The Rhythm of the Heart Beat. I—Location, Action Potential, and Electrical Excitability of the Pacemaker

By J. C. Eccles and H. E. Hoff

(The Physiological Laboratory Oxford)

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Anatomical and physiological investigations on the heart during the last fifty years have contributed a sound body of knowledge concerning the location of its rhythmic centre (the pacemaker) and the spread thence of excitation. The classical controversy between the exponents of the neurogenic view and of the myogenic view of the origin of the heart beat, may now be regarded as settled in favour of the latter, for the evidence against even the nerve fibre modification of the neurogenic theory is overwhelming, and none of the evidence supporting it stands the test of modern criticism. There remains the more fundamental problem of the nature of those processes in the rhythm centre which are responsible for its recurrent discharge. There has been much speculation concerning them, but no systematic attempt at elucidation.

Engelmann (1895, 1897) postulated a constant weak "inner stimulus," to which the centre is sensitive in varying degree; this sensitivity (considered to be identical with its sensitivity to electrical stimulation) gradually increases during diastole, until a threshold is reached and discharge occurs. Gaskell (1900, p. 190) expressed an essentially similar view (cf. Adrian, 1930), and this view has some support in the evidence of Ishikawa (1924), who found that the excitability of the frog's sinus, but not of ventricle or auricle, increases throughout diastole until the next beat occurs. Langendorff (1902) suggested that the inner stimulus might be provided by the products of dissimilation (Lebensprodukt).

In a series of papers largely theoretical, Hering (1901, 1912, a, 1912, b) gradually built up a theory of rhythm which is the most elaborate yet attempted. His inner stimulus (Reizbildung) was not continuous, but intermittent with an independent rhythm of its own; the sensitivity of the centre to this stimulus (Reaktionsfähigkeit), normally identifiable with its electrical excitability, was supposed to follow a time-course initiated by the previous beat. Hering's
theory in general lacks experimental foundation, and in particular the independence he assumes for the rhythm of his "Reizbildung" cannot be reconciled with the change of phase produced by premature beats. Andrus and Carter (1924) found that alterations in the perfusing fluid caused changes in the rate of the perfused heart, and on this inadequate evidence concluded that the rhythmic excitatory process is a disturbance of the ionic equilibrium between the cells and the surrounding fluid. Rothberger (1926) made a similar suggestion, without bringing any further evidence. Finally, von Brücke (1930) saw no justification for postulating a continuous inner stimulus, and attributed the interval between one heart beat and the next partly to refractory period and partly to other inhibitory influences.

In the present series of papers an attempt is made to investigate systematically the behaviour of the pacemaker of the heart, under all those experimental conditions which seem likely to throw light on the nature of the physiological processes underlying its rhythmic production of impulses. In the first paper the pacemaker is located as accurately as possible, and electrical records taken from it. Its recovery of excitability after a normal beat is determined in the usual way by the direct application of induction shocks of varying strengths, and the effect on the recovery curve of vagal slowing and of accelerantes quickening is investigated. The second and third papers deal with the effect of premature beats on the rhythm of the pacemaker, and we hope to publish later an analysis of the action of the vagus.

Method of Experiment

The following account will serve as a general description of the experimental procedures employed throughout the whole investigation. Special modifications will be mentioned in the appropriate sections.

The animal (cat) having been anaesthetized (ether only) was decerebrated by the trephine method and the anaesthetic was then discontinued. A longitudinal skin incision extending from the second to the sixth rib was made two to three centimetres to the right of the sternum. The fourth rib was laid bare and about two centimetres of its sternal end removed after ligation of the intercostal artery. Light artificial respiration by a pump was begun and continued throughout the experiment at just that intensity which allowed the normal respiratory movements to continue. In most experiments the upper lobe of the right lung was ligated at its base and removed in order to give a sufficient exposure of the heart, but this practice was discontinued in the later
experiments. The pericardium was opened along a line from the apex of the ventricles to the superior vena cava thus forming a flap which was sewn to the chest wall so as to prevent the lungs from moving over the exposed surface of the heart during respiration. In this procedure the heart rotates somewhat to the left giving a good exposure of the right auricle and the superior vena cava, but care has to be taken to prevent any kinking of the vena cavae.

