little larger in each successive beat. Presently a beat is missed—then several are passed again and so forth.
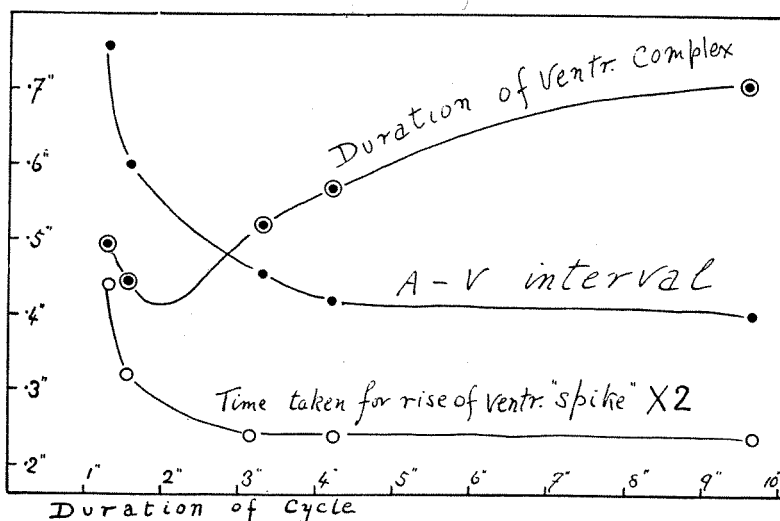
Fig. 15.

Again, if the period is adjusted so that the auricular excitations are followed alternately by ventricular responses (half-block) it is found that if several excitations are cut out, by closing an additional short-circuit key in the secondary, when the stimuli are admitted again at the same rhythm, two or three beats will pass in succession before the half-block is re-established.

Thus, approached abruptly, a rhythm is transmitted of higher frequency than could be transmitted if approached gradually.

In these experiments I found always that the auricle was able to respond to a rhythm of higher frequency than that capable of transmission from auricle to ventricle.

Refractory phase.

In sharp contrast to these relations stand those between the rhythm of stimulation and the response of a single chamber. If the electrodes are placed directly on the ventricle and the stimuli sent at shorter and shorter intervals, the duration of the ventricular complex of the electrogram becomes shorter, though not in the same proportion. It has often been remarked that the duration of the refractory period in heart muscle is related to the duration of the electrical response. In view of the data recorded in this paper a new and simple test of this notion is possible. If the absolute refractory phase of the ventricular muscle is directly related to the duration of the electric disturbance in the muscle, the ventricle should be able to take a higher rate of rhythm if this rate is approached gradually than if approached abruptly.

This deduction I have tested repeatedly with definite results. It is best demonstrated in the following way. The atropinised ventricle of the frog is arranged for stimulation with the apparatus described. Very thin platinum wires are tied on to the ventricle, care being taken that they do not touch any remnant of auricle or bulbus. The stimuli are sent in at first slowly, the rhythm is gradually quickened and the increase in frequency of the stimuli continued with the aid of the fine adjustment until the condition of half-rhythm appears—*i.e.* the ventricle responds to every other stimulus. The frequency at which this condition appears is noted. The rhythm is then slowed down until the ventricle again follows every stimulus. The rhythm is next increased gradually until it reaches a frequency somewhat less than that at which half-rhythm came on in the first trial. The ventricle continues to follow this regular rapid rhythm. If two or three of the induction shocks are short-circuited, and then the stimuli are sent in again at the same rate as before, it is found now that the ventricle responds only to every alternate stimulus. The explanation is simple enough. After the pause, the next response of the ventricle has a longer electric response and a longer absolute refractory period: the second stimulus of the new series therefore falls within the refractory phase and produces no response. The third stimulus finds the muscle excitable, the fourth inexcitable, and so on. But when the same rate of stimulation was approached by a gradual acceleration, each stimulus fell just outside the refractory period of the response due to the last, and thus while the

rhythm was accelerated the duration of the refractory period, like that of the electric response of the ventricle, became shorter and shorter.

Either of these conditions of equilibrium for this particular rhythm of stimulation may remain stable for a considerable time. The case provides a most interesting example of the way in which the previous history of the tissue may influence its immediate behaviour.

The same arrangement enables us to get a quantitative measure of the refractory phase of individual beats with two different rates of excitations. The procedure is as follows. The atropinised ventricle is stimulated with shocks at a frequency of say one in two seconds. The ventricle responds to every shock. The rate of stimulation is then very gradually increased so that each cycle is a very little shorter than that preceding it. The ventricle continues to follow the accelerated rhythm until a critical value is reached when it drops abruptly to half-rhythm. The stimulus first missed fell just inside the refractory phase due to the response aroused by the preceding stimulus. The rate at which stimuli are being delivered is now determined accurately by counting the revolutions of the stimulating apparatus in one minute. The period of the cycle is then very slightly less than the refractory phase of the ventricle when beating at the high speed. By moving the adjusting screw through a definite fraction of a turn each time, and turning it back this fraction when the half-rhythm is assumed, a more accurate measure of the cycle and refractory phase is obtained, but the difference between this and the other method is very slight. After having obtained the measure of the refractory phase at the highest frequency of response of which the ventricle is capable under the conditions of the experiment, the next step is to reduce the frequency of the excitations. It is found that the heart continues to respond to every second stimulus only, even when the frequency is reduced far below the value at which, on the ascending scale, every stimulus was followed by a mechanical response. By continuing the gradual retardation of the excitations a rate is ultimately reached at which the heart suddenly resumes the same frequency as the stimuli. The period of the cycle is now very slightly greater than the refractory period of the ventricle when beating at the low rate (see Fig. 16). The results of such an experiment will best be appreciated from diagrammatic presentation as given in Fig. 17.

