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Atrial Fibrillation as a Self-Sustaining Arrhythmia Independent of Focal Discharge

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All of the theories advanced to explain atrial flutter and fibrillation are variations of the circus movement and ectopic focus theories. Circus movement about an obstacle has been established experimentally by Rosenblueth and Garcia-Ramos,^{1,2} and it is likely that nature sometimes performs a similar experiment. Ectopic focal activity has also been produced experimentally by Scherf,³ and some rapid atrial mechanisms in patients may well have their genesis in unifocal or multifocal ectopic pacemakers. Since both circus movement and ectopic focus mechanisms have been produced experimentally, it is unrealistic to propose that only one of these mechanisms can exist in patients.

Both theories differentiate between flutter and fibrillation in terms of the frequency of the governing agency. Flutter is considered to be rapid enough to show continuous atrial activity in the electrocardiogram and slow enough to permit essentially uniform activation of the atria. Atrial flutter can certainly be produced by repetitive discharge from an ectopic focus at an appropriate frequency. It can also be produced, within the normal parameters of atrial conduction velocity and refractory period, by circulation of an excitation wave about an obstacle of suitable circumference. In the former case, arrest of the flutter will be expected when the ectopic pacemaker is suppressed; in the latter case the dysrhythmia will end if the circus path is interrupted.

The term "atrial fibrillation" is applied both clinically and experimentally to tachycardias so rapid that uniform atrial excitation does not occur. Because of the irregular atrial activity it becomes difficult to prove which of several possible mechanisms exists. It is conceivable that a circus movement could

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exist in a path in which the refractory period is briefer than in the rest of the atrium. In this situation the circuit length might be short enough to result in a frequency of impulse discharge exceeding the capacity of the atria to follow regularly. It is also conceivable that an ectopic pacemaker could fire at a frequency taxing the properties of the surrounding atrial muscle. It is, however, difficult to believe that either of these mechanisms would be endowed with sufficient stability to persist for years as fibrillation often does.

Fibrillation may be started by a rapidly discharging focus or even by a single premature systole. The initiating agency may be a stimulus from electrodes, a rapidly discharging aconitine focus, a spontaneous premature beat, or a circus movement whirling about an obstacle. Whatever the initiating mechanism, fibrillation may persist after that mechanism ceases to operate. It becomes necessary then to consider this arrhythmia as a stable state compatible with the normal parameters of atrial behavior but independent of its progenitor, whether this be a circus path or an ectopic focus. Neither of the current theories provides a satisfactory explanation of this phenomenon. The necessity for an alternative explanation for "true" (independent and self-sustaining) fibrillation as contrasted to simple rapid and irregular atrial excitation is apparent.

It is the purpose of this report to present evidence that fibrillation can exist as a stable state, self-sustained and independent of its initiating agency, and to present a hypothesis which explains these and other features of fibrillation.

METHODS

Dogs of both sexes, weighing from 6 to 20 kilograms and anesthetized with pentobarbital, 30 mg./Kg., or thiopental, 20 mg./Kg., followed by barbital, 200 mg./Kg., were used in all experiments. Under artificial respiration the heart was exposed through a mid-sternal incision and cradled in the opened pericardium. Both vagi were cut in the neck, and stimulating electrodes were applied to the right nerve below the point of section. Stimulating electrodes and one or more pairs of recording electrodes were attached to the surface of the right atrium, and recording electrodes were applied to the surface of the right ventricle. Responses were recorded on a Grass ink-writing polygraph.

Atrial dysrhythmias were produced by repetitive stimulation of the right atrium, or by application of aconitine in concentrations of 1:2000 to 1:500, usually by injection of 0.01 to 0.03 c.c. into the atrial muscle near the tip of the right appendage. On occasion the site of aconitine injection was blocked off by application of a rubber-shod intestinal clamp across the base of the appendage.

RESULTS

Response of Atrium to Electrical Stimulation.—According to the unitary hypothesis, it is implied that flutter differs from fibrillation only in the frequency of one or more ectopic foci and the degree of regularity of the atrial response. Experiments were performed to determine the frequency at which flutter, as defined in these terms, merged into fibrillation. Through electrodes attached to the tip of the right atrial appendage, driving stimuli were applied at frequencies increasing gradually from about 4 per second up to 20 per second. Since vagal stimulation is known to increase the likelihood of fibrillation during rapid excitation of the atria, responses were recorded with and without excitation of the right vagus at various frequencies.

