Electrical conversion of atrial flutter to atrial fibrillation

*Flutter mechanism in man*¹

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If human atrial flutter is due to re-entrant excitation, depolarization as well as repolarization must continue throughout the entire atrial cycle. It follows that the atrial vulnerable period for inducing atrial fibrillation is also continuous rather than discrete. This hypothesis was examined during cardioversion of 133 patients with atrial flutter who received 280 low-energy shocks. A composite analysis of these patients demonstrated that all intervals of the flutter cycle were equally susceptible to shock-induced atrial fibrillation. The optimal energy was found to be 10 Wsec. The development of atrial fibrillation was independent of the state of digitalization and was not prevented by pretreatment with atropine or propranolol. These findings are consistent with re-entry as the basic mechanism of human atrial flutter.

Attempts to clarify the mechanism of atrial flutter have engaged the energies of numerous physiologists and clinical investigators over more than half a century. Polemics have raged as to whether the arrhythmia is sustained by a single discharging focus or by a circulating wave front of depolarization. In the experimental animal there is persuasive evidence that a flutter-like arrhythmia can result from either of these mechanisms. When protoplasmic irritants such as aconitine (Hayden, Hurley, and Rytand, 1967; Ishikawa, 1967; Prinzmetal *et al.*, 1952; Scherf, 1947; Scherf and Terranova, 1949; Scherf, Romano, and Terranova, 1948) or delphinine (Scherf *et al.*, 1960; Scherf, Blumenfeld, and Yildiz, 1963) are applied to the atria, the ensuing flutter-like disorder emanates from the site of drug application. The extensive investigation of Thomas Lewis (1925) adduced evidence that flutter might also result from a circus movement. Decisive corroboration was provided by the experiments of Rosenbluth and Garcia Ramos (1947). They were able to initiate and

maintain a circulating wave front around an obstacle in the right atrium produced by a crush between the vena cavae. The relevance of these animal models to the disorder encountered in man remains uncertain.

The hypothesis in current favour is that clinical flutter is due to a re-entrant mechanism. As classically formulated by Lewis (1925), an advancing front of depolarization is separated from its tail of refractoriness by fully recovered tissue, the so-called excitable gap. Some portions of the atria are, therefore, undergoing depolarization at all times, while other portions are either in a state of refractoriness or completely repolarized. It would be inferred that if flutter is the result of re-entry, vulnerability to fibrillation should also be present throughout the cardiac cycle. By contrast, in the presence of sinus or single focus ectopic tachycardia, the vulnerable period is located in a discrete part of the cardiac cycle and is of brief duration (Lown, Kleiger, and Williams, 1965).

The opportunity to test the extent of the vulnerable period in patients with atrial flutter presents itself during cardioversion of this disorder to sinus rhythm. Low energy electrical discharges may convert flutter to atrial fibrillation (Lown, 1967). The vulnerable period is generally activated by a narrow range of low discharge energies. If the trans-

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TABLE 1 *Underlying heart disease in 144 patients with atrial flutter subjected to cardioversion*

Disease	No. of patients
Rheumatic heart disease	53
Coronary artery disease	32
Lone flutter	23
Pulmonary disease	12
Congenital heart disease	9
Hypertensive heart disease	4
Pericarditis	4
Other	7

formation in atrial rhythm from flutter to fibrillation is dependent upon the stimulus exciting the atria during their vulnerable period, only a limited range of energies should be shown to be effective. If the mechanism of atrial flutter is due to re-entry, it should be possible to produce atrial fibrillation by a single electric shock from any part of the cardiac cycle. The present clinical study provides information relating to each of these questions.

Methods

This study involved cardioversion of 144 consecutive patients with atrial flutter admitted to the Peter Bent Brigham Hospital between August 1962 and July 1970. There were 96 men and 48 women. The patients ranged in age from 19 to 89 years. Table 1 lists the cardiovascular diseases encountered.

