The Mechanism and Control of Fibrillation in the Mammalian Heart.

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The results of the present investigation are founded on a very extended study of the subject, carried on from time to time during the past 30 years, in the course of very numerous experiments (hundreds) on the mammalian heart.

These results establish the conclusion that in fibrillation there is an essential change in the manner of conduction of the excitation process in the cardiac musculature; the relation of this change to the excitability of the muscle determines the appearance and characters of the different forms of "fibrillar" action that may be observed. The conduction of the excitation is essentially altered, inasmuch as it is propagated along the muscular fibre systems or fasciculi, instead of travelling directly through the muscular substance, without obvious regard to the arrangement of the fibres, as in the normal beat of the heart.* Fascicular dissociation is an essential feature of fibrillation, which is, strictly speaking, a condition of "fasciculation" rather than "fibrillation." The essential change in conduction may be induced in very different ways. The state of fibrillation is rendered persistent by a disturbance in the normal relations of conduction time and refractory period in the cardiac musculature, resulting in the establishment of a mechanism of circulating excitations.

The cat's heart was the one most largely investigated, but those of rabbits, guinea-pigs, rats, etc., were also employed. The heart action was usually examined and recorded with the thorax open, while artificial respiration, by means of a pump or by continuous insufflation of the lungs with oxygen, was maintained. A myocardiograph of the type described by Cushny† was employed, arterial blood pressure or pulse being often registered at the same time. Intra-cardiac pressure records were often made from the auricles and the ventricles on the principles described by Frank. Anæsthesia was maintained by chloroform, ether, urethane, morphia, chloretone, paraldehyde, or combinations of these. In a number of experiments the method of decapitation was used. The perfused heart was frequently utilised, records being

* See the electrocardiographic evidence advanced by Lewis and Rothschild, 'Phil. Trans.,' vol. 206, p. 181 (1915).

† 'Heart,' vol. 2, p. 1 (1910–11).

made by (*a*) the myocardiograph, used in the same way as with the heart *in situ*, and (*b*) by a rubber bag placed in the left ventricle and connected with a Hürthle manometer, the system being filled with liquid. All the tracings are to be read from left to right; they are all ventricular (L.V. of cat) records except where otherwise noted.* The time is shown in seconds.

For the more accurate use of faradic currents, a Kronecker's inductorium was employed, with two volts in the primary circuit; the values of the units stated are to be taken as obtained with this E.M.F. in each case. For obtaining series of shocks at different rates, a Brodie cut-out arrangement was used, giving either make or break shocks at regular intervals; these shocks were recorded on the tracings by an electrical signal. The shocks were often applied through the myocardiograph, so that they traversed a considerable amount of the cardiac substance; at other times they were sent through electrodes about 1 mm. apart, etc.

The Conduction of the Excitation in Fibrillation.

Instead of travelling uniformly right through the mass of muscle without evident regard to the direction of the fasciculi or bands of muscle, as under normal conditions, the excitation wave in fibrillation travels most easily along the complexly-arranged fasciculi, there being an impairment or failure of propagation at most of the inter-fascicular connections. Such a mode of propagation of the rapidly-recurring contraction waves may be clearly perceived on direct inspection of the heart, and on palpation of the ventricles the apical portion being held between the finger and thumb with varying degrees of light pressure. In the latter case, instead of the normal uniform hardening of the muscular wall at systole, there is a striking want of synchronism in the hardening of the constituent fasciculi, short contraction waves in rapid succession hardening different sets of fibres, while others are relaxed and soft, the contracted ones momentarily standing out and giving a characteristic "wiry" feeling among the quiescent fasciculi; the impression of an incessant turmoil of dissociated or in-coördinated activity is a vivid one. The myocardiograph record shows a series of rapid irregular oscillations, varying to some extent from place to place in rate and in range of excursion. Similar records are obtained from the perfused heart.

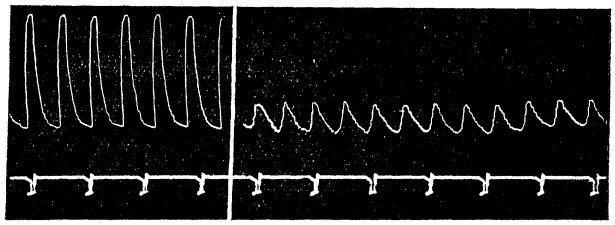
The failure of normal conduction may be induced in two ways: (1) by depressing agencies acting directly on conductivity, and causing more or less extensive blocking in the most susceptible parts, the inter-fascicular junctions, while the intra-fascicular connections remain functional. This effect may be produced even with a moderate or slow succession of

* Upward movement of the ventricular lever = systole.

contractions, but is greatly favoured by rapidity of sequence of the contractions. Such depressing agencies are of various kinds—cooling, intra-vascular injection of potassium salts, bile, over-doses of many drugs, etc., including some substances that are in suitable doses useful as remedial agents promoting recovery from fibrillation; (2) by excessive rapidity of excitation, *e.g.*, by electrical stimulation. This (2) may be the sole cause of the alteration in conduction, or it may co-operate with a depressing influence acting directly on conduction, *i.e.* a combination of (1) and (2) is specially effective.

Change in Mode of Conduction due to Direct Depression.

Fibrillar Beats.—That depression of conductivity is of fundamental importance is evidenced by the fact that individual beats may be "fibrillar" in character (fig. 1). This is strikingly realised on palpation; instead of the



A. B.

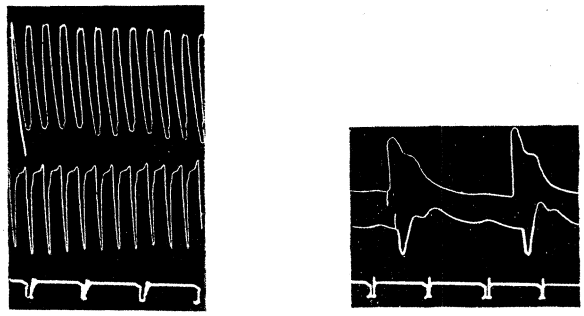
FIG. 1.—The systolic movement of the lever is upward. A = normal beats. B = fibrillar beats, which are strikingly wiry on palpation.

usual sensation of uniform hardening at each systole, the contraction is felt to be passing in asynchronous fashion along the different systems of fasciculi or bands of fibres, some feeling firm and contracted, with the characteristic wiry feeling, while others are soft and relaxed. On the surface of the ventricles the contraction wave is visibly slowed, and in the auricles this may be very strikingly evident in its progress over the muscle.* In this condition the nature of the ventricular beat is similar, whether it occurs in response to an impulse travelling down the A–V. conducting system, or is excited by a direct stimulus applied to the outer surface of the ventricles. The fascicular dissociation is evident even when the impulse is distributed through the endings of the Purkinje system of fibres (fig. 2).