In the absence of vagal stimulation the atrium followed driving frequencies up to 6 or 7 per second without intermission and without irregularities of the electrical responses. At slightly higher frequencies electrical alternation often appeared, but so long as the atria followed the driving stimulator regularly, cessation of stimulation was promptly followed by resumption of the sinus rhythm. At frequencies of 9 to 11 per second, at a sharply demarcated point in time, the atrial electrical responses became grossly irregular (Fig. 1,*A*). Beyond this point the atrial arrhythmia often persisted for a few seconds after cessation of stimulation.

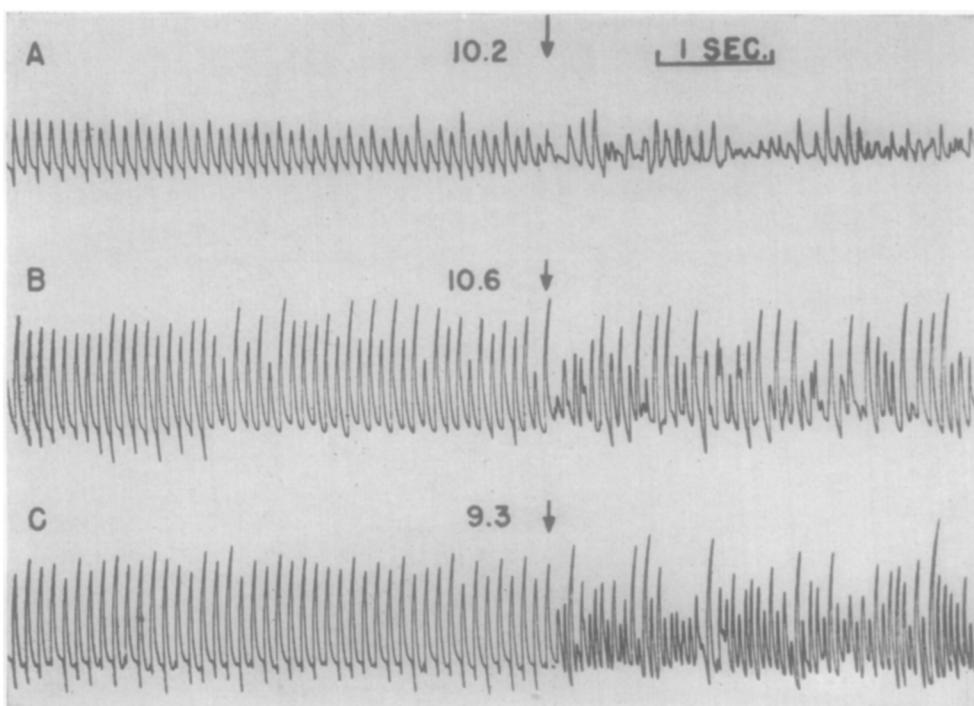


Fig. 1.—Dog weighing 15 kilograms and anesthetized with pentobarbital. Vagi cut. Records of electrical activity of right atrial appendix during gradual acceleration. *A*, Without vagal stimulation. *B*, During stimulation of right vagus at 5 cycles per second (sufficient to reduce spontaneous sinus frequency from 198 to 111 per minute). *C*, During vagal stimulation at 10 cycles per second (sinus frequency reduced from 198 to 69 per minute). Arrows indicate point at which atria fail to follow stimulus frequency regularly. Figures indicate driving frequency during 1 second just preceding irregular atrial responses. Time calibration is shown at right of upper record.

Although it might be expected that vagal stimulation, by abbreviating the atrial refractory period, would permit the atria to follow the stimulator regularly to higher frequencies, it was found that the point at which the atrial electrical responses showed alternation of configuration, and the point at which complete degeneration of the responses occurred, were almost precisely the same during vagal stimulation as during control observations (Fig. 1,*B* and *C*). In fact, if the atria were accelerated rapidly, fibrillation occurred at lower frequencies dur-

ing vagal stimulation. As in control observations, the normal sinus rhythm was immediately resumed if the stimulator was turned off while responses were still regular in rhythm. If stimulation was carried beyond the point at which the responses became irregular, the arrhythmia persisted after cessation of atrial stimulation as long as vagal stimulation was maintained, and ceased within seconds when vagal stimulation was discontinued.