In another experiment the following values were obtained:

Duration of cycle	·71″	1·94″
Refractory period	·71″	·97″

It is seen that over a quite considerable range of frequencies of excitation, there exist two possible equilibria, stable so long as the heart continues beating regularly and without interruption. We have seen how in this meta-stable condition, the transition from "whole" to half-rhythm may be brought about by the intermission of one or more excitations. The reverse transition, from "half" to "whole" rhythm may be brought about while the rhythmic stimuli from the apparatus continue. This is done by interpolating an extra stimulus at the proper time. An extra stimulus, applied shortly after the stimulus to
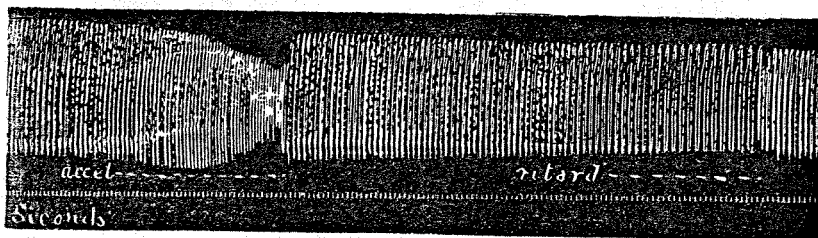
Fig. 16.
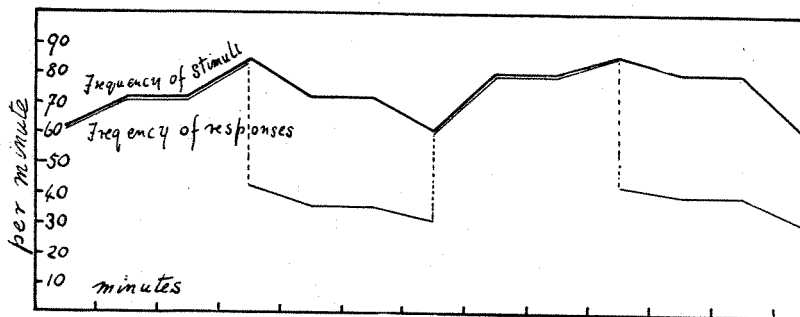
Fig. 17.

which response is missing, may provoke an extra systole. The extra systole will of course have a refractory phase shorter than the refractory phase of the preceding beats, and although the next of the rhythmic series of excitations will fall within it, the next but one (belonging to the hitherto "unaccented" series) will find the tissue ready to respond. But it will also reach the ventricle sooner after a response than has an effective stimulus before; thus the refractory phase will be shorter again, and probably so short that the next stimulus falls outside the refractory phase. Once started the new heart rhythm continues. The nature of the mechanism by which one single extra systole may under

certain circumstances produce enduring effects on the heart rhythm is thus quite evident.

The transition from whole to half-rhythm is not always so simple. Particularly when the ventricle has been suspended for some time, the condition of alternation makes its appearance and complicates matters to some extent. The refractory phase of some portions of the muscle differs from that of other portions, and therefore the frequencies at which they adopt the new manner of response are different. Fig. 18 was taken from the same experiment as Fig. 16 but 20 hours later, the ventricle meanwhile remaining suspended in moist air. It is seen from the tracing that the transition from one rhythm to the other is marked by a period of alternation. Sometimes there is a period of partial tetanus.
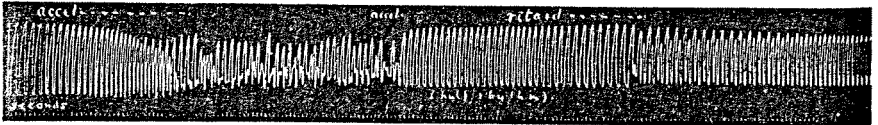

Fig. 18.

Alternation.

The condition in which cardiac muscle acted upon by evenly-spaced stimuli (either natural or artificial) responds with alternate large and small contractions, has been of late the subject of much discussion. The explanation offered in 1882 by Gaskell for the condition observed by him in the frog's ventricle has been often misinterpreted. Properly understood, it seems to account for all the diverse phenomena of alternation. "Owing to some cause which affects the ventricle unequally, the excitability of the ventricular muscle is at the time not absolutely the same throughout, so that, although the impulses remain the same in strength, yet certain parts which possess a lower excitability are able to respond only to every second impulse while the rest of the tissue responds to every impulse" (Gaskell, *loc. cit.*). In other words, while some of the muscle follows the rhythm of the stimuli, other parts take the half-rhythm. The mistake which has been made in interpreting this hypothesis is to assume that the portions of the muscle which take the half-rhythm all follow the odd or all follow the even series of stimuli (Muskens, 1907 ; Hering, 1908). Yet there is no ground for such an assumption : indeed it is incompatible with many experimental results.