Fibrillar beats are often able to give considerable excursions of the recording lever, and they are often able to pump out a very appreciable amount of blood into the aorta. The contraction and relaxation phases are

* In the ventricles waves can often be plainly seen entering at or emerging from the vortex.

both prolonged; the systolic power is relatively small. The individual beats are quite discrete; there is a very definite interval, varying in duration, of



A. B.

FIG. 2.—A shows normal curves, the upper one ventricular (systolic movement upward) and the lower auricular (systolic movement downward). B shows two fibrillar beats at a later phase of the experiment. Simultaneous points are marked by short vertical lines at the first beat. The Au. and V. contract together; the excitation apparently originates in the A–V. junctional tissues.

complete quiescence between them (fig. 2). The excitability of the cardiac muscle is low when such separate beats are present; the refractory period is long. The occurrence of these fibrillar beats shows that the "fibrillar" mode of contraction is not essentially dependent on or necessarily associated with rapidity of succession at all, though the latter is a very striking feature of typical "fibrillation," giving complexity of movement, complete in-coördination, and mechanical ineffectiveness as regards expulsive power.

Continuous Series of Fibrillar Beats as seen in a More Excitable Heart.

When the excitability is at a higher level, or when stimulation is applied to make the fibrillar beats follow one another more quickly, a continuous succession of contraction waves appears; one fibrillar beat excites another, and they are thus strung in a series, constituting a slow coarse fibrillation (fig. 3). The rate depends on the excitability of the muscle, the degree of

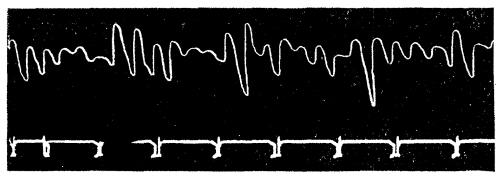


FIG. 3.—Continuous irregular series of fibrillar beats, each beat exciting a subse quent one through the mechanism of circulating excitation. An overdose (intra-vascula r) of sodium carbonate induced this condition.

dissociation varies with the rate of succession—the faster the rate the higher the grade of dissociation. In some cases the depression of conduction may be of such a degree that a beat coming after a long interval may show no distinct sign of dissociation by inspection or palpation, whereas, when a quick series occurs, each beat is markedly dissociated, giving the characteristic " wiry " feeling on palpation (fig. 4). When the excitability of such a

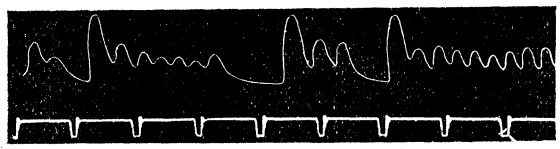


FIG. 4.—The quick series of beats are fibrillar in character. The larger beats coming after long intervals do not show evidence (on palpation) of that character.

heart gradually rises, *e.g.*, under the influence of massage, improved nutrition, certain remedial drugs, removal of depressing influences, etc., the rate of continuous movement may increase, with an accompanying increase in the grade of dissociation.

There is a very definite gradation from (*a*) the phase of discrete fibrillar beats, through (*b*) slow and then quicker series of successive contraction waves, up to (*c*) the rapid and mechanically ineffective oscillations of typical fibrillation. The increase in rate depends on the augmented responsiveness of the more excitable muscle. The degree of asynchronism or dissociation increases with the rise in the rate of succession, the partial blocking between the larger fasciculi or bands and layers of fibres giving the lower grade of dissociation seen in slow coarse fibrillation, while the higher grades of dissociation between fasciculi are present in the condition of rapid fine fibrillation.

Similarly with diminishing excitability and conductivity, a downward gradation may be observed from typical fibrillation, through grades of slower and coarser fibrillation, to the phase of individual fibrillar beats.

Change in Mode of Conduction Due to Excessive Rapidity of Excitation.

When the rate of beat is excessively accelerated by a series of induction shocks of increasing rapidity, a gradation of changes is observable as the rate of succession rises. The individual contractions become briefer and gradually give smaller and smaller excursions of the recording lever. Inspection shows evidence of dissociation becoming very pronounced at the higher rates, so as to bear a close resemblance to the familiar appearance of the ventricular surface in typical fibrillation. Palpation at the same time reveals increasing degrees of asynchronism as the rate rises, until the characteristic wiry

wriggling feeling, practically indistinguishable from that of true fibrillation, becomes very marked, instead of the solid push normally given to the palpating finger. These phenomena are obviously due to the rapid series of short contraction waves traversing, at relatively slowed rates, the various layers, bands or fasciculi of the ventricular musculature according to the lower or higher grades of inter-fascicular blocking and dissociation that are present, thus giving asynchronous contractions at different parts of the thickness of the muscular walls. These changes in their various grades are attended by related degrees of lowering of the arterial pressure, and by auricular acceleration and irregularity. At high rates the force and range of the contractions become small, the output from the ventricles is cut down and a great fall of arterial pressure results.

When the rapidly stimulated ventricles have been brought into the condition above described—presenting many features of resemblance to true fibrillation but not identical in mechanism as will be explained later—diminishing rates of excitation are attended by graded changes of converse order—slower succession of contractions, less dissociation, quicker conduction, apparent coarsening of the oscillations and a gradual return, as the rate falls, to the characters of normal beats.

Pseudo-fibrillation and Fibrillation.