The technique for cardioversion has been described previously (Lown, Amarasingham, and Neuman, 1962a; Lown, Kleiger, and Wolff, 1964). A DC cardioverter was employed, and the electrode paddles were positioned anteroposteriorly. All patients were pretreated with 100 mg pentobarbitone sodium given orally one to two hours

TABLE 2 *Energy content of initial transthoracic cardioversion shock administered to 133 atrial flutter patients*

Energy (Wsec)	Shocks (No.)	Per cent
1	45	24.8
5	35	19.3
10	20	11.2
25	28	15.5
50	44	24.3
100 and >	9	4.9
Total 181*		100

* Some patients were subjected to cardioversion more than once, thus accounting for the additional 48 initial shocks.

before the procedure. Anaesthetics included thiopentone sodium, methohexitone sodium, combinations of pethidine hydrochloride and pentobarbitone sodium or pethidine hydrochloride and promethazine hydrochloride. Over the past four years diazepam was used almost exclusively. In 61 patients, the doses ranged from 2.5 mg to 40 mg, with a mean dose of 13.5 mg. An initial dose of 2.5 mg to 5.0 mg intravenously was followed by 2.5 mg increments every two minutes until light sleep was induced. Blood pressure was checked between successive doses.

A complete 12-lead electrocardiographic tracing was recorded before the cardioversion procedure. The standard limb lead with the most distinct flutter waves was selected for monitoring throughout the procedure. In the majority of cases, lead II was employed. A special damping circuit protected the electrocardiographic recorder and resulted in an isoelectric artefact lasting an average of 1.8 seconds. After each shock, the cardiac mechanism was identified in lead II; the rhythm was then confirmed in lead VI. This was generally accomplished within 5 to 10 seconds after the emergence of the first post-shock complex. One of four types of response was identified: (1) persisting atrial flutter, (2) atrial fibrillation, (3) normal sinus rhythm, (4) junctional or other mechanisms. Of the 299 cardioversion shocks employed, 19 shocks in 11 patients were excluded from analysis because of the presence of electrical artefacts or uncertainty as to the underlying rhythm. Thus, the analysis to be described was carried out on the response to 280 shocks in 133 patients.

At the beginning of this study all cardioversions were carried out with an initial setting of 100 Wsec. As it became evident that atrial flutter could be reverted with lesser energies, the initial discharge energy was progressively reduced. Distribution of energies of the first shock administered to the 133 patients in this study is shown in Table 2. In 55.3 per cent, the initial shock was 10 Wsec or less. If sinus rhythm did not result, the energy content of successive shocks was increased. The following sequence was usually employed: 1 Wsec, 5 Wsec, 10 Wsec, 25 Wsec, 50 Wsec, 200 Wsec, 300 Wsec, 400 Wsec. If no reversion to sinus rhythm occurred with a 400 Wsec discharge, the procedure was stopped. In 5 patients, the clinical objective of cardioversion was to change the rhythm to atrial fibrillation: this was accomplished with low energy shock.

The location of the cardioversion discharge in the flutter cycle varied in different patients. Two factors determined where the shock fell in relation to the flutter wave, namely the degree of AV block and the voltage rise time of ventricular depolarization which triggered release of the electric discharge. Analysis of the location of the electrical discharge in relation to the flutter wave was carried out on records of 159 shocks delivered to 79 patients. These were selected because the flutter wave, designated as P', could be precisely defined. The interval between the nadirs of successive flutter waves in lead II (P'P') was measured in

milliseconds. The point of interception of this interval by the shock, designated as S, provided the P'S interval. The ratio of these two intervals, $P'S/P'P'$, defined the position of the electrical discharge in the flutter cycle. $P'S/P'P'$ ratios were divided into quartiles. Thus, if the shock fell 160 milliseconds after the nadir of the P' wave and the P'P' interval was 200 msec, the resulting ratio was $160/200$, or 0.80. This was grouped with all ratios occurring in the quartile of 0.75 to 0.99 (Fig. 1).