In particular I would call attention to the cases, not infrequent, where a marked alternation of the electrogram exists in the absence of any apparent mechanical alternation (Mines, 1912, Figs. 8 and 10).

If we call the whole musculature under consideration V and the muscle whose excitability is lower than the rest v, this portion must be subdivided according as it chances to respond to the odd or the even series of excitations. The alternating series will usually run thus: $V-v_1$, $V-v_2$, $V-v_1$, $V-v_2$, etc. not simply V, $V-v$, V, $V-v$. The latter respresents indeed one special case, but cannot be reconciled with the condition of *p. alternans celatus* which I have described, nor yet with many clinical observations. On the rational interpretation of Gaskell's hypothesis, *p. alternans celatus* represents the case where $v_1 = v_2$, so that their mechanical effects are alike, but owing to their different positions in relation to the electrodes, their effects on the electrogram are dissimilar.

In 1909, Hering arrived at a correct interpretation of Gaskell's hypothesis which he expressed by saying that in the alternating ventricle e v e r y beat is a partial asystole.

Against this view, H. Fredericq has levelled strongly adverse criticism. He maintains that the "partial asystole" hypothesis is upset by some observations made by himself (1912) and by Weekers (1906). Fredericq's objections are as follows: (*a*) Even in a small strip of muscle exhibiting alternation he has failed to see alternate contraction of different parts of the muscle. (*b*) If the rate of stimulation is reduced, alternation may continue over a considerable range. (*c*) The periodic variation in height of contraction may be sometimes more complex than mere alternation. (*d*) Alternation may be elicited from auricular muscle as well as from ventricular.

I shall examine these objections in order.

(*a*) There is no reason to expect that the portions of muscle which exhibit periodic asystole should form circumscribed masses. They may consist equally well of fibres distributed pretty evenly through the muscle and not necessarily in direct connexion with each other. Under such circumstances mere naked-eye inspection will certainly fail to show whether movement of some portion of the muscle is active or passive.

As a matter of fact, in advanced alternation of the frog's ventricle it sometimes happens that the alternate asystole of some portion of the muscle can be made out by simple inspection. But this is not usual.

(*b*) If the refractory phase remained of constant length under various conditions it would certainly be hard to understand why, on the

"partial asystole" hypothesis, reduction in frequency of stimulation of an alternating strip should not immediately abolish alternation, the stimuli falling outside the refractory period of the "asystolic" portions of the muscle. But, as I have shown, reducing the frequency of excitation increases the duration of the refractory phase of each excitation. Therefore alternation may sometimes persist over a considerable range of frequencies.

(c) This offers no real difficulty. The condition in which the muscle responds to every third stimulus is stable over a certain range of excitability and of frequency of excitation. So also is the condition in which every third stimulus fails to excite a response. Now if some portions of the "periodically asystolic" muscle are in either of these relations while other portions are in the simple "alternating" relation, it is obvious that such a condition offers a reasonable basis for a great variety of complex rhythms. In this way such rhythms as that seen in
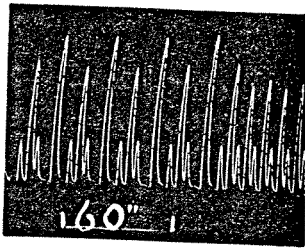
Fig. 19.

Fig. 20.

Fig. 19. Auricle strip from tortoise stimulated with strong induction shocks at regular intervals.
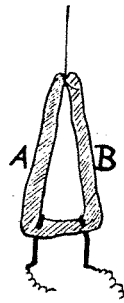
Fig. 19 receive their easiest explanation. Yet since the ranges of excitability and of stimulation frequency over which the $\frac{1}{3}$ rhythm or the missed third beat are stable are much narrower than those compatible with simple alternation, it is not surprising that the latter is a much commoner condition than the more complex types of rhythm.

(d) The phenomenon of alternation in the auricle has been seen less often than alternation in the ventricle because the majority of observations have been made on naturally beating hearts. The duration of the refractory phase in the auricle is less than that in the ventricle, and while the natural rhythm of the sinus fairly often reaches such a frequency that portions of the ventricle drop to half-rhythm, this rarely

obtains for the auricle. Yet by artificial stimulation, as Fredericq has shown, the auricular muscle will show the condition of alternation.

Although Gaskell's hypothesis does not require that the portions of muscle which fail to respond to alternate excitations shall be visibly separated, yet it is possible to arrange experimentally that they shall be. The experiment I shall now describe shows very clearly that a series of similar stimuli, passing through one and the same region, may excite two different tracts of muscle alternately. It also affords direct evidence in support of an hypothesis advanced elsewhere to account for the fact, observed by Windle (1910) and others, that the interpolation of an extra systole is very liable to alter the course of alternation, but may either increase or diminish it.