The above-described condition into which the ventricles may be brought by rapidity of excitation (graduated series of shocks or faradic currents of suitable strength) short of the rate necessary to induce true fibrillation, may for convenience be termed pseudo-fibrillation (figs. 5 and 6). As regards the evidence afforded by inspection, palpation, tracings of the oscillations, fall of blood-pressure, etc., the two conditions may be difficult or impossible of distinction, but they differ strikingly as regards persistence; pseudo-fibrillation ceases immediately or at varying short periods after the cessation of the stimulation, while true fibrillation in ordinary circumstances, in the absence of remedial measures, goes on as a rule to the death of the heart. (The duration of pseudo-fibrillation after cessation of the stimulation varies according to the excitability of the stimulated area, the strength and duration of the stimulating current, etc.) The difference depends on the fact that in true fibrillation a mechanism of circulating excitation has been established, whereas in pseudo-fibrillation this is not so. The latter condition depends on the emanation of an excessively rapid series of excitation waves from the area of stimulation; these short waves travelling at reduced speed over the interlaced fasciculi give rise to the condition described. But as soon as the issue of excitations from the stimulated area ceases, the disturbance ceases and the conditions revert to the

normal. The pseudo-fibrillation at once ceases when the stimulated area is disconnected from the rest of the muscle, *e.g.*, by forcible clamping, etc., or

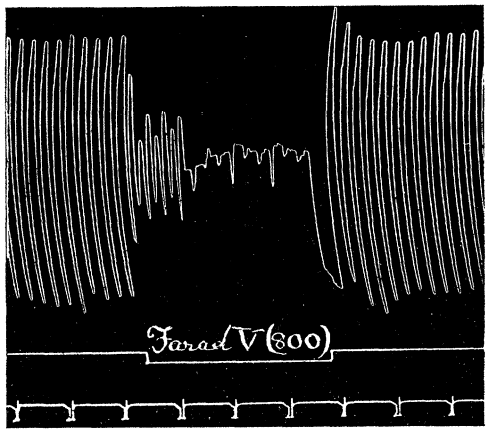


FIG. 5.—Rabbit's heart (R.V.). Faradisation with 800 units induced first a rapid tachycardia, then pseudo-fibrillation which promptly stops at the end of the faradisation. A blood-pressure record taken at the same time showed a great fall, with minute oscillations showing on the tracing.

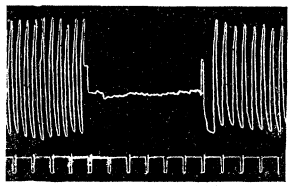


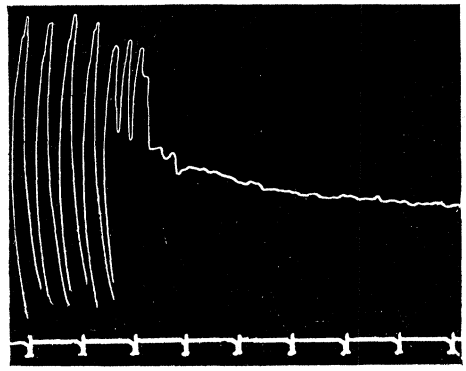
FIG. 6.—Pseudo-fibrillation induced almost immediately in fully developed form by faradisation ; it ends with a larger oscillation when the stimulation ceases.

when it is cut off—as may be done in the perfused heart—or when it is rapidly cooled. In pseudo-fibrillation there has not been established in the mass of the muscle outside the stimulated region a mechanism which ensures the continuance of the movement after the impulses emanating from the excited area have ceased or have been excluded—in striking contrast to what holds good in the case of true fibrillation. This method of differentiating between pseudo-fibrillation and fibrillation may be more easily applied in the case of the auricles, by isolation of the appendix after the stimulation has been applied to the tip.

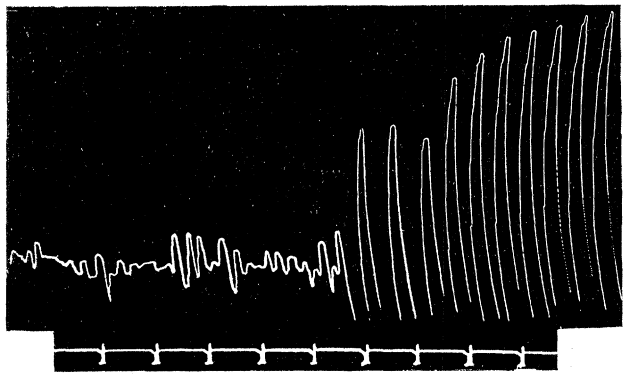
Mode of Recovery from Fibrillation.

When the ventricles are recovering from the state of typical fibrillation, with the aid of massage and of drugs, as stated later, the oscillations visible

on the surface become more vigorous and clearly much coarser, the dissociation becoming much less fine and larger groups of fasciculi contracting together; there is evidently an extension of conduction through inter-fascicular junctions that were formerly blocked. On palpation the muscular substance feels of good tone, and the gradation from fineness to coarseness of fibrillation is very clearly realised—the sensation of universal turmoil due to the fine rapid dissociated twitchings throughout the ventricular walls grading into more vigorous contraction waves of coarser type, and these again into beats giving the normal feeling of uniform hardening of the muscle (figs. 7 and 8).



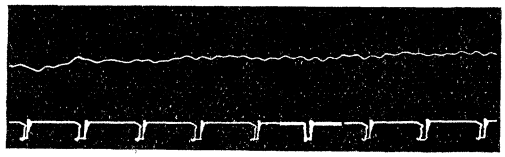
A.



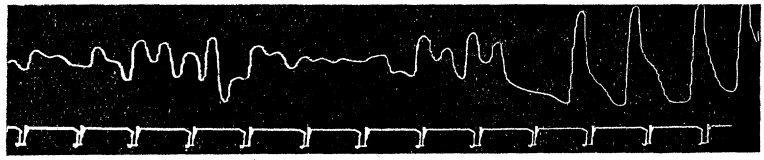
B.

FIG. 7.—Spontaneous recovery from fibrillation in 30 seconds, preceded by coarsening of the fibrillar movement. Urethane, 2·5 grm., had been given hypodermically, in addition to chloroform. In A, the fibrillation was caused by shocks sent into the ventricle at the rate of 480 per minute. A brief tachycardia precedes the fibrillation. In B, recovery is seen, preceded by slower and coarser oscillations.