To determine whether the emergence of atrial fibrillation was related to shock-induced release of neurohumoral agents (Amory and West, 1962; Blinks, 1966; Cobb, Wallace, and Wagner, 1968; Nelemans, 1951; Ten Eick *et al.*, 1967; Vincenzi and West, 1963; Whalen, Fishman, and Erickson, 1958), selected patients were pretreated with either atropine or propranolol. Twelve patients received atropine intravenously, in doses of 0.6 to 2.2 mg, five minutes before administering the cardioversion discharge. Ten patients were given oral propranolol, in doses ranging from 30 mg to 200 mg daily, for two days preceding cardioversion, as well as on the day of the reversion. One patient, subjected to cardioversion on two different occasions, received both atropine and propranolol. Necessarily, these patients were receiving other drugs that may have influenced the result of cardioversion. Of the 133 patients, 116 were on maintenance digitalis therapy, 11 had not received cardiac glycoside at any time, and in 6, digitalis had been discontinued five or more days before cardioversion. Seventy-eight patients were pretreated with quinidine, in a dose of 0.8 to 1.2 g, for the 24- to 48-hour period preceding the reversion procedure.

Results

The 133 patients with atrial flutter received 280 transthoracic shocks. Of this number, 82 resulted in atrial fibrillation and 96 were restored to sinus rhythm; the flutter mechanism persisted after 87 shocks and in 15 there ensued a junctional or an unidentifiable rhythm. An example of induction of atrial fibrillation is illustrated in Fig. 2. The median shock energy which resulted in atrial fibrillation was 10 Wsec (Table 3). A high incidence of atrial fibrillation was also observed after discharges of 5 Wsec. When results of shocks at these two energies are combined, out of 101 discharges 49, or 48.5 per cent, resulted in atrial fibrillation. Provocation of atrial fibrillation diminished as the energy content of the shock was increased.

After many of the shocks sinus rhythm, junctional rhythm, or some other mechanism developed precluding the emergence of atrial fibrillation. The data were therefore analysed to exclude those who had these rhythm alterations. Only those shocks that were fol-

FIG. 1 The $P'S/P'P'$ ratio was calculated as indicated in this figure.

lowed by either atrial fibrillation or persisting atrial flutter were included. The energy most effective for inducing atrial fibrillation was 10 Wsec, with 66.7 per cent of subjects who received this energy developing atrial fibrillation. There was a stepwise reduction in occurrence of atrial fibrillation at lower and higher shock energies (Fig. 3). There was an increase in incidence of atrial fibrillation at energies of 100 Wsec or greater; however, only 10 shocks were available for the analysis. The existence of a specific effective energy was shown strikingly in one patient. After 1 and 5 Wsec discharges, the atrial flutter remained unaltered. After 10 Wsec the mechanism persisted, how-

FIG. 2 Patient with chronic atrial flutter at a rate of 300 a minute. After a 5 Wsec shock synchronized to discharge in the QRS, atrial fibrillation ensued and is clearly seen in lead V₁. (In this and subsequent figures notation for watt seconds is WS.)

ever, the wave form was changed and the atrial rate increased slightly. When the energy of the next shock was reduced to 2.5 Wsec, atrial fibrillation resulted (Fig. 4). The fact that atrial fibrillation was produced at a specific low energy suggested that this phenomenon was related to the atrial vulnerable period.

The next question examined was whether the vulnerable period was discrete or continuous. The point at which the electrical discharge intercepted the flutter cycle ($P'-S/P'-P'$ ratio) was examined after 109 shocks which either resulted in atrial fibrillation or continued as atrial flutter (Table 4). When the cycle was divided into quartiles, it became evident that no part of the flutter cycle was impervious to the development of atrial fibrillation. In fact there was no statistically significant difference between quartiles (χ^2 analysis, $P=0.5$). Similar results were obtained for shocks of 10 Wsec or less. These findings indicated that there was no distinct part of the flutter cycle that was exclusively susceptible to the provocation of atrial fibrillation by electrical discharge.

It is possible that the occurrence of atrial fibrillation was related to release of neurotransmitter by the cardioversion discharge. This question was, therefore, examined in a small group of patients.

Atropine Twelve patients were given atropine in doses of 0.6 to 2.2 mg intravenously within five minutes before cardioversion. A total of 25 shocks was delivered. Of these, 11 shocks resulted in atrial fibrillation, 5 in sinus rhythm, and 9 remained in atrial flutter. Thus, in 55 per cent of patients given atropine atrial fibrillation followed a transthoracic discharge. The median effective energy in this group was also 10 Wsec (Fig. 5).