As electrodes we used small silver hooks soldered on to fine enameled wires. As far as possible they have been passed through the superficial epicardium only, but doubtless the deeper tissues have also at times been locally injured. When in position the hooks have been closed so that they retained their position despite movements of the heart, and, after packing the aperture in the chest wall with dry cotton-wool in order to keep the wires apart, the edges of the wound have been clipped together. In this way the heart may be investigated with closed chest wall and under conditions as near normal as possible. In the usual arrangement three electrodes have been applied to the heart, one being both the cathode of the stimulating circuit and the earthed lead to the amplifier of the recording circuit. This common lead has been placed as close to the pacemaker as possible (see p. 311), while the respective positions of the anode of the stimulating circuit and of the grid lead have usually been in the region of the tail of the sino-auricular node and on the right auricle, the three leads forming approximately the apices of an equilateral triangle.

Usually both vagi were cut in the neck during the preparation, but in some experiments on vagal tone they were cut during the course of the experiment; rarely they were left intact throughout. The nerves were freed for stimulation by careful dissection so as to preserve the blood supply intact as far as possible, and stimuli were applied through glass-shielded silver electrodes which were sewn in position during the initial preparation.

The nervi accelerantes were approached through the axilla with the fore-limb extended above the head. A skin incision along the inferior border of the pectoralis major was followed by a dissection exposing the second rib, and as much as possible of this was excised subperiosteally. The stellate ganglion was then exposed by blunt dissection, and completely excised except when the nervi accelerantes were to be stimulated, when all the branches of the ganglion except the nervi accelerantes were cut and the latter nerves were freed until their junction with the vagus. The ganglion was left attached merely as a convenience when applying the electrodes, but it was functionally disconnected by pinching the nervi accelerantes at their point of entry. A
specially shaped shielded-glass electrode with silver electrodes was then applied
to the nervi accelerantes and sewn in position, the skin being then clipped
together around the wires leading to the electrodes.

In the first experiments in which both nervi accelerantes were cut, the
additional dissection appeared to affect the condition of the animal so unfavourably that we adopted as a usual procedure the excision of the right nerve
only. It was later realized that in the decerebrate preparation there is a
considerable tonic acceleration through the left nerve alone, so the bilateral
operation was again adopted and fortunately was not then found to react
unfavourably on the condition of the animal.

After suitable amplification the action potentials from the heart were led
to a Matthews oscillograph and photographed by a falling plate camera. In
order to shorten the effect of the necessarily large stimulus artefact 0·002 \mu F

coupling condensers have usually been used throughout the amplifier. The
resulting great distortion of the action potential was of no consequence as we
were only concerned with the action potential as a standard of comparison.
In fact the smaller condensers would serve to sharpen the differential features
of the records. In most experiments stimulus escape was also reduced by
earthing the animal through a metal plate surrounded by cotton-wool soaked
in Ringer and placed subeutaneously in the lumbar region. In some experi-
ments the action potentials from an additional pair of leads were led to a string
galvanometer and simultaneously photographed on the same plate. In all
records time was registered simultaneously by photographing the movements
of a small needle attached to the free vibrating end of a 100 d.v. tuning fork.

Premature beats have been set up by break induction shocks from one or
two coreless coils, the circuits being broken by a Lucas pendulum which had
an electromagnetic release worked by the camera. As a further precaution in
minimizing stimulus artefacts in the records a 40,000 ohm non-inductive
resistance was placed in the secondary circuit. The stimulus artefact, how-
ever, served a useful purpose, as its beginning signalled the exact moment of
the stimulus. In the primary were a 12-volt accumulator battery and a
variable resistance which was used in adjusting the strength of the induction
shock, the coupling between the primary and secondary coils being kept
constant. Repetitive stimuli from a neon tube oscillator were applied to the
vagus or accelerantes nerves at a rate usually about ten a second.

The temperature of the animal was maintained by the heated table on which
it lay. By suitable adjustment this temperature was almost always kept
between 36 and 38°C.
The Pacemaker.