In the case of a heart which is showing individual fibrillar beats of the nature already described the process of recovery under the influence of



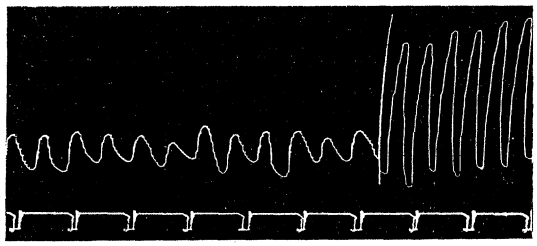
A.



B.

FIG. 8.—R.V. recorded. Fibrillation from application of faradic current (200 units). A is taken 7 seconds after beginning of fibrillation. B shows recovery occurring after fibrillation had lasted 75 seconds, massage being done at intervals. Adrenaline, 0·27 mgrm., had been injected previously, and this probably favoured recovery. Marked coarsening of the movement (followed by a long pause) is seen prior to recovery.

massage, removal of depressing influences, etc., is usually a more elaborate one. The phase of slow coarse fibrillation has to be passed through, with a gradual increase in the rate and the grade of dissociation as excitability is restored; this leads up to the condition of rapid fine fibrillation—from which recovery occurs in the fashion stated above. But treatment with certain doses of adrenaline, etc., may sometimes change the fibrillar beats into co-ordinated ones without a transition through the various phases just enumerated (fig. 9).



A. B.

FIG. 9.—A shows slow coarse fibrillation—a series of irregular fibrillar beats. B is taken shortly after the injection of 0·2 mgrm. adrenalin into the L.V. (1 in 5000 solution used). The fibrillar beats are changed into normal ones.

The coarsening of the rapid oscillation in the process of recovery is quite different from a coarse slow movement that is not on the way to recovery at all and where the muscle is lax and feeble. It is also different from the apparent coarsening with slowing of the oscillations in the graphic record due, as direct inspection of the heart shows, to irregular summation of fine feeble twitchings which are present with a high degree of dissociation and which may gradually become weakened to extinction. It is important to correlate the information derived from (*a*) inspection, (*b*) palpation, and (*c*) graphic records.

Rates of Stimulation Necessary to Establish the Mechanism of Circulating Excitations.

With excitable ventricles in good condition high rates of excitation by induction shocks of moderate strength are necessary to overpass the phase of pseudo-fibrillation and induce true fibrillation, *e.g.*, single induction shocks at rates of 450–500 per minute are commonly effective, but the duration of the application of the series of shocks has an influence in this respect; with longer application lower rates may suffice. When faradic currents are employed the current has to be of such a strength and duration as to raise the rate of responsive contractions to about the above rates. Beyond such rates the state of pseudo-fibrillation is not as a rule maintained, but gives place to true fibrillation as soon as the mechanism of circulating excitation has been established, this point being often recognisable on the tracing by a change from the rapid and more or less irregular curves of small excursion that are present during rapid tachycardia or pseudo-fibrillation to the much smaller and entirely irregular oscillations of true fibrillation (fig. 11).

The conductivity of the muscle plays an essential part in regard to the rate of stimulation needed to cause fibrillation; the necessary rate is not a constant or absolute one, but varies much in relation to the state of the conductivity at the time. The lower the conducting power, the lower is the rate of stimulation required to establish the circulating mechanism, since under these conditions the normal relations between conduction time and refractory period are more readily upset, a relatively low grade of acceleration sufficing to cause slowed excitation waves to reach different parts of the fascicular systems after the refractory period is over in these situations. Agents that depress conduction, *e.g.*, potassium salts, bile, cooling, etc., can be used in such a way and to such a degree as not to induce fibrillation by themselves, but to render the muscle prone to fibrillate with unusually low rates of excitation. Thus the minimal rate of stimulation which induces true fibrillation affords an indication of the state of conductivity. In

conditions of greatly depressed conduction power stimuli not faster than rates commonly seen when the heart is beating in co-ordinated fashion may cause fibrillation. The rate of oscillation when fibrillation is established in such hearts is naturally a slow one, as the excitability is commonly reduced as well as the conductivity.

In such conditions of depressed ventricular conductivity, it is sometimes, though rarely, possible to excite ventricular fibrillation by faradisation of the auricles or of the sino-auricular junction in the region of the S.A. node. Such a result has been quite definitely obtained in a very few cases. The A–V. conducting mechanism was apparently able to transmit a series of impulses to the ventricles sufficient to excite in the latter the relatively low degree of acceleration necessary, in presence of their lowered conductivity, to establish the circulating mechanism.

Rates of Oscillation in Fibrillation.

As has been stated, the rates of oscillation are usually high when fibrillation is induced, and they remain high for some time; if massage is employed, quick oscillation may be maintained for an hour or more. But when, in the absence of massage, etc., the excitability of the muscle becomes lowered, as happens even with massage after a variable time under the usual experimental conditions—the rate of oscillation falls markedly, the less excitable muscle being unable to give such rapid responses to the circulating excitations. And in conditions where the excitability is depressed when fibrillation is induced, the rate of oscillation is, from the beginning, very much slower than usual; such rates as about 280, 250, 240, 140, etc., being seen, *i.e.* rates sometimes below the rhythm of a normally-beating heart when acting rapidly. It must be noted that the graphic records of the oscillations have to be interpreted with caution. For the oscillations caused by contraction waves coursing along the interlaced fasciculi are very complex and irregular and do not denote the succession of contractions in any one fasciculus. Still, the rates observed are, within certain limits, quite definite and significant, though on account of the irregularity precise figures may not be obtainable. Such records must be controlled by the methods of inspection and palpation, and, as a rule, yield results that are in accordance with the evidence afforded by the latter methods.

Influence of Duration of Stimulation.

