On circulating excitations in heart muscles and their possible relation to tachycardia and fibrillation.

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§1 *The propagation and duration of the excited state in heart muscle.*

If a strip of heart muscle, living but not exhibiting spontaneous activity, is touched at one end with the point of a needle, an altered state is aroused at the point stimulated which is rapidly propagated over the strip. This altered state, the "excited state," is characterised essentially in two ways—by a difference of electrical potential between the part of the tissue in the excited state, and a part not excited and by the inability of the tissue to respond to a second stimulus (absolute refractory period). The onset of the excited state is normally followed very shortly by a mechanical movement, which continues as contraction until the excited state disappears and then gives place to relaxation.

The relation between the mechanical response and the excited state is such that the former can, under certain conditions such as the removal of calcium, be abolished while the latter remains. Contraction is not an essential part of the excited state.

The excited state is propagated in the ventricle of the frog or the tortoise at room temperature at the rate of about 10 cms. per second, while it persists at any one point a considerable time, e.g. 1″ or 2″. Thus if the strip is only 3 or 4 cms long, the excited state will still be present at the point stimulated when it has reached the other end of the strip, and for a time the whole strip will be in the excited state. In other words the wave of excitation is longer than the strip of tissue. But if now a second stimulus is applied so as to start a second wave in the tissue as soon as possible after the subsidence of the first wave

[1] Owing to the sudden death of the Author before this paper was printed, the proofs have been read by Dr. T. G. Brodie, who desires to be held responsible for the corrections.

at the point first stimulated, this second wave presents two important points of difference from the first wave. The second wave is propagated more slowly, and it lasts a shorter time at any point in the tissue.

Since the second wave lasts a shorter time than the first, a third wave can be started sooner after the beginning of the second wave than could the second after the beginning of the first. This third wave is again slower in its rate and shorter in its duration at any one point. By several repetitions it is possible thus to get a succession of waves each of which is actually shorter than the strip of tissue.

Thus by the time a wave has reached the far end of the strip it has left the end to which the stimulus was applied.

A series of similar waves can be kept going by a series of evenly spaced stimuli at this rapid frequency; but if a few members of the series of stimuli be cut out and then the series resumed, the responses will be of a different character and the heart muscle will respond only to every second stimulus. The slow propagation and short duration of the waves of excitation are characteristic of the tissue when it is thrown into activity with but very brief periods of rest.

Let us suppose we have the strip now being stimulated at such a rhythm that the waves of excitation are shorter than the strip. So far as we can make out, the conduction of the excited state is fairly expressed thus:—when one region of the muscle becomes excited and is in physiological connexion with a neighbouring region which is excitable but not excited, the excited state is induced in that neighbouring region, and so on.

Be it noted that our statement implies the assumption that the "excited state" the rate of travel and the duration of which we measure by the electrical disturbance and the refractory phase, is as it were a self-propagating affair. The only justification for such an assumption is that we can demonstrate no change antecedent to these signs of the excited state. The possibility that there is some antecedent change which is the thing really propagated and that the excited state is called forth at successive points in the muscle by the passage of a preliminary wave, must not be lost sight of.

An observer of the mechanical response in the muscle, seeing the wave of contraction start at the point stimulated, and course over the muscle at a rapid rate, might well imagine that conduction meant that when one region contracted it caused the neighbouring region to contract and so forth. But a study of other changes in the muscle shows very definitely that the mechanical contraction is a change called forth at each point in the muscle, by an antecedent change in the muscle. The wave of contraction reflects precisely enough the

rate of propagation of this change, but the contraction is in no way essential to the propagation. However, at present we have no sufficient reason to assume any wave *preceding* the excited state, and we may return to our discussion of the behaviour of the strip. Suppose it to be in a condition where a wave of excitation is shorter than the strip, and now suppose that the ends of the strip are united so as to form a ring. Under such circumstances, the wave having made one circuit of the ring would continue to propagate itself, finding the place where it started excitable when it reached it again.