A—The Location of the Pacemaker

The term "pacemaker" is here applied only to that part of the sino-auricular node in which the impulse originates (cf. Lewis, 1925, p. 525; Meek and Eyster, 1914), not to the whole "sinus" as well as the "presinus" (Rijlant, 1932). Lewis, Oppenheimer and Oppenheimer (1910), Sulze (1913), and Lewis, Meakins and White (1914), place it in the head of the sino-auricular node very close to the cavo-auricular angle. Eyster and Meek (1914) come to a similar conclusion in most of their experiments, but in some place it is nearer the middle of the node, in agreement probably with Wybauw (1910). Those results were all obtained with electrical recording, but with one exception no attempt was made to discriminate between points less than 5 mm apart. A more precise localization was claimed by Rijlant (1925, 1931), who in some of his experiments found the initial negativity developing in a circumscribed area about 1 mm in diameter (the "presinus") between the head of the sino-auricular node and the superior vena cava, while the main activity of the whole node (the "sinus") followed about 5 σ later.

In the conditions of most experiments the pacemaker appears to remain fixed, but under the influence of strong vagal inhibition it has been shown to move to a position nearer the tail of the node (Meek and Eyster, 1914; Lewis, Meakins and White, 1914).

For the purposes of the present investigation, the electrode common to the stimulating and the recording circuits must be applied as accurately as possible over the pacemaker itself, and the accuracy of its placing must be tested in every experiment. Two methods have been employed:

Method 1—Determination of the point associated with the first detectable action potential

This is the classical method. An extra pair of electrodes is fixed to the right auricular appendage, and connected with a string galvanometer. The action potentials recorded by this instrument are photographed simultaneously on the same plate as those recorded by the oscillograph and provide a fixed point of reference. The earthed lead of the oscillograph amplifier is then applied in various positions on and around the sino-auricular node the grid being on the auricle near the sino-auricular node, and records are taken, each position being noted on an outline drawing of the heart. That position which gives the longest interval between the first deflection of the oscillograph record and the galvanometer record, is nearest to the pacemaker. Thus in fig. 1, Plate 15, observations
2 and 3 are made with the earthed lead in position 4 of fig. 2, and the action potential recorded by the oscillograph begins about $1.5\sigma$ earlier than in observations 1 and 4, corresponding to position 5 of fig. 2. Position 4 is therefore nearer the pacemaker than position 5, and in this experiment it was also found to be nearer than any of the other positions of fig. 2. Subsequent histological examination showed that it lay over the upper part of the head of the sino-auricular node. In two other experiments precisely the same location was found; it corresponds to that of Lewis and his co-workers, and Sulze.

In five experiments, however, the pacemaker was found to lie further down the sino-auricular node, e.g., position 2 of fig. 2. In three of these the string galvanometer was not used, but the main deflection of the oscillograph record was used instead as a point of reference. This appears to be allowable, in experiments such as these in which the grid lead was from a fixed point on the body of the auricle; for the main deflection is not altered appreciably by moving the earthed lead to various parts of the sino-auricular node, and in experiments where the string galvanometer was used the main deflection always bore a constant time relation to the galvanometer deflection. These experiments indicate that the main deflection arises in the auricle and not in the sino-auricular node.

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**Fig. 2**—Drawing of the right auricle and ventricles to show positions of leads. 6 was the grid lead in all observations, and 4 and 5 were the ground leads used for the observations of fig. 1, Plate 15. Position 4 was closest to the pacemaker.
The Pacemaker.

Method 2—The determination of the point at which a stimulus applied late in the cycle sets up a premature beat which is identical with a normal beat (cf. Lewis, 1910)

The identity can be established by two criteria:

(a) The action potential of the premature beat must resemble that of a normal beat. Since the very small coupling condensers of the amplifier (0.002 μF) cause the oscillograph deflections to approximate to the rate of change of electrical potential between the leads, this criterion is a particularly rigorous one.

(b) The interval between the first deflection of the normal action potential and its main deflection must be the same as the interval from the stimulus to the corresponding main deflection of the premature beat. This condition is found to hold when a premature beat is set up by a stimulus applied through an electrode (cathode) which Method 1 shows to be close to the pacemaker.

It has been seen above that the main deflection arises from the grid lead on the auricle, so the interval from the first sign of the action potential to the main deflection is the conduction time to the grid lead. The similar time from the stimulus artefact to the main deflection of a premature beat indicates that the stimulus sets up a premature beat after a negligibly short latent period; a conclusion in agreement with the results of von Frey (1915) and Schellong (1925). When a stimulus falls very soon after the end of the absolutely refractory period, the main deflection of the premature beat may have a latent period even longer than 30 σ, but close inspection with sufficient amplification always reveals small waves throughout this apparently long latency. It would seem that this long latency was due to slow conduction in the relatively refractory period (Drury and Regnier, 1928).