Propranolol Ten patients received a total of 20 shocks at a time when they were receiving propranolol hydrochloride in doses ranging from 30 mg to 200 mg daily. Atrial fibrillation followed after five shocks, sinus rhythm after seven, and the rhythm remained unaltered after eight. One patient was twice subjected to cardioversion while pretreated with both atropine and propranolol. On each occasion 1 Wsec was without effect; 5 Wsec during the first cardioversion and 10 Wsec during the second resulted in atrial fibrillation (Fig. 6).

Since it has been shown that cardioversion enhances the arrhythmogenic action of digitalis (Lown *et al.*, 1965; Kleiger and Lown, 1966), the possible role of digitalis glycosides

TABLE 3 Result of 280 shocks delivered to 133 patients with atrial flutter as function of energy of electrical discharge

Energy of shock (Wsec)	Number of shocks at each energy	Response			
		Atrial fibrillation	Sinus rhythm	Persisting flutter	Other rhythms
1	48	13	3	32	0
5	56	27	5	24	0
10	45	22	9	11	3
25	50	13	25	8	4
50	59	3	43	6	7
100 and > 100	22	4	11	6	1
Total	280	82	96	87	15

in the emergence of electrically induced atrial fibrillation was examined. Only patients on maintenance digitalis therapy but not receiving quinidine were examined. This group included 55 patients who were subjected to 83 cardioversion shocks. In 28, or 34 per cent, atrial fibrillation resulted. A nearly identical result was observed in 10 patients who received neither digitalis nor quinidine; atrial fibrillation followed 37 per cent of the shocks.

Discussion

The mechanism of human atrial flutter remains undefined. Two major and opposing theories have long held sway, namely, that the underlying basis is a rapid firing of an ectopic focus or, that it results from circus movement or re-entry of an entrapped wave. The arguments in favour of each of these hypotheses have been extensively reviewed (Hecht *et al.*, 1953; Katz and Pick, 1960; Rytand, 1966; Scherf, Schaffer, and Blumenfeld, 1953).

TABLE 4 Distribution of cardioversion shocks in quartiles of flutter cycle expressed as ratio in $P'S/P'P'$

	Quartiles of $P'P'$ cycle			
	0.00-0.24	0.25-0.49	0.50-0.74	0.75-0.99
A. Total no. of shocks	18	17	39	35
No. with atrial fibrillation	7	10	22	17
% Atrial fibrillation	39	59	57	49
B. Total no. of shocks	13	13	27	25
No. with atrial fibrillation	4	8	12	11
% Atrial fibrillation	31	62	44.5	44

Data based upon an analysis of 109 shocks in 79 patients, of which 56 resulted in atrial fibrillation. (A) represents all energies employed, while (B) only energies of 10 Wsec or less. (The differences are not statistically significant.)

At the turn of this century, the American marine biologist, A. G. Mayer, induced a continuous recirculating wave of excitation in a ring of tissue cut from the bell of the large medusa, *Cassiopea* (Mayer, 1906). In one specimen the pulsation persisted for 11 days (Mayer, 1916). Some years later, Mines (1913) induced a similar circulating wave of contraction in the tortoise heart from which the sinus venosus had been excised. He noted that, 'the contractions are easily upset by the occurrence of an extrasystole'. The term 'circus contraction' was introduced by Garrey (1914), who noted that a critical mass of heart muscle was required and who also recognized the importance of a localized depression in conduction as a condition favouring such arrhythmia.

It was Thomas Lewis (1925) who provided the essential theoretical frame of modern thinking on re-entrant rhythms. He amassed a wealth of data derived from galvanic stimulation of dog atria and from analysis of electrocardiographic records of patients with flutter. In animals having atrial flutter, as the brief after-effect of rapid electrical stimulation, Lewis, Feil, and Stroud (1920) explored the arrival of the depolarization wave at various atrial sites. They concluded that some new part of atrial muscle was activated throughout the entire atrial cycle and that the propagated excitation traversed a fixed pathway around the orifices of the vena cavae. A limitation of these studies was the failure to define the entire pathway of excitation in the left atrium. Modern techniques have permitted Kimura *et al.* (1954) to remedy this deficiency in method and confirm Lewis's conclusions.