We do not know at present how to bring the ends of a strip of muscle into physiological continuity, but we can easily obtain closed conducting rings by cutting them from a large piece of heart muscle

§ 2. *Circulating excitations.*

It was shown in 1908, by A. G. Mayer[1] that in a ring of excitable tissue cut from the bell of the large Medusa Cassiopeia it is possible to establish a local block and by stimulating on one side of it to set going a wave which travels in one direction only. Removing the block before the circuit was completed by the wave, the wave continues to circulate round the ring indefinitely.

In a former paper[2] I have explained the theoretical and experimental considerations which led me to seek the production of a similar phenomenon in heart muscle. I there gave a short account of experiments in which the circulating waves, or as I prefer to call them, circulating excitations, were set going.

(a) in rings including portions of auricle from the tortoise.

(b) in rings cut from the auricles of elasmobranch fishes.

Last autumn, through the kindness of Professor Yves Delage, I had the opportunity of making further experiments at the Station Biologique in Roscoff.

I will describe one typical experiment which illustrates several points.

Large Dog-fish (Acanthias). Killed by decapitation. Spinal cord pithed. Heart excited and placed in a dish with blood. Beats continue regularly, starting in sinus. Scratching the bulbus aortae produces the effect described by Gaskell with great ease. Beats start in bulbus at a faster rhythm and are transmitted backwards over ventricle and auricle for five or six beats, then the normal sequence is resumed.

After half-an-hour the heart is beating well. Cut away sinus: the auricle and ventricle stop. Cut off auricle, slit it up to form a ring,

[1] A. G. Mayer. Popular Science Monthly. Dec. 1908. p. 481.

[2] G. R. Mines. Journ. of Physiol. *46*. p. 349, 1913.

spread it out on a glass plate, pour on serum and cover up with a vaselined watch-glass. Preparation remains quiescent for quarter of an hour. Pricking with a needle point provokes a strong contraction. Wave runs round ring in each direction; the waves meet on the opposite side of the ring and die out. Repeated the stimulus at diminishing intervals and after several attempts started a wave in one direction and not in the other. The wave ran all the way round the ring and then continued to circulate going round about twice a second. After this had continued for two minutes extra stimuli were thrown in. After several attempts the wave was stopped. The preparation then remained at rest for ten minutes. The circulating excitation was again started in the same way as before. This time there was considerable difficulty in stopping the wave. A number of attempts caused slowing of the wave in its passage over part of the course, but failed to arrest it. Presently a single stimulus was so timed as to arrest the wave. The preparation then remained absolutely quiescent. There was no sign of 'automatic' rhythm throughout this experiment. After cutting through the ring in one place, the strip of tissue responded with a single contraction to each of a series of stimuli if suitably spaced. It was found impossible to get more than one response to a single stimulus.

I have repeated the experiment successfully on five preparations from dog-fish auricles. A large heart must be taken otherwise it is difficult to secure that the duration of the refractory state shall be shorter than the time taken by the wave to pass round the ring. The chief error to be guarded against is that of mistaking a series of automatic beats originating in one point in the ring and travelling round it in one direction only owing to a complete block close to the point of origin of the rhythm on one side of this point. The cleanest experiments are those, such as that quoted above, in which the auricle showed no tendency whatever to give spontaneous beats. Severance of the ring at that point will obviously prevent the possibility of circulating excitations but will not upset the course of a series of rhythmic spontaneous excitations unless by a rare chance the section should pass through the point actually initiating the spontaneous rhythm.

Ordinary graphic records either mechanical or electrical are of no value in attesting the occurrence of a true circulating excitation in rings of this kind, since the records show merely a rhythmic series of waves and do not discriminate between a spontaneous series of beats and a wave of excitation which continues to circulate because it always finds excitable tissue ahead of it. The only method of recording the phenonenon which I have found of any use is cinemato-

Fig. 1.