A ring is cut from the auricles of a tortoise. It is suspended from a thread tied round at one point so as to produce block. The ring is caught below by two stout platinum hooks (see Fig. 20). A single stimulus applied anywhere to the quiescent ring causes contraction in all parts of it. With the apparatus before described break induction shocks of equal strength and evenly spaced are passed through the platinum electrodes. The whole ring responds to every stimulus. The frequency of the stimuli is increased until a stage is reached when the whole ring responds to every second stimulus. Thus:

St.	St.	St.	St.
$A+B$	—	$A+B$	—

If now a mechanical or electrical stimulus is applied to one side or the other, so as to provoke an extra systole (it must come, of course, shortly before the effective member of the rhythmic series which is being continued), the character of the responses at once changes to this:

St.	St.	St.	St.
A	B	A	B

Another extra systole, or the intermission of a few of the rhythmic stimulations, will restore the first condition where A and B go off together. It seldom happens that A and B are of equal strength and thus the record made by a lever to which the string is attached will show alternation in height of responses when A and B contract alternately. Tracings for such a preparation are shown in Fig. 21.

The experiment provides a coarse model of extreme alternation in which the alternating portions of muscle are separated visibly. Its real interest lies in the fact that at any time, if the rather rapid rhythmic series of stimuli is interrupted, a stimulus applied to the region A or to

B causes response all over the muscle. Their apparent independence during the course of alternation is essentially due to a special condition of the muscle which characterises its dynamic equilibrium at a rather high level of activity.

Reciprocating rhythm.

I shall now describe a type of rhythm which I have observed occasionally in the course of experiments where two chambers of the heart were used and where rhythmic stimulation at a fairly high pace had been applied. The phenomenon to which I refer may be called reciprocating rhythm. I have seen it in three experiments on the auricle-ventricle preparation of the heart of the electric ray, and in one experiment on the ventricle-bulbus preparation from the frog[1]. The preparations were, before stimulation, either quiescent or giving infrequent spontaneous beats.
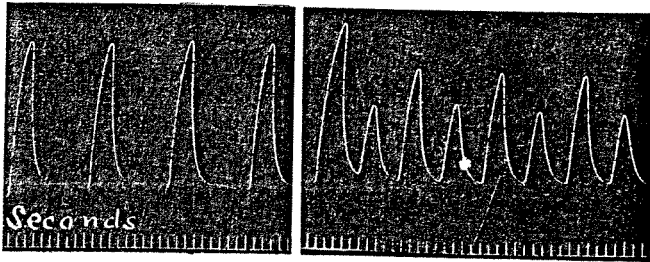
Fig. 21. From preparation shown in Fig. 20. Rate of stimulation the same in both pieces of tracing. See text.

After the application of rhythmic stimuli at some particular rate, the cessation of the stimuli was followed by a quick reciprocating movement of auricle and ventricle or of ventricle and bulbus. The appearance of the heart gave the impression that the beats of the ventricle were caused by those of the auricle or bulbus, while these in turn were caused by the ventricle. This was confirmed by observation of the effect of sending in a single shock, either to the auricle or to the ventricle. This, if timed properly, instantly arrested both chambers; its effect was not due to stimulation of the intracardiac vagus since in one of the experiments the heart was atropinised (see Fig. 22).

The rhythm of each chamber was directly dependent on that of the other. The rhythm was rapid and the interval between the auricle

[1] In each experiment the condition was produced and abolished repeatedly.

and ventricle contractions was apparently the same as that between the ventricle and auricle contractions. What explanation can be offered? Let us start with the auricular excitation. This is transmitted over the slowly conducting tissue to the ventricle. But immediately after, the excitation of the ventricle is transmitted back to the auricle. It is unlikely that the actual tissue which transmitted the impulse from auricle to ventricle could immediately transmit another impulse in the reverse direction. Therefore in all probability the portion of the auriculo-ventricular connexion responsible for the transmission from ventricle to auricle was quiescent during the previous transmission from auricle to ventricle. The connexion between the auricle and ventricle is never a single muscular fibre but always a number of fibres, and although these are ordinarily in physiological continuity,
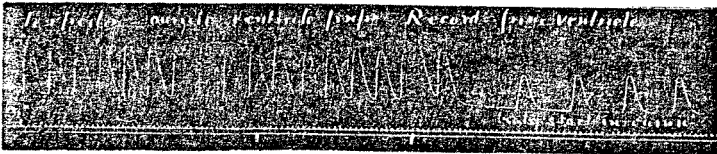

Fig. 22. The bottom line indicates single induction shocks thrown in. See text.

yet it is quite conceivable that exceptionally, as after too rapid stimulation, different parts of the bundle should lose their intimate connexion in precisely the way in which different parts of the ventricular muscle contract independently in the condition of *pulsus alternans.*

A slight difference in the rate of recovery of two divisions of the A–V connexion might determine that an extra systole of the ventricle, provoked by a stimulus applied to the ventricle shortly after activity of the A–V connexion, should spread up to the auricle by that part of the A–V connexion having the quicker recovery process and not by the other part. In such a case, when the auricle became excited by this impulse, the other portion of the A–V connexion would be ready to take up the transmission again back to the ventricle. Provided the transmission in each direction was slow, the chamber at either end would be ready to respond (its refractory phase being short) and thus the condition once established would tend to continue, unless upset by the interpolation of a premature systole. The experiments I have been able to make have given results in accord with this conclusion.