When electrical stimulation, *e.g.*, faradisation, is used to excite fibrillation, its efficiency shows a marked relation to the duration of its application, as well as to the strength of the current; a longer application, *e.g.*, 10 seconds,

may elicit persistent fibrillation when a shorter one, *e.g.*, 3 seconds, only causes a rapid tachycardia or pseudo-fibrillation. The greater effect of the more prolonged application may be ascribed to at least two factors:—

1. The time needed for the current to produce its full effect in the way of acceleration of the succession of contractions. With suitable strengths of current, the tracings clearly show an increasing acceleration for some little time after the beginning of the application, the excursions become more rapid and smaller until, when the circulating mechanism is established, fibrillation supervenes with its very irregular oscillations. With strong currents the characters of fibrillation may become manifest in the tracing immediately or almost immediately. It is evident that, with relatively weak currents, some time is needed to get up the full rate, with its influence in promoting fibrillation by shortening the refractory period and slowing and impairing the propagation of the excitations.

2. A continuance for some time of the rapid succession of contractions may be assumed to promote fatigue in the more vulnerable parts of the inter-fascicular connections (in analogy to what is known of fatigue of the A–V. conducting mechanism) by an unduly early repetition of an impulse to be conducted. Continuance of the stimulating current after the circulating mechanism has been established seems to be of no importance.

Parallelism between Auricles and Ventricles.

There are close analogies between the behaviour of the auricular and the ventricular muscular systems as regards (1) the occurrence of single contraction waves passing slowly through the muscle, constituting fibrillar beats in the ventricles, and (2) the development of (*a*) regular tachycardias, (*b*) irregular tachycardias, (*c*) pseudo-fibrillation, and (*d*) fibrillation, as results of graduated artificial stimulation.

The persistence or non-persistence of fibrillar movements is clearly explicable on the same principles in both auricles and ventricles—by the altered relation between conduction and refractory period—and the mode of conduction in fibrillation is, as in the ventricles, a fascicular one, depending on the presence of more or less extensive blocking in the inter-fascicular connections. Slow coarse fibrillation may be seen in the auricles as in the ventricles, and separate waves of contraction sweeping over the auricles in irregular fashion, more or less resembling what have been described as fibrillar beats in the ventricles, are often very striking in conditions of depressed conductivity; the progress of the greatly slowed wave can be followed by the eye with the greatest ease. And, with some increase of excitability, the wave of excitation may excite another, just as in the

ventricles, and so set up a continuous slow series—slow here also because of obviously depressed excitability, as shown by diminished readiness to respond to stimuli of definite strengths.

Pseudo-Fibrillation and Fibrillation in the Auricles.

Under gradually increasing electrical stimulation, the auricles, like the ventricles, show higher and higher grades of disturbance: (1) extra-systoles, (2) regular tachycardia, (3) irregular tachycardia, (4) pseudo-fibrillation, and, at least in certain conditions of the auricular muscle, (5) fibrillation. The gradually increasing rate of auricular response rises through the grades of tachycardia or flutter, with diminishing range of lever excursions, up to a condition of rapid tremulous movement (pseudo-fibrillation), with irregular succession and range of oscillations more or less closely approximating to the characters of true fibrillation and often hard to distinguish with certainty from the latter, either by inspection of the auricles or in the tracings, though in pseudo-fibrillation the oscillations are commonly larger and of a less high grade of irregularity than in fibrillation. The movement may last for variable periods after the stimulation has been discontinued.

A ready method of discriminating between the two conditions is afforded by the experiment of isolating the stimulated area (by clamping, etc.). Tachycardia or pseudo-fibrillation is at once arrested, while true fibrillation is not affected.

In the majority of the animals examined special conditions are necessary in the auricular muscle for the production of true fibrillation with its essential mechanism by faradisation, etc., the stimulation *per se* is not, as a rule, sufficient in the easier conditions of quick conduction normally present in the auricles. Contractions in very rapid sequence, *e.g.*, 500–600 or more per minute, may be excited without establishing the mechanism of persistent fibrillation. Certain conditions involving an alteration of conductivity without a great lowering of excitability, are often effective in determining the occurrence of fibrillation, *e.g.*, vagus influence, defective blood supply, certain phases in the action of some drugs, such as chloroform, paraldehyde, pilocarpine, etc.

"Spontaneous" fibrillation, *i.e.* when the precise exciting cause cannot be defined, depends no doubt on the presence of irritation *plus* an altered state of conductivity. The latter is sometimes supplied, under experimental conditions, by the tonic influence of the vagus centre exercised through either the right or the left vagus, as can be seen when only one nerve is intact; section of the nerve in such cases is speedily followed by recovery from fibrillation which may have persisted during the whole preceding part of the

experiment, or at least since the heart was exposed. Such vagus control has not appeared as a common cause of auricular fibrillation in these experiments, but in some instances its influence has been unmistakable.

The simplest and most easily available method of producing true auricular fibrillation for a time is by a combination of electrical stimulation and vagus stimulation. Rapid tachycardia set up by electrical stimulation is converted by vagus influence into true fibrillation which persists as long as the vagus influence is maintained in sufficient strength to provide the condition in the auricular musculature necessary for the keeping up of circulating excitation; the fibrillation so excited goes on under vagus influence long after the electrical stimulation has been discontinued; the latter may indeed have been applied only for a second or two. Under vagus influence the fibrillation oscillations, though very rapid, become greatly weakened, the irregular movements of the recording lever becoming minute. With pretty strong vagus control this weakening may go on to invisibility, so that the auricles look entirely quiescent, even when their surface is scrutinised with a lens. As the vagus influence wears off during prolonged stimulation of the nerve, very fine fibrillation oscillations again begin to become perceptible, and these gradually gain in vigour and range until after a variable time the normal type of beat replaces the fibrillation movement.

A similar sequence of events, more quickly passed through, is evident when vagus stimulation is diminished or discontinued instead of the influence of the nerve being allowed to wear off during continued stimulation. What evidently occurs in these cases when the auricles become motionless under vagus influence, is that the mechanism of circulating excitation goes on working in spite of the inhibitory influence which cuts down the mechanical response to invisibility; there is no true inhibition of the essential mechanism of fibrillation.

The experiment may be done in another way. Instead of first exciting the tachycardia and then stimulating the vagus, the latter may be brought into action first so as to reduce the auricles to complete quiescence; during this period an electrical current is applied briefly (*e.g.*, for one or two seconds) to the auricle; a fine tremulous (fibrillation) movement of small range may at once appear and continue until the vagus influence wanes or is discontinued.

