PHARMACOLOGICAL MECHANISMS OF EXPERIMENTAL AURICULAR FLUTTER AND FIBRILLATION

T H E S I S

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I. A B S T R A C T

This study was undertaken to clarify the controversy about the mechanism of experimental auricular flutter and fibrillation. Acetylcholine infusion produces generalised fibrillation, and this activity is enhanced by simultaneous infusion of adrenaline and noradrenaline. Topical application of acetylcholine produces localised fibrillation, while untreated areas exhibit impure flutter. A method is described for producing prolonged episodes of fibrillation in the intact dog, following acetylcholine infusion. Nodal tissues play no part in the maintenance of fibrillation.

The mechanism of impulse formation within aconitine-induced ectopic focus is re-entrant excitation, and not repetitive discharges from a single cell. Thus the only difference between ectopic focus and circus movement theories, is that, there is no fixed pathway for impulse circulation in the former. This will explain why both respond to cholinergic influences by increase in rate.

Post-stimulatory flutter is due to classical circus movement. Reversal of sequential activation phenomenon in direct auricular leads and of flutter waves in limb leads, in the same or consecutive episodes of flutter is described. Two distinct patterns of flutter waves in the limb lead records of clinical flutter are pointed out.

Both cholinergic and adrenergic influences increase the flutter rate, which is frequently converted into fibrillation. Atropine completely blocks the fibrillatory response, but only partially blocks the rate increasing effect. A dual action of aconitine, on isolated guinea-pig auricle and ileum is described.

Cholinergic influences are essential to produce auricular fibrillation, but not flutter. The cause of fibrillation is multiple re-entries produced by shortened refractory period and accelerated conduction, and not repetitive discharge or classical circus movement.

The similarities of cholinergic influence in experimental flutter and of digitalis in clinical flutter are discussed. The return of flutter in some cases, is due to re-establishment of circus movement. The clinical use of acetylcholine in the treatment of auricular flutter is suggested.

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II. INTRODUCTION

The nature of auricular flutter and fibrillation has been the subject of an intensive investigation ever since these conditions were first produced experimentally in animals (Vulpian, 1874; McWilliams, 1888), and later found to occur spontaneously in Man (Ritchie, 1905; Hertz & Goodhart, 1908; Rothberger & Winterberg, 1909; Lewis, 1909). A number of theories have been advanced from time to time by different workers to explain the mechanism of these arrhythmias in experimental animals and in Man, but no single theory has gained universal acceptance.

Generally speaking all these theories are variants of the two widely accepted concepts, viz. (a) ectopic focus theory, advanced by Engelmann (1896) and Rothberger & Winterberg (1914), and (b) circus movement theory, based on the work of Mines (1913, 1914) and Garrey (1914, 1924), and advanced in its present form by Sir Thomas Lewis (1920). The proponents of the former theory believe that auricular flutter and fibrillation is due to repetitively discharging ectopic focus or foci. The supporters of the latter theory believe that in these arrhythmias a central wave of excitation is propagated through the auricles via a narrow circular pathway embracing the openings of the two venae cavae, in a clockwise or counterclockwise direction and re-enters the original pathway on the completion of the circuit. Centrifugal daughter waves arising from the central wave activate

the auricular myocardium.

With the advent of the circus movement theory, the ectopic focus theory fell into disrepute, until Scherf & Terranova (1949) and Prinzmetal et al. (1952) produced strong experimental evidence in its favour. This led to the resumption of the arguments for and against each of these theories. Scherf & Terranova (1949) believe that the findings obtained by cooling and clamping experiments in aconitine-induced flutter and fibrillation are not compatible with the circus movement theory, and can best be explained on the basis of ectopic focus theory. Again Prinzmetal et al. (1952) who studied these arrhythmias by direct auricular leads and high speed cinematography, found no evidence of circus movement and suggested that auricular flutter and fibrillation are due to a repetitively discharging ectopic focus. Dawes (1952) has questioned the validity of these interpretations on the ground that it is not possible to cool a single point on the surface of the auricle, the effective cooling must spread around the thermode and that high speed cinematography will not rule out the existence of a localized circus movement, if the mass of the auricular tissue involved is too small to be seen.

Though the cooling and clamping experiments of Scherf & Terranova (1949) prove the focal origin of aconitine-induced flutter and fibrillation, they reveal nothing about the mechanism of impulse formation in the ectopic focus. Evidence has been

presented by Scherf et al. (1953 a, b), mainly on the basis of findings obtained in the nervous tissue that a repetitive focal discharge is the basic mechanism of impulse formation in the aconitine-induced ectopic focus, but it must be borne in mind that a localized circus movement will also behave like a repetitively discharging focus. McWilliams (1918) showed that localized circus movements could occur and cause fibrillation which could be stopped by the clamping off or cooling of a small area. The path of such a small circus movement was found to be 2.5 to 3.8 mm. in diameter. No other experimental evidence is available to prove or to disprove this possibility. Further, the experimental observations of Rosenblueth & Garcia Ramos (1947 a, b); Brown & Acheson (1952) and Lanari et al. (1956) have provided strong support for the circus movement theory.

According to both these theories, the only difference between auricular flutter and fibrillation is that of rate of discharge of the governing agency (Lewis, 1925; Prinzmetal et al. 1952). Recently Moe & Albidskov (1959) showed that auricular fibrillation can be maintained as a self-sustaining phenomenon independently of the focal discharge that initiated it, in the presence of adequate cholinergic influence, implying thereby that the mechanisms of flutter and fibrillation are not the same. This finding needs further investigation since on the basis of the observations of Scherf et al. (1953 b), it could

be argued that the fibrillation was maintained due to the development of the ectopic foci in the sino-auricular and auriculo-ventricular nodes, under cholinergic influence.

Cholinergic influences have been implicated in the production and maintenance of auricular fibrillation (Lewis, 1925; Nahum & Hoff, 1940; Scherf & Chick, 1951; West et al. 1954; Loomis & Krop, 1955; Burn et al. 1955; Moe & Albidskov, 1959), and to convert auricular flutter into fibrillation (Rothberger & Winterberg, 1910; Robinson, 1913; Lewis et al. 1921 a; Brown & Acheson, 1952; Lanari et al. 1956). Nevertheless, it is quite clear that acetylcholine is not the only factor involved in the production of auricular fibrillation since vagal stimulation or acetylcholine alone rarely produce fibrillation. In addition to acetylcholine, a source of rapid impulse formation is essential for the precipitation of fibrillation (Burn et al. 1955; Leveque, 1957; Holland & Burn, 1957). The role of acetylcholine in the production and maintenance of stable auricular flutter is not clear, as the available evidence is conflicting. Wedd (1924) demonstrated that following the administration of atropine in auricular flutter in Man, the only effect observed was a slight decrease in rate, the termination of flutter never occurred. On the other hand Scherf et al. (1953b, 1955), showed that aconitine did not produce auricular flutter in the atropinised

dogs. Further, Torchiana & Angelakos (1961) have recently suggested that acetylcholine may be concerned in the development of all types of auricular arrhythmias.

Very little is known about the role of catecholamines in the production and maintenance of auricular flutter and fibrillation. Winterberg (1907, 1908) and Scherf (1949) showed that sympathetic stimulation increased the rate of the fluttering auricles. Frequently, flutter was converted into fibrillation, but only if the vagus nerves were intact. Grant et al. (1949) demonstrated that adrenaline injection and vagal stimulation can act synergistically to incite auricular fibrillation in the dog, but Burn et al. (1957) showed that simultaneous infusion of adrenaline antagonised the fibrillatory activity of acetylcholine in the heart-lung preparation of the dog. Thus the exact role of catecholamines is still far from clear.

It was, therefore, considered worthwhile to study the mechanism of experimental auricular flutter and fibrillation, in the dog by employing direct auricular leads from both auricles simultaneously. The main aims and objects in carrying out this work were (i) to elucidate the mechanism of impulse formation within the ectopic focus and to look for further evidence, in order to determine, if possible, whether the ectopic focus theory or circus movement theory is correct; (ii) to find out whether

the mechanism of auricular flutter and fibrillation is the same or different; (iii) to study the mechanism of the fibrillatory activity of acetylcholine and to determine its role, if any, in the production of stable auricular flutter; (iv) to study the role of catecholamines in the production and maintenance of auricular flutter and fibrillation; (v) to correlate the experimental findings with the available data on auricular flutter and fibrillation in Man.

III. HISTORICAL SURVEY

1. EARLY WORK

Cardiac arrhythmias did not attract much attention until the beginning of the 19th Century, although a number of them have been noted ever since Galen described them in the Second Century A.D. (White, 1957). The first person to describe a peculiar type of pulse called 'pulsus caprisans' was Herophilus of Alexandria in 300 B.C. He likened it to the 'leap of a goat'. It is possible that he had observed premature systoles (Garrison, 1929). Like his contemporaries, Herophilus also believed that arteries were filled with air. Montagnana in the 15th Century A.D., described an abnormal rhythm of the pulse called 'motus tremulans et bipulsus cordis', and as pointed out by Herrick (1942) this irregularity of the pulse might be that of auricular fibrillation. Senec in 1749 recommended the use of quinine in 'rebellious palpitation', an arrhythmia now recognised as auricular fibrillation.

According to Hoff (1942), Fontana (1785) was the first to advance the general concept of refractory period. He concluded from his animal experiments that the heart does not contract immediately after relaxation because it does not recover its normal irritability until later. Bouilland in 1836, first described the indirect diagnosis of auricular fibrillation at the bedside, in the detection of 'pulsus irregularis, inequalis, deficiens and intermittens'. Schiff (1850) studied the changes in the

irritability of the heart during phases of contraction and used the term 'refractory' in referring to the heart's periodic inexcitability. Bowditch (1871) reported that the frog's heart did not respond to repetitive stimuli in the same fashion as did skeletal muscle. This was confirmed by Marey (1876), who concluded that the heart responded irregularly to high frequency of stimulation.

Vulpian in 1874, converted the normal systole of the auricle into tremulous movement by faradic stimulation. He called this arrhythmia fibrillation 'movement fibrillaire'. In the same year Aubert and Dehn advanced the first hypothesis about the nature of fibrillation. These workers believed that the fibrillation was produced by injury to a 'nervous co-ordination centre' in the heart. This view got the support of Kronecker and Schmey, (1884), but was disproved in 1887 by McWilliams, who argued that the cause was to be found in the condition of the muscle itself. He stressed the importance of state of excitability of the cardiac muscle, and formulated the hypothesis of re-entrant excitation, very similar to the one put forward by Mines and Garrey many years later. McWilliams clearly recognised that a single stimulus may pass more than once through the same tissue and that two or more beats may result from a single impulse. Subsequent work of Mines and Garrey provided the experimental proof for this hypothesis.

In 1888, McWilliams used the term 'auricular flutter' to describe the very rapid and regular action imparted to the dog's auricle by faradic stimulation.

The concept of polytopic impulse formation was advanced by Engelmann in 1896, and it gained the support of his contemporaries, Lewis (1910) and Winterberg (1910), until it was abandoned in favour of circus movement hypothesis in 1920. Mathews (1897) produced cardiac irregularities by intravenous injection of aconitine in the frog. Cushny (1899) was the first to suggest the possibility of the occurrence of auricular fibrillation as a clinical phenomenon, but it remained unconfirmed until 1909. Hering in 1903 described a type of arterial pulse called 'pulsus irregularis perpetuus' and in 1908, he added evidence of supraventricular formation of ventricular impulses in this condition, which soon got recognised as auricular fibrillation. He also stressed the gradual transition from a single ectopic beat to fibrillation, frequently observed in one and the same patient.

Mayer (1908 a,b) was the first to produce experimental evidence in support of the re-entry concept of McWilliams, by demonstrating the circus movement in the umbrella of jelly fish and later in the rings cut from the turtle's heart. He found that if the ring of tissue was stimulated in such a way that the impulse travelled only in one direction, a circus movement was established and may continue for many minutes or hours. This

lead was taken up by Mines (1913, 1914), who confirmed and extended Mayer's observations. He studied the factors underlying circus movement and observed that (i) an area of muscle refractoriness must exist so that the wave of contraction can progress only in one direction and along one path, (ii) the original area of refractoriness must have recovered by the time the excitation wave again reaches it, so that an excitable gap of the tissue always exists. He used his observations on the 'ring' preparations as a basis for explaining the continuous activity of auricular flutter and fibrillation. Garrey (1914) made similar observations independently and showed that in a ring cut from the fibrillating muscle, a single wave of contraction continues to circulate.

Einthoven's (1903) string galvanometer has played a very important part in the study of cardiac arrhythmias by enabling us to determine the site of impulse formation and its direction of spread. Another important milestone which undoubtedly provided the chief impetus for work on the nature of auricular flutter and fibrillation, was the discovery of these conditions in Man. Ritchie in 1905, and Hertz and Goodhart in 1908, were the first to describe auricular flutter in Man. Jolly and Ritchie (1911) applied the term 'auricular flutter' to the clinical arrhythmia and established the diagnosis electrocardiographically. The identity of experimental

auricular fibrillation with clinical condition termed 'delirium cordis' was first described by Cushny & Edmunds (1907), Hirschfelder (1908), Rothberger & Winterberg (1909) and by Lewis (1909). To Carlson (1906, 1907) goes the credit for coining the terms 'relative' and 'absolute' refractory period.

In 1907, Sir James Mackenzie classified cardiac arrhythmias into different types. He also suggested that auriculoventricular node was the pacemaker in auricular fibrillation, and labelled the arrhythmia 'auriculoventricular nodal rhythm'. This was disproved by Lewis in 1909, who conclusively showed that auricular fibrillation and nodal rhythm were two dissimilar phenomenon. Rothberger & Winterberg (1914), were the first workers to employ direct auricular leads to the study of flutter and fibrillation in the animals, and advanced the concept that the rapid tachycardia originated from a single ectopic focus. They also emphasized the close relationship of auricular flutter and fibrillation. By studying the action of vagal stimulation and of drugs like physostigmine, they demonstrated that cholinergic influences facilitate the production of auricular fibrillation, and can convert flutter into fibrillation. A few years later Lewis et al. (1921a), made similar observations in post-faradic flutter and fibrillation, and ascribed the

action of vagal stimulation to a shortening of the relative refractory period. The existence of a phase of 'supernormal' excitability just after the end of relative refractory period was first described by Adrian (1920, 1921), in the frog heart.

Although the re-entry concept of McWilliams (1887), the ring experiments of Mayer (1908 a,b) and Mines (1913 a,b) and the writings of Garrey (1914, 1924), provided the basis for circus movement concept, the widespread acceptance accorded to this theory may be attributed to the work of Sir Thomas Lewis and his associates (1925). It may be interesting to recall at this stage that until 1918, Lewis not only leaned to the view that irritable foci in the muscle underlay fibrillation, but he actually criticized the work of Mines (Lewis, 1914). He embarked on his classic studies in the hope of disproving the circus movement concept of Mine's, but ended up by putting it on a much more secure footing.

Lewis's outstanding contribution dealt with the nature of auricular flutter and fibrillation. He studied these arrhythmias in the experimental animals using direct auricular leads, and postulated the 'circus movement theory'. He observed that a main excitation wave is propagated through the auricles via a narrow circular pathway, embracing the two venae cavae. The main wave pursues a unidirectional course and re-enters the original pathway on the completion of the circuit.

Small daughter waves are presumed to arise from the main wave and they spread over the remaining musculature of the auricles. In this single auricular pathway, the impulse always encounters responsive muscle between the head and tail of the unresponsive 'ring' muscle, and the area of responsive muscle fibres 'the excitable gap' circulates in the mother ring at the same speed and thus keeps ahead of the impulse. In auricular flutter, the mother ring and the pathways taken by its offshoots are believed to form a regular pattern. In auricular fibrillation, the mother ring is still believed to be present but its diameter is smaller and the pattern of both its path and that of its offshoot's is variable. Unfortunately, Lewis could not adequately explore the path of the returning cycle in the left auricle and he presumed that it did return towards the inferior vena cava. Lewis also applied the results of his animal experiments to the analysis of clinical auricular flutter and fibrillation and concluded that the circus movement concept is fully applicable in these cases.

Findings incompatible with the circus wave theory were soon reported. Brams and Katz (1931), severed the hypothetical circus pathway but the postfaradic flutter did not terminate. Despite these objections, the evidence advanced by Lewis was considered to be so complete that circus movement theory has been accepted as an established fact in the majority of standard textbooks when discussing the mechanism of auricular flutter and

fibrillation, and has been generally accepted by the pharmacologists as an explanation for the antifibrillatory action of drugs.

Andrus and Carter (1930) induced auricular fibrillation in the dog by applying a single stimulus shortly after the end of the relative refractory period during vagal stimulation. Nahum and Hoff (1940) produced auricular fibrillation in the dog by the topical application of methacholine to the right auricle, while Iglauer, Davis and Altschule (1941) used intravenous methacholine to produce this arrhythmia. This confirmed the observations of Rothberger and Winterberg (1914) and of Lewis et al. (1921a), that cholinergic influences facilitate the production of auricular fibrillation.

2. RECENT WORK

The experimental observations of Rosenblueth & Garcia Ramos (1947 a,b) have provided more powerful support for circus movement theory, than any other evidence reported since the classic studies of Sir Thomas Lewis. They showed that prolonged episodes of post-stimulatory auricular flutter occurred in the dog when the intervenae caval bridge was either crushed or blocked with cocaine, before the electrical stimulation. The intervenae caval crush or block provided an obstacle to short cuts across the auricle, thereby preventing

deviations of the impulse from circus pathway that might terminate the arrhythmia. Other workers have also confirmed the finding that preliminary crush or block of the intervenae caval bridge, facilitates the production of prolonged episodes of post-stimulatory auricular flutter (Brown, 1952; Brown & Acheson, 1952) and that the basic mechanism of this type of flutter was a circus movement (Brown & Acheson, 1952; Kimura et al. 1954; Lanari et al. 1956).

Cabrera Cossio & Sodi-Pellares (1947) by analysing the electrocardiographic tracings demonstrated the existence of circus movement in two patients with spontaneous auricular flutter. Similar observations were made by Wenger & Hofmann-Credner (1952) in six cases of auricular flutter in Man.

Scherf, et al.(1953b) presented an alternative explanation to account for post-stimulatory flutter. They stated that the crushed area may be capable of rapid impulse formation, thus acting as a rapidly discharging ectopic focus. They also stressed the possibility that the crushed region may contain elements of sino-auricular node and damaged nodal tissue may act as a rapidly discharging ectopic focus. The hypothesis is certainly very attractive but it failed to explain the timing of the intrinsic deflections in direct auricular leads that Rosenblueth & Garcia Ramos (1947 a,b) advanced as evidence of a circus movement. The demonstration of reversal of the pathway

of impulse circulation in the same animal by Lanari et al. (1956), supports the view of Rosenblueth & Garcia Ramos .

Among the first workers who seriously challenged the circus movement theory, was Scherf (1947) who produced auricular flutter in the dog by establishing an ectopic focus with topical application of aconitine to the right auricle. When the aconitine-treated area was cooled, the arrhythmia disappeared and sinus rhythm returned. The arrhythmia reappeared within few seconds, when the cooling was stopped. Again, when the aconitine treated area was functionally isolated from the rest of the auricle by a clamp, sinus rhythm returned in the body of the auricle but flutter persisted in the isolated part (Scherf & Terranova, 1949). These observations on aconitine-induced auricular flutter have been regarded as an evidence against the presence of self-perpetuating circus movement, and have been explained on the basis of ectopic focus theory (Scherf, 1947, 1948, 1951; Scherf & Terranova, 1949; Scherf et al., 1948; 1949 a,b; 1950 a,b; 1953 a,b). Dawes (1952) objected to the interpretations of Scherf and his associates on the ground that it was almost impossible to cool a single point on the surface of the auricle, the effective cooling must spread over an area surrounding the thermode. He argued without experimental proof that any stimulus, for instance one arising from the sino-auricular node and entering the aconitine-treated

area recovering from cooling, might restart the circus movement. Wilson (quoted by Kennamer & Prinzmetal, 1954) proposed a modification of the original circus movement theory that appeared to be compatible with the findings of Scherf and his associates. He suggested that each flutter beat may originate from an ectopic focus, pursue a circus pathway around the auricle and terminate on the completion of the circuit. Another version of the circus movement theory was offered by Katz & Pick (1953, 1956, 1959). They suggested that multiple simultaneous circulating waves may be present in auricular flutter. The multiple re-entries perpetuate the vulnerable period of the cardiac cycle. Either a normal sinus beat or an ectopic focus could give rise to the initiating impulse.

Prinzmetal and his associates (Prinzmetal, et al., 1950; 1951 a,b; 1952; 1953; 1955; Kennamer et al; 1957), studied experimental auricular flutter and fibrillation in the dog and spontaneous flutter and fibrillation in Man by using direct auricular leads and by high speed cinematography. Motion pictures of the fluttering and fibrillating auricles were taken at 2000 frames per second and projected on a screen at 8 frames per second, the movement could thus be slowed by 250 times. Auricular events of one second took four minutes to view on the screen. The picture was magnified 100 times or more on projection. Both factors indicated that the waves

originated from ectopic focus, and spread out in radial fashion in all available directions simultaneously. Evidence of a primary wave that returned towards the focus or of small circulating waves was not found. Burning and cutting of the Lewis's circus pathway failed to arrest the arrhythmia. These workers, therefore, concluded that auricular flutter and fibrillation in animals, as well as in man was due to a rapidly discharging ectopic focus. Dawes (1952) has argued that cinematographic studies would not rule out the presence of circus movement if the mass of the muscle involved was too small to be seen. This objection seems to be quite relevant in the light of McWilliams (1918) observations. He demonstrated that localized circus movements could occur and cause fibrillation, which can be interrupted by clamping off or cooling of a small area. The path of such a small circulating wave was estimated to use a circuit with a diameter of only 2.5 to 3.8 mm.

Dawes & Vane (1951a) studied the mechanism of the repetitive discharges in the isolated driven guinea-pig auricles and concluded that a rapidly discharging ectopic focus was the basic mechanism. Later they analysed the electrical events in greater detail and ascribed this arrhythmia to a circus movement (Dawes, 1952). Brown & Acheson (1952) produced the aconitine-induced and post-stimulatory auricular flutter simultaneously in the same auricle in the dog under certain experimental

conditions, and ascribed the aconitine-induced flutter to a rapidly discharging ectopic focus and the post-stimulatory auricular flutter to a circus movement.

Widely varying views concerning the mechanism of auricular arrhythmias were reflected at a symposium held in 1953. Rosenblueth (1953) stated unequivocally that auricular flutter and fibrillation in both Man and laboratory animals involved a circus movement. Prinzmetal (1953) attributed these arrhythmias in Man to a rapidly discharging ectopic focus. The mechanism of flutter and fibrillation in the experimental animals was thought to vary with the method of production. Hecht (1953) agreed that flutter and fibrillation in the experimental animals and in Man may exhibit different mechanisms. Katz & Pick (1953) considered no single theory adequate to explain all the experimental and clinical features of flutter and fibrillation. They advanced a compromise hypothesis by which both arrhythmias were assumed to initiate from a discharging ectopic focus and to persist through a mechanism of multiple re-entries.

Brooks et al. (1955) advanced the concept of the role of electrotonic currents in the production and maintenance of fibrillation. They presume that all provocative agents create an unequal effect on cardiac tissue, leading to an asymmetrical propagation of excitation wave. Any active area or depolarised region of cell membrane gives rise to electrotonic

currents. This current spreads through all adjacent conducting media and if sufficiently strong will excite tissues through which it passes. When heterogenous states of excitability exist, certain cells will respond to a nearby focus of activity before neighbouring cells which may be close to already depolarised 'sink area'. These cells will fire and stimulate their neighbours thus initiating new foci of activity. Because of their earlier activation these cells will recover earlier than their neighbours and may be re-excited from an adjacent area but not necessarily the contiguous area of the myocardium, this will favour re-entry.