Investigation of the arrhythmia in man was more indirect and consisted of mapping the time course of the flutter wave by determining the change in atrial electrical axis during the cardiac cycle (Lewis, Drury, and Iliescu, 1921). As studied by vectorial analysis, the manifest atrial potential appeared to rotate 360° . This circulation was believed to account for the continuous undulation of the electrocardiographic baseline seen in cases of pure flutter (Lewis *et al.*, 1920). Prinzmetal *et al.* (1951) later challenged this interpretation. They ascribed baseline motion not to circus movement, but to the sequence of depolarization and repolarization which altered direction of the atrial vector.

Attempts to define the flutter mechanism in man have since been largely directed to mapping the time course of arrival of the excitation wave described by Lewis to travel upward in the left atrial wall and downward in the taenia terminalis of the right atrium (Lewis, 1925). Since vectorial analyses have

FIG. 3 Incidence of atrial fibrillation after different energy shocks tabulated both as percentages of total shock and of effective shocks, i.e. those shocks that were followed by either persistent atrial flutter or development of atrial fibrillation (see also Table 3).

yielded conflicting results (Cabrera and Sodi Pallares, 1947; Duchosal and Sulzer, 1949), many studies aimed to achieve greater proximity by means of oesophageal and right intra-atrial electrodes (Duchosal and Sulzer, 1949; Enselberg, 1951; Giraud, Latour, and Puech, 1955; Grishman *et al.*, 1950; Groedel and Miller, 1950; Kato *et al.*, 1956, 1957; Kossman and Berger, 1941; Prinzmetal *et al.*, 1953; Rosenbluth, 1953; Rytand, 1966; Wenger and Hofmann-Credner, 1952). Oesophageal electrocardiography confirmed, in

FIG. 4 Shocks of 10 Wsec (5 Wsec and 1 Wsec not shown) failed to induce atrial fibrillation though there occurred a slight acceleration in atrial rate and change in atrial morphology. After 2.5 Wsec atrial fibrillation resulted.

most cases, a caudocephalic direction of the depolarization wave in the left atrial wall, though the opposite direction was occasionally noted (Cabrera and Sodi Pallares, 1947; Duchosal and Sulzer, 1949; Enselberg, 1951; Grishman *et al.*, 1950; Kossmann and Berger, 1941; Prinzmetal *et al.*, 1952). Direct mapping of the path of the excitation wave was only rarely attempted and the results have been inconclusive (Groedel and Miller, 1950; Prinzmetal *et al.*, 1953).

Recently Kishon and Smith (1969) have addressed themselves to this question. In 10 patients with flutter, they timed arrival of the intrinsic deflection by recording simultaneously from oesophageal and right atrial electrodes at different levels. In 4 patients, atrial activation progressed cephalad in the left atrium and caudad in the right atrium. Though exploration of the excitatory pathway was incomplete, almost two-thirds of the atrial cycle could be defined. They judged these findings to be consistent with a circus movement. In the 6 other patients no such sequence was recorded, the excitation wave occupied only one-third of the atrial cycle and spread cephalad simultaneously in both atria. They concluded that two mechanisms operated in human flutter. Kishon and Smith (1969) acknowledged that if the circus pathway was located low in the atrium, it would not have been detected by the techniques employed in their investigation.

The present study of the flutter mechanism is also indirect but is based upon an entirely different approach. The ability to convert flutter to fibrillation at a discrete low energy suggests excitation of an atrial vulnerable period. The observation that vulnerability is present throughout the entire atrial cycle suggests that this is also true for the atrial depolarization-repolarization sequence. Andrus, Carter, and Wheeler (1930) first showed that the dog's atrium possessed a sharply demarcated vulnerable period. Single electrical

FIG. 5 After 1 mg atropine intravenously 5 Wsec shock did not alter flutter mechanism; however, a 10 Wsec discharge induced atrial fibrillation.

pulses when discharged during this time interval of the cardiac cycle produce atrial fibrillation. Electrophysiologists (Brooks *et al.*, 1951) have confirmed the existence of such a discrete zone in the atrium, which coincides with the dip in the atrial excitability curve. Lown (unpublished data) looked for the atrial vulnerable period in the intact dog with transthoracic shocks and found it to have a duration of 10 to 20 msec, with 1 Wsec being the optimal energy. The vulnerable period was located consistently during inscription of the terminal portion of the QRS complex.