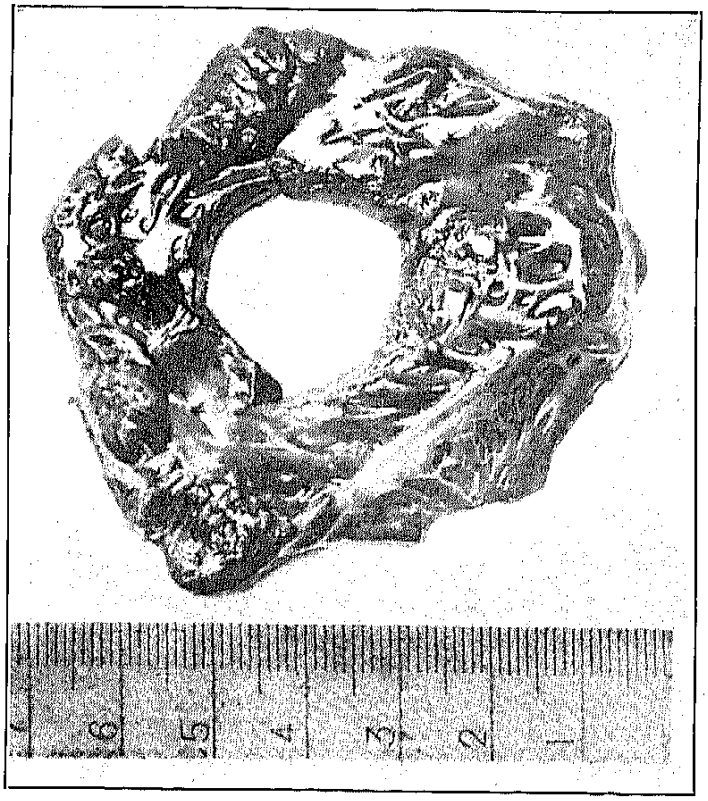

Fig. 2.

graphy. Fig. 1. is enlarged from one image taken from a cinematograph film of an auricle ring exhibiting circulating excitation.

I have also succeeded in producing excitations in rings of mammalian ventricle. In many cases I have failed to get the requisite conditions, but in seven experiments on the ventricles of large dogs and in one cat's heart I have been able to demonstrate conclusively the production of true circulating excitations. In the best experiments the procedure was as follows:—

The heart was excised from the anaesthetised animal (usually at the conclusion of some other experiment) and placed on a glass table. The right side of the ventricular wall was then cut out. The act of cutting generally provoked fibrillation. In the sheet of muscle thus obtained a large hole was cut (see Fig. 2.) During this operation the fibrillation died out and the preparation became quiescent. The rest of the experiment followed a course similar to that described above for the auricle rings, except that the time during which the muscle remained excitable was very much shorter.

In a favourable experiment the vigorous circulating wave and its instantaneous arrest by section of the ring is a sight not easily forgotten.

Garrey[1] has recently described experiments made about the same time and independently of mine, on the production of circulating waves in rings cut from the base of the ventricles of large water turtles.

Garrey has succeeded in getting a number of waves following one another round the ring at the same time—just as Mayer did with the Medusa rings. This very interesting effect evidently depends on two factors, the large size of Garrey's ring, and the fact that when starting the wave the tissue was fibrillating and therefore ready to give the type of wave characteristic of the very active tissue —a short wave slowly propagated.

Garrey very justly emphasises the fact that for a circulating wave a uni-directional block is a necessary condition. In his experiments he was able to demonstrate uni-directional block repeatedly: "it appeared to be related to the irregular width of the blocking and consequently the differences in strengths of the inpulses passing a given point of block." Erlanger had previously noted uni-directional block in strips of auricle. In the frog's heart, when exhausted, I have occasionally observed uni-directional block between auricles and ventricle. In some cases the direction blocked was from ventricle to auricle; in other cases from auricle to ventricle. In the latter case it is very curious to see the auricular contractions not followed by

[1]Amer. Journ. Physiol. *33*. March 1914. p. 397.

any movement of the ventricle, yet the ventricle ready to respond to direct stimulation and to call forth an extra beat of the auricles.

The cause of uni-directional block may very likely be expressed thus in terms of Adrian's work. The region of blocks is a region of decrement, situated between two normal regions. If the decrement is uniform, then the system is symmetrical and the blocking should be equal in the two directions. But if the decrement is greater at one end of the "depressed" region than at the other, we have the possibility that transmission in one direction may be easier than in the other.

It is evident that the uni-directional block need not necessarily persist for more than a very short while in order to start a circulating excitation.