Scherf et al. (1960) produced auricular flutter and fibrillation in the dog by topical application of delphinine, an alkaloid closely related chemically to aconitine. Yelnowsky and Clark (1960) studied aconitine-induced tachycardia in the isolated rabbit auricles and concluded that the arrhythmia was due to the stimulation of the sino-auricular node. They found that aconitine failed to induce tachycardia in the isolated non-driven left auricle. However, Dawes & Vane (1956) found that aconitine regularly induced tachycardia in the isolated driven left auricle of the guinea-pig.

Thus, it is apparent that much disagreement still exists about the mechanism of auricular flutter and fibrillation.

Recently the role of acetylcholine in the production

and maintenance of auricular fibrillation has been extensively studied. Scherf & Chick (1951); Hoff & Geddes (1955), and Loomis & Krop (1955), showed that acetylcholine or methacholine applied topically to a small area of the auricle regularly produced fibrillation, either spontaneously or following mechanical or electrical stimulation. Dawes & Vane (1951b), DiPalma & Mascatello (1951), West et al. (1954), Holland & Burn (1957) and West & Cox (1960), observed that fibrillation resulted consistently when the isolated rabbit auricles were stimulated electrically in the presence of acetylcholine. This profibrillatory action of acetylcholine was also noted by Burn et al. (1955 a, b; 1956) in the heart-lung preparation of the dog. Cholinesterases were also found to produce auricular fibrillation (Burn & Walker, 1954); and to convert aconitine-induced auricular flutter into fibrillation (Burn et al. 1956), in the heart-lung preparation of the dog. Scherf et al. (1953 a), Brown & Acheson (1952) and Lanari et al. (1956) showed that aconitine-induced, as well as post-stimulatory auricular flutter was converted to fibrillation under cholinergic influence. The profibrillatory action of acetylcholine has been ascribed to its excitatory action, that was first described by Rothberger & Sachs (1938), to a shortening of the refractory period (Lewis et al. 1921 a; Hoffmann & Suckling, 1953; Burgen & Terroux, 1953) and to an increased permeability of the myocardia cell

membrane to potassium (Burn, 1956; Harris & Hutter, 1956; Holland, 1957; Leveque, 1957).

Burn (1953) postulated that for the maintenance of heart beat, an optimal concentration of acetylcholine was required and acetylcholine has been shown to stimulate the auricles which had ceased beating either spontaneously or after exposure to quinidine or to cold (Burn & Vane, 1949; Bulbring & Burn, 1949; Briscoe & Burn, 1954; Marshall & Vaughan Williams, 1956). Marshall (1957) showed that acetylcholine re-started the cold arrested isolated auricles by raising the resting potential of the auricular fibres, thus making the pace-maker potentials effective. If the pacemaker potentials were absent, acetylcholine failed to re-start the auricles. This showed that acetylcholine acts by facilitating the transmission of the impulses from the sino-auricular node to the auricular myocardium and not by a stimulant action on impulse generation in the sino-auricular node.

Alessi et al. (1958) demonstrated that the effect of vagal stimulation on the refractory period of the auricles was not uniform and Moe & Albidskov (1959) showed that auricular fibrillation can persist as a self-perpetuating arrhythmia, independent of focal discharge that initiated it, if adequate cholinergic influence was present.

Thus the role of acetylcholine in the production of

auricular fibrillation seems to be well documented. This fibrillatory action of acetylcholine is completely blocked by atropine (Scherf et al. 1953 a; Burn et al. 1956). It is, however, not known with certainty whether acetylcholine plays a part in the establishment of stable auricular flutter. Scherf et al. (1953 b, 1955) showed that aconitine did not produce flutter in the atropinised animal, and Angelakos & Torchiana (1961) suggested that acetylcholine may be concerned in the development of all types of auricular arrhythmias. This hypothesis needs further confirmation.

On the other hand, little is known about the role of catecholamines in the production and maintenance of auricular flutter and fibrillation. Winterberg (1907, 1908) showed that stimulation of the sympathetic nerves produced an increase in the rate of post-stimulatory auricular flutter. Cowan & Ritchie (1922) and Rosenblum et al. (1933), showed that adrenaline injection may induce auricular fibrillation in the intact animal and in perfused hearts. They did not study the mechanism of fibrillation. Scherf (1949) demonstrated that sympathetic stimulation increased the rate of aconitine-induced auricular flutter. Frequently, the flutter was converted into fibrillation; this effect was blocked by atropine. Grant et al. (1949) produced auricular fibrillation by adrenaline injection in the dog. They demonstrated that adrenaline produced fibrillation only if

functional vagi were present and that adrenaline and vagus nerve stimulation can act synergistically to incite auricular fibrillation. However, Burn et al. (1957) showed that simultaneous infusion of adrenaline antagonised the fibrillatory action of acetylcholine in the heart-lung preparation of the dog, this is not in agreement with the findings of Scherf (1949) and Grant et al. (1949) mentioned above.

This fibrillatory action of adrenaline appears to be cholinergic in nature, since it is blocked by atropine. DiPalma (1956, 1959) showed that acetylcholine and adrenaline were the two vital hormones concerned in the maintenance of normal sinus rhythm and that adrenaline facilitated the induction of arrhythmias by suppressing the dominance of the sino-auricular node. Further, McKendrick & Godfrey (1959) showed that adrenaline was even more effective than acetylcholine in restarting the fatigue-arrested isolated rabbit auricles. None of the preparations that failed to respond to adrenaline, responded to acetylcholine but all the preparations that failed to respond to acetylcholine, responded to adrenaline. This finding supports the hypothesis advanced by DiPalma, that both acetylcholine and adrenaline regulate the maintenance of normal sinus rhythm.

IV. MATERIALS AND METHODS

(1) Selection of methods

Many methods have been described for producing experimental auricular flutter and fibrillation in the intact animal (Rothberger & Winterberg, 1914; Lewis et al. 1920a, Andrus & Carter, 1930; Brams & Katz, 1931; Nahum & Hoff, 1940; Iglauer, Davis & Altschule, 1941, Burn et al. 1955a; Ellis, 1956, Winsbury, 1956.

In the present study, the following three methods were used to induce auricular flutter and fibrillation in the intact dog, under positive pressure artificial respiration.

(i) Acetylcholine-induced auricular fibrillation (Scherf & Chick, 1951).

(ii) Aconitine-induced auricular flutter and fibrillation (Scherf, 1947).

(iii) Postelectric-stimulatory auricular flutter (Rosenblueth & Garcia Ramos, 1947a, b).

These three procedures were selected as the basis for this study, for the following reasons:-

(a) The arrhythmias persist for prolonged periods of time, and are not fatal.

(b) They show some resemblance to auricular flutter and fibrillation in Man. The acetylcholine and aconitine-induced arrhythmias are believed to be due to a rapidly discharging ectopic focus or foci

(Scherf et al. 1953a, b; Prinzmetal et al. 1951a, b). The post-electric stimulatory flutter is thought to be due to circus movement (Rosenblueth & Garcia Ramos, 1947a, b; Brown & Acheson, 1952; Lanari et al. 1956).

(c) These procedures have been extensively used by other workers to study the mechanism of auricular flutter and fibrillation and for screening quinidine-like drugs (Brown, 1952; Brown & Acheson, 1952; Scherf et al. 1953a, b; Winbury & Hemmer, 1955; Lanari et al. 1956).

(d) The resulting arrhythmias can be induced more than once in the same animal and the results are easily reproducible in different animals.

(2) Acetylcholine-induced auricular fibrillation

The procedure described by Schallek (1952) was used, which is a modification of the method of Scherf & Chick (1951).

Mongrel dogs of either sex (8 - 15 kgm. weight) were anaesthetised by the intravenous administration of 35 mg/kg. pentobarbitone sodium. Under positive pressure artificial respiration through the tracheal cannula, the chest was opened by midline incision, splitting the sternum longitudinally into two and the cut ends were retracted to give a clear exposure of the heart. The pericardium on the upper right quadrant

of the heart was incised and its edges stitched to the chest wall, thereby exposing the sino-auricular node and the right auricle. The left auricular appendage was exposed through a left thoracotomy in the 4th intercostal space.

The right femoral vein was cannulated for giving intravenous injections. Direct electrograms from the sino-auricular node, tip of the right auricular appendage, tip of the left auricular appendage and conventional bipolar lead II were recorded simultaneously on a Siemen Ediswan 4-channel ink writing oscillograph. Clip electrodes mounted on flexible enamelled copper wire were used as leads for direct electrograms. The Goldberger common terminal was used as the reference electrode, and in some experiments the unipolar and bipolar limb leads were also recorded.

After recording at least three control electro-cardiograms, a small pledget of cotton, soaked in 5% acetylcholine chloride solution was placed at sino-auricular node, or on the right or left auricular appendage. Fibrillation developed spontaneously in some experiments, while in others it was induced by gentle stroking of the auricle with a forceps one minute later. As long as the acetylcholine pledget remained on the auricle, the fibrillation persisted, which was over 10 minutes in all the experiments. Normal sinus rhythm returned after 15 - 30 minutes, but the process could be expedited, if need be, by removing the acetylcholine pledget.

Application of a fresh acetylcholine pledget re-induced auricular fibrillation. Thus it was possible to induce several episodes of auricular fibrillation in the same animal.

In some experiments acetylcholine was infused intravenously with a slow injector, at a constant rate. Fibrillation was evoked by gently stroking the right auricle with a blunt instrument.

(3) Aconitine-induced auricular flutter and fibrillation

The method described by Scherf (1947) was used in all essential details.

Mongrel dogs of either sex (8 - 18 kg. weight) were anaesthetised by intravenous administration of 35 mg/kg. pentobarbitone sodium. In exactly the same manner as described above, the chest was opened and the sino-auricular node, right and left auricular appendages were exposed. The same electrocardiographic leads as mentioned above were recorded simultaneously.

A small pledget of cotton, soaked in 0.05% solution of aconitine nitrate was applied to the tip of the right auricular appendage (Fig. 1). This was done to facilitate the functional isolation of the auricular appendage from the body of the auricle by a clamp. Care was taken to avoid any accidental contact of aconitine with the ventricular myocardium, as such an incident invariably resulted in fatal ventricular

fibrillation. In some experiments a few crystals of aconitine nitrate were applied directly to the auricular appendage at the root of the recording electrode. This was done to avoid any movement of the electrode per se that may occur when aconitine is applied with a cotton pledget.

In some experiments, aconitine was applied to the left auricular appendage and clamping and cooling experiments were repeated.

The paper was kept running to study the evolution of auricular flutter in detail. Within 2 minutes auricular flutter developed and reached a stable state within 5 minutes. In some experiments fibrillation appeared instead of flutter.

For evaluating the effect of acetylcholine and adrenaline these drugs were either applied topically to the auricles or injected intravenously. A rubber shod stout haemostat was used to effect the functional separation of the aconitine-treated area from the rest of the auricle. In the cooling experiments, a small cube of ice was applied directly to the aconitine-treated area or on the region of sino-auricular node.

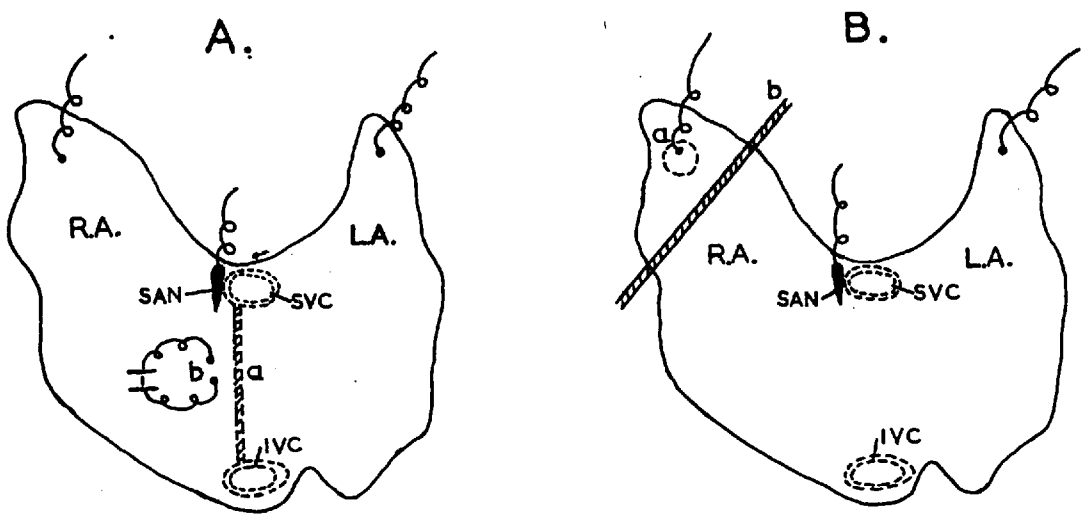


FIG.1

Fig. 1

(A) Method of producing post-stimulatory auricular flutter

(a) represents the inter-venae caval bridge, which is crushed with a stout haemostat.

(b) site of electrical stimulation (square wave pulses of 1 m. sec. duration; 20 volts; 20/sec; for not more than 15 sec. at a time).

(B) Method of producing aconitine-induced auricular flutter

(a) represents the site of application of aconitine nitrate (0.05% solution in physiological saline, with a small cotton wool pledget).

(b) represents the site where clamp is usually applied to isolate the aconitine-treated area from the rest of the auricle.

S.A.N. = sino-auricular node.
R.A. = right auricle.
L.A. = left auricle.
S.V.C. = superior vena cava.
I.V.C. = inferior vena cava.
The sites from where direct electrograms are recorded are depicted by coiled lines.

(4) Post-electric-stimulatory auricular flutter

Mongrel dogs of either sex (8 - 19 kg. weight) were anaesthetised by intravenous pentobarbitone sodium 35 mg/kg. The sino-auricular node, right auricle and left auricular appendage were exposed by a mid-line incision and left thoracotomy, and the direct auricular, unipolar and bipolar limb leads were recorded in exactly the same manner as outlined above.

Auricular flutter was induced in all the experiments by the injury-stimulation procedure of Rosenblueth & Garcia Ramos (1947 a, b). The intervenae caval bridge was crushed with a haemostat and the intact area of the right auricle surrounding the injured zone, was stimulated electrically for 15 seconds (Fig. 1). The stimulation parameters used were square wave pulses of 1 m. sec. duration; frequency 10 - 20/sec; and 10 - 20 volts. This procedure usually resulted in the production of long-lasting, self-perpetuating auricular flutter. The arrhythmia was allowed to continue for 20 min. before experimental observations were started.

The arrhythmia could be terminated at will by brief electrical stimulation and re-induced by electrical stimulation as mentioned above. Spontaneous reversions of flutter that had persisted for over 20 minutes were not observed.

For cooling purposes, a small cube of ice was applied directly on the crushed region, sino-auricular node or auriculo-ventricular node.

For evaluating the effect of acetylcholine and adrenaline on atrial flutter, these drugs were either applied topically to the auricles or injected intravenously.

(5) Vagal stimulation

For purposes of vagal stimulation, the right vagus nerve was exposed and divided in the neck and the peripheral stump stimulated electrically (square wave pulses of 0.5 m. sec. duration; frequency 5 - 20/sec; 5 - 20 volts) for not more than 15 seconds at a time.

In some experiments the left vagus nerve was also used for stimulation.

(6) Blockade of acetylcholine synthesis by hemicholinium

Hemicholinium (d d dimethylethanolamino 4, 4' - biacetophenone dibromide) a drug known to produce a failure of response to cholinergic nerves (McIntosh et al. 1956; Reitzal & Long, 1959a, b; Wilson & Long, 1959) and to block synthesis of acetylcholine (McIntosh et al. 1956; Gardiner, 1957), was administered in a dose of 10 mgm/kgm. intravenously in 0.5% solution in isotonic saline over 10 minutes. The effects were observed for up to 2 hours. The effect of vagal stimulation was completely blocked by

hemicholium at this dose level.

(7) Sympathetic stimulation

Shielded electrodes were placed between stellate and 2nd thoracic ganglia. All the preganglionic sympathetic connections (1 - 5th thoracic) were cut off. The stimulus parameters used were square wave pulses of 0.1 m. sec. duration; 10 - 20 volts; frequency 5 - 20/sec. for not more than 15 sec. at a time.

(8) Depletion of catecholamines by reserpine pretreatment

Reserpine was administered in a dose of 0.5 mg/kg. intraperitoneally daily; on two consecutive days. The animals were used for experimentation 48 hours after the last dose. Reserpine at this dose level is known to produce a complete depletion of cardiac noradrenaline in the dog. Adrenaline content though markedly reduced is not totally depleted (Paasonen & Krayer, 1958; Arora & Sharma, 1960).

(9) Acute cardiac denervation

The animals were anaesthetised and the chest opened by a mid-line incision; in exactly the same manner, as mentioned above.

Both the vagus nerves were dissected in the neck and divided. The chest was rotated to the left side to facilitate access to the costo-vertebral groove. The

right lung was displaced towards the diaphragm with gauze packing, and the stellate ganglia and 2 - 5th thoracic sympathetic ganglia were excised and removed on the right side. The chest was now rotated to the right side and the same procedure was repeated on the left side.

The chest was restored to the midline position, the pericardium incised and the heart was cradled. A period of 30 minutes was allowed for the heart rate to stabilise. Auricular flutter or fibrillation was then induced in the same manner as mentioned above.

(10) Isolated guinea-pig auricle:

Immediately after stunning the animal by a blow on the back of the head, the thorax was opened and the entire heart removed and placed in oxygenated nutrient fluid at room temperature. The auricles were carefully dissected from the ventricles by cutting along the auriculo-ventricular junction and then were cleared of adjacent tissue and suspended vertically in a muscle chamber, filled with 20 ml. of Burn's mammilian ringer solution (NaCl, 9.0 g; KCl, 0.42 g; $CaCl_2$, 0. 24 g; $NaHCO_3$, 0. 2 g; Glucose, 1. 0 g; distilled water, 1000 ml.), at 29° C. The tip of the left auricle was anchored to the tissue holder and the tip of the right auricle was attached to a light writing lever by a silk thread. The working volume of muscle chamber was 20 ml.

Auricular rate was monitored electrocardiographically, using thin enamelled copper wire leads. The fluid was aerated with 95% oxygen and 5% carbondioxide. Each drug was allowed to act for 30 sec. and then the bath fluid was changed twice.

(11) Isolated guinea-pig ileum:

A piece of terminal part of guinea-pig ileum was set up in a bath at 32°C, filled with 20 ml. Tyrode's solution (NaCl, 8.00 g; KCl, 0.2 g; Ca Cl_2, 0.2 g; NaH_2PO_4, 0.05 g; Mg Cl_2, 0.20 g; $NaHCO_3$, 1.00g, glucose, 1.00 g; distilled H_2O, 1000 ml.) through which was bubbled a mixture of 95% oxygen and 5% carbon dioxide. The responses were recorded on a smoked drum, using a frontal writing-point lever. The drugs were allowed to act for 30 sec. and after each addition, the bath fluid was changed twice.

(12) Drugs used

1. Acetylcholine chloride.
2. Aconitine nitrate.
3. Atropine sulphate.
4. Adrenaline hydrochloride.
5. Noradrenaline bitartrate.
6. Hemicholinium (HC - 3).
7. Eserine sulphate.
8. Barium chloride.
9. Nicotine hydrogen tartrate.
10. Histamine acid phosphate.

All the drugs were dissolved in 0.9% sodium chloride solution. In all cases the dose refers to the salt used and all drug solutions were prepared fresh on the day of the experiment.

V. RESULTS

1. ACETYLCHOLINE-INDUCED AURICULAR FIBRILLATION

Auricular fibrillation was induced by topical application of acetylcholine to the auricular appendage or by continuous intravenous infusion of acetylcholine.

(i) Auricular fibrillation induced by topical application of acetylcholine

A total of 10 experiments were performed in 10 dogs. When a pledget of cotton soaked in 5% acetylcholine solution was applied to the auricle, the first effect noted was sinus bradycardia. The bradycardia was most marked when the acetylcholine was applied directly to the sino-auricular node, in some cases nodal rhythm followed. The slowing was least marked when the acetylcholine was applied to the auricular appendages. If spontaneous fibrillation did not result within one minute, a gentle tap on the right auricle with a blunt instrument, always precipitated this rhythm. The duration of fibrillation varied between 9 - 22 minutes, if the acetylcholine pledget was allowed to remain on the auricle. The fibrillation rate varied between 1440 - 2750/min. The rate declined gradually, as acetylcholine was being destroyed by the enzyme cholinesterase, transient auricular flutter intervened in most cases and finally the arrhythmia came to an abrupt end, and sinus rhythm returned.

Direct auricular leads, recorded simultaneously from the sino-auricular node, right, and left auricular appendages, showed that the fibrillatory activity of acetylcholine was very

localised. In Fig. 2, the occurrence of inter-auricular and intra-auricular dissociation, following topical application of acetylcholine has been demonstrated. When acetylcholine was applied to the right auricular appendage, the fibrillation was confined to the right auricle, the left auricle recorded impure flutter (excerpt B), the reverse was also true (excerpt D). When acetylcholine was applied to the right auricular appendage, intra-auricular dissociation was also seen in that the sino-auricular electrode also recorded impure flutter and not fibrillation. When acetylcholine was also applied to the sino-auricular node the intra-auricular dissociation disappeared, excerpts B and C). No dissociation was observed when acetylcholine was applied to both the auricles (excerpt E). The auricular complexes in lead II were either upright, inverted, biphasic or isoelectric and frequently varied in contour from beat to beat, showing that the beats were not originating from any single area of the auricles.

(ii) Auricular fibrillation-induced by intravenous infusion of acetylcholine

When acetylcholine was infused intravenously at a constant rate, 1 - 4 mg./min. (12 experiments in 5 dogs), fibrillation resulted spontaneously in 8 experiments. In the remainder, gentle stroking of the auricle produced fibrillation, which lasted for the duration of the infusion of acetylcholine (up to 30 min.) and disappeared within 30 sec.

of stopping the infusion. The fibrillation could be induced again by repeating the procedure. No auricular dissociation was seen. The fibrillation rate varied between 1200 - 3480/min., depending upon the dose of acetylcholine employed.

A typical experiment is shown in Fig. 3. Acetylcholine was infused at the rate of 2 mg./min. Gentle stroking of the auricle precipitated auricular fibrillation with marked A-V block. Both the auricles fibrillated simultaneously and no dissociation was seen. When the acetylcholine infusion was stopped, the fibrillation rate slowed, transient impure flutter intervened and then the arrhythmia stopped abruptly and sinus rhythm returned.

(iii) Acetylcholine-adrenaline interaction

When adrenaline was infused intravenously at the rate of 100 - 200 µg./min., gentle stroking of the auricle produced short runs of fibrillation (8 experiments in 4 dogs). In one dog the fibrillation lasted for the duration of the infusion (5 min.) and sinus rhythm returned 48 sec. after the infusion was discontinued. In another dog auricular flutter resulted, which stopped 42 sec. after discontinuation of the infusion (Fig. 4). Noradrenaline infusion (100 - 200 µg./min.) produced only short runs of fibrillation (6 experiments in 3 dogs).

To study the acetylcholine-adrenaline interaction the rate of acetylcholine or adrenaline infusion was so adjusted that stroking of the auricle only produced short runs of fibrillation.