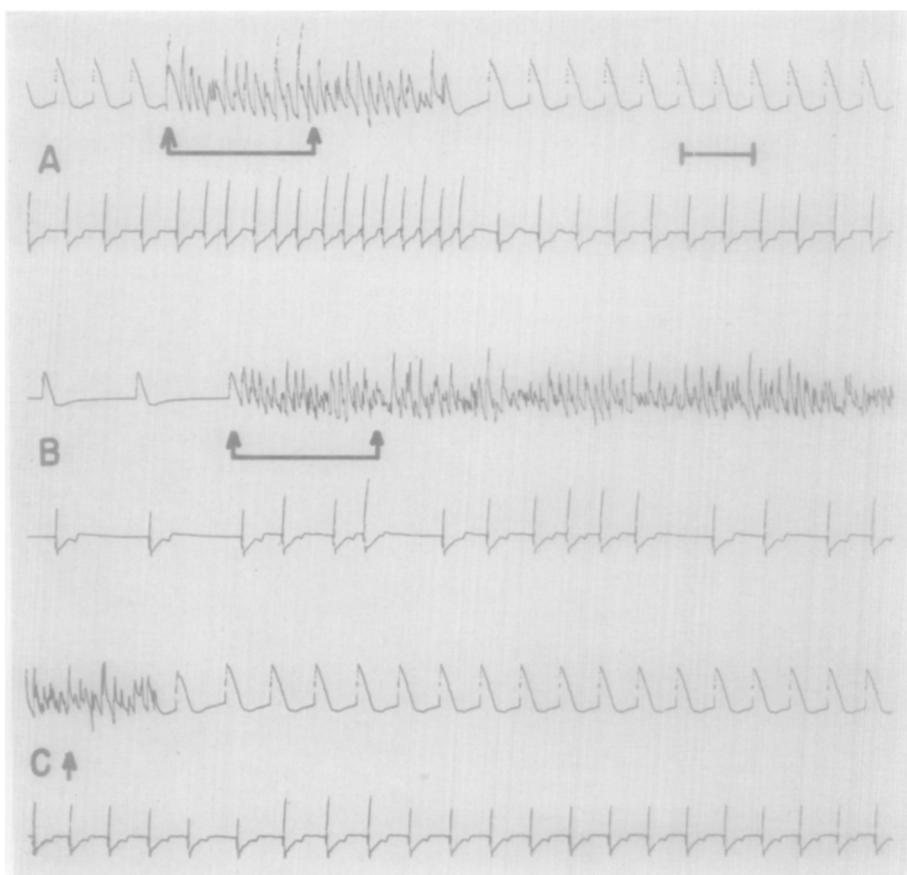


Fig. 2.—Dog weighing 9.8 kilograms and anesthetized with pentobarbital. Vagi cut. Upper record, atrial electrogram; lower record, ventricular electrogram. Time calibration at right of part A is 1 second. A, Without vagal stimulation; atrial stimulation at 20 cycles per second between arrows. B, During right vagal stimulation; atrial stimulation at 20 cycles per second between arrows. Between B and C, 12 seconds elapsed. At arrow in C, vagal stimulation stopped.

In other experiments the dependence of sustained fibrillation upon cholinergic stimulation was tested by subjecting the atria to brief periods of stimulation at a frequency of 20 per second, with and without simultaneous excitation of the right vagus nerve. Fibrillation, as defined by rapid and irregular electrical activity in the atria, rarely outlasted the atrial stimulation by more than a few seconds in the absence of vagal stimulation, but always persisted for the

duration of vagal stimulation if the latter was sufficiently intense. Fig. 2 illustrates such an experiment. In part A, without vagal stimulation, electrical stimulation of the atrium at 20 per second was applied for 2 seconds, as indicated by the arrows. The irregularity persisted for less than 2 seconds after atrial stimulation was discontinued. In Fig. 2,B, atrial stimulation was applied for 2 seconds during vagal stimulation strong enough to slow the sinus frequency by slightly more than 50 per cent. Fibrillation persisted until vagal stimulation was stopped (at the arrow in Fig. 2,C), about 20 seconds later.