Figs. 3 and 4, Plate 15, exemplify the use of these criteria. In fig. 3 the action potentials of the premature beats in observations 1 and 5 are indistinguishable from the normal action potentials; in each the interval from stimulus artefact to main deflection is only very slightly shorter than the interval from the first tiny wave of a normal action potential (indicated by an arrow in the more highly amplified observation 6) to its main deflection. It may therefore be concluded that the electrode common to recording and stimulating circuits has lain very close to the pacemaker, since criteria a and b are satisfied. It was in position 2 of fig. 2. Fig. 4 is similar, but the disturbance of rhythm produced by the premature beats is also shown (see next paper).
In most of the experiments to be described the common lead was first placed in positions 2 of fig. 2, and records made of normal beats, and of premature beats late in the cycle using a stimulus well above threshold. If these records satisfied the criteria of Method 2, the lead was left in that position throughout the experiment; if not, the procedure was repeated with alternative positions until a satisfactory one was found. The more laborious Method 1 was used only in the experiments on the excitability of the pacemaker, where the advantage given by its greater accuracy was highly important. The constancy of the shape of the action potentials obtained throughout a given experiment was taken as sufficient indication that the pacemaker had not materially shifted during the course of the observations.

**B—The Action Potential of the Pacemaker**

Some physiological process in the pacemaker must be conceived of as preceding and conditioning the production of the impulse, and it is possible that this process might be associated with a slight and gradual change of electrical potential preceding the rapid potential changes produced by the propagation of the impulse. With this in view, records have been made with large coupling condensers of 4 μF in the amplifier; the deflection produced by a constant potential then fell to half its initial value in slightly less than one second. Fig. 5, Plate 15, is a record obtained in this way, with the leads to the amplifier in positions 4 and 6 of fig. 2. It shows two auricular action potentials with the ventricular action potential following the first. There is no slow change of electrical potential preceding the sudden upward deflection (shown by the arrow) which signals the propagation of the impulse. The small slow wave between the ventricular and the next auricular action potential is the ventricular T wave. Similar results have been obtained in four other experiments.

These results are in agreement with Adrian’s (1931) observations on the frog’s sinus. However, still more refined technique may yet detect some changes [cf. Adrian and Gelfan’s (1933) results with rhythmic beats of skeletal muscle fibres], but artefacts due to the incessant movement of the tissues will be difficult to exclude. At present it is clear that any electrical changes possibly present in the latter part of diastole can only be of a very much smaller order than those associated with the appearance and propagation of the impulse.
C—The Electrical Excitability of the Pacemaker during its Rhythmic Cycle

No previous attempt appears to have been made to measure the electrical excitability of the mammalian pacemaker itself. Observations on other parts of the heart have shown that a beat is followed in turn by an absolutely refractory period and then a relatively refractory period, but opinion is divided as to whether in the last part of diastole the excitability continues to increase or attains a constant level. In frog's auricles and ventricles, Trendelenburg (1911), Adrian (1921), Ishikawa (1924), Schellong and Schütz (1928) and Buchthal (1931) found a longer or shorter period of constant excitability at the end of diastole, while Engelmann (1895) found none. Ishikawa (1924) found that the excitability of the frog's sinus increased till the end of diastole. In mammalian auricle and ventricle, Cushman and Matthews (1897) found a rising excitability at the end of diastole, but Cushman later (1912) failed to confirm that result. Drury and Regnier (1928), using mammalian auricles driven by direct stimulation, found a fairly long period of constant conductivity in the latter part of diastole.

We have used the technique already described in an attempt to measure the excitability of the pacemaker itself. In every experiment the electrode common to stimulating and recording circuits was placed over the pacemaker, using Method 1 (p. 311). Single break induction shocks of varying intensity were applied at random in all phases of the cardiac cycle, and with each strength of stimulation records were taken until the critical point at which recovery was just sufficient for the stimulus to excite was fairly accurately fixed. From these results the usual recovery curves were constructed.