To test the hypothesis, I devised another experiment, which I carried out on the heart of a tortoise. The heart was excised and the sinus venosus cut away. A longitudinal incision was then made extending through the anterior and posterior walls of the auricle and ventricle, so that the heart was converted into a ring, as shown in Fig. 23. The auricles were connected with the ventricle in two places, and across each of these junctions it was found that excitation

Fig. 23.

could pass. The experiment was made at a temperature of 21° C. On stimulating any part of the heart there was, after a slight pause, contraction in each of the other parts. After stimulating several times, the following condition appeared. The four portions of the heart marked V_1, V_2, A_1, A_2, contracted in the order given, with distinct pauses between the successive portions. This cycle of events was repeated over and over again without any further external stimulation. When V_1 became excited the excitation spread to V_2 but not back to A_2 which was still refractory. From V_2 it spread to A_1, from A_1 to A_2, now recovered from its refractory state, and then again from A_2 to V_1. While the cycle was being regularly repeated, the application of an external stimulus to either of the chambers, if out of phase with the cycle, stopped the contractions, showing that they were not originated by an automatic rhythm in any part of the preparation, but were due to a wave of excitation passing slowly round and round the ring of tissue.

It seems then that the reciprocating rhythm may reasonably be regarded as due to a circulating excitation.

The circumstances under which the phenomenon made its appearance were such as to produce the favourable conditions of slow conduction and short refractory period. By its continuance the circulating rhythm would tend to maintain these conditions. The conditions are easily upset by the occurrence of an extra systole and they may be re-established by other extra systoles. I venture to suggest that a circulating excitation of this type may be responsible for some cases of paroxysmal tachycardia as observed clinically.

The to-and-fro character of the movement in the cases of reciprocating rhythm which I have described recalled in a curious way the appearances sometimes seen in fibrillation of the mammalian heart, with the difference that in fibrillation, different portions of the muscle in a single chamber, instead of separate chambers of the heart, appear to exhibit reciprocating rhythm.

Fibrillation.

The data provided by the experiments recounted in this paper suggest an explanation of the important and interesting condition of *delirium cordis* or fibrillar contractions. As is very well known, this condition is brought on in the mammalian heart with great ease by the stimulation of the surface of the heart with strong faradic currents. The stimuli must be applied usually for some seconds before the condition develops; it then continues, often for a long while, after the stimuli cease. Now the effect of a faradic current on the muscle will be like that of a series of induction shocks at gradually decreasing intervals, beginning with an interval just greater than the refractory phase of the chamber as measured for the first beat of the series considered. Each cycle becomes a little shorter than its predecessor, and hence the duration of the electric response and the refractory phase becomes shorter, while the rate of transmission of the excited state gets slower. The effects of such alteration on the condition of affairs in the heart muscle will be profoundly important. The wave of excitation in cardiac muscle is normally very rapid in propagation but also very long in duration. On increasing the frequency of excitation, the wave becomes both slower and shorter. Under these circumstances it becomes possible for the whole wave to be present at one time on the muscle column.

The results described are capable of simpler expression in the following way. The effect of increased activity of the heart muscle is to decrease the rate of propagation and to decrease the length of the wave of excitation. Ordinarily, in the naturally beating heart, the wave of excitation is so long and so rapid that it spreads all over the ventricle long before it has ceased in any one part. Under the altered conditions of increased frequency it is possible that this should be no longer the case, and thus that, the wave being slow and short, more than one could exist at one time in a single chamber.

No fact is better established concerning the histological structure of cardiac muscle than that there exist numerous connexions between the various portions or columns of cells. There exist therefore closed circuits in the myocardium. Supposing an excitation to be started in such a closed circuit and supposing that for some reason it travels in one direction but not in the other. If the rate of propagation is rapid as compared with the duration of the wave, the whole circuit will be in the excited state at the same time, and the excitation will die out.

This is represented diagrammatically in Fig. 24*a*. But if, on the other hand, the wave is slower and shorter (and it is made slower and shorter by the conditions which produce fibrillation) the excited state will have passed off at the region where the excitation started before the wave of excitation reaches this point on the circle at the completion of its revolution. Not only so, but there will have been time for the excitability of the muscle to return to something near the value it had at the time of the first excitation. Under these circumstances, the wave of excitation may spread a second time over the same tract of tissue; once started in this way it will continue unless interfered with by some external stimulus arriving during that part of the cycle when the portion of the muscle stimulated is neither in the excited state nor in the condition of depressed excitability which outlasts it (Fig. 24*b*). The condition of depressed excitability which persists after the absolute refractory phase has passed (relative refractory phase) is represented in the diagram by dots.
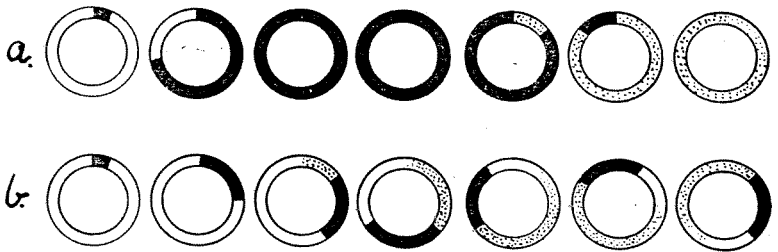

Fig. 24.

The circulating rhythm here described[1] is precisely comparable to the state of affairs produced in rings cut from the bells of Medusae in the experiments of A. G. Mayer.

Mode of conduction in the normal heart.