There has been no systematic exploration for an atrial vulnerable period in man. Atrial fibrillation at times has been noted to occur during right atrial pacing (Ross, Linhart, and Braunwald, 1965). In a retrospective analysis, Haft and coworkers (1968) found 26 episodes of atrial fibrillation or flutter-fibrillation in 3 normal subjects during single or paired pacing of the right atrium. The interstimulus interval or the P-stimulus interval for initiating arrhythmia was the same and ranged from 180 to 280 msec. In over 200 other patients, atrial fibrillation was never seen during right

FIG. 6 In a patient pretreated with both atropine and propranolol, atrial fibrillation was not prevented after a 5 Wsec cardioversion discharge.

atrial pacing outside this time period. Additional support for an atrial vulnerable period derives from the findings of Killip and Gault (1965) that atrial premature beats which occur early in the cycle are associated with a high incidence of atrial fibrillation.

Is a vulnerable period present when sinus rhythm is replaced by an ectopic tachycardia? No data are available for atrial tachyarrhythmias. However, the vulnerable period appears unaltered when the mechanism is ventricular tachycardia. Lown *et al.* (1965) explored the cardiac cycle with low energy cardioversion pulses during ventricular tachycardia induced by digitalis overdose. They found a single sharply demarcated vulnerable period for producing ventricular fibrillation which was of the same duration and energy threshold as determined during sinus rhythm. It therefore appears that when a tachycardia emanates from a single ectopic site, it is associated with a discrete rather than a continuous vulnerable period. If repetitive discharge from a single ectopic focus accounted for atrial flutter in man, a similarly circumscribed period of atrial vulnerability should have been observed. The contrary findings of the present investigation, that fibrillation could be induced equally well throughout the atrial cycle, is thus consistent with the circus movement hypothesis.

A limitation of the present study needs to be emphasized. The presence of a continuous vulnerable period in atrial flutter was deduced from a composite view derived from many discrete observations, where each patient provided but a single point of datum. It was not based on a systematic exploration of the entire flutter cycle in a single individual. Even if this were ethically permissible, it would have been difficult to accomplish. Since there was frequently but one chance to test for vulnerability, once atrial fibrillation was induced, the mechanism usually persisted or reverted to sinus rhythm. There is, however, additional evidence to support the concept that the change from flutter to fibrillation was due to stimulation of an atrial vulnerable period. If this rhythm alteration was simply a shock-induced disorganization in heart rhythm, it would have varied directly with the energy of discharge. This is the case when long AC pulses are administered transthoracically (Lown *et al.*, 1962b). While at 75 volts the incidence of atrial fibrillation is 40 per cent, it progressively increases reaching 100 per cent with a shock level of 450 volts. On the other hand, when single short DC pulses are delivered to the heart during the atrial or ventricular vulnerable period a narrow range of low energies exists which is optimal for induc-

FIG. 7 Low energy cardioversion discharge changed direction of flutter wave without significantly altering atrial rate.

ing fibrillation. In the present study, the peak incidence of atrial fibrillation occurred at 10 Wsec, with less effectiveness resulting from either lower or higher energies.

A phenomenon encountered in 5 of the patients lends additional support to the circus movement hypothesis. After a low energy shock the flutter mechanism persisted, but closer inspection of the electrocardiographic record revealed a change in morphology of the atrial complex. In fact the flutter waves were a mirror image of their former contour (Fig. 7). An additional shock at a higher energy resulted in atrial fibrillation. It is difficult to explain this occurrence if the arrhythmia resulted from discharge of an ectopic pacemaker. One would have to entertain a number of assumptions, namely, the existence of two ectopic sites, one held in abeyance by the other and both discharging at nearly identical rates, furthermore, that they were situated at opposite atrial poles to permit a precise mirror imaging in wave form. If one holds to the circus movement hypothesis, such compounding of improbable assumptions is unnecessary. A reversal of direction of the entrapped wave from counterclockwise to clockwise, when viewed sagittally from the left, would account for the observation.