3. Tachycardia and circulating excitations.

It is a fact familiar to the physician and to the physiologist that a heart which has been beating regularly and in normal sequence may sometimes suddenly exhibit a new rhythm of a totally different character. While in some cases the new rhythm is related to the original rhythm in some simple ratio, and is explicable on the hypothesis of partial heart blocks between the region originating rhythm and the rest of the heart or between auricles and ventricles, there are other instances where there is no such relation to be made out between the normal and the abnormal rhythms.

Last year I showed that certain instances of tachycardia observed during experiments on cold-blooded hearts, where the excitations of the auricle and ventricle were proved to be mutually dependent, might best be explained as circulating excitations, the impulse passing from auricle to ventricle by one path and returning from ventricle to auricle by another path.[1]

I ventured then to suggest that some instances of paroxysmal tachycardia observed in man where auricles and ventricles beat with the same frequency might conceivably be explained along somewhat similar lines. I now repeat this suggestion in the light of the new histological demonstration by Stanley Kent[2] that the muscular connexion between auricles and ventricles in the human heart is multiple.

Stanley Kent shows that an extensive muscular connexion is to be found at the right-hand margin of the heart at the junction of the right auricle and right ventricle.

Supposing that for some reason an impulse from the auricle reached the main A-V bundle but failed to reach this "right lateral"

[1]Mines, loc. cit.

[2]Stanley Kent, Quart. Journ. Exper. Physiol. VII, p. 193. 1913.

connexion. It is possible then that the ventricle would excite the ventricular end of this right lateral connexion, not finding it refractory as normally it would at such a time. The wave spreading then to the auricle, might be expected to circulate around the path indicated. But if the recovery of the main A-V connexion or of the ventricle itself was not sufficiently rapid, the circulating wave could not continue and what would be observed would be a series of groups of this type aur.-ventr.-aur. ——— aur.-ventr.-aur ——— aur.-ventr.-aur. etc. a type of rhythm known to occur both under experimental conditions and in disease.

We know enough of the physiological properties of heart muscle and the arrangement of the fibres in the human heart to enable us to speak of a circulating excitation between auricles and ventricles as a theoretical possibility and to say that if it did occur, auricles and ventricles would beat at a much more rapid rate than normal and that the onset and the disappearance of the abnormal rhythm would be abrupt.

Fibrillation.

The suggestion that the abnormal character of the heart's activity in fibrillation depends essentially on abnormality of conduction was put forth by W. T. Porter in 1898. Porter's view has recently received very strong support from the experiments of Garrey,[1] to whose admirable paper I would refer the reader. Garrey points out that fibrillation is more easily aroused and is more persistent in large than in small pieces of heart muscle and he shows that it is most unlikely that the self-maintained activity in fibrillation is due to an exaggerated power of ectopic impulse formation. Garrey arrives independently at a closely similar conclusion to that which I expressed in a recent paper,[2] namely, that fibrillation is due to waves travelling in closed circuits in the syncytium.

Garrey observes that if the above conclusion is correct, it is not surprising to find the onset of fibrillation induced by such conditions as local differences of temperature or the application of certain drugs which may reach one region sooner than another. Professor Starling has mentioned to me that in the course of his numerous experiments on heart-lungs prepared from the dog, a detail of technique which he found of some importance was to avoid touching the surface of the heart with a cold instrument, since this was found very frequently to start fibrillation.

The most certain method of starting fibrillation is by the application of a faradic current directly to the heart. The rapid series of

[1] Garrey. Amer. Journ. Physiol. *33*. p. 397. March, 1914.

[2] Mines, loc. cit.

induction shocks has the same effect as a series of stimuli so spaced that one is thrown into the muscle just after the conclusion of the absolute refractory period associated with the response to the last stimulation. Thus the duration of the excited state of each response becomes shorter and the rate of propagation becomes slower until the characteristics essential for the circulating wave are attained. Once started the existence of fibrillation tends to maintain the conditions necessary for its appearance.

Yet under some conditions a stimulus of very brief duration may induce fibrillation. I propose to describe here some experiments showing how the relation of the time of application of such a brief stimulus to the cardiac cycle may be of great importance in determining whether or no the stimulus will initiate fibrillation.

The production of fibrillation in the cooled ventricles of the rabbit by the application of a properly timed stimulus.