The peculiar character of the heart movements during fibrillation has been adduced by Kronecker and by L. Fredericq (1906) as one of the strongest pieces of evidence that the propagation of excitation in the auricles and ventricles in ordinary co-ordinated contractions is by nervous paths. The argument is charmingly simple. It may be stated thus. The propagation of contraction during fibrillation is so slow that it can be followed by the naked eye. It is therefore due to muscular conduction. The propagation of contraction when the heart

[1] See Addendum, p. 383.

is beating in a normal fashion is very much faster and presents a different appearance. It is therefore not muscular, except in the bundle of His, but nervous.

Evidently this argument might be started at either end. It merely insists on the difference in rate of propagation of the excited state in fibrillation and in ordinary contraction and assumes that the difference is explicable only by conduction through different sorts of tissue in the two cases. But, as I have shown, with increase in the frequency of excitation of the heart muscle the rate of propagation of excitation falls off along a smooth curve. And whether the rapid succession of excitations is maintained by artificial stimuli or automatically as in fibrillation, the rate of conduction in heart muscle which is so often excited becomes extremely slow. If this slow conduction were due to a different tissue from the quick conduction the curves relating rate of conduction to frequency of excitation must show a sudden break, instead of a continuous relation. Accordingly the only possible conclusion is that the conduction in fibrillation is through the same tissue as in the normally beating heart. According to Kronecker and L. Fredericq the path in fibrillation is certainly muscular.

Relations between duration of electrical response and amplitude of mechanical response.

It has been remarked before that there often appears a relation between the amplitude of the mechanical response of the ventricle and the duration of the electrical response. A longer electrical response is often accompanied by a greater mechanical response. This appears, for example, very clearly in many of the experiments published by Miss Dale and myself (1913). In many cases the parallelism is so striking that it is impossible to dismiss it as accidental. Yet such a parallelism is by no means invariable. And, as usual, it is precisely to the exceptions that we must look in seeking an interpretation of the phenomenon.

The most important cases where there is divergence between changes in duration of the electric response and amplitude of the mechanical response are as follows :

(1) In the absence of calcium, the contractile mechanism is thrown out of gear, while the general metabolism of the muscle continues. As has been pointed out before (Mines, *loc. cit.*), the removal of calcium probably causes the dissociation of some calcium compound of which the actual contractile strands are built. Where the contractile mechanism

is thus directly upset it is unlikely that changes in the events antecedent to the shortening process can be reflected in the shortening process.

(2) There is a limit set to the possible amount of shortening of the contractile mechanism. If the duration of the electrical response is increased when this limit has been reached, it is obvious that the relation we are considering cannot be manifested. This appears to be the case when Sr is substituted for Ca in the perfusion fluid (Mines, *loc. cit.*). The contractions being already as large as they ever can be, the substitution of Sr lengthens the electrical disturbance and also the mechanical response, but it cannot increase the height of the latter.

(3) A most interesting exception occurs after a rather long pause, when the " Treppe " is well marked in the mechanical responses. In such cases the first of the mechanical responses of the new series is smaller than its successors; but the first of the electrical responses is longer than those which follow. For example :

Frog. Atropinised Stannius preparation. Stimulation of auricle. Induction shocks at intervals of 2·18″.

A–V interval	Duration of ventr. electrogram	Amplitude of mech. response
·45″	1·22″	26 mm.
·46	1·22	26
Three stimuli cut out.		
·38	1·30	23
·44	1·26	26·5
·44	1·26	27

(4) Another interesting exception has been noted as a result of stimulation of the sympathetic. Miss Dale and I have shown that stimulation of the sympathetic, increasing the frequency of the beat, may produce at the same time shortening of the electrical response of the ventricle and increase in the amplitude of the beats. But, as we have shown, the reduction in duration of the electrical responses which results from increased frequency brought about by sympathetic stimulation is not nearly so great as the reduction which results from increase in the frequency apart from the sympathetic stimulation. For the direct effect of the sympathetic on the ventricle (that is to say the effect obtained after elimination of the effects due to change in frequency) is an increase in the duration of the electric response.

On the general hypothesis of the nature of the processes involved in muscular contraction which has been outlined in a previous paper (1913), the electrical response has been regarded as an immediate indication of the liberation of acid in the tissue. It is but a slight extension of the

hypothesis to suggest that the duration of the electric response bears a direct relation to the amount of acid liberated. If the contractile act depends, as has been supposed, upon the action of acid on some material which, like catgut, shortens upon the application of acid, then other things being equal, the liberation of a larger amount of acid will determine a greater amount of shortening. But it is certain that the amount of shortening will not depend simply on the amount of acid liberated, but rather on the concentration of acid present around the contractile elements during or after the liberation of acid. If for example the acid is liberated into a medium already alkaline, the resultant acidity will be less than if the medium at the start were neutral. It is only when the hydrogen ion concentration is raised above a certain value that the effect on the contractile material will appear. If the general hydrogen ion concentration is much below this critical value, even a large liberation of acid may cause less effect than will be produced by a smaller liberation of acid when the acidity is nearer the critical value[1]. Now after a prolonged pause, the hydrogen ion concentration is certainly lower than after a period of activity. Oxidative removal of lactic acid is a slow process (Fletcher and Hopkins, Hill), and during the pauses between successive contractions of the heart, the removal is certainly not complete. A longer pause will mean more complete removal.

In this way we can harmonise the results described in the previous sections of this paper.