Mechanism of Circulating Excitations without Contractions.

But if the vagus is strongly inhibiting the muscle when the electrical current is briefly applied, there may be no visible effect at all; the auricles remain perfectly motionless until the vagus control has become weakened, when the fine tremulous movement usually appears and gradually gains in

vigour as in the former experiment, after a time giving place to normal action. What has happened in this case is that the electrical stimulation, falling within the period of vagus influence, is effective in setting up the mechanism of circular excitation, while the latter finds no expression in contractile movement on account of the mechanical response to excitation being kept in abeyance by the vagus inhibitory power. When the latter wanes and the mechanical response again becomes manifest, the circulating excitations are attended by the circulating contractions of visible fibrillation.

When the electrical stimulation is applied in the foregoing way without apparent effect on the inhibited auricles, the subsequent appearance and development of fibrillation as described above is not affected by the stimulated area (*e.g.*, auricular appendix) being isolated from the rest of the auricle shortly after the brief application of the stimulating current and while the auricles are still kept in complete quiescence by the vagus; the subsequent fibrillation involves the whole of the auricular muscle, apart from the isolated area. It is plain that the mechanism of excitation necessary for fibrillation has been established in the mass of the auricular muscle, and that it is independent of a continued emission of impulses from the stimulated area—now isolated. In these experiments the isolation was effected (*a*) by clamping off or (*b*) by section, after a weak clip or a ligature not too tightly drawn had been applied along the base of the appendix to prevent hæmorrhage. In some cases rapid cooling of the stimulated area was employed instead of isolation. Control experiments were made to determine that the methods used do not themselves cause fibrillation in the conditions present, under vagus influence, etc.* The vagus evidently can act more strongly on auricular contraction force, if not also on conductivity, than on excitability, for the latter property must remain functional (though depressed) in auricles that respond by subsequently manifested fibrillation movements to an electrical stimulus applied during the period of mechanical quiescence of the muscle.

As a rule, as stated above, the auricular muscle is not sufficiently depressed by vagus influence to prevent excitation occurring in response to adequate stimulation, or to stop the circulation of excitations once this mechanism has been established, though the normally-associated mechanical response may be cut down to the point of invisibility. But in some instances the vagus seems to be able to act so strongly on excitability that after electrical stimulation during the vagus period, fibrillation does not gradually appear in the usual way as the vagus control is passing off, but visible action recommences

* Under certain conditions it is clear that mechanical stimulation may sometimes excite auricular fibrillation.

in the form of slowed auricular *beats*. This is to be ascribed to the vagus acting more strongly than usual on excitability, in addition to the usual effects on contraction force and conductivity.

When the influence of the vagus in converting a rapid tachycardia or flutter into fibrillation was first studied, the question naturally arose as to whether the changes visible on inspection and in the graphic records might not be due simply to the cutting down of the force of the rapidly-recurring contractions, the mechanical limitation of the range of movement associated with distension of the auricular chambers, etc. But the clamping-off experiment brings out there is an essential difference in the mechanisms in the two cases.

The vagus alters or depresses conductivity in the auricles in such a way that the inter-fascicular connections are unable to functionate normally when the succession of excitations is much accelerated. (Distinct from this is the question of the power of the vagus to slow the conduction along the main transmitting paths in the auricles.) Certain other depressant agencies have an influence on the inter-fascicular connections in the ventricles (already described), which resembles that of the vagus in the auricles, and these agencies, when acting in great intensity, may have the further result of causing obvious and striking retardation in the passage of the contraction wave both in the ventricles and the auricles, even when the sequence is not a rapid one, but may indeed be slower than the normal.

Some Differences in the Behaviour of Auricles and Ventricles.

While the analogies between the various phenomena are very close in the auricles and ventricles, certain points of difference may be noted.

1. Electrical stimulation of strength adequate to give a sufficiently excessive rate of beat is, by itself, a ready means of exciting ventricular fibrillation, though, as has been stated, the addition of some influence depressing conductivity causes fibrillation to develop when the rate of beat is not nearly so rapid as would otherwise be required. Auricular fibrillation, on the other hand, is not, in most cases when the heart is in good condition, excited by electrical stimulation *per se*, but requires an alteration of conductivity (in the sense already defined) by some other agency, *e.g.*, vagus influence, defective nutrition, toxic substances, etc. The reason of this difference is probably to be found in conduction being less easily upset in the auricles with their simpler structure and easier conditions of rapid conduction, as compared with the highly elaborate ventricular architecture with the much slower rate of conduction in the ventricular muscle proper—apart from the Purkinje system.

2. The relation of the vagus to fibrillation is quite different in auricles and ventricles; in the auricles the vagus favours fibrillation in the presence of some irritation, *e.g.*, electrical stimulation; in the ventricles vagus influence can often be clearly shown to retard or prevent fibrillation, while not able to remove the latter once it has been established. The difference is due to the stronger action of the vagus on conductivity than on excitability, as a rule, in the auricles; this naturally promotes fibrillation. In the ventricles, on the other hand, in regard to these two properties, the main, if not the sole, incidence of the vagus influence is on excitability; this, of course, tends to repress the development of fibrillation. Pilocarpine, in suitable doses, acts similarly to the vagus, and its relation to fibrillation in auricles and ventricles is to be explained on the same lines.

3. Some drugs and toxic substances, etc., have a different incidence on the auricles and ventricles respectively both in regard to promoting and retarding fibrillation.

Confirmation of Former Views.

So long ago as 1887 the writer* put forward the view that the essential mechanism of typical fibrillation is explicable not simply as an excessive acceleration of rate *per se* or on the assumption of a mechanism of a different nature, in the sense of muscular *v.* nervous, from that concerned in the normal beat, but in a disturbance in the relation between the refractory period and the conduction time in the cardiac musculature; that when this relation is upset by shortening of the refractory period or lengthening of the conduction time or a combination of such changes, the excitation wave, in spreading over the muscular systems, reaches fibres in which the refractory period has already ended and further excitation occurs; the co-ordinated beat is thus abolished and replaced by a rapid and continued series of in-coördinated fibrillar contractions. The alteration in conduction—the passage of the slowed contraction waves in peristaltic fashion along the various complexly-arranged bundles of the ventricular wall at different points of time was described—and also the important fact that single beats may in certain circumstances be fibrillar in character.