In these experiments the hearts of rabbits were profused with Ringer's solution (NaCl 0·9%, KCl 0·042%, $CaCl_2$ 0·024%, $NaHCO_3$ 0·1%) by Langendorff's method, using the perfusion apparatus of Brodie. The perfusion was started at body temperature but was allowed to fall gradually to room temperature. A thread attached to the apex of the heart and to a lever enabled the ventricular movements to be recorded on a kymograph. As a rule, non-polarisable electrodes were placed in contact with an auricle and a ventricle and connected to an Einthoven galvanometer so that records of the electrical changes could be recorded when desired. A pair of platinum electrodes, separated by two or three millimetres, rested against one of the ventricles. These were connected with the secondary of an induction coil. Stimuli were delivered by single taps of a Morse key connected with the primary of the stimulating coil by means of a double relay so arranged that the moment of application of the stimulus was signalled by the simultaneous use of a sparking coil connected by a short air-gap with the insulated metal pointer and to the drum. It was found in a number of experiments that a single tap of the Morse key *if properly timed* would start fibrillation which would persist for a time which varied in different cases from a few seconds up to over three hours, then giving place suddenly to a normal sequence of beats. The fibrillation affected the ventricles only and was never transmitted back to the auricles.

The point of interest is that the stimulus employed would never cause fibrillation unless it was set in at a certain critical instant. Figures 3, 4, and 5 illustrate the phenomenon. In Fig. 3 the first stimulus applied falls within the refractory phase and does not in-

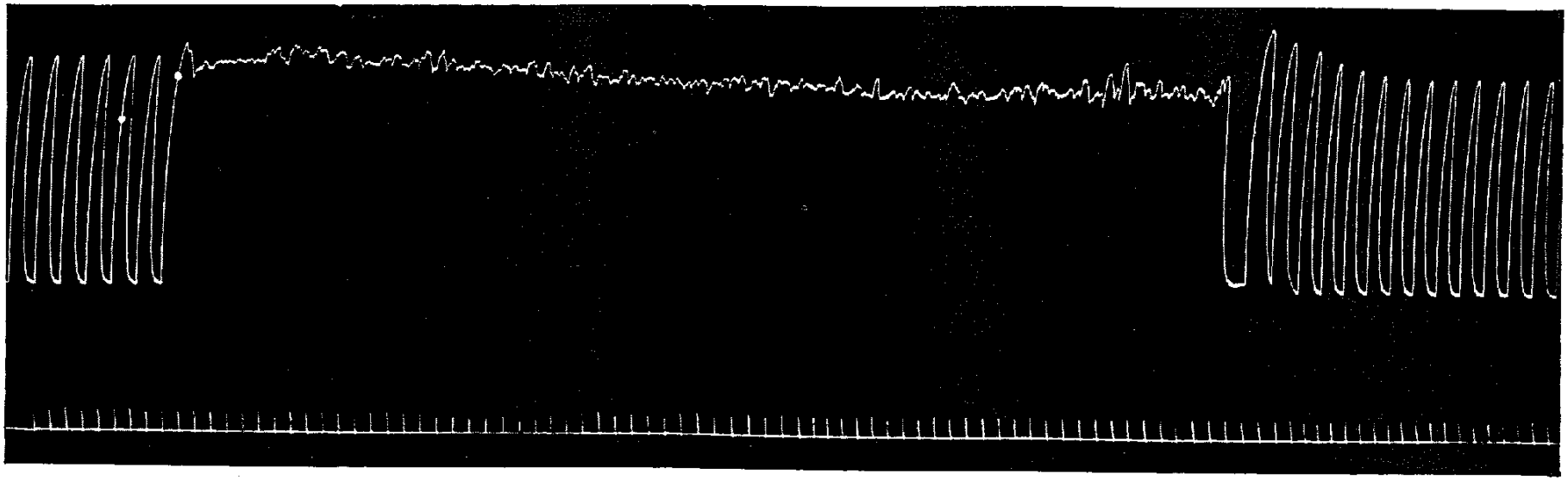

Fig. 3.