In the heart of the tortoise or frog at 15° C. and without perfusion the following relations hold.

With increased length of pause, the duration of the electric response to excitation after the pause increases. With increased length of pause the amplitude of the mechanical response to excitation increases up to a certain point and then decreases. To put it in another way, the optimal rhythm for amplitude of mechanical response is a quicker rhythm than the optimal rhythm for duration of the electrical response. The former is slow, but the latter is so slow that we have never yet waited long enough to reach it!

. If we assume that the duration of the electrical response gives an indication of the amount of lactic acid liberated, the general nature of the explanation offered for the relations described may be presented by the diagrams in Figs. 25 and 26. In these diagrams the areas of the

[1] Clearly, not only the $C_{H^{.}}$ but also the 'reaction-inertia' (Walpole) will be of importance.

circles represent the amount of lactic acid liberated in one contraction. The position of the centre of the circle (on the vertical axis) represents the level of acidity in the region of the contractile elements just before the acid is liberated. The horizontal line indicates the level of acidity which must be reached before the contractile elements begin to shorten. The portion of the circle which is blackened represents therefore the portion of the liberated acid which is effective in the production of contraction.

In Fig. 25 is shown the supposed effect of a short pause. After the pause, the liberation of acid is greater, and since the pause was short
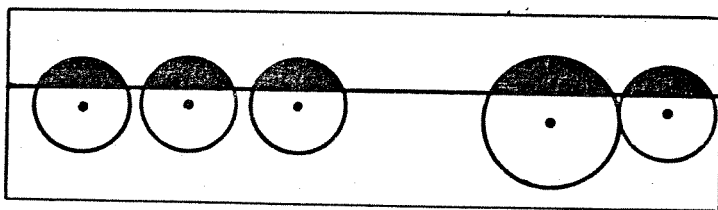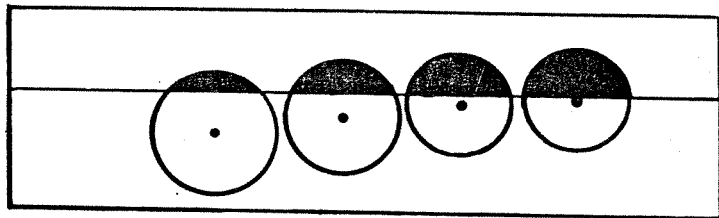

Fig. 25.

Fig. 26.

the general level of acidity has not fallen much. The effective concentration of acid is therefore greater than that due to the preceding or the succeeding excitations. Fig. 26 represents the other case. Here the events supposed to occur after a prolonged pause are represented. The liberation of acid is greatest in the first response of this series and in successive responses it diminishes. But the first, large, discharge is made at a low level of acidity, therefore but a small fraction is available to cause contraction. The succeeding liberations, though smaller, are more completely utilised in producing contraction, because of the remaining effect of the preceding excitations. The contractions therefore exhibit the staircase effect.

Interpretation of the effects upon the electrogram of altered frequency.

I shall conclude this paper with a brief discussion of the significance of the effects here described in the light of facts presented elsewhere concerning the influence of hydrogen ion concentration on various properties of the muscle.

The C_H. in any region of the muscle depends on a very complex equilibrium, in which the following factors take part:

(*a*) The periodic liberation of lactic acid in the muscle which follows each successful stimulation.

(*b*) The diffusion of the acid away from the points where it is produced.

(*c*) The oxidative removal of the acid.

(*d*) The C_H. of the fluid bathing the muscle.

It is certain that increased activity of the muscle or increased C_H. of the fluid bathing the muscle will both tend to shift the equilibrium so as to cause increase in the mean C_H. at any point in the muscle. It would appear that the mean C_H. of some region in the muscle has an important influence on the rate of propagation of the disturbance following stimulation of the muscle. Further, this region is much more accessible to the acid change from within than to change in the fluid bathing the muscle.

Transmission in the A–V connexion. I have shown in a previous paper that an effect of a small increase in C_H. of the fluid perfusing the heart is an increase in the duration of the A–V interval. The A–V interval may be greatly lengthened in this way without slowing the propagation through the ventricle.

Similarly, by increasing the activity of the heart muscle the propagation through the A–V connexion is slowed before any effect is produced on the propagation rate in the ventricle. There is a great difference in the rate of attainment of equilibrium in the two cases. Changing the frequency of excitation of the heart muscle, the new equilibrium value for the A–V interval is reached in the course of a few beats. But on altering the C_H. of the perfusion fluid there may be progressive change for half an hour or more.

Transmission in the ventricle. The rate of propagation of the excited state is slowed by increasing the frequency of the heart; the increase needed being greater than that required to slow conduction in the A–V connexion. Although a small change in the C_H. of the perfusion fluid does not appreciably alter the rate of propagation in the ventricle

it has been shown by Burridge (1912) that treatment of the heart with a strongly acid solution causes great slowing in the rate at which contraction appears to spread over the ventricle. The slow passage of the visible contraction certainly indicates here a slow propagation of the event which precedes contraction—the propagated disturbance.

Heart block. It has been shown that the A–V connexion fails to transmit excitations if these are sent in too rapid succession. The condition of partial block is produced also very readily by perfusing the heart with acid solutions.