(a) The Normal Recovery Curve—Fig. 6 is a typical example of the curves obtained in 12 out of 17 experiments. The strength of the stimulus is plotted along the ordinate, and its time of application along the abscissa; the latter is measured by the interval between the beginning of the action potential of the previous beat and the stimulus artefact. For each strength of stimulus two points are plotted, the earliest time at which it evokes a premature response, and the latest time at which it fails to do so. These are joined by a short horizontal line, and the whole recovery curve is a smooth curve passing as nearly as possible through these lines. Its lower end is seen to run horizontally through the latter part of diastole at a strength of stimulus just on the threshold, i.e., it sometimes excited and sometimes failed to excite a response. Fig. 7 is a similar example.
Fig. 6—Recovery curve of "pacemaker." Ordinates, strength of stimuli in arbitrary units, abscissæ intervals in sigma after the beginning of the previous normal beat. The arrow shows the time of the next normal beat. Each horizontal line joins the longest interval at which that stimulus failed to excite to the shortest interval at which a premature beat was set up.

Fig. 7—Recovery curve of "pacemaker" in the same experiment as figs. 1 and 2. The cathode of the stimulating circuit was in position 4 of fig. 2.
The Pacemaker.

In the remaining 5 of the 17 experiments, of which fig. 8 is an example, the threshold increased during the latter part of the cycle, i.e., the excitability reached its maximum relatively early in diastole and then decreased progressively until the end of the cycle. A similar "supernormal" phase of excitability was described by Adrian (1920) and Wastl (1922) in frogs' ventricles. It was not affected by tetanic stimulation of the accelerantes, and could not be attributed to faulty artificial ventilation, for it occurred when this was so adjusted that normal respiratory movements were present.

![Graph](image_url)

Fig. 8—Recovery curve of "pacemaker" in another experiment.

A possible source of error in observations such as these performed on a moving tissue must be mentioned, namely, variations in tissue resistance and in shunting through inexcitable parts caused by the movements. Three rough determinations of the resistance of the tissues between the stimulating electrodes showed that its average value was 3500 ohms, with a variation of about 500 ohms during the cycle. In the presence of a 40,000 ohm resistance in the secondary circuit, the effect of this variation on the strength of the stimulus would be negligible. Variations in the amount of shunting by such inexcitable structures as connective tissue or blood in the auricular cavity, cannot be
measured, but the constancy of the threshold in the latter part of diastole in the 12 experiments is presumptive evidence that these variations are not a serious source of error.

The 17 experiments therefore provide clear evidence that, in the later part of diastole, the electrical excitability of the structure stimulated remains constant, or passes through a supernormal phase and then slightly decreases: in any event it does not rise as the next spontaneous beat approaches. It remains to ask, what exactly is the structure stimulated? The common electrode was placed with all care as near as possible to the pacemaker, and it may reasonably be assumed that in some experiments at least the pacemaker was directly stimulated. But the stimulating current would also have passed through adjacent fibres of the sino-auricular node, and, if at any time these fibres possessed a lower threshold to electrical stimulation than the pacemaker itself, then the observations made at that time concern these fibres and not the pacemaker. We have no means of detecting whether or when this happens, but the behaviour of such rhythmic centres is probably very similar to the actual pacemaker, which is generally believed to be that particular rhythmic centre possessing the most rapid intrinsic rhythm. Thus it may reasonably be assumed that any changes found in the excitability of these more highly excitable fibres will be similar to changes occurring in the adjacent pacemaker itself. We may therefore treat the curves as recovery curves of the pacemaker.

(b) Influence of Tetanic Accelerantes Stimulation on the Recovery Curve—This was investigated in seven experiments. In all the acceleration of rhythm was accompanied by a shortening of both the absolutely and relatively refractive periods; the total shortening, expressed as a fraction of the total refractory period, was less than the shortening of the cycle, expressed as a fraction of the whole cycle. In the example shown in fig. 9 the cycle was reduced by 16%, the refractory period by about 6%. In some experiments, though not in that of fig. 9, the threshold reached at the end of the relatively refractory period was lowered a little by the accelerantes stimulation.

In a complementary experiment, the spontaneous accelerantes tone was abolished by division of the nerves. The cycle lengthened from 259 $\sigma$ to 348 $\sigma$ (34%) and the refractory period from 127 $\sigma$ to about 150 $\sigma$ (18%).