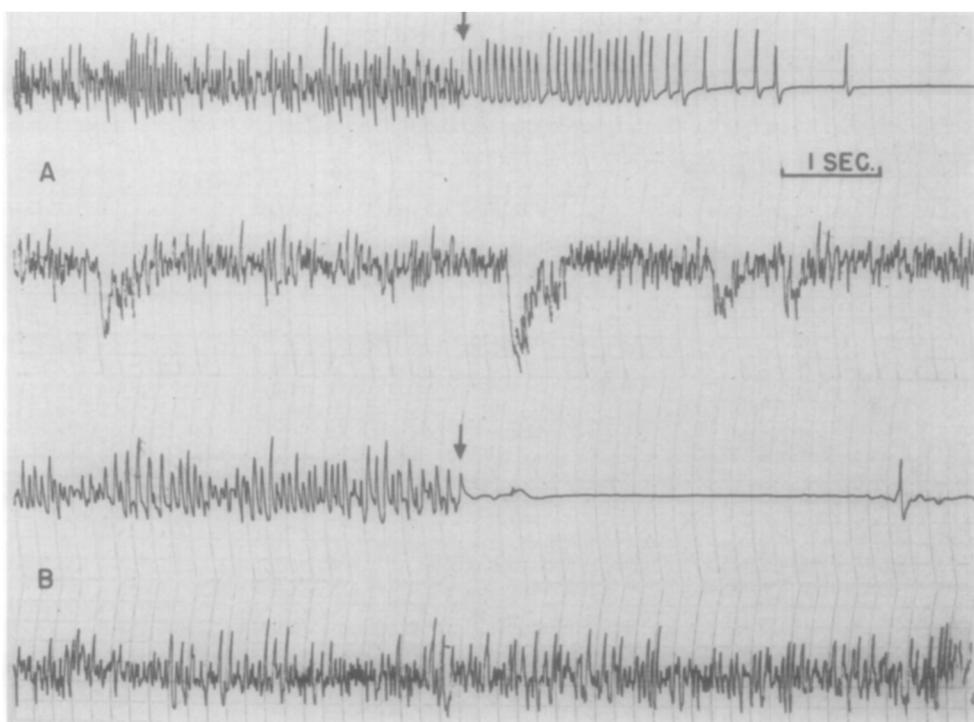


Fig. 3.—Dog weighing 15 kilograms and anesthetized with pentobarbital. Vagi cut. Upper tracing, electrogram taken near tip of right atrial appendage; lower tracing, from body of right atrium. Fibrillation was induced by a brief period of stimulation at the tip of the auricle during vagal stimulation. At arrow in A, the clamp was applied with moderate pressure across the base of the auricle. At arrow in B, the clamp was applied with crushing force during the second episode of fibrillation.

By all criteria of direct observation and of the electrical records of atrial and ventricular activity, the arrhythmia produced by rapid atrial excitation during vagal stimulation was fibrillation, and it persisted after the precipitating focus (the stimulator) was turned off. It was considered remotely possible, however, that rapid electrical excitation of the atrium created an ectopic focus which continued to fire from the site of stimulation after the driving stimulator was stopped. If this were the case, it would be expected that application of a clamp across the base of the atrial appendage should result in arrest of fibrillation in the body of the atrium, and persistence of rapid activity in the isolated

appendage. Accordingly, recording electrodes were attached to the atrial appendage near the stimulating electrodes and to the body of the right atrium near the superior vena cava. After fibrillation was established by a brief period of rapid atrial stimulation during strong vagal stimulation, a clamp was applied to the base of the auricle. When the clamp was closed with moderate pressure,