The two drugs were then infused simultaneously and the duration of fibrillation noted. A typical experiment is illustrated in Fig. 5. In this experiment, acetylcholine (0.5 mg./min.) or adrenaline (50 µg./min.) produced only short-lived arrhythmia when the auricle was stroked. When the two drugs were infused simultaneously, stroking of the auricle produced auricular fibrillation which lasted for the duration of the infusion (7 min.), sinus rhythm returned 28 sec. after the infusion was discontinued. The procedure was repeated and a prolonged episode of fibrillation resulted once again. Acetylcholine and adrenaline were then infused separately and did not produce prolonged fibrillation.

This finding is not in agreement with the observations of Burn et al. (1957), who reported that adrenaline antagonised the fibrillatory activity of acetylcholine, in the heart-lung preparation of the dog.

(iv) Role of nodal tissue in acetylcholine-induced auricular fibrillation

Scherf et al. (1953b) observed that the acetylcholine-induced auricular fibrillation was due to the development of ectopic foci in the sino-auricular and auriculo-ventricular nodes. This hypothesis was tested in clamping experiments (4 experiments in 4 dogs).

A typical experiment is illustrated in Fig. 6.

Methacholine chloride 2.5% solution was applied to the tip of the right auricle (acetylcholine was not used because of its short duration of action). Gentle stroking of the auricle produced fibrillation. Both inter-auricular and intra-auricular dissociation are present. If fibrillation was due to the development of ectopic foci in the nodal tissue, it will not explain why the sinus node and the left auricle beat at a slower rate than the methacholine-treated area. This suggested that impulse formation was occurring in the treated area. Clamping experiments proved that this was true. When the treated area was clamped to prevent the entry of the sino-auricular impulses into the treated area and vice versa, the arrhythmia continued on both sides of the clamp for 72 sec. Then the arrhythmia in body of the right auricle abruptly stopped and sinus rhythm returned but fibrillation continued in the isolated area for several minutes and then stopped abruptly.

Fresh application of methacholine did not induce fibrillation in the isolated area but fibrillation lasting several minutes could be induced by electrical stimulation of the treated area (Fig. 7), while sinus rhythm continued elsewhere. Focal cooling of the sinus node produced slow rate nodal rhythm.

(v) Effect of catecholamines depletion on the production of acetylcholine-induced auricular fibrillation

The cardiac catecholamines were depleted with reserpine treatment and acetylcholine-induced fibrillation was produced 48

hours after the last dose of reserpine. Topical acetylcholine application produced fibrillation as usual in all the 4 experiments. There was no significant increase in the duration of the fibrillation but the auricular rates were somewhat higher than the control experiments.

(vi) Effect of cardiac denervation

In 5 experiments, the acute denervation of the heart did not affect the production of the acetylcholine-induced auricular fibrillation. There was no significant effect on the fibrillation rate or on the duration of the arrhythmia, as compared to the control experiments.

(vii) Summary

1. The fibrillatory activity of acetylcholine applied topically to the auricle is very localised, as seen from the auricular dissociation phenomenon. No dissociation is seen when acetylcholine is infused intravenously.

2. A method for the production of prolonged episodes of auricular fibrillation in the intact dog, by continuous intravenous infusion of acetylcholine is described. The advantages of this method over the heart-lung method will be discussed later.

3. Simultaneous infusion of adrenaline or noradrenaline enhances the fibrillatory activity of acetylcholine, which itself is blocked by atropine.

4. Nodal tissues are not essential for the maintenance of auricular fibrillation, since this rhythm can be induced in a part of the auricle devoid of nodal tissue.

5. Neither catecholamines depletion nor acute cardiac denervation affect the production of the acetylcholine-induced auricular fibrillation.

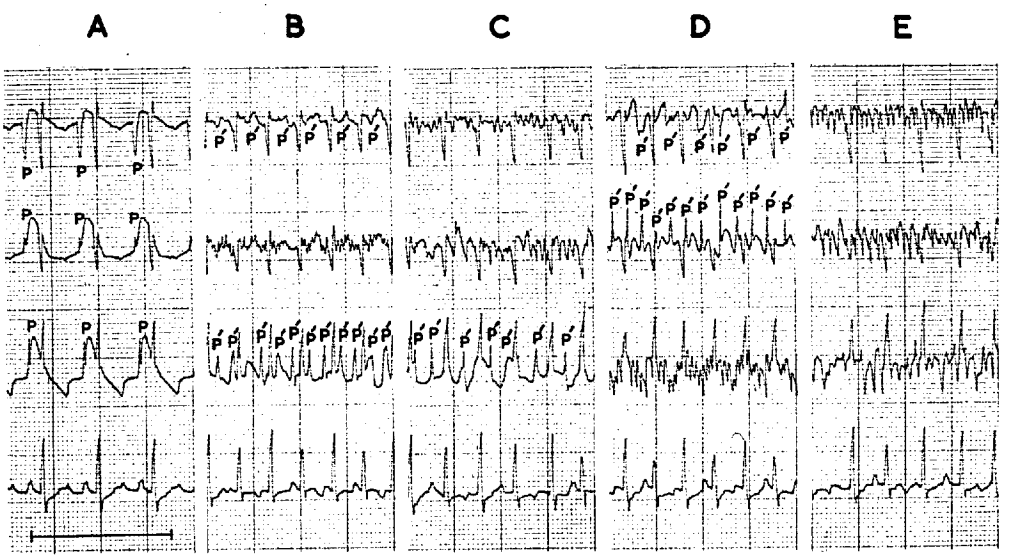


FIG. 2

Fig. 2

Auricular fibrillation induced by topical application of acetylcholine

From top to bottom, electrograms from the sino-auricular node, tip of the right auricular appendage, tip of the left auricular appendage and conventional bipolar lead II.

P = normal sinus beats.

P' = flutter beats, some flutter waves are lost in QRS deflections and are not labelled.

(A) Control, heart rate is 150/min.

(B) Acetylcholine 5% sol. was applied topically to the right auricular appendage, the resulting fibrillation (2340/min.) is confined to this area alone. Elsewhere impure auricular flutter (rate varying between 480 - 600/min.) is present. The dissociation is both inter-auricular and intra-auricular.

(C) Acetylcholine applied to sino-auricular node as well, the right auricle now records fibrillation (1620/min), the left auricle still flutters (480 - 600/min.) The acetylcholine pledgets were removed and in a few minutes, sinus rhythm returned.

(D) Acetylcholine applied topically to the left auricular appendage, only left auricle fibrillates (2160/min), the right auricle is fluttering (480 - 610/min.)

(E) Acetylcholine applied to both auricles, fibrillation exists everywhere. Removal of acetylcholine pledgets resulted in the cessation of fibrillation and sinus rhythm returned.

Time scale = 1 sec.

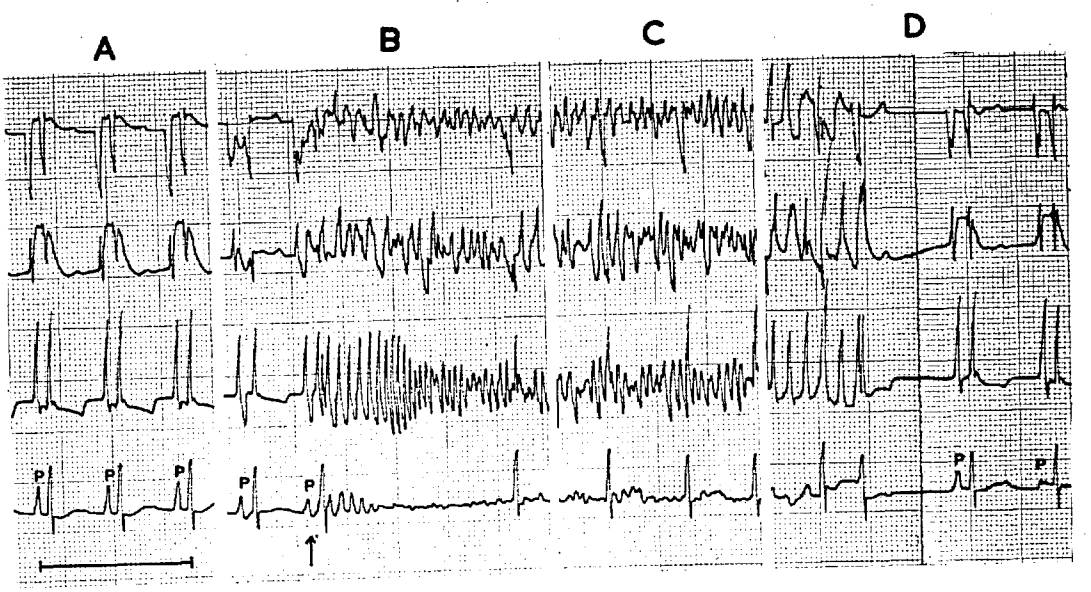


FIG. 3

Fig. 3

Acetylcholine-induced auricular fibrillation

From top to bottom, electrograms from the sino-auricular electrode, tip of the right auricular appendage, tip of the left auricular appendage and conventional bipolar lead II.
P = sinus beats.

(A) Control, heart rate is 132/min.

(B) Acetylcholine at the rate of 2 mg/min. was infused intravenously. At the arrow, a gentle stroking of the auricle with a blunt instrument resulted in auricular fibrillation, with very marked A - V block.

(C) 3 min. after the start of fibrillation. The fibrillation was allowed to continue for 5 min., then the acetylcholine infusion was stopped.

(D) 24 sec. after the stoppage of acetylcholine infusion, the fibrillation has changed into impure flutter and then the arrhythmia stopped abruptly and sinus rhythm returned at the rate of 106/min.

Time scale = 1 sec.

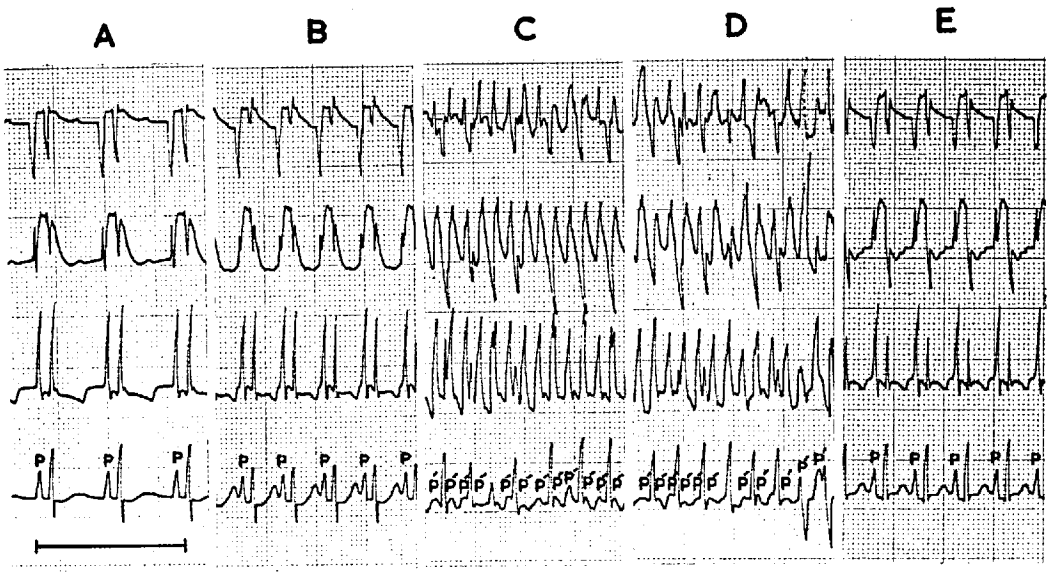


FIG. 4

Fig. 4

Adrenaline-induced auricular flutter

From top to bottom, electrograms from the sino-auricular node, tip of the right auricular appendage, tip of the left auricular appendage and conventional bipolar lead II. P = sinus beats, P' = flutter beats.

(A) Control, heart rate is 136/min.

(B) Adrenaline 100 µg./min. intravenously by continuous infusion. The rate has increased to 192/min.

(C) Immediately after the application of electrical stimulation (square wave pulses of 1 m. sec. duration; 20 volts; frequency 20/sec. for 5 sec.), to the right auricle. Auricular flutter at the rate of 620/min. is present.

(D) 4 min. after electrical stimulation, flutter rate is 610/min. The adrenaline infusion was then stopped.

(E) The flutter stopped abruptly 42 sec. after the stoppage of adrenaline infusion, and sinus rhythm at the rate of 225/min. returned.

Time scale = 1 min.

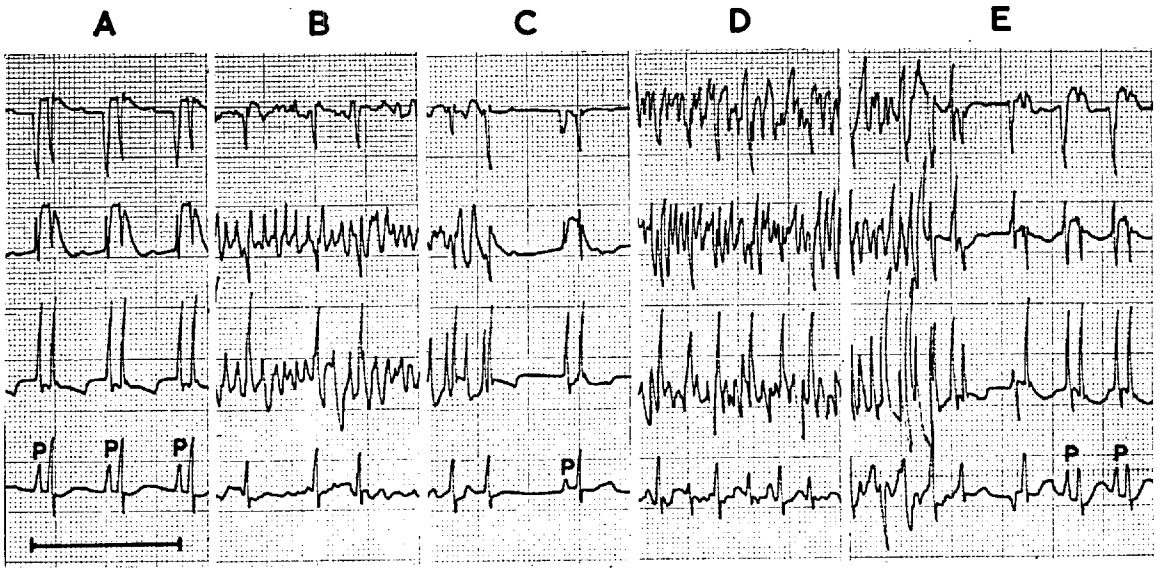


FIG. 5

Fig. 5

Effect of simultaneous infusion of adrenaline on acetylcholine-induced auricular fibrillation

From top to bottom, electrograms from the sino-auricular node, tip of the right auricular appendage, tip of the left auricular appendage and conventional bipolar lead II. P = sinus beats.

(A) Control, heart rate is 130/min.

(B) Acetylcholine 0.5 mg./min. was injected intravenously, gentle stroking of the auricle resulted in coarse auricular fibrillation.

(C) The fibrillation reverted after 10 sec., subsequent stroking of the auricle failed to induce prolonged episode of fibrillation.

(D) Adrenaline 50 µg./min. was given, along with acetylcholine 0.5 mg./min. Long-lasting fibrillation resulted. The infusion was stopped after 7 min.

(E) 28 sec. after stoppage of the infusion, the fibrillation rate has declined and then suddenly the arrhythmia stopped, and sinus rhythm at the rate of 184/min. returned.

Time scale = 1 sec.

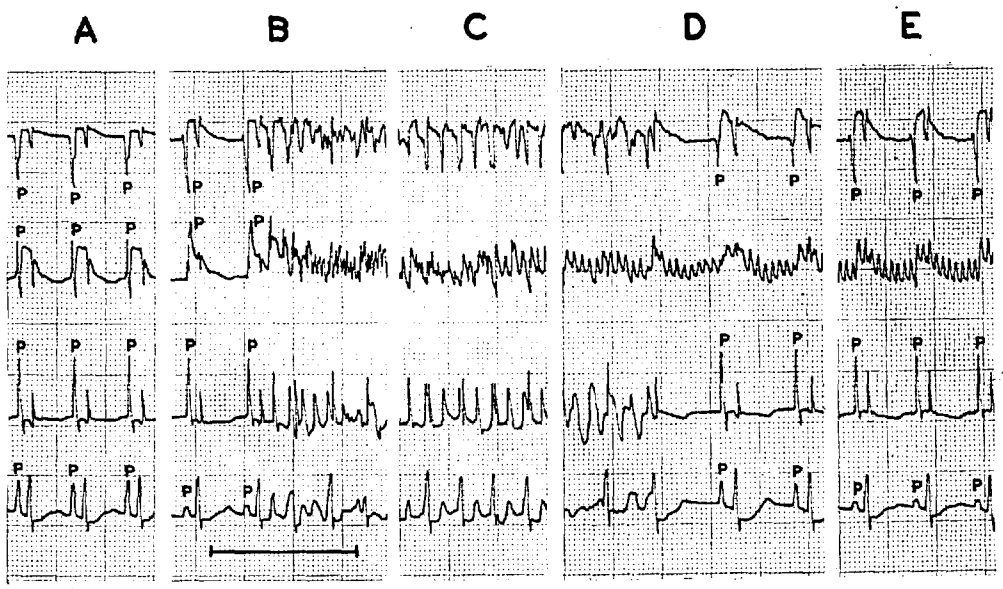


FIG. 6

Fig. 6

Illustrates that the methacholine-induced auricular fibrillation is not due to ectopic foci situated in the sino-auricular and auriculo-ventricular nodes

From top to bottom, electrograms from the sino-auricular node, tip of the right auricular appendage, tip of the left auricular appendage and conventional bipolar lead II.

P = normal sinus beats.

(A) control, heart rate is 165/min.

(B) 50 sec. after the topical application of 2.5% methacholine chloride to the right auricular appendage, fibrillation developed spontaneously, the rate is 2160/min. The left auricle is beating at a slower rate, 600 - 720/min.

(C) 30 sec. after the start of fibrillation. Auricular dissociation is seen, in that only the tip of right auricular appendage is fibrillating (1620/min), the sino-auricular and left auricular electrodes record impure flutter(rate 514 - 600/min.)

(D) The right appendage was clamped for one minute. This excerpt has been recorded 10 sec. after the release of the clamp. While fibrillation (1140/min) continued in the methacholine-treated area, note the sudden cessation of the arrhythmia in the rest of the auricle and return of sinus rhythm (120/min).

(E) Recorded 2 min. after release of the clamp. The fibrillation continues in the right auricular appendage (1320/min). while elsewhere sinus rhythm exists (146/min).

Time scale = 1 sec.

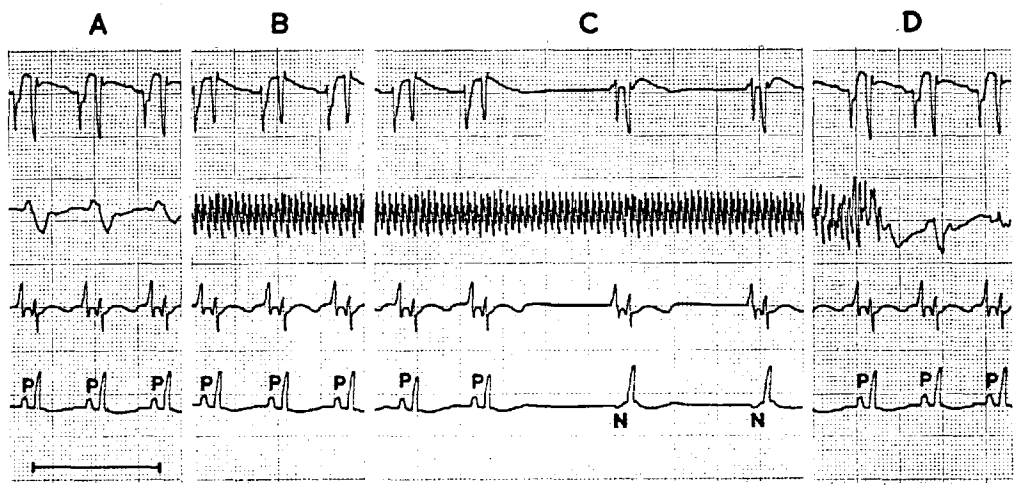


FIG. 7

Fig. 7

Production of auricular fibrillation
in the functionally isolated right auricular appendage

From top to bottom, electrograms from the region of the sino-auricular node, tip of the right auricular appendage, tip of the left auricular appendage and conventional bipolar lead II.

P = normal sinus beats.

N = nodal beats.

(A) control, heart rate is 124/min.

(B) methacholine chloride 2.5% solution was applied topically to the right auricular appendage which was isolated from the rest of the auricle by a clamp for one minute. One minute later electrical stimulation was applied to the treated area (square wave pulses of 5 m. sec. duration; 20 volts; 10/sec.) for 5 sec. This excerpt was recorded immediately after stimulation. Fibrillation is confined to the methacholine-treated area alone.

(C) 10 min. after the end of stimulation, fibrillation is still present in the treated area. Sinus node is beating at the rate of 120/min. Focal cooling of the sinus node revealed that auriculo-ventricular node was also not concerned in auricular fibrillation.

(D) 14 min. after stimulation, the fibrillation rate has slowed down. Note the abrupt disappearance of fibrillation.

Time scale = 1 sec.

2. ACONITINE-INDUCED AURICULAR FLUTTER AND FIBRILLATION

The topical application of aconitine nitrate to the right auricular appendage resulted in the development of auricular flutter; in some experiments auricular fibrillation resulted but changed into flutter after a few minutes. The auricular rates at the start of the arrhythmia were irregular in all the experiments but reached a steady level within 2 - 3 min. The experimental observations were, therefore, not started for at least 10 min. The arrhythmia persisted for over 3 hours in the control experiments.

The mean auricular flutter rate in 40 dogs was 447 ± S.E.7.16/min. There was a latent period of 76 ± S.E.8.43 sec., before the aconitine-induced arrhythmia started. The onset of the arrhythmia was of three types:

(a) the first abnormality noted was the appearance of premature systoles either singly or in pairs which soon led to short runs of auricular tachycardia and finally auricular flutter resulted. This was the commonest pattern (18 dogs).

(b) auricular fibrillation developed suddenly in 14 dogs. In 9 dogs it soon changed into auricular flutter, in the remainder auricular fibrillation continued for several minutes and then changed into auricular flutter.

(c) Sudden auricular tachycardia developed in 8 dogs and soon auricular flutter resulted. No premature systoles were seen.

(i) Genesis of aconitine-induced auricular flutter

The different stages in the development of aconitine-induced arrhythmia were studied in those dogs in which flutter developed gradually. Three typical electrocardiographic records are illustrated in Fig. 8 - 10.

The first abnormality noted was the occurrence of premature systoles occurring singly, in pairs or as short runs of auricular tachycardia. All the single premature systoles and the first beat of a pair of premature systoles or of a short run of tachycardia (which have been serially numbered in Fig. 8 - 10), showed fixed coupling to the preceding sinus beat and were of the same form and amplitude. This showed that they were all arising from one area of the auricular myocardium. When regular tachycardia and later flutter resulted, the form of beats remained the same as that of preceding premature systoles.

Another important feature of short runs of tachycardia and early stages of flutter was an irregularly irregular rate and slight variation in the contour of the auricular complexes from beat to beat. After a few minutes, as the aconitine effect reached its peak, the rate became quite regular but some variation in the duration of flutter cycles did persist.