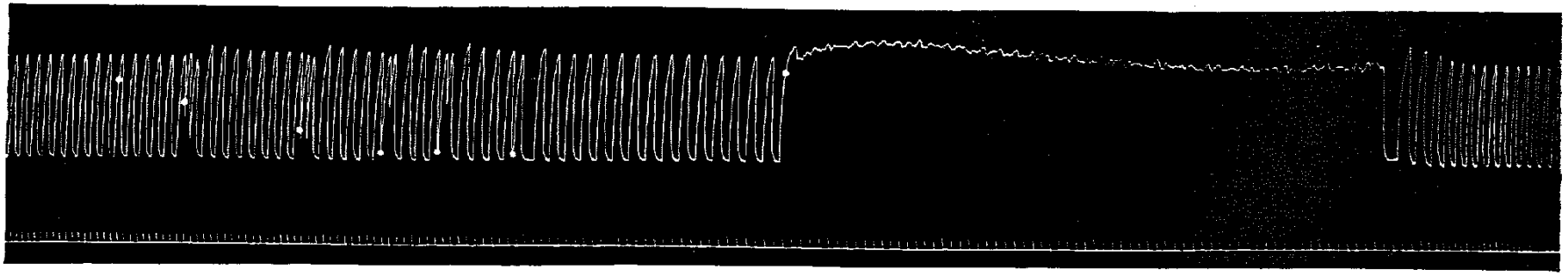

Fig. 4.

fluence the rhythm. The next stimulus, coming a little later in the cycle, set up fibrillation which persists for a certain length of time and then suddenly ceases. In Fig. 4 it is seen that stimuli coming later than the critical instant for the production of fibrillation merely induce an extra-systole, while a comparison of the position of the last stimulus shown with the first, indicates that the critical instant for the production of fibrillation is immediately after the close of the refractory phase. In figure 5 are given some examples of electrograms taken before and during fibrillation set up in the manner described. The appearances of the electrograms are compatible with the idea of a rapid periodically repeated change under the electrode on the ventricle.

In the production of fibrillation in the manner just described, the stimulus apparently arrives at some part of the ventricular muscle just at the end of the refractory phase and probably before the refractory phase has ended in some other regions of the muscle. If this is so, we have again a difference in condition of different regions of the muscle as a basis for the inauguration of the state of fibrillation. It seems possible that circulating excitations may play an important part in the maintenance of fibrillation, but it seems to me that there is another possibility which deserves careful testing. Suppose that A and B are two regions of heart muscle close together. If the region A, is thrown into the excited state, in the ordinary course of events the region B immediately after enters the excited state itself; this is the ordinary conduction process. Now suppose that at the time when excitation is set up in A, B is in the refractory state. It cannot then be excited by A. But the excited state set up in A will persist for a considerable time, and the refractory state will disappear from B before the excited state has ceased in A. The question is: Is it ever possible that under these circumstances A will excite B ?

Conceivably such a state of affairs may arise only under particular conditions of the heart muscle. If we can, we have in such residual excitations a basis for several varieties of anomalous cardiac activities of which fibrillation is one.

DESCRIPTION OF FIGURES.

Fig. 1.—Ring cut from auricle of Acanthias vulgaries, in which a circulating excitation was produced. From a cinematograph film. About three quarters natural size.

Fig. 2.—Ring cut from right ventricle of dog. A centimetre scale photograph beside the muscle. Circulating excitations were set going in this preparation.

Fig. 3.—Kymograph record of lever attached to ventricles of a rabbit's heart, profused with Ringer's solution by the coronary system. The bottom line marks time in seconds. The white spots on the heart tracing were produced by sparks from the pointer, employed to signal the moment of stimulation of the ventricle by induction shocks. The first stimulus applied fell within the refractory phase, the second stimulus, just outside the refractory phase, produced fibrillation. Temperature 24·7°C.

Fig. 4.—From same experiment as previous figure but one hour later. Temperature 22·5°C. Signals as before. Shows that stimuli too early or too late are ineffective in producing fibrillation. The last stimulus applied arrives at the critical instant.