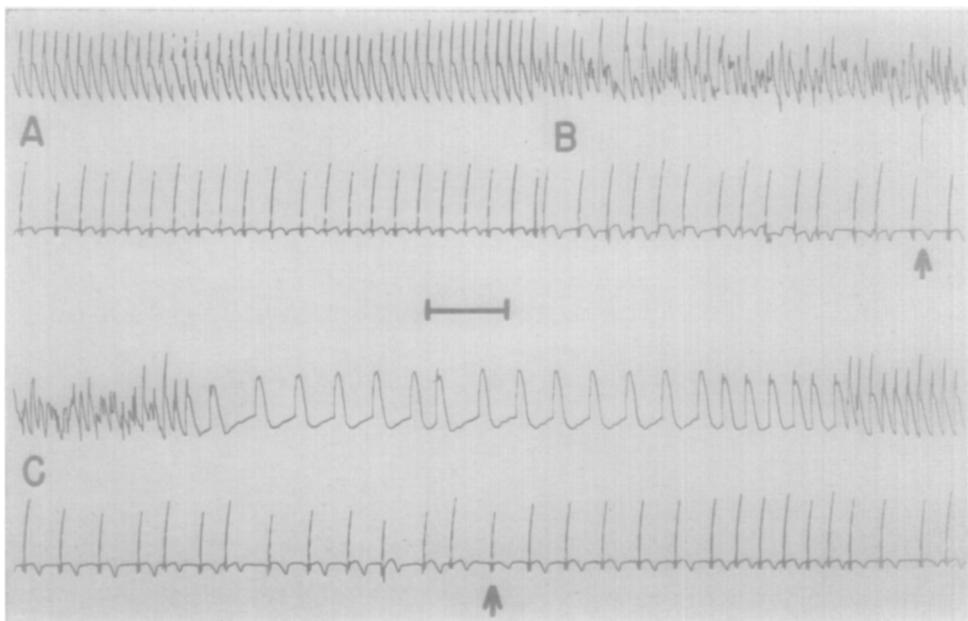


Fig. 4.—Dog weighing 15 kilograms and anesthetized with pentobarbital. Vagi cut. Upper tracing, electrogram taken from body of right atrium; lower tracing, ventricular electrogram. A, Flutter recorded 30 seconds after intramural injection of 0.02 c.c. of 1:500 solution of aconitine near tip of auricular appendage. B, One minute later, fibrillation. Application of the clamp across the base of the auricle (arrow in B) was followed within 3 seconds by resumption of sinus rhythm (in record C, which is continuous with B). Release of the clamp (at arrow in C) was followed by resumption of ectopic rhythm. Time calibration is 1 second.

fibrillation continued in the body of the atrium, but was replaced by a tachycardia decelerating within a few seconds to complete inactivity in the auricular appendage (Fig. 3,A). When the clamp was applied abruptly and with crushing force, activity in the appendage ceased promptly (Fig. 3,B) while fibrillation continued unchanged in the rest of the atrium. On other occasions the clamp was applied during rapid stimulation of the auricular apex; fibrillation continued on both sides of the clamp as long as atrial stimulation was continued, but stopped in the clamped-off appendage as soon as the stimuli were cut off. On the other hand, if the clamp was similarly applied and vagal stimulation was then stopped, fibrillation stopped promptly in the body of the atrium but continued in the auricle until the driving stimulator was turned off.

Response of the Atrium to Aconitine.—Injection of small volumes of aconitine solution in low concentration into the atrial muscle near the tip of the appendix resulted in atrial tachycardia at 5 to 8 per second. At these "flutter" frequencies,

as with electrical stimulation in the same range, the electrical responses of the atrium were regular and uniform; vagal stimulation did not alter atrial behavior. Application of the clamp at the base of the auricle resulted in immediate resumption of sinus rhythm in the body of the atrium while the tachycardia persisted in the auricle, whether or not the vagus was stimulated.