In another experiment (Fig. 11), the re-appearance of the arrhythmia following its arrest by focal cooling was very gradual. Here too, premature systoles with fixed coupling

preceded auricular tachycardia, and auricular rate was irregularly irregular.

(ii) Effect of aconitine on the auricular electrogram

Bipolar direct electrograms were recorded from the tip of the right auricular appendage. A few crystals of aconitine were carefully applied to the root of one of the electrodes and the paper was kept running.

Within 6 sec., monophasic action potentials (MAP) developed at the right auricular electrode. The amplitude of MAP increased gradually and the peak effect was reached after about 30 - 40 sec. After this the amplitude of the MAP decreased somewhat. Then the premature systoles appeared and passed into auricular flutter. A typical experiment is illustrated in Fig. 12. The development of MAP in the aconitine-treated area showed that the drug was producing tissue injury.

(iii) Role of sino-auricular impulses in the initiation of aconitine-induced auricular flutter

In 4 dogs, the right auricular appendage was functionally separated from the body of the right auricle by a clamp, to prevent the entry of the sinus impulses into the isolated area. Aconitine was then applied to the isolated area. Auricular flutter did not develop for the duration of the clamp (up to 10 min.) Normally the arrhythmia always appeared within 2 min.

When the clamp was removed, arrhythmia developed spontaneously in 3 experiments. In the 4th experiment, flutter started after the application of electrical stimulation to the aconitine-treated area (square wave pulses of 5 m. sec. duration; 20 volts; 10/min; for 10 sec.) The flutter developing after removal of the clamp was confined to the aconitine-treated area, elsewhere sinus rhythm continued. A typical experiment is illustrated in Fig. 13. It is very unlikely that the failure of the arrhythmia to develop in the clamped area could be due to anoxia since Resnik (1925), Smith & Wilson, (1944), and Horlick & Surtshin (1949) showed that anoxia, in fact, favoured the development of auricular arrhythmias. Further, when the clamp was applied during fully developed flutter, the arrhythmia continued in the clamped part for over 10 minutes.

The results show that the initiation of aconitine-induced arrhythmia is dependent upon the entry of the sino-auricular impulses into the aconitinised area. Once flutter was fully developed, it was independent of sino-auricular impulses and persisted in the isolated appendage if the clamp was reapplied.

Role of sino-auricular impulses in the re-appearance of aconitine-induced auricular flutter after its arrest by focal cooling

Eight dogs were used in the cooling experiments. A typical experiment is illustrated in Fig. 14. When the aconitine-treated area was cooled, the flutter rate slowed down and finally disappeared, but re-appeared within few seconds when the cooling was discontinued. This procedure was repeated at least three times in each experiment and then the procedure was modified to assess the role of sino-auricular impulses in the re-appearance of the arrhythmia.

Focal cooling was done as before until the arrhythmia disappeared and sinus rhythm returned. The aconitinised area was clamped to prevent the entry of sinus impulses into the treated area and cooling was stopped. The arrhythmia did not return for the duration of the clamp (up to 10 min.) The clamp was then removed and the arrhythmia returned within 3 min. and was confined to the aconitine-treated area, elsewhere sinus rhythm continued. Focal cooling of the sino-auricular node had no effect on the flutter rate in the isolated area.

Focal cooling of the isolated aconitinised area slowed and finally abolished the arrhythmia. Stoppage of cooling was followed by the return of arrhythmia within few sec. However, if the aconitinised area was reclamped before stopping the focal cooling, the arrhythmia did not return for the duration of the clamp. The arrhythmia returned within 3 min. after the clamp was

removed. A typical experiment of this group is illustrated in Fig. 15.

The results show that while fully developed flutter is independent of sino-auricular impulses, its re-appearance after its arrest by focal cooling is once again dependent upon the entry of sinus impulses into the aconitine-treated area.

(iv) Cholinergic influences in aconitine-induced auricular flutter and fibrillation

The role of cholinergic influences was studied in two ways (a) by increasing the cholinergic influences through vagal stimulation or acetylcholine, (b) by antagonising the existing cholinergic influence with atropine or by blocking the synthesis of acetylcholine by hemicholinium.

Effect of vagal stimulation on established auricular flutter

A total of 22 observations were made in 8 dogs. Vagal stimulation converted flutter into fibrillation in 16 experiments, auricular flutter at the pre-stimulation rate returned in all the cases, within 5 sec. The highest rate of fibrillation recorded in this series was 1620/min. In majority of experiments the rate varied between 720 - 1440/min. In 6 experiments, vagal stimulation increased the flutter rate (up to 600/min), but did not produce fibrillation.

A typical experiment is illustrated in Fig. 16. Under vagal stimulation both the auricles fibrillated simultaneously. The stimulation of the right or of the left vagus nerve produced

identical results, except that the latter produced a higher degree of auriculo-ventricular block. This fibrillatory activity of vagal stimulation was completely blocked by 0.1 mg./kg. of atropine sulphate injected intravenously.

Effect of injected acetylcholine on auricular flutter

Acetylcholine chloride (200 - 1000 µg. in 1 ml. of physiological saline, injected in 5 sec.) injected intravenously, produced an effect qualitatively similar to that of vagal stimulation but quantitatively its effect was much more pronounced. A total of 30 observations were made in 14 dogs. Auricular fibrillation resulted in all the experiments. The highest rate of fibrillation recorded in this series was 3960/min. In the majority of experiments, the rate varied between 1800 - 2760/min.

When acetylcholine was injected intravenously (into femoral vein or into superior vena cava), auricular dissociation was seen in that the right auricle fibrillated earlier than the left. The latter did not fibrillate until 5 - 7 sec. after the former. A typical experiment is illustrated in Fig. 17.

Since no dissociation was observed after vagal stimulation, it was possible that this dissociation could be due to earlier arrival of acetylcholine into the right auricle than in the left. To test this possibility, acetylcholine was injected directly into the left ventricle, so that it reached simultaneously in the two auricles via their arterial blood supply, the two

auricles now fibrillated simultaneously, as illustrated in Fig. 18. Both Fig. 17 and Fig. 18 were recorded from the same animal, auricular dissociation is present in the former but not in the latter.

Following the intravenous injection of acetylcholine, there was a latent period of 6 - 13 sec., before the effect on auricular flutter was noticeable. Following the left ventricular injection, the latent period was much shorter and varied from 2 - 5 sec. This fibrillatory activity of acetylcholine was completely blocked by 0.1 mg./kg. atropine sulphate injected intravenously.

Effect of topical application of acetylcholine on auricular flutter

The effect of topical application of acetylcholine on aconitine-induced auricular flutter was studied in 7 dogs. Topical application of 5% solution of acetylcholine with a cotton wool pledget, to the right or to the left auricle also showed the phenomenon of auricular dissociation. A typical experiment is illustrated in Fig. 19. The application of acetylcholine to the tip of the right auricular appendage showed that the dissociation was both inter-auricular and intra-auricular. The fibrillation was recorded at the right auricular electrode only, the sino-auricular and left auricular electrodes recorded auricular flutter. The occurrence of fibrillation in the left auricle after topical

application of acetylcholine, while the right auricle containing the aconitine-induced ectopic focus continued to flutter is a finding of considerable interest since it shows that the mechanism of flutter and fibrillation is unlikely to be the same.

The latent period before localised fibrillation appeared varied from 30 - 60 sec., and the effect of acetylcholine completely disappeared in less than 10 min., with the return of auricular flutter at the control rate.

Differential effect of acetylcholine on sinus rhythm and on aconitine-induced auricular flutter

A total of 12 experiments were done in 6 dogs. Aconitine was applied to the tip of the right auricular appendage and when flutter developed, this area was isolated from the body of the right auricle by a clamp for 1 min. After removal of the clamp, the aconitine-treated area showed flutter, while sinus rhythm returned elsewhere. Acetylcholine was given intravenously and its effect on the two rhythms was observed. Acetylcholine increased the flutter rate and fibrillation resulted in the isolated area, but the rate of sinus rhythm was markedly slowed. A typical experiment is illustrated in Fig. 20. Aconitine-treated area was beating at the rate of 395/min., elsewhere sinus rhythm was present at the rate of 140/ min. Administration of 1 mg. of acetylcholine (in 1 ml. of

physiological saline in 5 sec.) intravenously increased the flutter rate to 840/min., while the sinus rate was decreased to 62/min.

Scherf et al. (1953b) offered an explanation to account for the differential effect of vagal stimulation. They suggested that acetylcholine exerted an inhibitory effect on slower rhythms (sinus rhythm) but stimulated the faster ones (ectopic rhythm). This possibility was tested in five experiments. Hemicholinium was administered intravenously to block the acetylcholine synthesis. This decreased the rate of ectopic rhythm but increased the rate of sinus rhythm, by blocking of the inhibitory vagal effect. A typical experiment is illustrated in Fig. 27., recorded from the same animal as Fig. 26., one hour after the administration of hemicholinium. The flutter rate has decreased to 256/min. from 395/min., while the sinus rate has increased to 225/min. from 140/min. Intravenous administration of 1 mg. acetylcholine still increased the flutter rate, though the rise was not as marked as that before hemicholinium. The sinus rate was slowed as before. This experiment clearly shows that the differential effect of acetylcholine was not due to the difference in the rate of the rhythms involved, since the difference in the rate of the two rhythms was only 31 beats/min., after the administration of hemicholinium.

Effect of atropine on established auricular flutter

In 6 dogs auricular flutter was produced by aconitine and atropine sulphate 1.0 mg./kg. was injected intravenously (in 20 ml. of physiological saline, slowly over a period of 5 min.) to block the cholinergic influences. The main effect observed was a marked decrease in flutter rate, but the rhythm continued to be ectopic. The electrocardiographic tracing of a typical experiment is illustrated in Fig. 22. In this experiment the control flutter rate was 410/min. After atropine injection, the rate decreased to 300/min. When the aconitine-treated area was isolated from the rest of the auricle by a clamp it continued to flutter at the rate of 272/min., while the rest of the auricle revealed sinus tachycardia at the rate of 180/min.

The results of all the six experiments are presented graphically in Fig. 24. The mean control flutter rate in these experiments was 444 $\pm$ S.E. 14.00/min., the slowest rate recorded after atropine was 256 $\pm$ S.E. 6.20/min. The peak effect was seen immediately after the injection of atropine, the rate then increased gradually to 310 $\pm$ S.E. 12.00/min. in an hour. This shows that at least part of the atropine-induced decrease in rate could be due to the direct depressant effect of atropine on the refractory period, and was not due to its anti-acetylcholine effect.

Similar results were obtained in another experiment illustrated in Fig. 23. In this experiment the aconitine-treated area was isolated from the rest of the auricle by a clamp before the administration of atropine. Atropine injection decreased the flutter rate, while the sinus rate was increased.

Effect of atropine pre-treatment on aconitine-induced auricular flutter

Six dogs were treated with atropine sulphate 1.0 mg./kg. intravenously, and aconitine was applied to the right auricular appendage 30 min. later. Aconitine regularly produced auricular flutter in the atropinised animals but the flutter rates were slower in the treated animals (257 - 360/min.) The slow rate flutter could be easily distinguished from the atropine-induced sinus tachycardia by isolating the aconitinised area by a clamp. The slow rate flutter persisted in the isolated area. The electro-cardiographic records of a typical experiment are presented in Fig. 25.

The results of all the 6 experiments are presented graphically in Fig. 26. The mean flutter rate in these experiments was 274 $\pm$ S.E.18.00/min. Clamping of the right auricular appendage (aconitinised area) revealed that the rate of atropine-induced sinus tachycardia was only 189 $\pm$ S.E.11.16/min.

Aconitine did not produce auricular fibrillation after atropine. In three experiments aconitine application to the

right auricle resulted in the development of auricular fibrillation. Atropine 0.1 mg./kg. injected intravenously promptly converted the fibrillation into flutter.

Effect of hemicholinium on aconitine-induced auricular flutter

In 5 dogs aconitine-induced flutter was produced and control flutter rates recorded. Hemicholinium (10 mg./kg., 0.5% solution in physiological saline, over 10 min.) was then injected intravenously to block the synthesis of acetylcholine. This produced a marked decrease in flutter rate. The peak effect was noted 1 hour after the injection of the drug.

The results obtained in all the 5 experiments are presented graphically in Fig. 27. The mean flutter rate in the control experiments was 457 $\pm$ S.E. 27.10/min., the lowest flutter rate recorded after hemicholinium was 319 $\pm$ S.E. 11.60/min. These results confirm the findings obtained with atropine.

(v) Adrenergic factors in aconitine-induced auricular flutter and fibrillation

The role of adrenergic influences was studied in two ways (a) by increasing the adrenergic influences through sympathetic stimulation or injection of adrenaline or noradrenaline, (b) by depletion of cardiac stores of catecholamines by reserpine pre-treatment.

Effect of adrenaline and noradrenaline on sinus rhythm and aconitine-induced auricular flutter

Twelve observations were made for each drug in 6 dogs. The results of a typical experiment are presented in Fig. 28. The aconitinised area was isolated from the rest of the auricle for 1 min. Flutter rate in the isolated part was 360/min., elsewhere sinus rhythm existed at the rate of 140/min. Both the drugs increased the rate of auricular flutter and of sinus rhythm. This is in contrast to the differential effect of acetylcholine. The effect of the two drugs was similar, except that after adrenaline injection, the effect reached its peak at 40 sec., the rate then fell gradually and a secondary rise occurred at about 100 sec. In 4 experiments an unusual response was seen (shown by dotted line), the fall in flutter rate after the peak effect was very marked and it fell below that of sino-auricular rate for a few seconds and then recovered gradually to the control value. The rate increasing effect of adrenaline was slightly more marked than that of noradrenaline. The effect completely disappeared in 3 min. There was a latent period of 8 - 14 sec., before the effect of these drugs could be noticed. In 5 experiments (3 adrenaline, 2 noradrenaline) auricular fibrillation resulted, flutter at the control rate returned as the drug effect disappeared.

Following atropine (0.1 mg./kg. i/v), adrenaline and noradrenaline still increased the flutter rate, but did not produce fibrillation.

Effect of sympathetic stimulation on aconitine-induced auricular flutter

A total of 20 experiments were done in 5 dogs. Sympathetic stimulation produced an increase in flutter rate (20 - 140 beats/min.) in all the experiments. In 6 experiments fibrillation resulted, flutter at the control rate returned 1 min. after the stimulation was discontinued. The rate increasing effect of sympathetic stimulation was not blocked by atropine (0.1 mg./kg. i/v), fibrillation, however, did not result after atropine.

Effect of catecholamines depletion on the production of aconitine-induced flutter and fibrillation

The cardiac catecholamines were depleted by reserpine treatment and aconitine-induced arrhythmia was produced 48 hours after the last dose of reserpine. A total of 5 experiments were done. Aconitine produced fibrillation in all the cases which lasted for over one hour. Bilateral vagotomy was followed by a decrease in fibrillation rate and within 30 min. the fibrillation was converted to flutter. Vagal stimulation again converted flutter into fibrillation for a few minutes. The flutter rate after vagotomy, varied between 450 - 514/min. Administration of hemicholinium 10 mg./kg. intravenously also converted aconitine-induced fibrillation into slow rate flutter (272 - 360/min).

(vi) Effect of cardiac denervation

In 5 experiments, acute denervation of the heart did not effect the production of auricular flutter by aconitine. There was no noticeable effect on the flutter rate and on the duration of the arrhythmia, as compared with the control experiments.

(vii) Dual action of aconitine on the isolated Guinea-pig auricles and isolated Guinea-pig ileum

Since aconitine-induced auricular flutter persisted in the atropinised animals, it was considered worthwhile to study the acetylcholine-aconitine interaction on the isolated guinea-pig auricles.

Five isolated guinea-pig auricle preparations were used. In smaller doses 1 - 5 µg. in a 20 ml. bath, aconitine produced a slight bradycardia but the rate decreasing effect of acetylcholine was not affected. At a dose level of 10 µg. it did not produce any slowing per se, the rate decreasing effect of acetylcholine was, however, significantly inhibited (35.5%). Unfortunately, the effect of higher doses of aconitine could not be studied in this preparation because of the rapid development of ectopic tachycardia. Further experimentation was, therefore, done on the isolated guinea-pig ileum.

Aconitine 200 µg. induced a contraction of the gut and relaxation followed while the drug was still in the bath fluid (Fig. 29), the acetylcholine response was partially blocked (26.3%).

The bath fluid was changed and acetylcholine response returned to normal. The aconitine-induced contraction showed a quick development of tachyphylaxis. Frequently, a second dose of aconitine failed to induce a contraction and in most of the experiments a rest interval of 30 - 60 min. was needed before the response could be elicited again. The aconitine-induced contraction was cholinergic in nature since it was completely blocked by atropine (Fig. 30). The aconitine induced contraction could still be elicited after the ganglia were blocked by repeated doses of nicotine. During aconitine tachyphylaxis, the effect of smaller doses of nicotine was blocked but larger doses of nicotine were still effective (Fig. 31). The blockade of smaller doses of nicotine could be due to the anti-acetylcholine action of aconitine at the peripheral nerve endings, rather than ganglionic blockade.

The log dose-response curve of acetylcholine-aconitine antagonism is presented in Fig. 32. The antagonism was of surmountable type, since larger doses of acetylcholine could overcome the block. Further, the presence of an anticholinesterase in the bath fluid, shifted the curve to the left (Fig. 33).

The contraction induced by eserine and pilocarpine was also gradually blocked by aconitine (Fig. 34). The barium chloride-induced contracture was, however, not affected by aconitine (Fig. 35).

These findings show that aconitine has a dual effect on the guinea-pig ileum. It produces a contraction which is cholinergic in nature and it also produces a competitive blockade of acetylcholine. The site of action of aconitine appears to be peripheral, most probably on the acetylcholine receptors.

(viii) Summary

1. The genesis of the aconitine-induced flutter is dependent on the entry of the sino-auricular impulses into the aconitinised tissue. In other words, a beating auricle is essential for the production of the arrhythmia. When the flutter is fully established it is independent of sinus impulses but when arrested by focal cooling its return is once again dependent upon the entry of the sinus impulses into the aconitinised tissue.

2. Premature systoles with fixed coupling (due to re-entrant excitation) precede the development of flutter. The form of the ectopic beats remains unchanged when premature systoles pass into flutter. Also the auricular rate is irregularly irregular in early stages of the arrhythmia.

3. Cholinergic factors increase the flutter rate and frequently the flutter is converted into fibrillation. Flutter at the control rate returns when the cholinergic influence disappears. This fibrillatory response is completely blocked by atropine. Transient auricular dissociation is seen after

intravenous injection of acetylcholine but not after the direct intraventricular injection or following vagal stimulation. Acetylcholine exerts a differential effect on the sinus rhythm and flutter. The former is inhibited while the latter is stimulated. This is due to the difference in the mechanism of impulse formation in the two rhythms and not due to the difference in their rate.

4. Cholinergic influences are not concerned in the development or maintenance of auricular flutter. Aconitine regularly produced auricular flutter in the atropine or hemicholinium treated animals. Atropine and hemicholinium also failed to terminate established auricular flutter, the only effect observed is a decrease in flutter rate. The slow rate flutter is easily distinguishable from the sinus tachycardia caused by atropine in the direct auricular leads but not in the limb leads.

5. Adrenergic influences also increase the flutter rate, frequently the flutter is converted into fibrillation. Atropine antagonises the fibrillatory response completely, the rate increasing effect is decreased but not abolished. In some experiments following adrenaline-induced increase in flutter rate, the rate transiently decreased to below the control value and then recovered gradually. This effect is not seen after noradrenaline or after sympathetic stimulation.

6. Aconitine produces fibrillation after the depletion of cardiac catecholamines by reserpine pre-treatment. Bilateral

vagotomy or hemicholinium convert fibrillation into flutter. Acute denervation of the heart, however, produced no significant effect on the production of aconitine-induced arrhythmia.

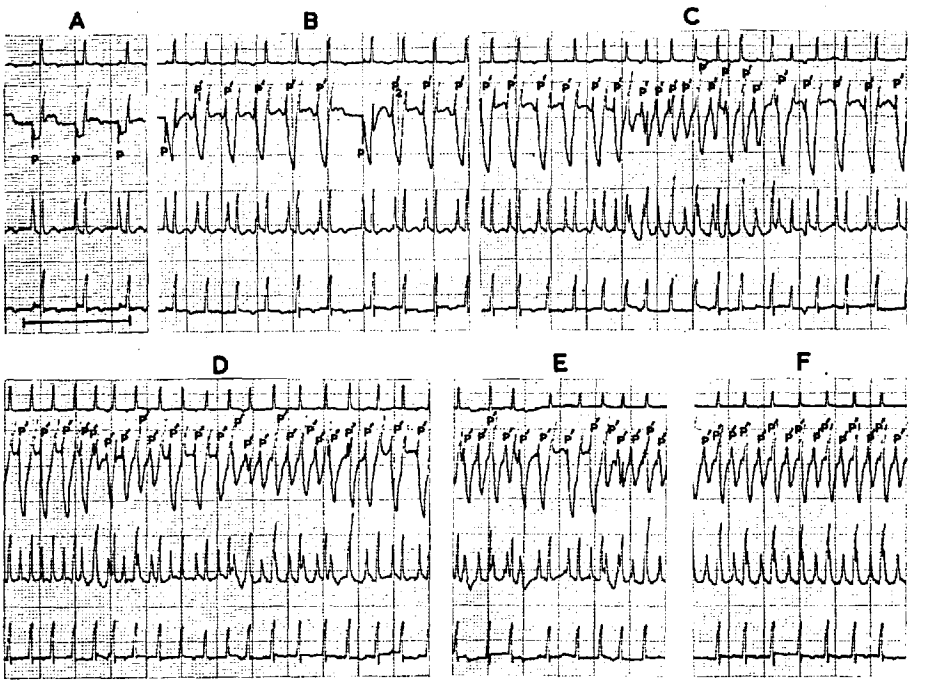


FIG. 8

Fig. 8

Stages in the development of aconitine-induced auricular flutter

From top to bottom, esophageal lead, electrograms from the right auricular appendage, from the region of the sino-auricular node and conventional bipolar lead II.

P = normal sinus beats.

P' = ectopic beats.

(A) Control, heart rate is 154/min.

(B) 68 sec., after the topical application of aconitine nitrate to the right auricular appendage. The first sinus beat is followed by five ectopic beats, then there is a single sinus beat which is followed by a persistent auricular tachycardia. Note that the first beat of the tachycardial episodes (labelled 1 & 2) shows a fixed coupling (0.25 sec.) to the preceding sinus beats.

(C) 80 sec., after aconitine, slow rate auricular tachycardia (212 - 225/min.) led to fast beats (450 - 480/min.) and then returned to the original rate.

(D) 86 sec., after aconitine, slow rate tachycardia (285 - 300/min.) led to two episodes of fast beats (450/min.) The auricular rate is irregularly irregular.

(E) 92 sec., after aconitine, auricular flutter at 450/min. is present. Three slow beats appear and their rate is irregular and then persistent flutter supervened but auricular rate is still somewhat irregular.

(F) 5 min., after aconitine, auricular flutter at the rate of 484/min. is present and the rate is quite regular. Note that the contours of the slow beats and fast rate flutter are very similar to one another.

Time scale = 1 sec.