Heart block can also be produced by a too rapid excitation. It appears that increased acidity of the conducting strands between auricle and ventricle produces a decrement in the transmission of the excited state at the same time as it produces slowing in the rate of propagation. It is at present uncertain how far the production of a decrement and the slowing are to be regarded as different aspects of the same change.

That acidity can produce a decrement leading to complete block in heart muscle is readily shown on the slit auricle preparation from the tortoise heart as described by Gaskell. The application of an acid solution to the auricle " bridge " results after some minutes in the production of block; the block is removed by washing with an alkaline solution. In the same way, making incisions in the muscle near the " bridge " often causes temporary block, which may well be due to the liberation of acid which Fletcher and Hopkins have shown to result from all forms of mechanical injury to muscle. The block is removed by washing—best with an alkaline solution.

Duration of ventricular electrical response.

It has been shown that the duration of the excited state in the ventricle (as determined by the ventricular electrogram) is reduced as the frequency of excitation is increased. The relation between this change and the changes produced by alteration in $C_{H^.}$ of the perfusion fluid of the heart is not at present clear.

It is difficult to avoid the conclusion that there is some connexion between $C_{H^.}$ in some part of the muscle and the length of the electrical disturbance, since it has been shown that alteration in the $C_{H^.}$ of the perfusion fluid can cause marked alteration in the duration of the electrogram. Yet although in some cases increased $C_{H^.}$ has led to decreased duration of the electrogram, in other more numerous instances, decrease in $C_{H^.}$ has resulted in decreased duration of the electrogram.

The data are not extensive enough to enable any definite conclusion on this matter to be reached at present, but two possibilities require consideration.

In the first place, it may be that there exists an optimum C_H. at which the electrogram is longest and that this optimum is so situated that the experiments on artificial modification of rhythm have always been on the "acid" side of it, while some of the perfusion experiments reached the "alkaline" side of the optimum. Another possibility is that the duration of the electrogram depends not, or not only, on the C_H. in some particular region, but on the difference of C_H. across some boundary separating two phases—just as the E.M.F. of a concentration cell depends on differences of concentration. In such a case the production of more acid on the "inner" side would result in the same sort of change as the application of a more alkaline solution outside.

The question may, I hope, be solved by the combination of the types of experiment described in this and preceding papers on single preparations.

SUMMARY OF CHIEF CONCLUSIONS.

The accuracy of the rhythm originating in the sinus venosus of various cold blooded hearts isolated from nerve influence is very high. With a cycle of 2″ there may be variation of less than 1 % in series of 20 beats or more.

A new method of detecting small changes in rhythm is described, and the influence of minimal changes in temperature demonstrated.

With increasing frequency of stimulation, each wave of excitation in the heart muscle is propagated more slowly but lasts a shorter time at any one point in the muscle. The wave of excitation becomes slower and shorter. Similarly the refractory phase (towards strong induction shocks) is shortened.

It follows that by gradual acceleration of the rate of stimulation, the ventricle can be caused to beat at a higher rate than if the rate of stimulation is abruptly raised. Thus with one and the same rate of stimulation there can exist two meta-stable equilibria, in one of which the responses are twice as frequent as in the other. Transition from one state to the other may be brought about by a suitably placed extra systole.

Certain of these results bear directly on the question of the nature of *pulsus alternans.* They afford strong confirmation of Gaskell's view

that this condition is dependent on local differences in the condition of the heart muscle.

If a closed circuit of muscle is provided, of considerably greater length than the wave of excitation, it is possible to start a wave in this circuit which will continue to propagate itself round and round the circuit for an indefinite number of times. The condition is readily upset by an extra systole. It is shown that these observations offer a simple explanation of certain cases of reciprocating rhythm between two chambers of the heart. It is capable of further extension to explain the condition of fibrillation, which arises under precisely those circumstances which produce the conditions in heart muscle essential for the manifestation of circulating excitation, namely a slow and short wave of excitation. Once started, the high frequency of repetition of the excitations tends to maintain the condition.

Certain relations between the duration of the electric response in heart muscle and the amplitude of the mechanical response are described and a simple theoretical interpretation is developed.

It is shown that certain of the changes in the electrocardiogram which result from increased frequency of heart beat may be accounted for by change in the C_H. of some region of the muscle.

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ADDENDUM.

On circulating excitations in the musculature of a single chamber.

Since the above paper was sent to press I have made further observations on circulating rhythm, which may be briefly noted here. The experiments were carried out at the Plymouth Marine Laboratory on ring preparations cut from the auricles of large rays. In such preparations a single stimulus applied to any point in the ring starts a wave in each direction. The waves meet on the opposite side of the ring and die out. But by the application of several stimuli in succession it is sometimes possible to start a wave in one direction while the tissue on the other side of the point stimulated is still refractory. Such a wave runs round the ring sufficiently slowly for the refractory phase to have passed off in each part of the ring when the wave approaches it. Thus the wave circulates and may continue to do so for fifty revolutions or more. Usually an interpolated extra stimulus stops the wave at once. The preparation may then remain quiescent or it may start beating with a slow spontaneous rhythm. In the latter case the totally different characters of the spontaneous rhythm and the circulating excitation are very striking.

Erratum. In l. 3, p. 232 of my paper in vol. XLVI. of the Journal "the muscle no longer, has" *should read* "the muscle, no longer has."