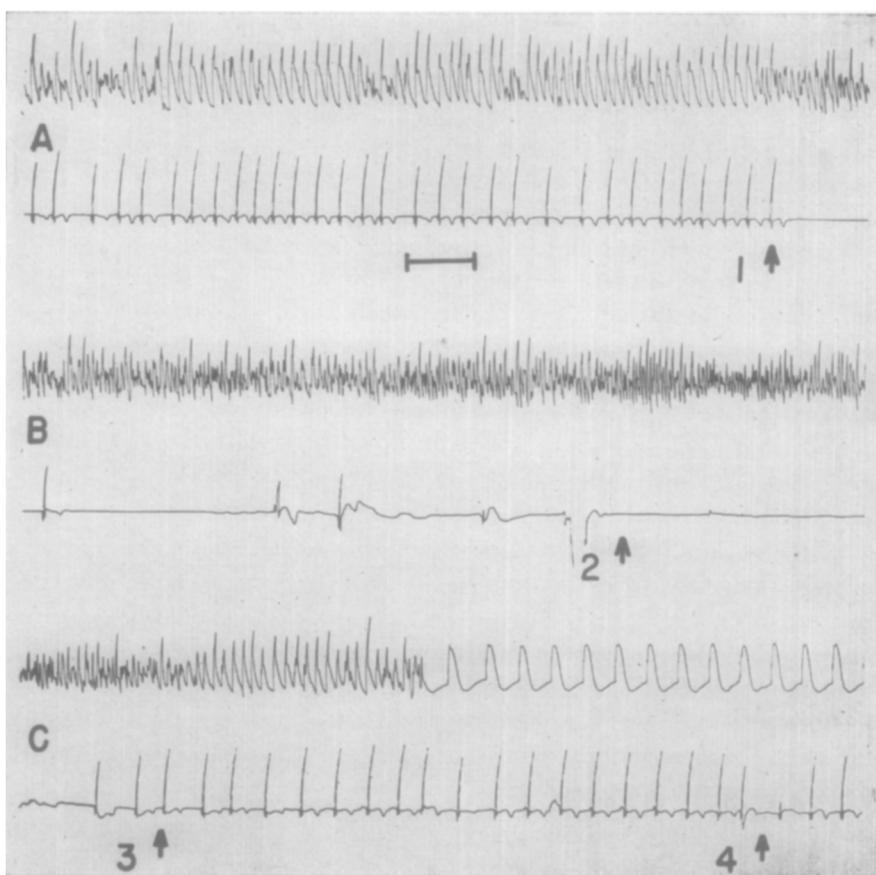


Fig. 5.—Same experiment as in Fig. 4; 2½ minutes after the injection of aconitine. At 1, vagal stimulation is begun; at 2, the clamp is applied across the base of the auricle. Lapse of 24 seconds between B and C. At 3, vagal stimulation is stopped. At 4, clamp is removed. Time calibration is 1 second.

After higher doses of aconitine, frank fibrillation developed, with characteristically rapid and irregular atrial activity. When the auricular clamp was applied without vagal stimulation, fibrillation was promptly replaced by sinus rhythm in the body of the atrium (Fig. 4). Even in the clamped-off auricle fibrillation was usually replaced by more regular patterns of tachycardia after clamping.

During vagal stimulation, application of the clamp never resulted in cessation of fibrillation in the body of the atrium. Fig. 5 illustrates this phenomenon.

In part *A*, vagal stimulation was begun at the first arrow during a period of rapid and irregular tachycardia induced by the injection of aconitine. At the second arrow (part *B*) the clamp was applied firmly across the base of the auricle. Fibrillation continued in the body of the atrium for about 30 seconds, and stopped only when vagal stimulation was discontinued (third arrow, part *C*). Removal of the clamp (at arrow 4) was followed within 25 seconds by resumption of fibrillation. The site injected with aconitine reacted in essentially the same manner as the electrical focus: fibrillation, once induced by either agency, was self-perpetuating in the body of the atrium as long as the vagus was stimulated, and was self-limited in the absence of vagal discharge.

When aconitine was injected in low doses, a prolonged period of slowly accelerating flutter preceded the development of fibrillation. If the vagi were stimulated during this early stage, the frequency of the atrial responses was not usually altered. On occasion, however, vagal stimulation "converted" flutter (apparent frequency 8 to 10 per second) to fibrillation (see Fig. 5,*A*), which reverted more or less promptly to flutter when vagal stimulation was stopped. Application of recording electrodes to the site of aconitine application in such instances revealed that the focus itself was discharging at a frequency double that of the body of the atrium (16 to 20 per second).

On several occasions when a rapidly firing aconitine focus was established in the auricle without vagal stimulation, application of the auricular clamp was followed by conversion of fibrillation to flutter rather than sinus rhythm in the body of the atrium. The flutter persisted even when the clamp pressure was increased sufficiently to cause permanent interruption of conduction between the atrium and its appendix. The flutter thus established could be captured and arrested, in the same manner as a circus movement flutter, by decelerating atrial stimulation starting at a rate exceeding the flutter frequency. It is likely that the site of the clamp itself supplied the obstacle for a self-sustaining circuit which then persisted independently of the original aconitine focus, as in the experiments of Brown and Acheson.⁴

When aconitine was applied on the atrial surface by means of small squares of filter paper soaked in the solution, atrial tachycardia developed much more gradually than following the injection of discretely localized doses. Once established, both flutter and fibrillation often failed to yield to application of the auricular clamp. It was likely that the aconitine in these instances had spread extensively from the site of application, so that clamping no longer separated the body of the atrium from all loci of action of the alkaloid. This probability was supported by the observation that acetylcholine similarly applied at the tip of the auricle caused prompt and profound slowing of the sinus node.

DISCUSSION

In the experiments described above, atrial flutter induced either by electrical stimulation or by injection of aconitine was abolished when the inciting agency was eliminated; atrial fibrillation, as judged by gross irregularity of the

atrial electrograms, could persist independently of the inciting agency; and independent survival of fibrillation was possible only in the presence of adequate cholinergic discharge.