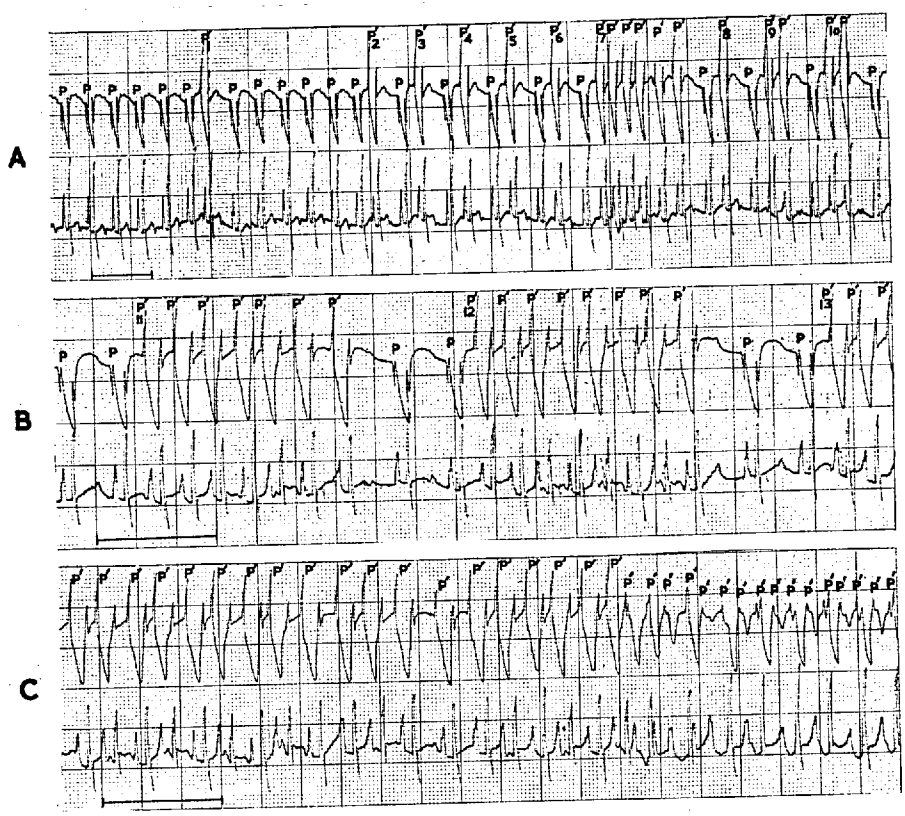


FIG. 9

Fig. 9

Stages in the development of aconitine-induced auricular flutter

Upper trace is electrogram from the tip of the right auricular appendage, the lower trace is conventional bipolar lead II.

P = normal sinus beats.

P' = ectopic beats.

(A) 72 sec., after the topical application of aconitine nitrate to the right auricular appendage. There occurs a single premature beat (marked 1) and later 5 more premature beats occur (marked 2 - 6) in a regular bigeminal pattern. The premature beat (marked 7) led to the development of a short run of auricular tachycardia, which is irregularly irregular in rate. Premature systoles (marked 8 - 10) show bigeminy and trigeminy, respectively.

(B) 88 sec., after aconitine, the speed has been doubled. Ectopic beats now occur in short runs and their rate is irregularly irregular. The intervening sinus beats show a regular rate of 134/min. Note that all the premature beats and the first beat of short runs of tachycardia (marked 1 - 13) show fixed coupling to the preceding sinus beat (0.26 sec.)

(C) 112 sec., after aconitine, persistent auricular tachycardia is present but the rate is still irregular. Towards the end of the excerpt, the rate is 430/min. and it is fairly regular. The contour of the ectopic beats is very much like the isolated premature beats in excerpt A.

Time scale = 1 sec.

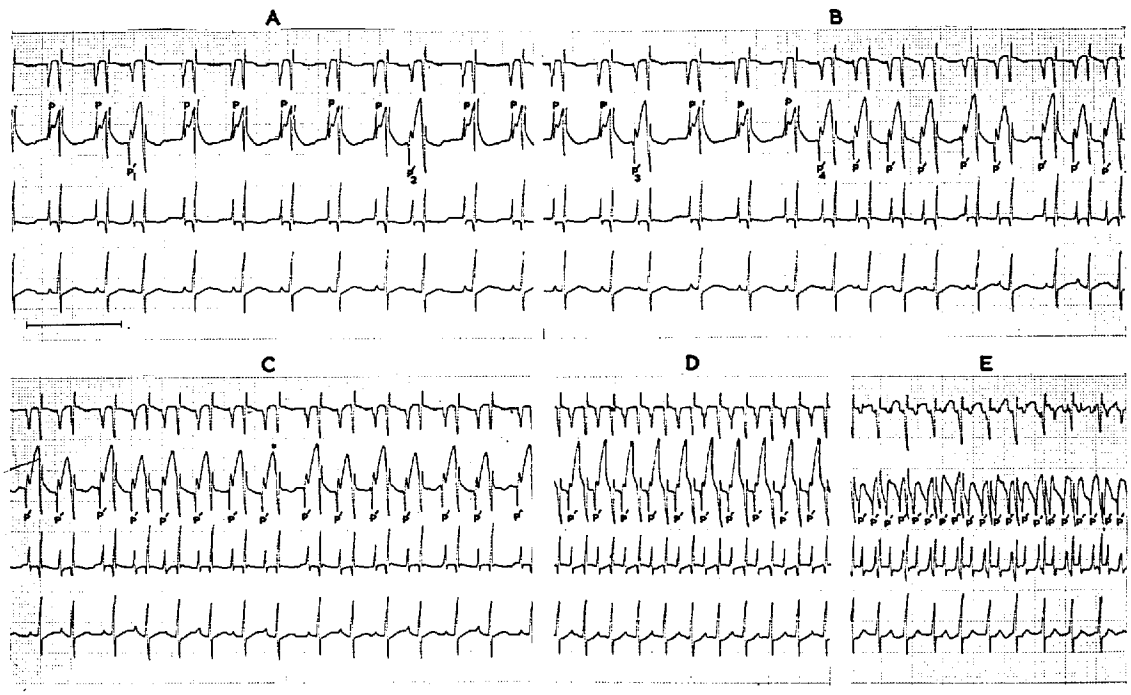


FIG. 10

Fig. 10

Stages in the development of aconitine-induced auricular flutter

From top to bottom, electrograms from the region of the sino-auricular node, tip of the right auricular appendage, tip of the left auricular appendage and conventional bipolar lead II.

P = normal sinus beats.

P' = ectopic beats.

(A) 48 sec., after the topical application of aconitine nitrate to the tip of the right auricular appendage. Two premature systoles (marked 1 & 2) appear. Both show a fixed coupling to preceding sinus beat (0.36 sec.)

(B) 54 sec., after the aconitine application, there is a single premature systole (marked 3) with the same fixed coupling (0.36 sec.) as 1 & 2, and then a slow tachycardia is established. The first beat of this tachycardial episode (marked 4) has the same fixed coupling as the three preceding premature beats and is of exactly of the same shape and amplitude. The auricular rate is irregularly irregular.

(C) 68 sec., after aconitine, slow rate tachycardia is present, the rate is still irregular and the shape and amplitude of the beats is very much like the isolated premature systoles, slight variations in their contour and amplitude are, however, seen from beat to beat.

(D) 80 sec., after aconitine, the tachycardia rate is 200/min., and is quite regular and the beats are of the same shape and amplitude.

(E) 96 sec., after aconitine, regular auricular flutter at the rate of 402/min., is present. The contour of the flutter waves at the right auricular electrode is still very much like the premature beats in excerpt A & B.

Time scale = 1 sec.

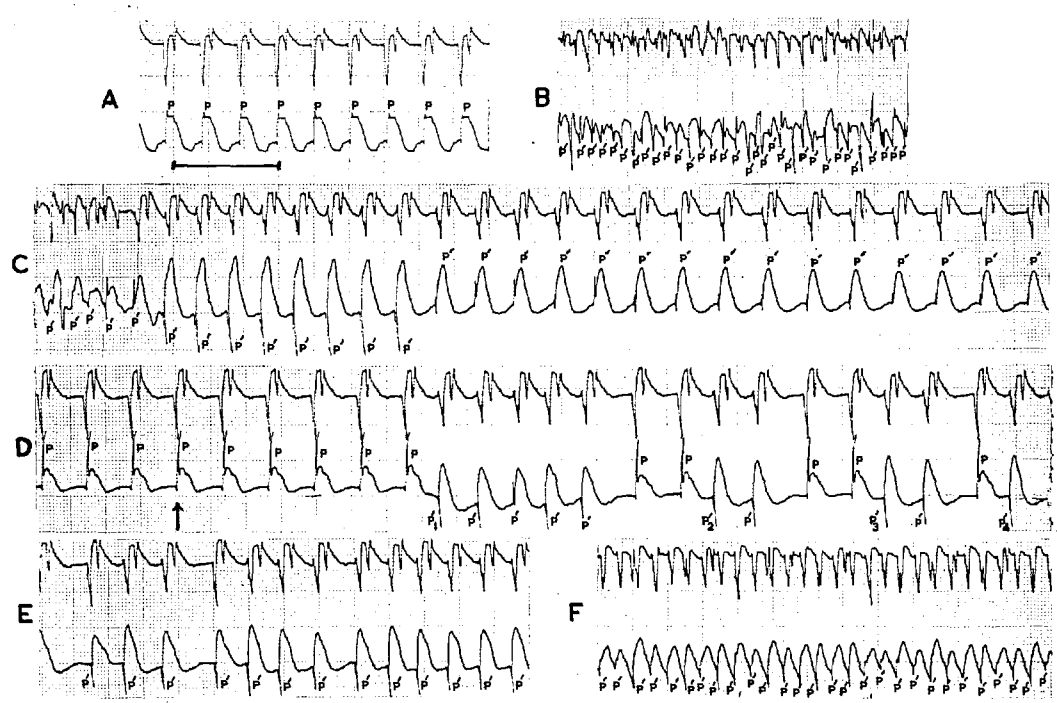


FIG. 11

Fig. 11

Illustrates the gradual re-appearance of aconitine-induced auricular flutter after its arrest by focal cooling

Upper trace, electrogram from the region of sino-auricular node. Lower trace, electrogram from the tip of the right auricular appendage.

P = normal sinus impulses.

P' = flutter beats.

(A) Control, heart rate is 176/min.

(B) 10 min. after the topical application of aconitine to the right auricular appendage. Flutter rate is 560/min.

(C) 4 sec. after the start of focal cooling, the flutter rate has decreased markedly but is still ectopic, as seen from the contours of the beats recorded from the sinus node electrode.

(D) 14 sec. after start of cooling, sinus rhythm has been established. The cooling was discontinued at the arrow and within 2 sec., ectopic beats reappear in a short run (5 beats), the next two beats are of normal sino-auricular origin, then two ectopic beats are followed by two sinus beats. This is followed by two ectopic beats and a sinus beat and finally ectopic rhythm is fully established. The first ectopic beat following the sinus beats (labelled 1 - 4) show fixed coupling to preceding sinus beats (0.30 sec.)

(E) This is continuation of excerpt D, the ectopic rate is slow and is irregular.

(F) 2 min. after discontinuation of focal cooling. The flutter rate is 410/min., and is regular.

Time scale = 1 sec.

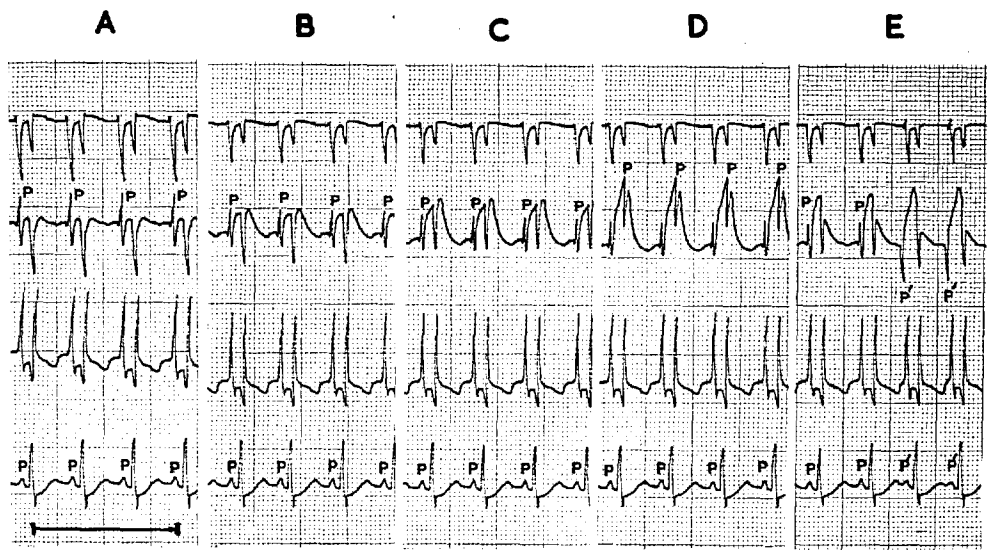


FIG. 12

Fig. 12

Illustrates the development of monophasic action potentials in the aconitine-treated area of the auricle

From top to bottom, electrograms from the region of the sino-auricular node, tip of the right auricular appendage, tip of the left auricular appendage, and conventional bipolar lead II.

P = normal sinus beats.

P' = ectopic beats.

(A) Control, heart rate is 168/min.

(B) 6 sec. after the topical application of aconitine at the root of the right auricular electrode. Small monophasic action potentials (MAP) are present.

(C) 14 sec. after aconitine, well marked MAP seen. Rate is still 168/min.

(D) 24 sec. after aconitine, MAP are fully developed, rate is still 168/min.

(E) 68 sec. after aconitine, the amplitude of MAP has slightly decreased. Note the development of ectopic beats. The wave form is reversed at the right auricular electrode, but not in lead II.

Time scale = 1 sec.

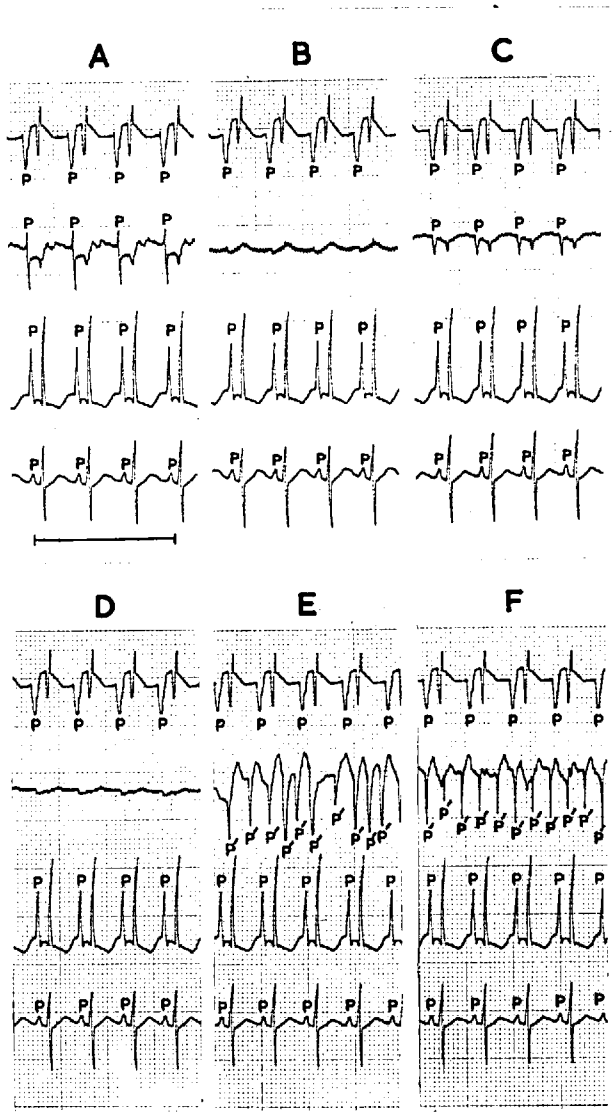


FIG. 13

Fig. 13

Role of sino-auricular impulses in the initiation of aconitine-induced auricular flutter

From top to bottom, electrograms from the region of sino-auricular node, tip of the right auricular appendage, tip of the left auricular appendage, and conventional bipolar lead II.

P = normal sinus beats.

P' = flutter beats.

(A) Control, heart rate is 184/min.

(B) The right auricular appendage was clamped and the sino-auricular impulses are not entering the isolated area.

(C) The clamp was released after 5 min. The sino-auricular impulses are once again being recorded in the right auricular appendage.

(D) The clamp was reapplied and aconitine nitrate applied topically to the isolated area. The arrhythmia did not develop in 5 min. Normally it develops in less than two minutes.

(E) The clamp was removed and flutter appeared in the isolated area in 15 sec., elsewhere sinus rhythm exists. The flutter rate varies between 400 - 600/min. and the rate is irregular.

(F) 5 min. after the removal of the clamp, flutter rate has stabilised at 484/min., and is fairly regular.

Time scale = 1 sec.

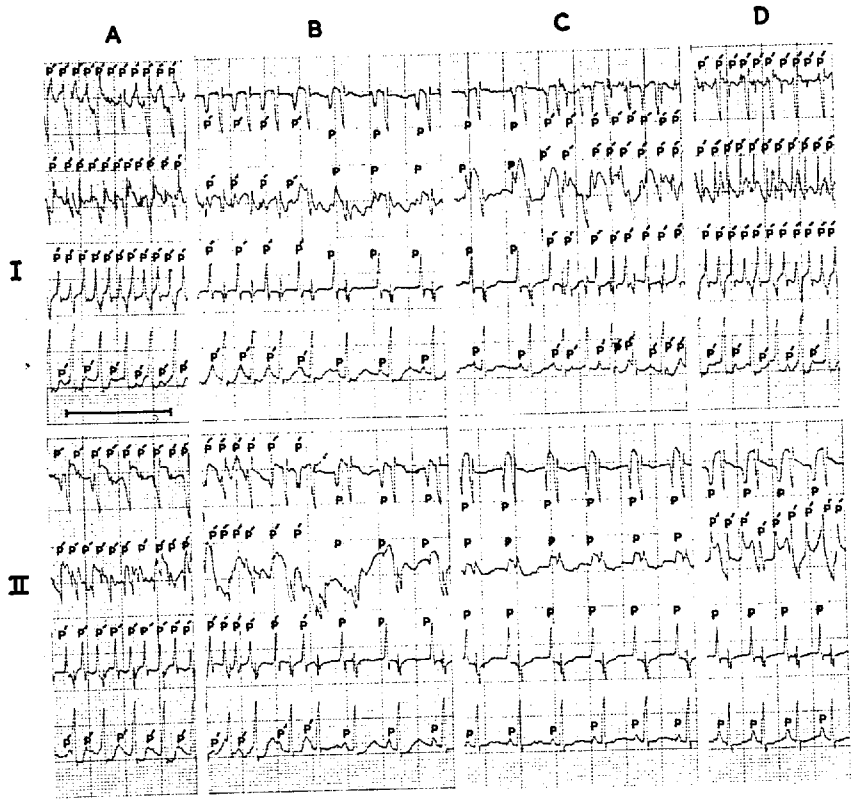


FIG.14

Fig. 14

Effect of focal cooling on aconitine-induced auricular flutter

From top to bottom, electrograms from the region of the sino-auricular node, tip of the right auricular appendage, tip of the left auricular appendage, and conventional bipolar lead II.

P = normal sinus beats.

P' = flutter beats, some of the flutter beats are incorporated in the QRS complexes and are not labelled.

Panel I

(A) Control flutter rate is 480/min., 10 min after the topical application of aconitine to the tip of the right auricular appendage.

(B) 2 sec. after the start of focal cooling of the aconitine-treated area. The flutter rate slowed down and finally disappeared, sinus rhythm at the rate of 152/min. returned.

(C) 1 sec. after discontinuation of focal cooling. Note the re-appearance of flutter.

(D) 5 sec. after stopping the cooling, flutter at the control rate has returned.

Panel II

(A) Control flutter rate in the same animal 20 min. after the aconitine application, rate is 464/min.

(B) 3 sec. after the start of focal cooling, the flutter has disappeared and sinus rhythm at the rate of 145/min. returned.

(C) The aconitine-treated area was clamped to prevent the entry of sino-auricular impulses into the aconitinised area, and the cooling was stopped. This excerpt has been recorded 1 min. after the cooling was stopped. Note that flutter has not returned.

(D) 30 sec. after removal of the clamp, the flutter has returned at the rate of 410/min. in the aconitinised area. Elsewhere sinus rhythm at the rate of 184/min. is present.

Time scale = 1 sec.

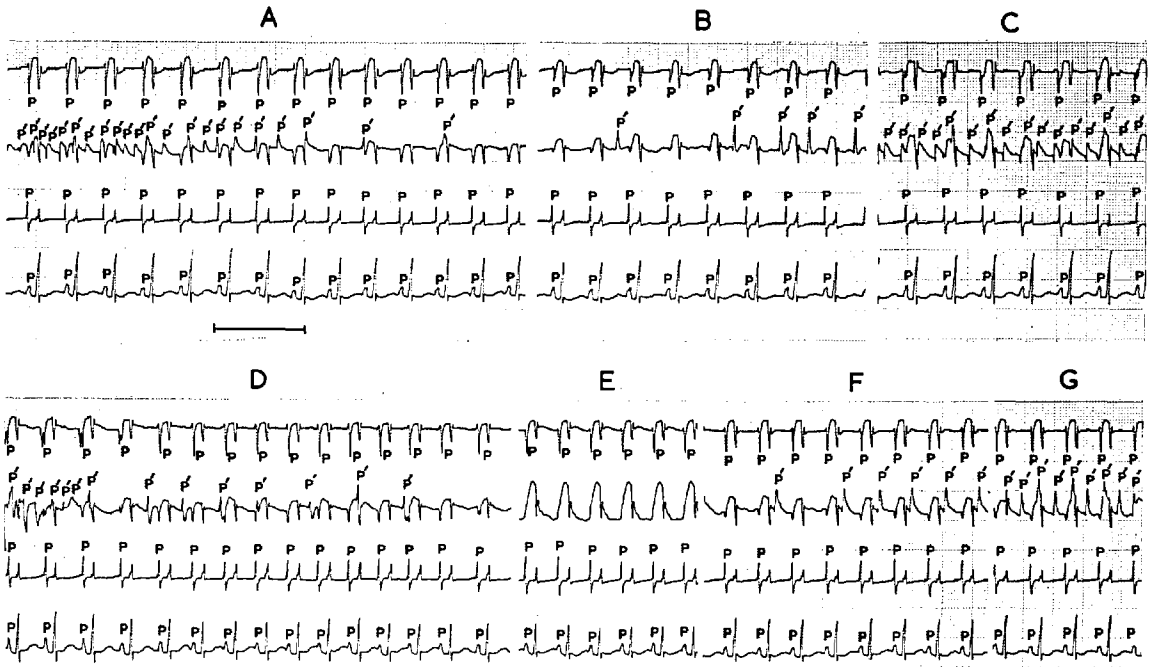


FIG. 15

Fig. 15

Role of sino-auricular impulses in the re-appearance of aconitine-induced auricular flutter following its arrest by focal cooling

From top to bottom, electrograms from the region of sino-auricular node, tip of the right auricular appendage, tip of the left auricular appendage, and conventional bipolar lead II.

P = normal sinus beats.

P' = flutter beats.

(A) Shows the presence of aconitine induced auricular flutter in the functionally isolated right auricular appendage. Focal cooling slowed and eventually arrested the arrhythmia.

(B) 2 sec. after the discontinuation of focal cooling, the ectopic rhythm is gradually re-appearing. The first two ectopic beats show fixed coupling (0.26 sec.) to the preceding sinus beats.

(C) 5 sec. after stoppage of cooling, the arrhythmia has fully returned.

(D) focal cooling done once again, the arrhythmia slowed and finally disappeared.