The results are in line with those of Andrus and Carter (1930), who found that adrenalin shortens the absolutely refractory period of cardiac muscle by as much as 40%.
(c) Influence of Tetanic Vagus Stimulation on the Recovery Curve—This was investigated in 14 experiments, in all of which submaximal stimulation was used, insufficient in intensity to cause a shift of the pacemaker to some other part of the sino-auricular node—a change easily recognized by the abrupt alteration in the shape of the action potential (p. 311). The lengthening of the cycle varied from 15% to over 50%. The effect on the recovery curve was variable.

In six experiments, one of which appears as fig. 10, the curve remained substantially unaltered, and in two others there was a doubtful slight shortening of the refractory period.

In the other six experiments the refractory period was shortened by amounts varying from 6%, fig. 11, to 50%. When the shortening was pronounced,
Fig. 10—Recovery curves of "pacemaker" both normal and during a vagal slowing of the heart which lengthened the cycle from 350 $\sigma$ to 530 $\sigma$. The circles represent the intervals obtained during the vagal slowing. The recovery curve seems unaltered.

Fig. 11—Recovery curves of "pacemaker" as in fig. 10 but in another experiment, the vagal slowing lengthening the cycle from 290 $\sigma$ to 450 $\sigma$ and being accompanied by a slight shortening of refractory period.
the threshold reached and maintained during the period of full recovery was
definitely lowered.

Taking all the experiments together, we found no relationship between the
degree of vagal slowing and the change in refractory period. Twice, indeed,
it was clear that a small change in rate during an experiment can be accom-
panied by a large change in refractory period: thus, after vagus stimulation
had lengthened the cycle from 360 \( \sigma \) to 630 \( \sigma \) (\(+75\%\)) and shortened the
refractory period from 190 \( \sigma \) to 114 \( \sigma \) (\(-40\%\)), the length of the cycle sponta-
nuously diminished to 550 \( \sigma \) (\(+53\%\)) through vagal fatigue, and at the same
time the refractory period increased to 182 \( \sigma \) (\(-4\%\)), almost its original
value.

The variability in the effects obtained with vagus stimulation might be due
to small differences in the placing of the stimulating electrodes causing the
sino-auricular node to be stimulated directly in some experiments and only the
auricular muscle in others. This would disturb the results only if the vagus
stimulation has a grossly different effect on the auricular muscle. We tested
this effect deliberately in three experiments: in two of them the rate was
slowed by 30\% to 40\% and the refractory period of the auricular muscle
remained unchanged; in the third, the rate was slowed by 43\% and the
refractory period of the muscle shortened from 180 \( \sigma \) to 75 \( \sigma \). In the latter,
the refractory period of the pacemaker was shortened almost to the same
extent, for the premature beats, with the possible exception of the one at
75 \( \sigma \), disturbed the rhythm of the pacemaker (see p. 356). It seems, then,
that the pacemaker and the auricular muscle are similarly affected by vagus
stimulation, and that the variability of the present results is not due to
inaccurate placing of the electrode.

Lewis, Drury and Bulger (1921) and Andrus and Carter (1930) found that
tetanic vagus stimulation invariably produced a great shortening of refractory
period in the mammalian auricle. The constancy of their results may be due
to the use of stronger vagus stimulation than we employed. On the other
hand, Ishikawa (1924) found that vagus stimulation had no effect on the
recovery curves of frog's sinus, auricle, and ventricle.

\(d\) The Recovery of Excitability after Premature Beats—This was examined
in 14 experiments, by applying to the pacemaker two stimuli, separated by a
varied short interval. The first stimulus set up a premature beat, and the
second tested the recovery of excitability after this beat. The refractory
period following the premature beat was always shorter than normal, and its
shortening was greater when the curtailment of the previous cycle was greater. Fig. 12 shows approximately a normal recovery curve (cf. fig. 6) and a recovery curve after a premature beat which curtails the previous cycle by one half. The curves are almost parallel; between them would lie the corresponding curves obtained after less curtailment of the previous cycle. Fig. 13 also shows recovery curves after a normal and an early premature beat; a supernormal phase is present, and moves earlier with the shortening of the refractory period.