Fig. 5.—Electrograms taken with Einthoven galvanometer from profused rabbit's heart. The abscissae represent fiftieths and tenths of a second. Temperature 26°C. Electrodes for galvanometer on rt. auricle and l. ventricle. (1) shows spontaneous beats, (2), (3), (4) shows stages of fibrillation induced by induction shock. The kymograph tracing at the bottom serves as a key. The electrograms were taken during the process of the kymograph record at the times indicated by the longer lines projecting from the time tracing, which represents seconds as before.

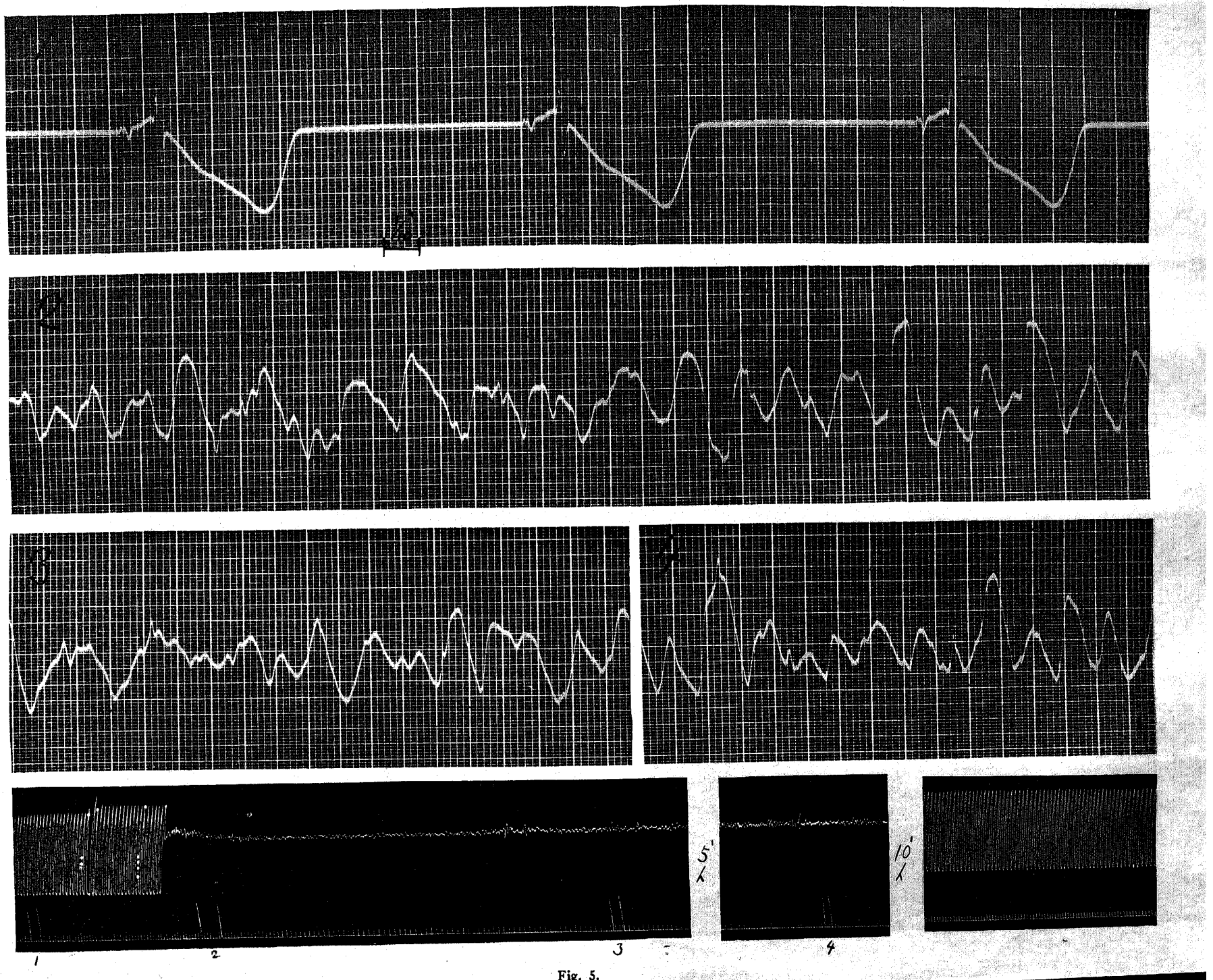

Fig. 5.