Control of Ventricular Fibrillation.

The various actions of different agencies, in promoting or retarding the development of fibrillation and of removing it after it has been established, are to be explained by their incidence on the functions of conduction and excitability and the effects which they bring about in the relations of these functions in different conditions of the cardiac muscle (as a whole) and in the different conditions that may obtain in the auricles and ventricles respectively.

* 'Journal of Physiology,' vol. 8, p. 296 (1887).

Any influence which depresses excitability without depressing—at least proportionately—the function of conduction naturally tends to be in some measure protective against the occurrence of fibrillation and favourable to recovery from that condition when once it has been established. A diminution of excitability opposes the attainment of acceleration sufficient to determine fibrillation; it also diminishes the responsiveness of the muscular fasciculi to circulating excitations. (The control of auricular fibrillation which differs in some respects from that of ventricular fibrillation will be dealt with elsewhere.) Similarly any agency which improves conductivity without unduly exalting excitability is inimical to the mechanism of circulating excitation. Obviously a combination of a depressing influence on excitability with the maintenance of a high level of conductivity would afford the most favourable condition for protection or recovery. Concurrent depressions or elevations of excitability and conductivity in proportionate degree naturally have no specific influence on the question of fibrillation. The agencies which operate successfully in opposing the development of fibrillation—either spontaneous (*i.e.* from unknown causes) or excited artificially by drugs, electrical stimulation, etc.—are often effective in restoring the normal action after fibrillation has been established. Remedies for fibrillation have commonly, in these experiments, been injected into the cavity of the left ventricle through the apex by means of a slender needle; sometimes intravenous injection (external jugular, etc.) was used, massage of the heart being done in both cases, while the artificial respiration is of course maintained. Smaller doses were sufficient by the intra-ventricular mode of injection. Approximately isotonic solutions were used, warmed to body temperature. The doses stated are for cats, usually weighing 2–3 kilos. but sometimes more.

Urethane.—Doses varying between 0·025 and 0·25 grm. injected into the left ventricle were found effective in removing fibrillation in very numerous experiments (fig. 10); 3 per cent. solutions were commonly used for

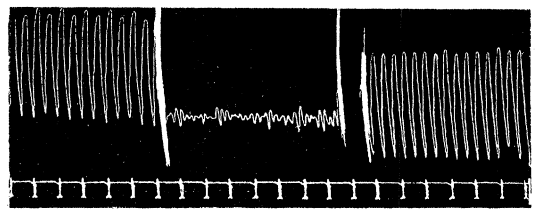
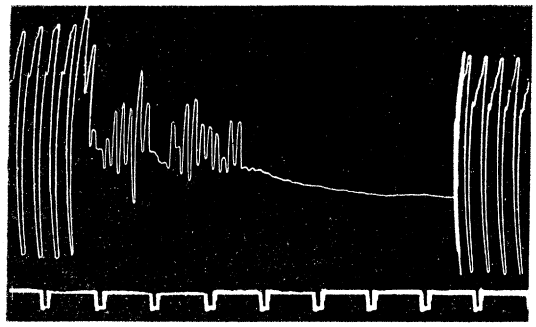


Fig. 10.—The middle portion of the tracing shows fibrillation caused by strong faradisation (5000 units). After it had lasted for 2 minutes (with occasional massage) 0·05 grm. urethane was injected into the L.V. The restored action is seen in the right-hand portion.

intra-cardiac or intra-vascular injections. Hypodermic doses of 0·5 grm. per kilogramme and upwards (given in 25-per-cent. solution, etc.) have a pronounced influence in protecting against fibrillation in light chloroform anæsthesia and in diminishing, though not always obviating, the danger of adrenaline fibrillation in the same grade of anæsthesia. Sufficient time has to be allowed for absorption before the effects are tested. Smaller doses suffice for this purpose when given by intra-vascular (*e.g.*, saphenous vein) injection.

Strontium Chloride was given in doses of 0·01—0·06 grm., a 1-per-cent. solution in dilute Ringer's fluid being usually employed.* Especially when applied at an early phase of the fibrillation this remedy often succeeded very well, and the condition of the heart and circulation were excellent afterwards (fig. 11). In other cases after fibrillation had lasted for a long time and other



A. B.

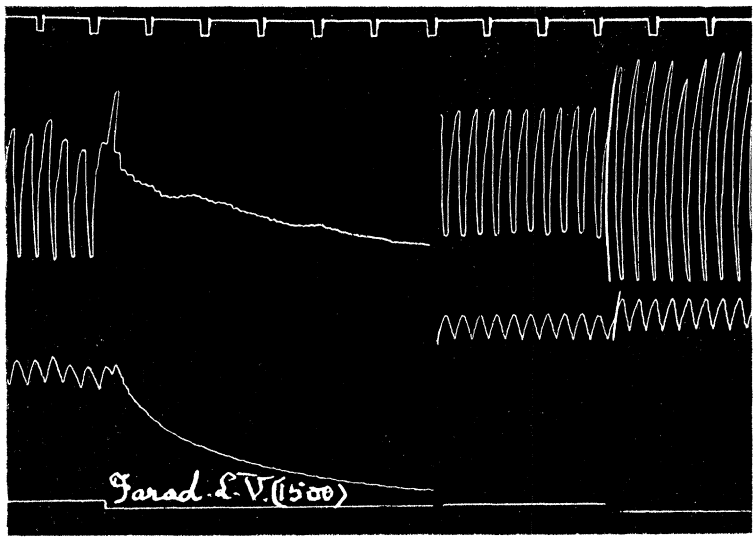
FIG. 11.—A, fibrillation, preceded by period of tachycardia and pseudo-fibrillation, from faradising with 500 units. Injection of 0·06 grm. strontium chloride was followed in 30 seconds by restoration of the normal action, shown in B, taken shortly after recovery. Soon afterwards faradisation with 1000 units again caused fibrillation; recovery followed injection of 0·03 grm., with the usual massage.

measures had been unsuccessful, this salt sometimes speedily induced recovery. Fibrillation, in its various phases, caused by potassium salts is, as might be expected, specially amenable to treatment with strontium in doses varying according to the toxic dose of potassium.