![Diagram](image)

**Fig. 12**—Recovery curves of "pacemaker," the one on the right side being the normal recovery curve (see fig. 6 for details of this), and the other the recovery curve after a premature beat set up after a curtailed cycle equal to 0·5 of a normal cycle. This curve is approximately drawn through the perpendicular lines which for each interval join the weakest stimulus which excited to the strongest stimulus which failed to excite. At an interval of 90 σ this perpendicular line had no length, for at a strength of 15·4 the stimulus sometimes excited and sometimes failed to excite.

The earlier recovery of excitability after a premature beat was discovered by Trendelenburg (1903) in frog's ventricle, and observed by de Boer (1916), Ishikawa (1924), Umrah (1925), Lewis and Master (1925), Schellong and Schütz (1928) and Buchthal (1931), the last two investigations showing that the shortening of refractory period corresponded with the shortening of the action potential of the premature beat.

**Discussion**

Any plausible theory of the production of rhythmic impulses by the pacemaker, must postulate some sort of continuous process or change in the pace-
The Pacemaker.

maker during the interval between two impulses. From the observations that have been described two general statements, both of a negative character, may be made about the nature of that process.

The first statement is that no demonstrable relationship exists between the course of that process, and the electrical excitability of the pacemaker. This rests on the following observations:—

1. The electrical excitability in the last third (approximately) of the normal cycle either does not alter, or shows a slight decline subsequent to a supernormal phase (Section C, (a)). All this time the hypothetical process must be continuing.

2. When the time-course of the hypothetical process is shortened by excitation of the accelerans, the refractory period to electrical excitation of the pacemaker is also shortened; but, when the time-course of the hypothetical process is lengthened by vagus excitation, no lengthening of the refractory period is found. On the contrary, it is often shortened, and that to a highly variable degree (Section C, (b), (c)).

3. In the cycle initiated by a premature beat, i.e., the premature beat cycle, the time-course of the hypothetical process is lengthened (see p. 335), but the refractory period is shortened (Section C, (d)).

The absence of relationship between the rhythmic process and extrinsic electrical excitability was inferred by Hering (1907) from the fact that some drugs which stop the heart-beat increase the excitability. Cushny drew the
same conclusion from evidence resembling that of observation 1 above. The present observations, however, with the application of stimuli as near as possible to the seat of the rhythmic process (the pacemaker) itself, place the generalization on a more secure basis. The only previous attempt to investigate directly the excitability of a rhythmic centre was Ishikawa's (1924) work on the frog's sinus, where he found that excitability increased through diastole right up to the appearance of the next beat; in this respect the frog's sinus and the cat's sino-auricular node would seem to differ.

The second statement is that, in the interval between two impulses, the hypothetical process in the pacemaker does not betray itself by giving rise to any detectable electrical potential (Section B).

According to the membrane theory an impulse in nerve or muscle is propagated as a change of polarization and permeability in certain membranes, and an impulse is set up by an extrinsic stimulus, e.g., an induction shock, when that stimulus produces a sufficiently great diminution in the polarization of the membrane in question (the conducting membrane). An attractive explanation of the intrinsic setting up of an impulse, e.g., the origin of a normal beat in the pacemaker, would be that the polarization of the conducting membrane suffered a progressive diminution until it passed the critical point and an impulse was then set up. But then one would expect the setting up of this impulse to be preceded by:

(a) a slowly developing electrical potential, the pacemaker becoming increasingly negative, and

(b) a gradual change in electrical excitability, the pacemaker becoming more and more easily excited; and these changes should continue right up to the moment at which the beat was set up.

Since neither of these effects are observed experimentally, the setting up of the impulse cannot be preceded by a gradual diminution in the polarization of the conducting membrane. The changes in this membrane signalled by the beginning of the action potential of the beat must be impressed on it by some other mechanism in which the gradual preliminary changes must have been occurring. It is this mechanism which is the seat of the rhythmic activity of the pacemaker. In the following papers this rhythmic mechanism will be subjected to a more direct investigation.

Summary

This paper is the first of a series in which an attempt has been made to investigate the mechanism responsible for the rhythmic production of beats by the pacemaker of the heart.
The position of the pacemaker has been determined by the usual methods. In some experiments it has been found to be situated in the head of the sino-auricular node (agreeing with Lewis and Sulze), but in other experiments it has been located more towards the middle of the node.