(E) The clamp was re-applied to prevent the entry of sinus impulses into the aconitine-treated area and focal cooling was stopped. This excerpt was recorded 1 min. after stopping the cooling. The arrythmia has not returned.

(F) 5 sec. after removal of the clamp, the ectopic beats re-appear and show fixed coupling (0.20 sec.) to the preceding sinus beats.

(G) 30 sec. after removal of the clamp. The arrhythmia is fully established.

Time scale = 1 sec.

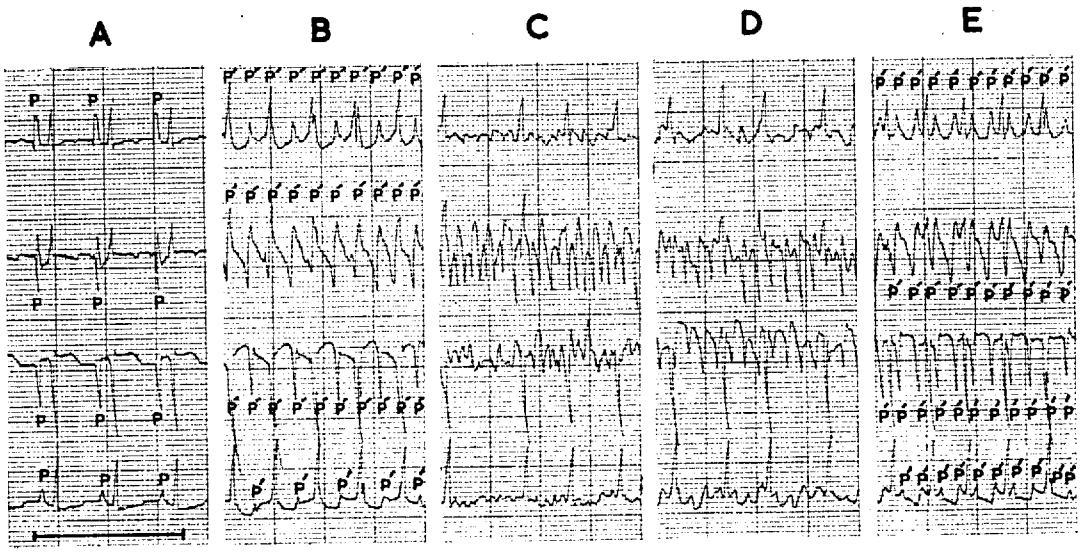


FIG. 16

Fig. 16

Effect of vagal stimulation on aconitine-induced auricular flutter

From top to bottom, electrograms from the region of sino-auricular node, tip of the right auricular appendage, tip of the left auricular appendage, and conventional bipolar lead II.

P = normal sinus beats.

P' = flutter beats, some of the flutter beats are incorporated in the QRS complexes and are not labelled.

(A) Control, heart rate is 150/min.

(B) 10 min. after the topical application of aconitine to the right auricular appendage, flutter at the rate of 424/min. is present.

(C) Immediately after the stimulation of the right vagus nerve (square wave pulses of 0.5 m. sec. duration; 20 volts; frequency 20/sec.) for 10 sec. Auricular fibrillation is present in both the auricles, A-V block has been enhanced. The fibrillation rate varies between 720 - 1260/min.

(D) 3 sec. after the end of vagal stimulation, fibrillation rate has decreased, the rate varies between 600 - 740/min.

(E) 6 sec. after the end of vagal stimulation, auricular flutter at the control rate has returned.

Time scale = 1 sec.

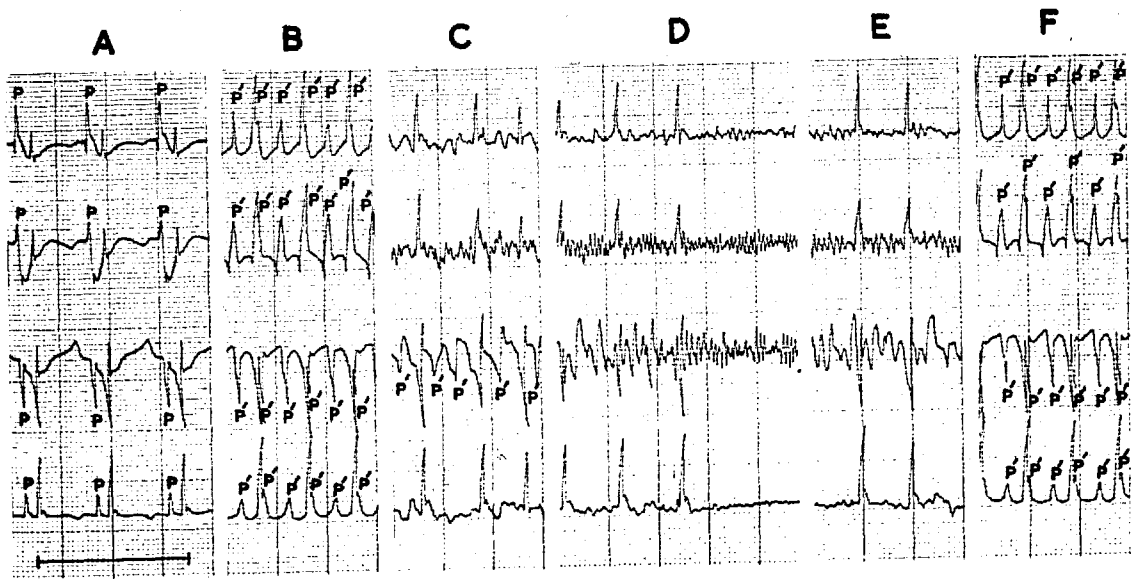


FIG.17

Fig. 17

Effect of intravenous acetylcholine on the aconitine-induced auricular flutter

From top to bottom, electrograms from the region of sino-auricular node, tip of the right auricular appendage, tip of the left auricular appendage, and conventional bipolar lead II.

P = normal sinus beats.

P' = flutter beats.

(A) Control, heart rate is 132/min.

(B) 20 min. after the topical application of aconitine to the right auricle, flutter rate is 400/min., with 2:1 A-V block.

(C) 8 sec. after the intravenous injection of 500 µg. acetylcholine chloride (in 1 ml. of physiological saline in 5 sec.) Note the auricular dissociation. The right auricle is fibrillating at the rate of 1820/min., while the left auricle is still fluttering at the rate of 400/min.

(D) 12 sec. after acetylcholine, the left auricle has also passed into fibrillation. The fibrillation rate in the right auricle is somewhat higher (2340/min.) than the left auricle (1980/min).

(E) 26 sec. after acetylcholine, the fibrillation rate has decreased in both the auricles.

(F) 46 sec. after acetylcholine, auricular flutter at the control rate has returned.

Both Fig. 17 and 18 are from the same animal.

Time scale = 1 sec.

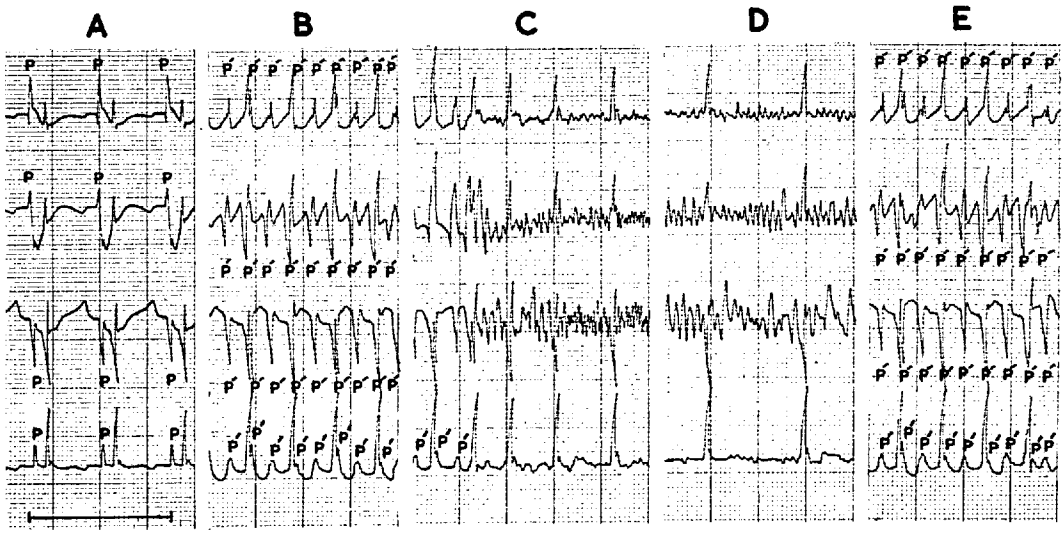


FIG. 18

Fig. 18

Effect of intra-arterial injection of acetylcholine on the aconitine-induced auricular flutter

From top to bottom, electrograms from the region of sino-auricular node, tip of the right auricular appendage, tip of the left auricular appendage, and conventional bipolar lead II.

P = normal sinus beats.

P' = flutter beats.

(A) Control, heart rate is 134/min.

(B) 10 min. after the topical application of aconitine to the right auricular appendage. The flutter rate is 400/min., with 2:1 A-V block.

(C) 3 sec. after the injection of 500 µg. of acetylcholine chloride directly into the left ventricle. Note the simultaneous development of auricular fibrillation in the two auricles. Auricular dissociation did not occur. The maximum fibrillation rate reached was 2760/min.

(D) 22 sec. after the acetylcholine injection, the fibrillation rate has slowed down.

(E) 54 sec. after the acetylcholine injection. Flutter at the control rate has returned.

Both Fig. 17 and Fig. 18 are from the same animal.

Time scale = 1 sec.

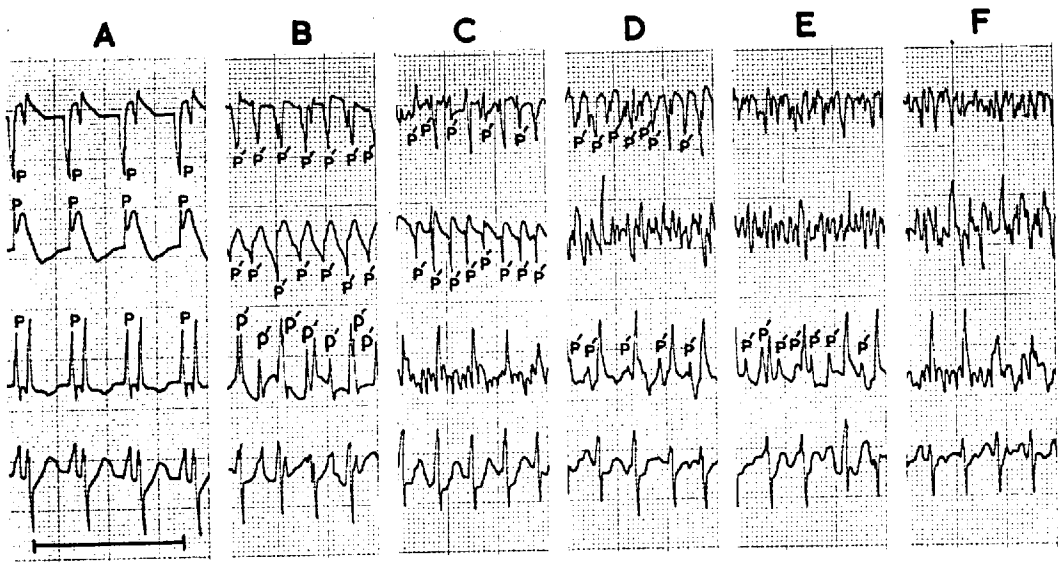


FIG. 19

Fig. 19

Effect of topical application of acetylcholine on the aconitine-induced auricular flutter

From top to bottom, electrograms from the region of sino-auricular node, tip of the right auricular appendage, tip of the left auricular appendage, and conventional bipolar lead II.

P = normal sinus beats.

P' = flutter beats, some of the flutter waves are incorporated in the QRS complexes and are not labelled.

(A) Control, heart rate is 170/min.

(B) 10 min. after the topical application of aconitine to the right auricular appendage, flutter rate is 402/min.

(C) 15 sec. after the topical application of 5% acetylcholine solution to the left auricular appendage. Note the inter-auricular dissociation. Only left auricle is fibrillating (1620/min), the right auricle is fluttering at the rate of 514/min. The acetylcholine pledget was removed and flutter returned in the left auricle in few minutes.

(D) 15 sec. after the application of the acetylcholine to the right auricular appendage. Note both inter-auricular and intra-auricular dissociation. Only the right auricular appendage is fibrillating (1440/min.) The sinus node and the left auricular electrode record flutter at the rate of 514/min.

(E) 15 sec. after the application of acetylcholine to the sinus node as well, both the right auricular and sinus node electrodes record fibrillation (1440/min). The left auricle continues to flutter at the rate of 514/min.

(F) 15 sec. after the application of acetylcholine to both auricles. Fibrillation is present everywhere.

Time scale = 1 sec.

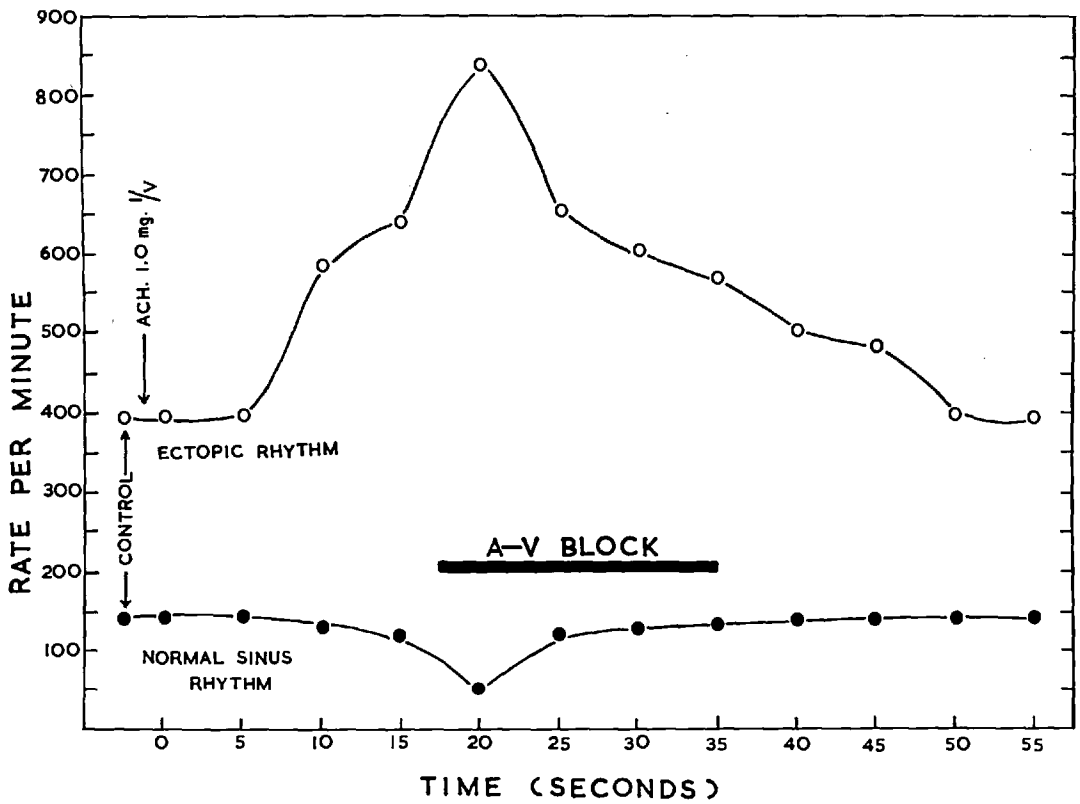

900
800
700
600
500
400
300
200
100
RATE PER MINUTE
ACH. 1.0 mg. IV
CONTROL
ECTOPIC RHYTHM
A–V BLOCK
NORMAL SINUS RHYTHM
0
5
10
15
20
25
30
35
40
45
50
55
TIME (SECONDS)

FIG. 20

Fig. 20

Differential effect of acetylcholine on the sinus rhythm and on aconitine-induced auricular flutter

Ordinate, auricular rate/min. Abscissa, time interval from the acetylcholine injection and the measurement of rate. Aconitine was applied topically to the tip of the right auricular appendage and when flutter fully developed, this area was clamped for one min. The aconitine treated area shows flutter at the rate of 395/min., the sinus rate is 144/min. Acetylcholine 1 mg. in 1 ml. of physiological saline was injected intravenously in 5 sec. The sinus rate decreased, the peak was reached 20 sec. after the injection and then the rate gradually returned to normal. The ectopic rate was markedly increased (maximum 840/min.), the peak effect was noted 20 sec. after the injection and the rate then gradually returned to normal.

Fig. 20 and Fig. 21 are from the same animal.

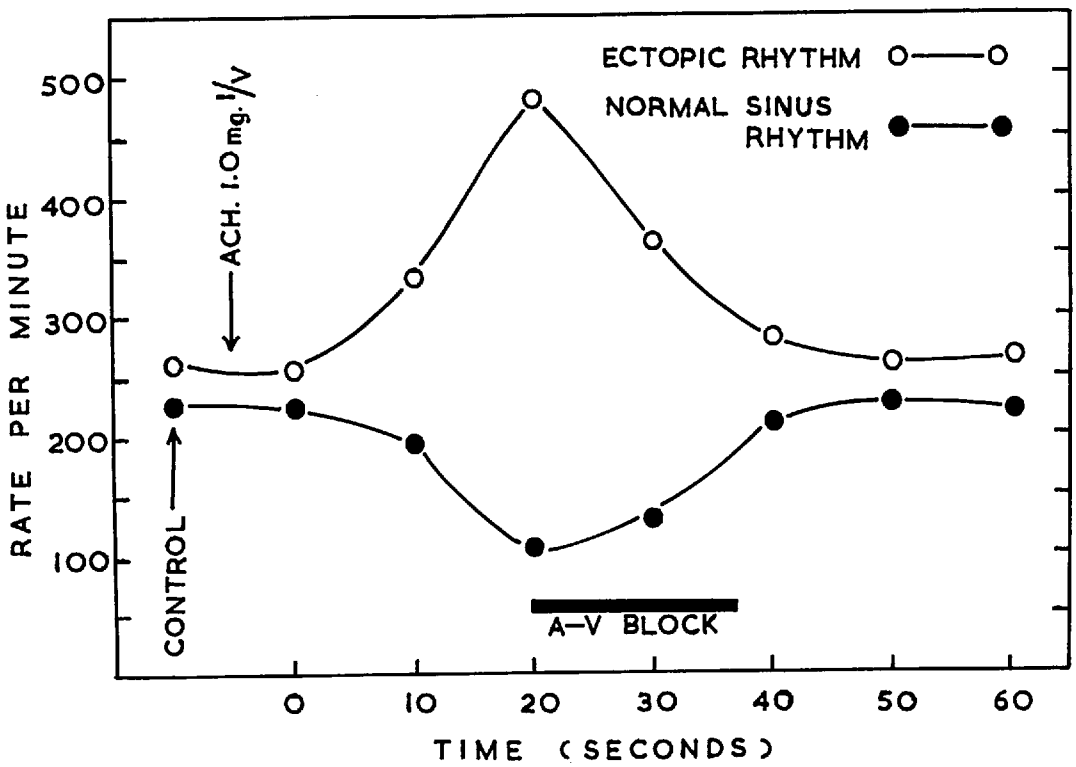

ECTOPIC RHYTHM
NORMAL SINUS RHYTHM
ACH. 1.0 mg. I/V
CONTROL
A–V BLOCK
RATE PER MINUTE
500
400
300
200
100
0
10
20
30
40
50
60
TIME (SECONDS)

FIG. 21

Fig. 21

Differential effect of acetylcholine on the sinus rhythm and on aconitine-induced auricular flutter

Ordinate, auricular rate/min. Abscissa, time interval from the acetylcholine injection to the determination of auricular rate. Aconitine was applied to the tip of the right auricular appendage and when the flutter fully developed, this area was isolated by a clamp for one min. The animal was treated with hemicholinium 10 mg./kg. intravenously. The control value was recorded 1 hour after hemicholinium, the ectopic rate is 256/min., sinus rate is 225/min.

Acetylcholine 1 mg. in 1 ml. of physiological saline was injected intravenously in 5 sec. The sinus rate has decreased, the peak effect was reached in 20 sec. The ectopic rate has increased markedly, reaching the peak value in 20 sec. and then gradually returned to the control value.

Both Fig. 26 and Fig. 27 are from the same animal.

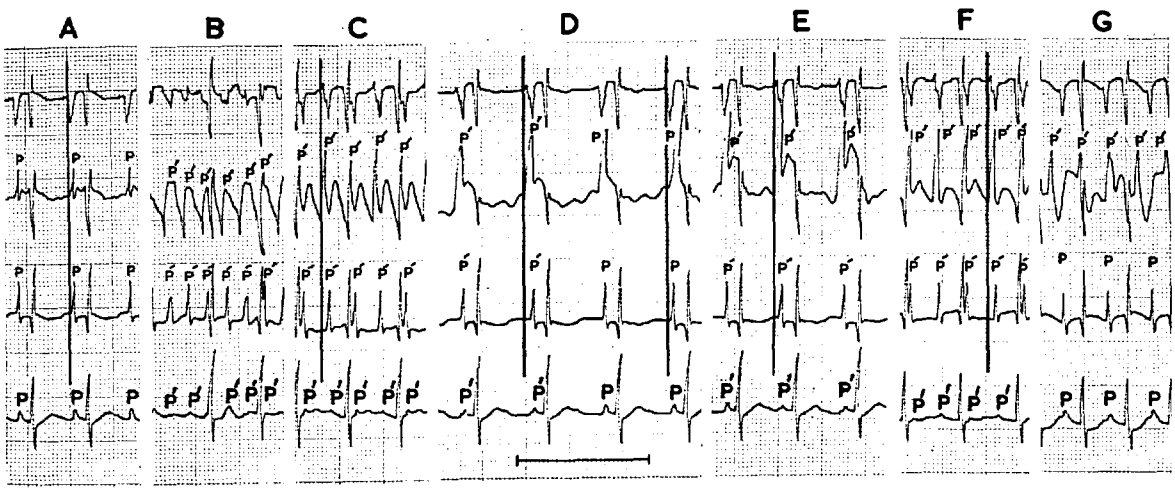


FIG. 22

Fig. 22

Effect of atropine on aconitine-induced auricular flutter

From top to bottom, electrograms from the region of the sino-auricular node, from the tip of the right auricular appendage, from the tip of the left auricular appendage and conventional bipolar lead II.

P = normal sinus beats.

P' = flutter beats, some of the flutter beats are incorporated in the QRS complexes and are not labelled.

(A) Control, heart rate is 140/min. The thick vertical line shows that the sinoauricular node records the activation process first and the two auricles are excited at almost the same time.

(B) 10 min. after the topical application of aconitine nitrate to the right auricular appendage. Flutter rate is 410/min The activation process now starts at the right auricular electrode.

(C) 10 min. after the intravenous administration of 1.0 mgm./kg. atropine sulphate, in 20 ml. of physiological saline over a period of five min. The flutter rate has decreased to 304/min. The activation of the right auricle still precedes that of sino-auricular node.

(D) 3 sec. after the start of focal cooling of the aconitine treated area. The first two beats are ectopic, though they very much look like sinus beats. The next two beats are sinus beats. The thick vertical line clearly shows the distinction between the sinus and the ectopic beats.

(E) 4 sec. after the discontinuation of focal cooling, all the beats are ectopic, as shown by the thick vertical line.

(F) 30 sec. after stopping the focal cooling, the flutter rate is now 284/min.