Adrenalin.—Solutions of 1 in 10,000 or 1 in 5,000 were commonly used; sometimes as strong as 1 in 1,000; in Ringer's fluid in each case. The dose varied from 0·1 to 1 mgrm. Successful results were very frequent in fibrillation which had been induced in various way—by electrical stimulation, chloroform, adrenalin injection during light chloroform anæsthesia (the

* The amounts here stated are of strontium chloride crystals ($SrCl_2+6H_2O$). The doses of the anhydrous salt would be represented by about 60 per cent. of the above amounts.

chloroform-adrenalin reaction described by Levy and abundantly illustrated in this investigation), intravenous injection of potassium salts, etc. In many instances fibrillation has been induced by a small dose (*e.g.*, 0·1 mgrm.) of adrenalin and remedied by the intraventricular injection of a very large dose (up to 1 mgrm.), the state of the heart and circulation remaining good afterwards (fig. 12). The excitability and conductivity of the muscle are



A. B. C.

FIG. 12.—The upper tracing is from the left ventricle, the lower indicates the blood-pressure. In A, fibrillation caused by faradisation with 1500 units lasted 6 minutes, recovery following injection of 0·5 mgrm. adrenalin in three doses. B is shortly after recovery. C, taken 1 minute later, shows much increase in the range of the lever excursions. Note that the blood-pressure is still elevated.

enhanced by a small injection and as early effects of a large injection; subsequently a pronounced depression of excitability occurs—shown in many cases by a great diminution in responsiveness when tested by graduated faradic currents; stimulation, that formerly induced fibrillation readily, now fails to do so even when strengthened to many times its former intensity. Diminished sensitiveness to faradic currents is often pronounced, while the blood-pressure is still elevated and the heart is beating very strongly. Adrenalin can thus act in two ways: (*a*) by reducing excitability, and (*b*) by improving conduction.

Hirudin.—Injections* (into the saphenous vein) of about 8–10 mgrm. per

* Doses of 0·3–0·5 mgrm. were often effective in removing fibrillation injected into the L.V. The solution of hirudin used generally contained 1 mgrm. in each cubic centimetre of Ringer's fluid.

kilogramme of body-weight showed striking effects in opposing the development of fibrillation, either "spontaneously" or in response to electrical stimulation, etc. Even powerful faradisation (often several thousand units) caused only a pseudo-fibrillation, ceasing almost immediately or lasting only a short time (seconds) after the stoppage of the current, or a true fibrillation, which is spontaneously recovered from—on account of the diminished responsiveness of the muscle to the circulating excitations.

Pilocarpine.—Intravenous injection (into jugular, etc.) of 0·0025 grm. (with massage of the ventricles) was often effective in arresting ventricular fibrillation. There was a good deal of variation in regard to this result; there seemed to be a parallelism between the efficiency of pilocarpine in this respect and the activity of vagus inhibition in the particular heart in question—as tested by stimulation of the vagus in the neck or, preferably, the inhibitory area on the dorsal aspect of the auricles. Though vagus stimulation has not been found to arrest fibrillation once it has been established, it has shown notable effects in opposing the development of fibrillation in certain circumstances. And pilocarpine is much more potent than the vagus, though its influence is in the same direction and of the same nature in many respects at least.

Similar remedies were found applicable to the perfused heart, also, a little of the solution of urethane, adrenalin, etc., being injected into the tube leading to the aorta; very small doses usually sufficed.

In some instances, where ventricular fibrillation does not yield so readily as usual to a single remedy, combinations such as urethane and adrenalin, or these followed by strontium chloride, prove very effective. After such treatment the ventricles commonly show a remarkably great resistance to electrical stimulation as far as the induction of fibrillation is concerned, very powerful currents up to 7,000–10,000 units, etc., often causing only pseudo-fibrillation, and, if true fibrillation, with its special mechanism, is induced, it very frequently shows spontaneous recovery after variable periods, frequently without any massage or with massage for some seconds. The difficulty in exciting fibrillation, and its notable tendency to recover, are often very striking, and are to be accounted for, in the main at least, by the diminished responsiveness of the muscle induced by the drugs.

Some relations of different remedial agents to special conditions of the heart may be noted. In very excitable hearts that have fibrillated, depression of excitability is the primary requirement. On the other hand, when direct depression of conductivity (*e.g.*, by potassium salts, bile, cooling, etc.) is the predominant factor in any particular heart, remedies calculated to enhance this function are obviously indicated, whether they act (*a*) by

direct improvement of conductivity or (*b*) secondarily through the slowing of the rate of succession which they may induce, *i.e.* by lowering excitability, provided that this effect is not attended by a proportionate lowering of conductivity. Adrenalin is notably useful in this respect, as indicated by the remarkable improvement in conduction often seen under its influence, especially evident in the auricles, where a strikingly slow contraction wave, present during gravely depressed conduction, may be replaced by an approximation or a return to the normal type. Hence the special utility of adrenalin in dealing with forms of slow coarse fibrillation, already described, and also with fibrillar beats—unless the damage in the latter case has been carried to an irreparable stage (fig. 9).

The success of the above-mentioned methods of obtaining recovery from typical fibrillation, induced by means that did not permanently damage the heart, has been such that in recent years of experimentation there has not been failure in any instance.

For valued assistance in some of the experiments of this investigation, I have to record my thanks to Drs. G. Spencer Melvin and J. R. Murray.

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The Artificial Production of Echinoderm Larvæ with Two Water-Vascular Systems, and also of Larvæ Devoid of a Water-Vascular System.

By E. W. MacBride, F.R.S.

(Received January 18, 1918.)

[Plates 4–10.]

The development of Echinoderms has been characterised, and with justice, as the most remarkable ontogenetic change in the animal kingdom. For the larva is an almost perfect example of a simple, bilaterally symmetrical Metazoon, and the amazing thing is, not that the radially symmetrical adult should develop out of a bilaterally symmetrical larva, but that the axis of symmetry of the radial adult should cut the principal axis of the bilateral larva at an angle which approaches 90°.

In the three orders Asteroidea, Ophiuroidea, and Echinoidea, the general