No potential changes have been detected in the pacemaker preceding those produced by the impulse, hence it is concluded that the processes responsible for setting up the beat are not associated with potentials of the same order of magnitude as those produced by the propagation of the impulse.

The recovery of excitability at various stages after a normal beat has been tested by applying at random stimuli of varying strengths. The recovery curves constructed from such experiments show the following features.

1. The absolutely refractory period usually lasts for about half the cardiac cycle and the relatively refractory period is very short, so that maximum excitability is always reached before two-thirds of the cycle have elapsed.

2. During the last third of the cycle the excitability usually remains constant, but it may decline so that a supernormal phase is present.

3. Stimulation of the nervi accelerantes slightly quickens all phases of the recovery curve.

4. Stimulation of the vagus may also quicken the recovery, but quite marked vagal slowing may be accompanied by no change in the recovery curve.

5. The recovery of excitability is always quickened after a premature beat, though the cycle after that beat is longer than normal.

On account of this complete lack of correlation between the recovery of excitability of the pacemaker and its spontaneous setting up of beats, it is concluded that the stimuli do not act directly on that part of the pacemaker responsible for this rhythmic production of beats, i.e., on the rhythmic mechanism of the pacemaker. Since the setting up of a beat is not preceded by any detectable action potential, it is concluded that the rhythmic mechanism is not situated in the surface membranes of the muscle fibres composing the pacemaker.

REFERENCES

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EXPLANATION OF PLATE

Fig. 1.—A series of records of action potentials from the beating heart. The white lines are records from the Matthews oscillograph, and the black lines (indicated by upper arrow, observation 3) show simultaneous string galvanometer records with both leads in a constant position on the body of the auricle. The grid lead to the Matthews oscillograph was in position 6 of fig. 2, while the earthed lead was in position 5 for observations 1 and 4 and position 4 for observations 2 and 3. The first arrow below the fourth observation indicates the small initial action potential arising from the sino-auricular node, the second arrow indicating the large auricular action potential, and the third arrow the ventricular action potential. The coupling condensers have a capacity of 0.02µF. This and all subsequent records read left to right, and an
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upward deflection indicates negativity of the earthed lead, i.e., the lead from the pacemaker. Tuning fork, 1 d.v. = 10σ.

Fig. 3—A series of action potentials of normal and premature beats recorded by the Matthews oscillograph. In observations 1 and 5 premature beats were set up by an induction shock, the cathode of the stimulating circuit being also the earthed lead of the recording system. The main auricular deflection of the action potential occurs after the record of the stimulus artefact (indicated by the arrow above observation 1). In observation 2 there is a record of the stimulus artefact which was too soon after the previous beat to set up a premature beat. The irregular series of deflections following this artefact is the ventricular action potential corresponding to the previous normal beat. Observation 6 is a more highly amplified record of a normal beat. Coupling condensers = 0·002μF.

Fig. 4—A series of observations similar to fig. 3 but taken with a slower plate in order to show the disturbance of rhythm produced by premature beats (indicated by arrow).

Fig. 5—Normal action potentials with leads in positions 4 and 6 of fig. 2. Coupling condensers = 4μF. The first arrow indicates the abrupt onset of the action potential and the second arrow indicates the ventricular T wave.

The Rhythm of the Heart Beat. II—Disturbance of rhythm produced by Late Premature Beats

By J. C. Eccles and H. E. Hoff
(The Physiological Laboratory Oxford)

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The disturbance of cardiac rhythm by a premature beat was first studied by Marey (1875), who found that the lengthening of the cycle following the premature beat usually just compensated for the shortening of the cycle preceding it, the two cycles together being equal to two normal cycles. The phase of the rhythm therefore suffered only a transient disturbance by the premature beat. Engelmann (1895) obtained similar results when premature beats were set up by stimulation of the frog’s ventricles, but later (1897) he stated that there was no lengthening of the cycle following the premature beat set up by stimulation of the vena cava. On the basis of these observations he put forward the suggestion that the ventricle beats in response to discrete impulses discharged rhythmically from the sinus. A premature beat set up by stimulation of the ventricle would be prevented from reaching the sinus by the