When an impulse is initiated in fully excitable atrial muscle, it may be expected to propagate rapidly and uniformly in all directions from the site of origin. Recovery from such a primary activation, while following roughly the same concentric pattern of spread, does not, however, progress so uniformly; i.e., the refractory state does not have precisely the same duration in all atrial fibers.⁵ It follows that the "spread" of recovery will have a serrated configuration: some fibers will be excitable at a time when closely adjacent fibers on either side are still refractory. Since conduction velocity is low in relatively refractory tissue, it follows that a second response initiated at the site of origin of the primary response will be irregularly propagated: it will rapidly invade those fibers in an advanced state of recovery and it will be retarded or altogether stopped by those fibers which are still partially or totally refractory. In other words, the advancing wave front of the second response must tend to conform itself to the retreating edge of the preceding response, and must also become serrated in contour. If this process is repeated a second or a third time, temporal dispersion of the processes of excitation and of recovery must become accordingly greater. One fibril may become activated while its nearest neighbor repolarizes; even the frequencies of individual elements, at least over a brief span of time, may be widely variant. Orderly spread of excitation will no longer be possible; the grossly irregular wave front becomes fractionated as it divides about islets or strands of refractory tissue, and each of the daughter wavelets may now be considered as independent offspring. Such a wavelet may accelerate or decelerate as it encounters tissue in a more or less advanced state of recovery. It may become extinguished as it encounters refractory tissue; it may divide again or combine with a neighbor; it may be expected to fluctuate in size and change in direction. Its course, though determined by the excitability or refractoriness of surrounding tissue, would appear to be as random as Brownian motion. Fully developed fibrillation would then be a state in which many such randomly wandering wavelets coexist.

The likelihood of persistence of this process should depend upon the number of wavelets present. If the number is large, there is little chance that all elements will fall into phase (i.e., be refractory or excitable simultaneously), but if the number is small there is a considerable probability that they may fuse and permit resumption of a sinus rhythm. The average number, in turn, will depend upon (1) the atrial mass, (2) the mean duration of the refractory period, and (3) the mean conduction velocity. Obviously, a larger mass of tissue can support a larger total number of independent wavelets. It is also obvious that a brief refractory period will allow a larger total number of coexisting wavelets than a long one. If the refractory period were sufficiently prolonged, the total atrial mass would soon be left in a refractory state; i.e., all wavelets would merge and fibrillation would cease. That conduction velocity must be a factor is also apparent, for if every impulse were rapidly propagated to the remotest extremity

of the atrium, fractionation and total disorganization of atrial behavior would not occur.

Emphasis on the importance of these factors recurs in many discussions of the mechanism of fibrillation. Garrey⁶ demonstrated that fibrillation stopped promptly when the mass of the tissue was reduced sufficiently by cutting, and it has been stated by Martinez⁷ that fibrillation cannot be sustained in less than 1 gram of cardiac tissue. Garrey, emphasizing also the importance of the shape of the tissue, showed that fibrillation cannot pass a narrow isthmus.

The importance of abbreviation of the refractory period has been recognized by almost all investigators. Mines⁸ considered the role of progressive shortening with induced acceleration; Rothberger and Winterberg⁹ assigned the effects of vagal stimulation and of vagomimetic drugs to their action upon the atrial refractory period; Burn and associates^{10,11} have recently emphasized the importance of cholinergic mechanisms in the genesis of sustained atrial fibrillation; and Holland and co-workers¹² have shown that fibrillation may be maintained in isolated rabbit atria exposed to depletion of potassium and acetylcholine, both of which reduce the refractory period.

The significance of depression of conduction velocity is recognized in all discussions of fibrillation which implicate propagation of impulses in the relatively refractory period, and was specifically considered by Moe, Harris and Wiggers¹³ and by Moe and Mendez¹⁴ as a factor in the induction of ventricular fibrillation.

Recognition of the importance of nonuniformity of these several attributes of myocardial behavior dates from Engelmann¹⁵ and has been repeated by Mines,⁸ Garrey,⁶ Rosenblueth and Garcia-Ramos,^{1,2} Wiggers,¹⁶ Alessi and associates,⁵ and Brooks and associates.¹⁷

In all these studies it is stated, assumed, or implied that fibrillation results from fractionation of early premature responses initiated in partially and irregularly excitable tissue. Responses initiated repetitively in partially refractory tissue will, when fractionated into small wavelets, yield rapid irregular activity, i.e., fibrillation. Whether the fibrillation will be self-sustaining is then a function of the combination of properties (mass, refractory period, conduction velocity) which exist or are induced in the tissue. Those factors which increase the degree of fractionation will increase the mean number of wavelets which may wander independently in the atria, and will correspondingly reduce the likelihood of spontaneous arrest (falling into phase). Large mass, short refractory period, and slow conduction will all favor perpetuation of the arrhythmia by permitting the coexistence of many independent, randomly wandering wavelets. The results of the present study may be interpreted in terms of this multiple wavelet hypothesis.