(G) The aconitine treated area was clamped for one min., to differentiate between slow rate flutter and atropine-induced sinus tachycardia. The aconitine-treated area shows flutter at the rate of 272/min., while elsewhere sinus tachycardia exists at the rate of 182/min.

Time scale = 1 sec.

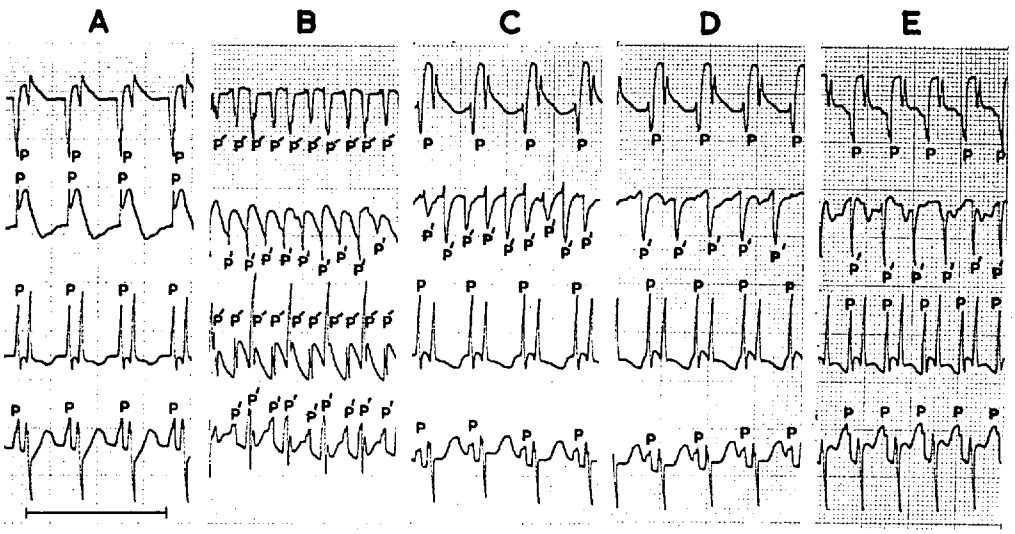


FIG. 23

Fig. 23

Differential effect of atropine on
aconitine-induced auricular flutter and on sinus rhythm

From top to bottom, electrograms from the region of the sino-auricular node, from the tip of the right auricular appendage, tip of the left auricular appendage and conventional bipolar lead II.

P = normal sinus beats.

P' = flutter beats, some of the flutter beats are incorporated in the QRS complexes and are not labelled.

(A) Control, heart rate is 168/min.

(B) 10 min. after the topical application of aconitine nitrate to the right auricular appendage. Flutter rate is 456/min.

(C) The aconitine-treated area was isolated from the rest of the right auricle by a clamp for 1 min. This excerpt has been recorded 5 min. after release of the clamp. Flutter at the rate of 410/min. is present in the aconitine-treated area, elsewhere sinus rhythm at the rate of 168/min. is present.

(D) Immediately after the intravenous administration of atropine sulphate 1 mgm./kg. in 20 ml. of physiological saline over a period of 5 min. Note the differential effect on the normal and the ectopic rhythm. The sinus rate has increased to 180/min., while the flutter rate has decreased to 256/min.

(E) 10 min. after atropine, the flutter rate has stabilised at 276/min., the sinus tachycardia rate is now 225/min. Note that the flutter beats occur independently of the sinus tachycardia caused by atropine.

Time scale = 1 sec.

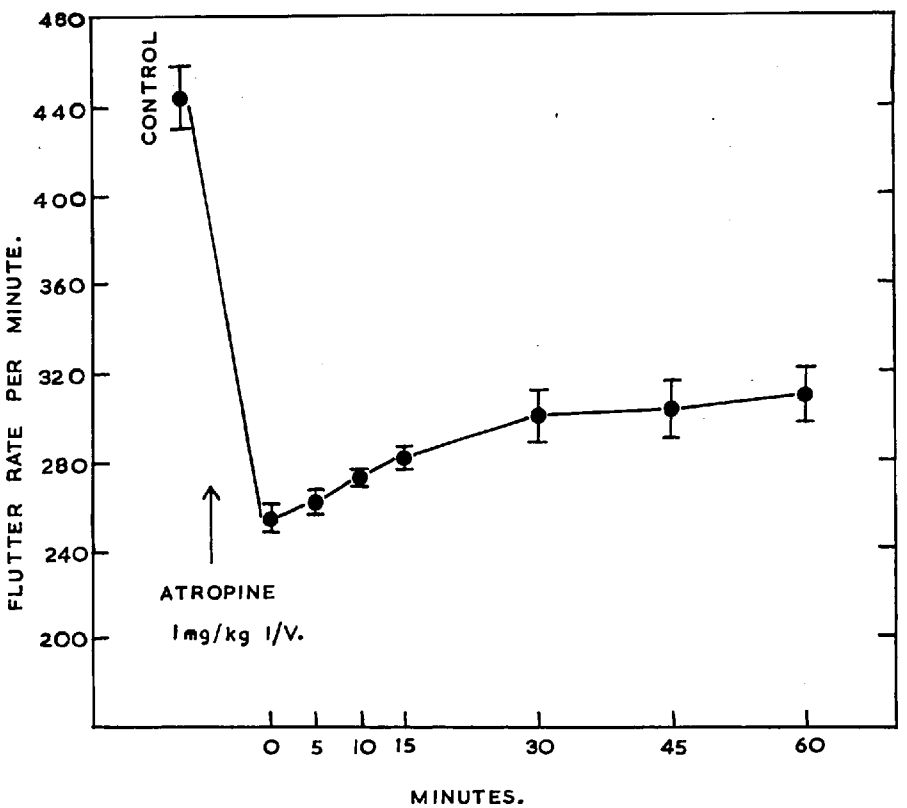

480
440
400
360
320
280
240
200
FLUTTER RATE PER MINUTE.
CONTROL
ATROPINE
1mg/kg I/V.
0
5
10
15
30
45
60
MINUTES.

FIG. 24

Fig. 24

Effect of atropine sulphate
on aconitine-induced auricular flutter

Ordinate, flutter rate/min. Abscissa, time interval from the injection of atropine and determination of rate.

Each point is a mean value ± S.E. (6 experiments). The maximum decrease in flutter rate occurred immediately after the administration of atropine, the rhythm continued to be ectopic and could be easily distinguished from sinus tachycardia in the direct auricular leads.

The drug was injected intravenously in 20 ml. of physiological saline, slowly over a period of 5 min.

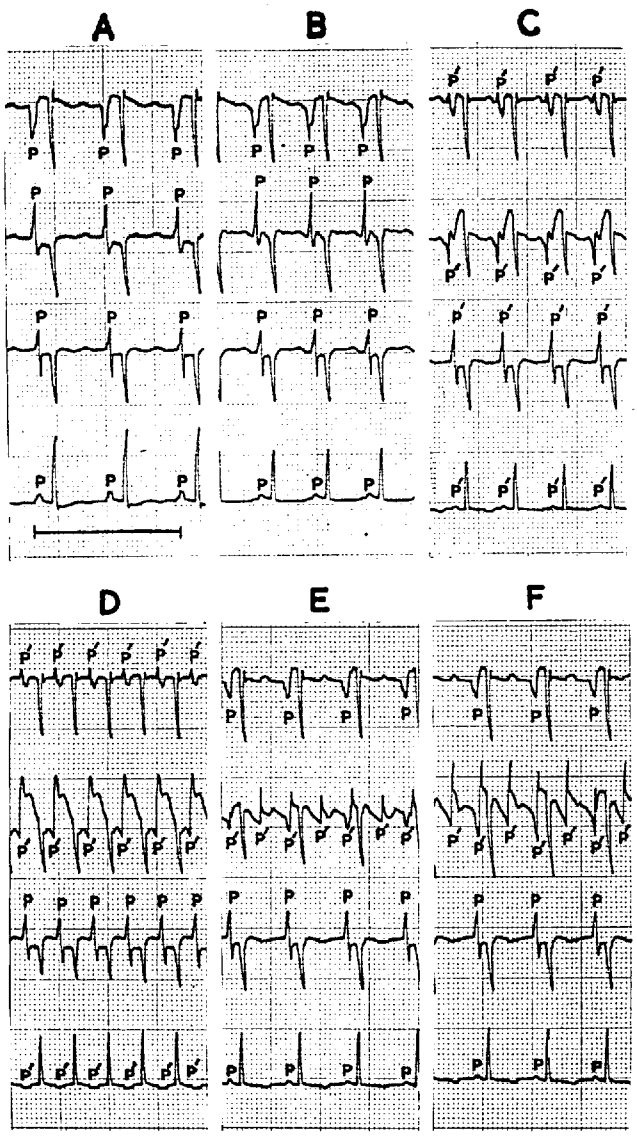


FIG. 25

Fig. 25

Aconitine-induced auricular flutter
in the atropine pre-treated dog

From top to bottom, electrograms from the region of the sino-auricular node, from the tip of the right auricular appendage, from the tip of the left auricular appendage and conventional bipolar lead II.

P = normal sinus beats.

P' = ectopic beats.

(A) Control, heart rate is 126/min.

(B) 10 min., after the intravenous administration of 1 mgm./kg., atropine sulphate, in 20 ml. of physiological saline over a period of five min. The heart rate has increased to 165/min.

(C) 108 sec., after the topical application of aconitine nitrate to the right auricular appendage. The heart rate has increased to 180/min. and is ectopic as evidenced by the reversal of wave form in the right auricular lead.

(D) 152 sec., after aconitine, the flutter rate has increased to 262/min. To differentiate the slow rate flutter from simple sinus tachycardia caused by atropine, the aconitine-treated area was clamped for one min.

(E) Immediately after the release of the clamp, the aconitine-treated area shows flutter at the rate of 272/min., elsewhere sinus tachycardia at the rate of 164/min. is present.

(F) 5 min. after the release of the clamp, the flutter rate has increased to 310/min., while the sinus rate is 162/min.

Time scale = 1 sec.

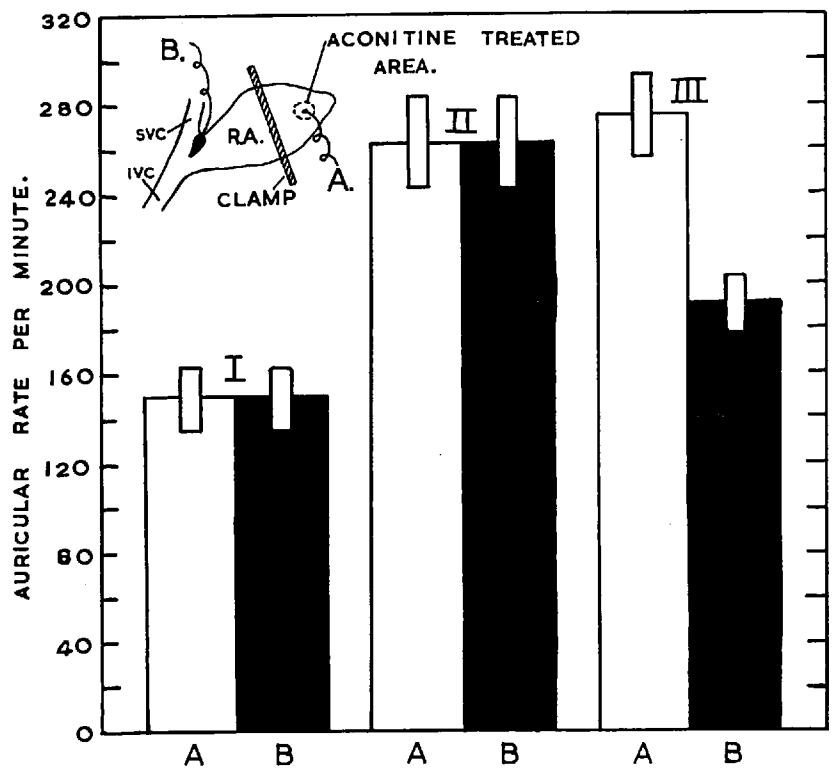

320
280
240
200
160
120
80
40
0
AURICULAR RATE PER MINUTE.
B.
ACONITINE TREATED AREA.
SVC
RA.
IVC
CLAMP
A.
I
II
III
A
B
A
B
A
B

FIG. 26

Fig. 26

Aconitine-induced auricular flutter in the atropinised animals

Ordinate, auricular rate/min. Abscissa, (A) rate at the tip of the right auricular appendage, (B) rate at the sino-auricular node (See the diagram for details, at the left hand, upper corner). Each trace is the mean value (7 experiments) $\pm$ S.E. (shown as rectangular bar at the top of each trace).

(I) normal sinus rhythm, heart rate is the same at (A) and (B). The animals were atropinised (1 mg./kg., 0.1% sol. in physiological saline, slowly over a period of 10 min.) 30 min. were allowed for full atropinisation and then aconitine was applied topically to the right auricular appendage.

(II) 10 min. after the application of aconitine. Slow rate flutter is present. The rate is the same at A & B.

(III) The aconitine-treated area was isolated from the rest of the auricle for 1 min. The rate was recorded 5 min. after release of the clamp. Note the differentiation between the slow rate flutter present in the aconitine-treated area, and simple sinus tachycardia due to atropine recorded at the sino-auricular electrode. The aconitine-treated area is beating at a faster rate and is completely independent of the sinus tachycardia.

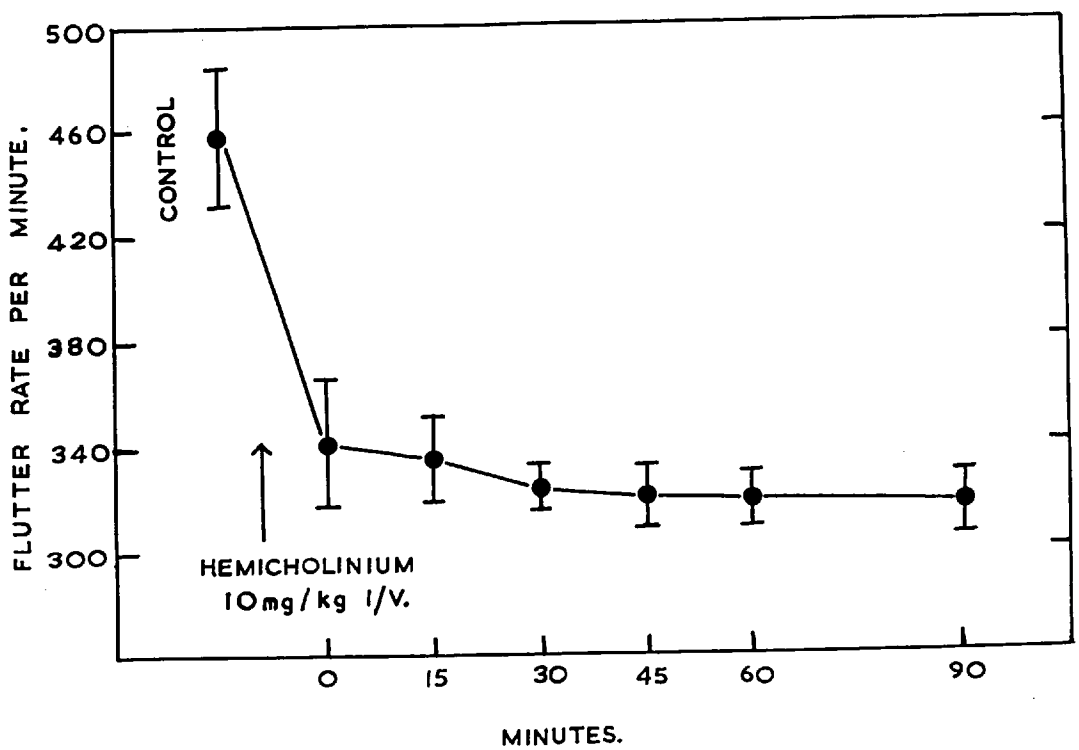

500
460
420
380
340
300
FLUTTER RATE PER MINUTE.
CONTROL
HEMICHOLINIUM
10mg/kg I/V.
0
15
30
45
60
90
MINUTES.

FIG. 27

Fig. 27

Effect of hemicholinium
on the aconitine-induced auricular flutter

Ordinate, flutter rate/min. Abscissa, interval between the injection of hemicholinium and the electrocardiographic determination of rate.

Each point is the mean value $\pm$ S.E. (5 experiments). The peak effect was reached 1 hour after the injection.

The drug was injected intravenously, 0.5% sol. in physiological saline, slowly over a period of 10 min.

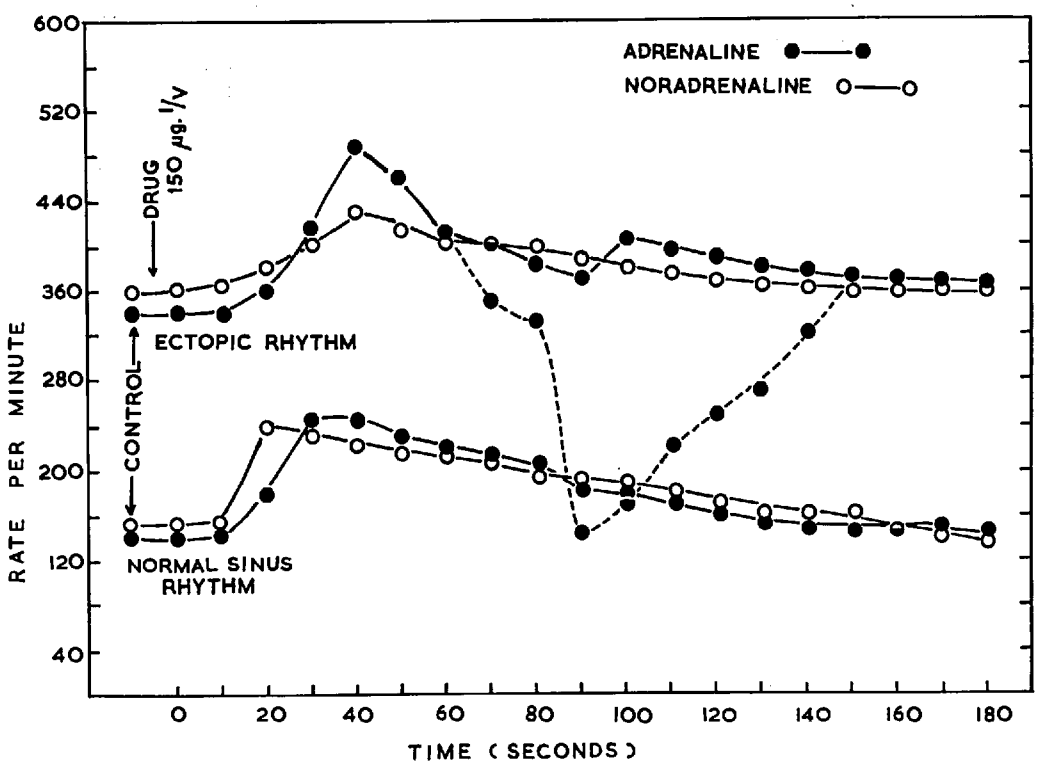

ADRENALINE
NORADRENALINE
DRUG 150 µg. I/V
CONTROL
ECTOPIC RHYTHM
NORMAL SINUS RHYTHM
RATE PER MINUTE
TIME (SECONDS)
600
520
440
360
280
200
120
40
0
20
40
60
80
100
120
140
160
180

FIG. 28

Fig. 28

Effect of adrenaline and noradrenaline
on the normal sinus rhythm and aconitine-induced auricular flutter

The aconitine-treated area was clamped for 1 min., and shows flutter at the rate of 364/min., the sinus rate is 142/min. The two rhythms are completely independent of one another.

Both adrenaline and noradrenaline increased the rate of sinus rhythm and of the ectopic rhythm. The peak effect on sinus rhythm was reached in 15 - 20 sec., while in the case of flutter it occurred at 40 sec. The effect completely disappeared in 3 min.

Qualitatively both the drugs produced similar effects, with one difference. With adrenaline after the initial increase in the rate of the ectopic rhythm, the rate decreased gradually and there was distinct secondary rise about 100 sec. after the injection. In some cases, however, the rate fell more rapidly after the initial rise and reached a level below that of the sinus rate (as shown by dotted line) and then gradually recovered to the control value. This effect was not seen with noradrenaline, the rate increasing effect of adrenaline was slightly more marked than that of noradrenaline.

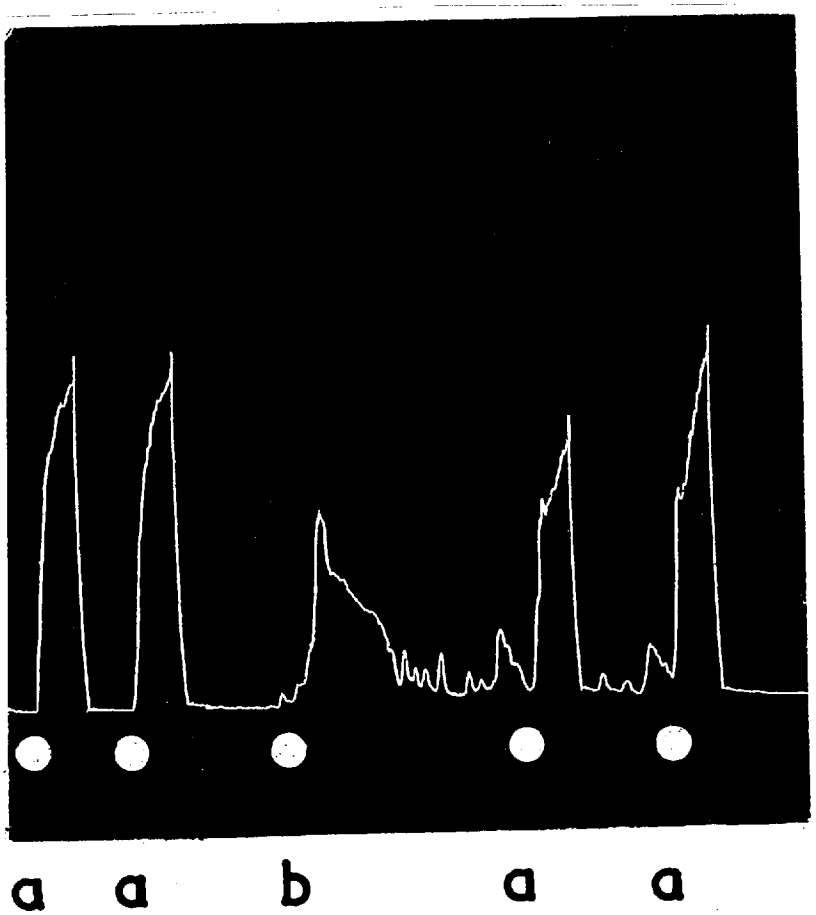


FIG. 29

Fig. 29

Response of the guinea-pig ileum to aconitine nitrate

(a) responses evoked by 1 µg. of acetylcholine chloride.

(b) 200 µg. of aconitine evoked a contraction, relaxation followed while the drug was still in the bath fluid. Without washing acetylcholine was added and its response has been partially (26.3%) blocked. The bath fluid was changed and the acetylcholine response has returned to normal.

Bath capacity = 20 ml.