A significant question is the frequency with which a circus movement operates as the mechanism of atrial flutter in man. The present study provides some information. At the most effective energy of 10 Wsec, 22 out of 33 episodes, or 66.7 per cent resulted in atrial fibrillation. It is possible that 10 Wsec was not the optimal energy in the 11 patients in whom failure was encountered at this energy setting. Indeed, in 6 of the 11, atrial fibrillation was produced at either higher or lower

energy settings, while in the remaining 5 sinus rhythm occurred in a succeeding shock. Thus, 28 of 33, or 85 per cent of the group, developed atrial fibrillation after a single low energy shock. It is not unreasonable to surmise that if the initial choice of energies were correct, the 5 who reverted to sinus rhythm would also have developed atrial fibrillation. Thus, it may be that, in 100 per cent of patients with flutter, it is possible to transform the rhythm to fibrillation by stimulating the vulnerable period randomly in the atrial cycle. The data suggest that human flutter is the result of but a single mechanism, namely, the circulation of an entrapped wave, as conceived by Lewis.

An alternative explanation for our data should be considered. It has been shown that electrical discharge releases acetylcholine and norepinephrine from nerve endings in the heart (Amory and West, 1962; Blinks, 1966; Cobb *et al.*, 1968; Nelemans, 1951; Ten Eick *et al.*, 1967; Vincenzi and West, 1963; Whalen *et al.*, 1958). It is conceivable that the change in rhythm resulted from neurotransmitter liberation. In the experimental animal it has been shown that cholinergic stimuli favour the emergence, as well as sustenance, of atrial fibrillation (Scherf and Schott, 1953). In man, carotid sinus pressure, which causes reflex vagus stimulation of the heart and acetylcholine release, may convert atrial flutter to atrial fibrillation (Anbe, Rubenfire, and Drake, 1969; Bussan, Reid, and Scherf, 1957; Lown and Levine, 1961; Rytand, 1967; Scherf, Cohen, and Rafailzadeh, 1966). Cobb *et al.* (1968) found that, in dogs, direct current trans-thoracic shock, even at a low setting of 1 Wsec, provoked vagal-like effects manifested by sinus slowing or sinus arrest. These could be prevented by administering atropine. It is unlikely that shock-induced acetylcholine release was responsible for the change from atrial flutter to fibrillation in man. If neurotransmitter liberation were the basis, one would anticipate the following: (1) A greater incidence of atrial fibrillation both at higher energy discharge as well as in patients on digitalis who are more sensitized to cholinergic stimuli; and (2) prevention of emergence of atrial fibrillation by atropine. None of these was observed. The fact that pretreatment with propranolol did not prevent induction of atrial fibrillation argues also against a role for catecholamine release.

Several recent reports (Haft *et al.*, 1967; Zeft *et al.*, 1969) indicate that atrial flutter may be reverted to sinus rhythm by rapid right atrial electrical pacing. The pacing rates employed have ranged from 180 to 600 a

minute. Atrial fibrillation was an intermediate rhythm in 12 of 13 patients. A similar method has been used to convert a disabling and frequently recurring atrial tachycardia, for a brief period, to atrial fibrillation (Wiener and Dwyer, 1968). Haft and coworkers (1967) postulated that frequent atrial stimulation allowed an impulse to fall within the atrial vulnerable period, thereby initiating unstable atrial fibrillation. They also suggested overdrive capture of an ectopic focus as the possible mechanism of conversion in one of their patients. Of interest is the observation of Zeft *et al.* (1969) that it was possible to restore sinus rhythm in one patient without intervening atrial fibrillation. This was accomplished by pacing at a rate of 180 a minute significantly slower than the atrial flutter rate of 330 a minute. It was suggested that an appropriately timed atrial stimulus interrupted a re-entry pathway of excitation, extinguishing the arrhythmia and permitting the sinus node to establish pacing hegemony.

The ability to terminate a number of arrhythmias with serial right atrial pacing (Massumi, Kistin, and Tawakkol, 1967; Durrer *et al.*, 1967), single pulses carefully timed in the excitation cycle of the tachycardia (Bigger and Goldreyer, 1970; Hunt *et al.*, 1968), low energy cardioversion shocks, and thump version (Lown and Taylor, 1970; Pennington, Taylor, and Lown, 1970) all point to the prevalence of re-entry as the fundamental mechanism in many diverse human rhythm disorders.

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