Stimulation of the atria at frequencies accelerating up to about 10 per second did not cause disorganization of atrial activity, while higher frequencies caused the irregular electrical responses characteristic of fibrillation. It may be assumed that the refractory period of *all* atrial cells was reduced to about 0.1 second by acceleration, but that the refractory period of some cells could not be further shortened. Intermittency and irregularity of the gross electrical behavior was,

of course, the inevitable result when frequencies above 10 per second were imposed. It is perhaps surprising that vagal stimulation failed to increase the maximum frequency which the atria could follow. It has been demonstrated recently, however, that the refractory period of some atrial fibers is almost unaffected by vagal stimulation.⁵ Since the upper frequency limit of regular response must be imposed by those fibers which have the longest refractory period, it becomes apparent that vagal stimulation cannot increase this limiting frequency. It is also apparent, since vagal stimulation causes marked shortening of the refractory period of some fibers, that fractionation of the wave front (and degeneration into independent wavelets) of an early premature response, and resultant fibrillation, is much more likely to occur during vagal stimulation. In fact, a single premature response initiated at a site subject to profound vagal influence often results in fibrillation, as reported by Alessi and associates.⁵

Self-sustained fibrillation always resulted when the atria were stimulated briefly at high frequency during adequate vagal excitation, but never when the vagi were at rest. In terms of the multiple wavelet hypothesis it appears that vagal stimulation, in addition to facilitating the initial fractionation of responses, reduces the *mean* refractory period of atrial cells, and thereby increases the total possible number of wandering wavelets.

In the absence of vagal stimulation, fibrillation could not sustain itself for more than a few seconds, suggesting that the limited number of wavelets that can be supported by the atria of the average dog is too small to prevent chance fusion and obliteration of the arrhythmia.

The importance of atrial mass and refractory period, implied above, is well illustrated by the experiments in which a clamp was applied across the base of the auricle during fibrillation sustained by vagal stimulation. Fibrillation persisted in the body of the atria, but stopped abruptly in the appendix. It was implied by Garrey,⁶ who performed similar experiments, that the mass of the isolated appendix was too small to support circus pathways of adequate dimension; in terms of the rather closely related wavelet hypothesis, it may be assumed that the mass of tissue remaining in the isolated auricle contained too few wavelets to permit a self-sustained arrhythmia, while the much larger mass of the body of the atrium supported an adequate number. Proponents of the ectopic focus hypothesis might object that the focus was not in the appendix, or that anoxia was produced in the tissue beyond the clamp, or that vagal influence (as a source of ectopic foci) was interrupted by the clamp. These possible objections, however, are of doubtful validity, for the appendix was the site of the stimulation which initiated the arrhythmia; anoxia could not have developed in the fraction of a second which elapsed between application of the clamp and arrest of fibrillation; and application of the clamp should have briefly stimulated those vagal fibers which passed through the crushed area.

The experiments with aconitine are in every respect analogous to those with electrical stimulation. So long as the aconitine focus discharged at a frequency of less than 9 or 10 per second, vagal stimulation failed to alter atrial behavior, and isolation of the aconitine focus by clamping resulted in resumption of sinus rhythm in the body of the atria. When the aconitine focus discharged

more rapidly, application of the clamp still abolished the arrhythmia in the atrium; but when the vagi were stimulated, fibrillation persisted on both sides of the clamp.

The results reported above are not consistent with a unitary hypothesis of atrial arrhythmias; neither are they consistent with a circus movement hypothesis in the sense commonly attributed to Lewis. They can be explained in terms of a wavelet hypothesis which has its origin in the observations of Garrey, anteceding both of the current controversial theories. They emphasize the necessity of a definition of fibrillation in terms of *mechanism* rather than in terms of the gross and superficial criterion of irregularity of electrical events in the atria. We may conclude that irregular activation of the atria may be produced by (1) a single rapidly discharging ectopic focus, whether electrically or chemically induced, (2) multiple rapidly discharging foci, or (3) a rapidly circulating circus movement (transit time less than 0.1 second, under the conditions of the present experiments). We may further conclude that true fibrillation may be self-sustained and independent of whatever initiating agency, provided the atria are large enough (as the adult human atria probably are) or have a sufficiently brief refractory period. It is conceivable that all possible mechanisms are encountered in the clinic.

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