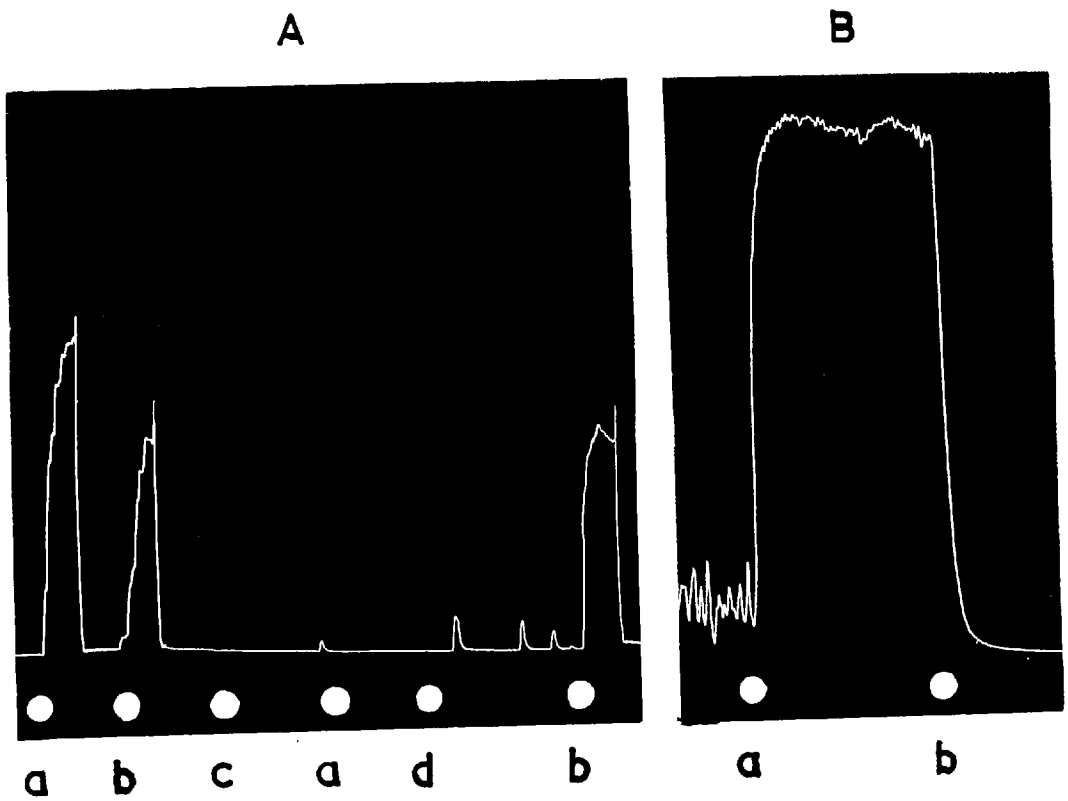


FIG. 30

Fig. 30

(A) Effect of atropine on the response of the guinea-pig ileum to acetylcholine, histamine and aconitine

(a) Acetylcholine 2 µg.

(b) Histamine 5 µg.

(c) Atropine 0.02 µg.

(d) Aconitine 200 µg. Note that atropine has completely blocked the effect of acetylcholine and aconitine, without affecting the response to histamine.

(B) Effect of atropine on aconitine-induced contraction of the guinea-pig ileum

(a) Aconitine 200 µg. evoked a marked and sustained contraction, at

(b) atropine 0.02 µg. was added and it has completely antagonised the aconitine response. Subsequent addition of another dose of 200 µg. of aconitine was also without any effect.

These findings suggest that the aconitine-induced contraction is parasympathomimetic in nature.

Bath capacity = 20 ml.

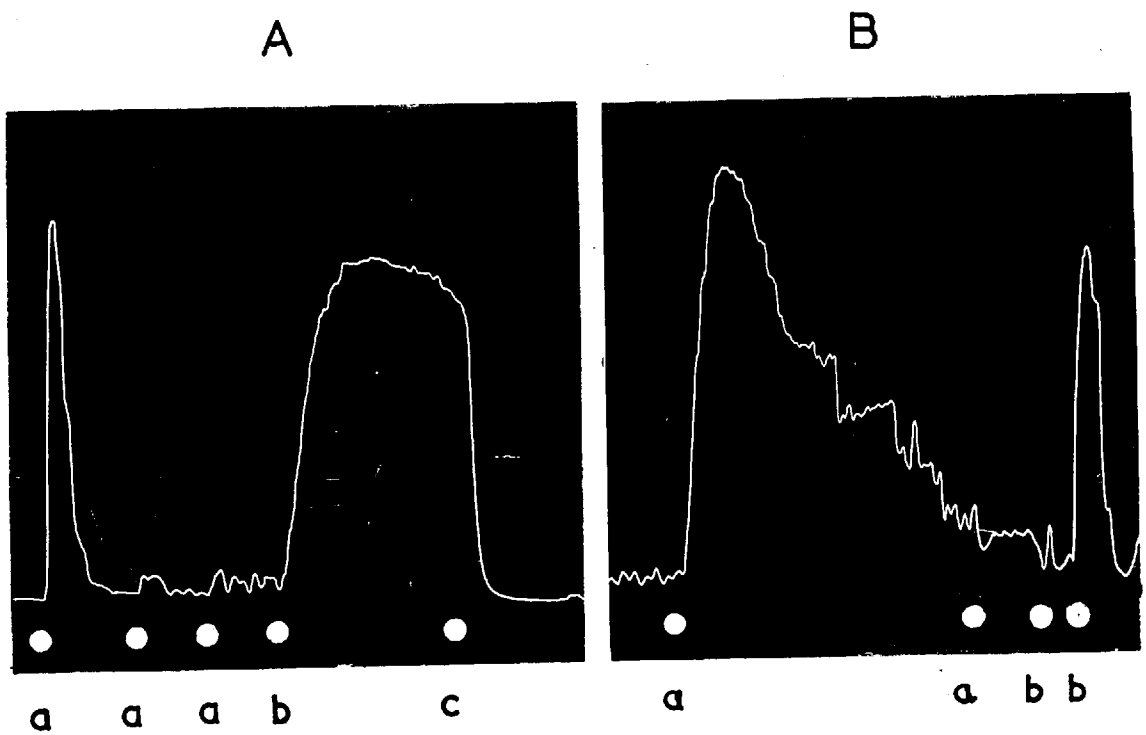


FIG. 31

Fig. 31

(A) Effect of nicotine tachyphylaxis on the aconitine-induced contraction of the guinea-pig ileum

(a) Nicotine 50 µg., added three times without washing produced complete tachyphylaxis.

(b) Aconitine 200 µg., still evoked a marked contraction, which was completely antagonised by 0.02 µg. of atropine added at (c).

(B) Effect of aconitine tachyphylaxis on the nicotine-induced contraction of the guinea pig ileum

(a) Aconitine 200 µg. evoked a marked and sustained contraction, gradual relaxation followed while the drug was still in the bath. Addition of another dose of 200 µg. of aconitine did not produce any effect. Nicotine 50 µg. did not produce any effect, but a larger dose of nicotine (200 µg.) produced a contraction.

These findings suggest that parasympathetic ganglia are not the site of action of aconitine.

Bath capacity = 20 ml.

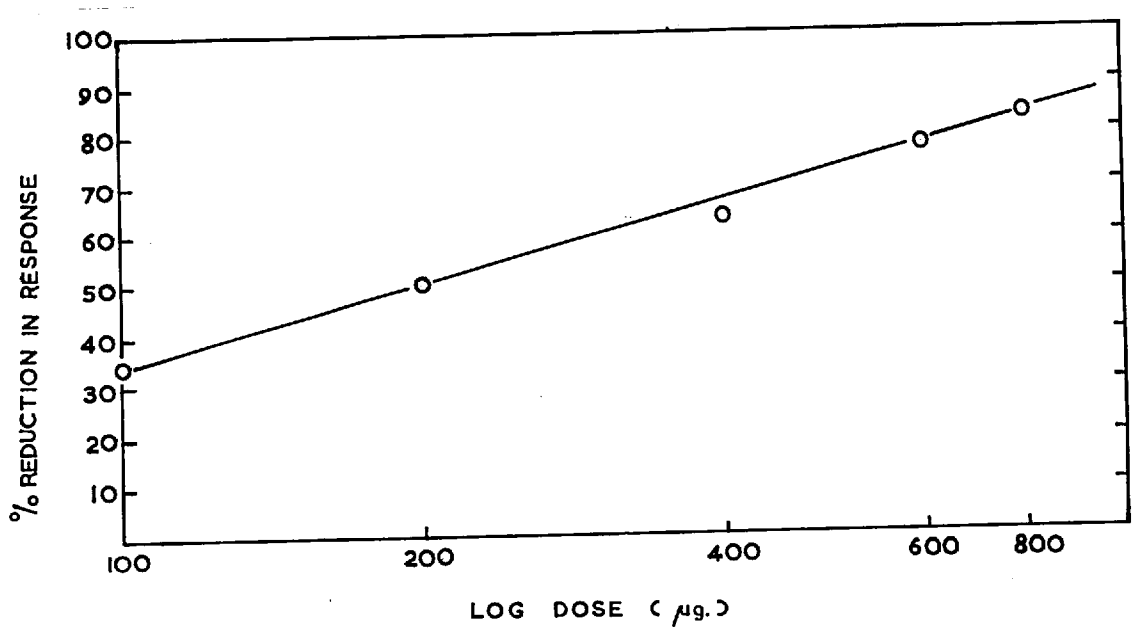

100
90
80
70
60
50
40
30
20
10
% REDUCTION IN RESPONSE
100
200
400
600
800
LOG DOSE (µg.)

FIG. 32

Fig. 32

Anti-acetylcholine action of aconitine nitrate on the guinea-pig ileum

Ordinate per cent reduction in the responses evoked by 1 µg. of acetylcholine. Abscissa, doses of aconitine nitrate (µg.) plotted on the logarithmic scale.

Bath capacity = 20 ml.

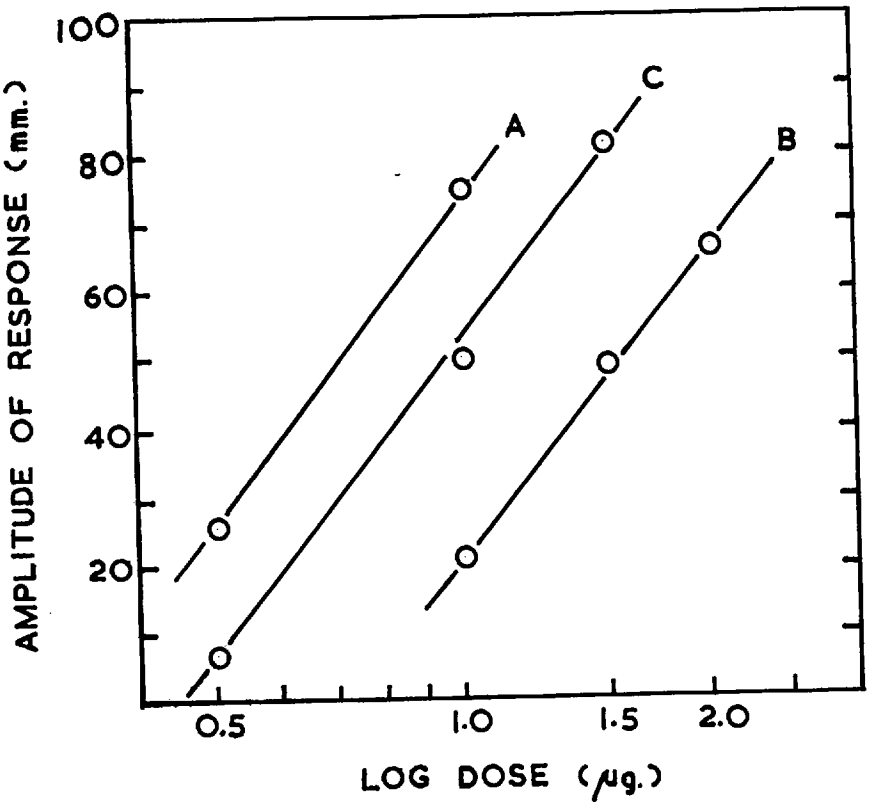

100
80
60
40
20
AMPLITUDE OF RESPONSE (mm.)
A
B
C
0.5
1.0
1.5
2.0
LOG DOSE (µg.)

FIG. 33

Fig. 33

Anti-acetylcholine action of aconitine nitrate on guinea-pig ileum

Ordinate, amplitude of responses evoked by acetylcholine (mm.)
Abscissa, doses of acetylcholine plotted on a logarithmic scale (µg.)

(A) Dose-response curve for acetylcholine alone.

(B) Dose-response curve for acetylcholine in the presence of 50 µg. of aconitine nitrate in the bath. Note the shift of the curve to the right.

(C) Dose-response curve for acetylcholine in the presence of 50 µg. of aconitine nitrate and 2 µg. of eserine sulphate.

The presence of the anticholine-esterase has partially antagonised the acetylcholine-aconitine antagonism, as shown by the shift of the curve to the left. The antagonism, therefore, appears to be of surmountable type.

Bath capacity = 20 ml.

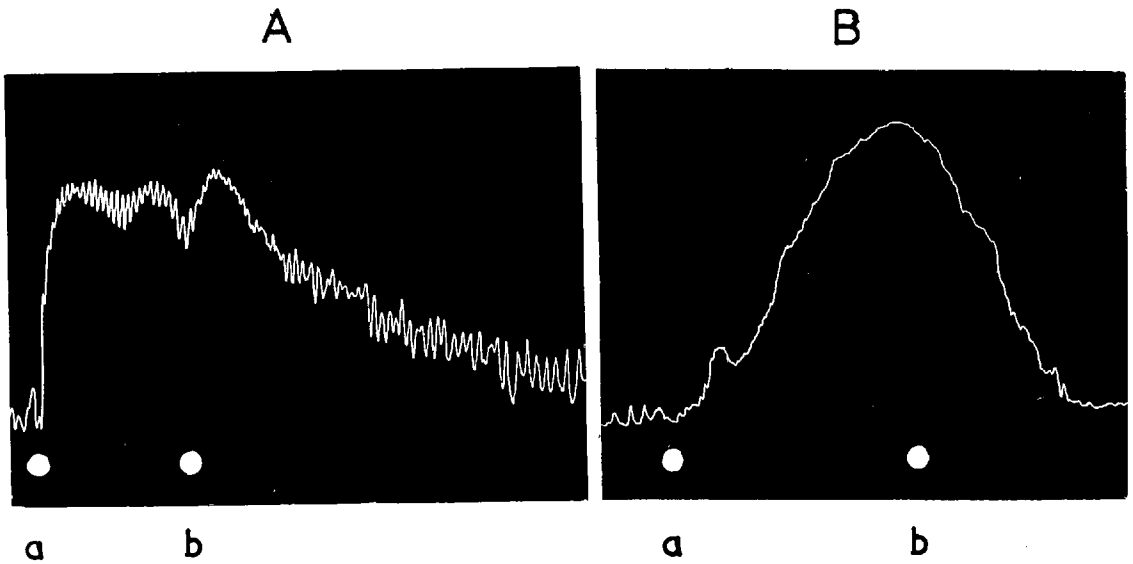


FIG. 34

Fig. 34

(A) Effect of aconitine nitrate on pilocarpine-induced contraction of the guinea-pig ileum

(a) Pilocarpine 50 µg. produced a sustained contraction.

(b) Aconitine 500 µg. produced a gradual relaxation of the gut, while the pilocarpine was still in the bath.

(B) Effect of aconitine on the eserine-induced contraction of guinea-pig ileum

(a) Eserine 20 µg. produced a sustained contraction of the gut.

(b) Aconitine 500 µg. produced a gradual relaxation of the gut while eserine was still in the bath.

Bath capacity = 20 ml.

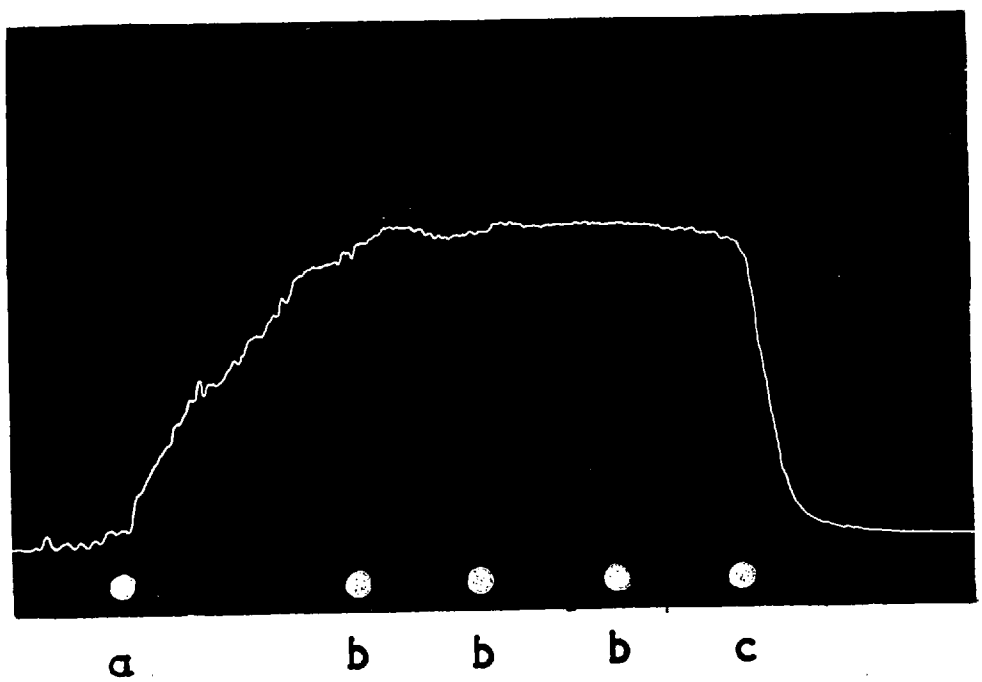


FIG. 35

Fig. 35

Effect of aconitine on barium chloride-induced contraction of the guinea-pig ileum

(a) Barium chloride 2 mg. produced a gradual and sustained contraction. (b) Aconitine added three times in doses of 500 µg., failed to affect the barium-induced contraction. (c) Papaverine 0.5 mg. quickly antagonised the barium-induced contraction. Addition of 2 mg. of barium chloride was without effect.

Bath capacity = 20 ml.

3. POST-STIMULATORY AURICULAR FLUTTER

A total of 46 dogs were used. The injury-stimulation procedure usually resulted in auricular flutter, with 2:1 A-V block. In some cases, however, irregular A-V block was noted. The rate of the fluttering auricles soon reached a steady level, from which it varied very little for the next two to three hours. The experimental observations were, therefore, not started until at least 20 minutes. Spontaneous reversions of auricular flutter which had persisted for this period were not observed in the control experiments. The mean flutter rate in the whole group was 462 $\pm$ S.E. 4.35/min.

(i) Cholinergic influences in post-stimulatory auricular flutter

The role of cholinergic factors was studied in exactly the same way as in aconitine-induced auricular flutter, i.e. by vagal stimulation and acetylcholine or by atropine and hemicholinium.

Effect of vagal stimulation on auricular flutter

A total of 32 observations were made in 8 dogs. Two types of responses were observed. In 12 experiments vagal stimulation increased the flutter rate, but did not result in fibrillation. The flutter rate returned to the control level within 5 sec. after the stimulation was discontinued. In the

remaining 20 experiments, vagal stimulation converted flutter into fibrillation. When the stimulation was stopped, the arrhythmia terminated abruptly. Sinus rhythm returned in all the experiments, except two. In both of them, as the fibrillation rate declined, flutter at the control rate returned. A typical experiment is illustrated in Fig. 36.

Under vagal stimulation both the auricles fibrillated simultaneously and auricular dissociation was not observed. In contrast to the observation of Lewis et al. (1921a), an abrupt termination of flutter at the beginning or during the course of vagal stimulation was not observed. Unless vagal stimulation converted flutter into fibrillation, the arrhythmia was never terminated. The stimulation of the right or of the left vagus nerve produced similar results, except that the latter produced higher degree of A-V block. The highest fibrillation rate recorded in this series was 1800/min. In the majority of experiments the rate varied between 600 - 1440/min. This fibrillatory activity of vagal stimulation was completely blocked by atropine (0.1 mg./kg. i/v).

Effect of injected acetylcholine on auricular flutter

Acetylcholine chloride (200 - 1000 µg., in 1 ml. of physiological saline, injected in 5 sec.) injected intravenously produced an effect very similar to that of vagal stimulation. A total of 46 observations were made in 10 dogs. Acetylcholine

converted flutter into fibrillation. The cholinergic influence was short lived and two types of after-effects were seen. In 37 experiments, the arrhythmia terminated abruptly and sinus rhythm returned within 50 sec. of the injection. A typical experiment is illustrated in Fig. 37. In the remaining 9 experiments. auricular flutter at the control rate returned, as the cholinergic influence disappeared.

After intravenous injection of acetylcholine, an unusual finding 'auricular dissociation' was seen in all the experiments, the right auricle fibrillating earlier than the left. The latter did not fibrillate until 4 - 7 secs. after the former. Since no dissociation was observed after vagal stimulation, it was possible that this dissociation could be due to earlier arrival of acetylcholine in the right auricle than in the left. To test this possibility, acetylcholine was injected directly into the left ventricle so that it reached the two auricles almost simultaneously via their blood supply, the two auricles now fibrillated simultaneously. This point is clearly demonstrated in Fig. 37 and Fig. 38, recorded from the same animal. In Fig. 37, acetylcholine 500 µg. was injected intravenously, auricular dissociation lasted for 4 sec. In Fig. 38, acetylcholine 500 µg. was injected into the left ventricle and both auricles fibrillated simultaneously.

Following the intravenous injection of acetylcholine there

was a latent period of 6 - 13 sec. before the effect on flutter was noticeable. Following the left ventricular injection the latent period was much shorter and varied from 2 - 5 sec. This fibrillatory activity of acetylcholine was completely blocked by atropine (0.1 mg./kg.i/v).

Effect of topical application of acetylcholine on auricular flutter

The effect of topical application of acetylcholine (5% solution in physiological saline) was studied in 6 dogs. The phenomenon of auricular dissociation was observed in all the experiments. Only that auricle to which acetylcholine was applied fibrillated, while the other continued to flutter. The latent period before localised fibrillation appeared varied from 30 - 60 sec., and the effect of acetylcholine completely disappeared in less than 10 min., with the return of flutter at the control rate. Careful application of acetylcholine to the tip of the right auricular appendage alone showed that the dissociation could be both inter-auricular and intra-auricular, since fibrillation was confined to the right appendage only, the electrodes at sinus node and the left auricle recorded flutter. When acetylcholine was applied to the crushed area, the fibrillation was confined to this area alone, both the auricular appendages recorded flutter. When the effect of acetylcholine disappeared the arrhythmia stopped abruptly with re-establishment of sinus rhythm. A typical experiment is illustrated in Fig. 39.

Effect of atropine sulphate on post-stimulatory auricular flutter

In 6 dogs auricular flutter was produced and atropine sulphate 1.0 mg./kg. was injected intravenously (in 20 ml. of physiological saline, slowly over a period of 5 min.), to block the cholinergic influences. The results of all the 6 experiments are presented graphically in Fig. 40. The mean flutter rate in these experiments was 468 $\pm$ S.E. 14.00/min. Atropine decreased the flutter rate, the slowest rate recorded after atropine was 416 $\pm$ S.E. 20.00/min. The peak effect was reached 5 min. after the injection of the drug.

Effect of hemicholinium on post-stimulatory auricular flutter

In 5 dogs, auricular flutter was produced and hemicholinium 10 mg./kg. was injected intravenously (0.5% solution in physiological saline, over a period of 10 min.) to block the acetylcholine synthesis. The results of all the five experiments are presented graphically in Fig. 41. The mean flutter rate was 446 $\pm$ S.E. 9.50/min. After hemicholinium, the flutter rate decreased, the lowest rate was recorded 20 min. after the drug administration, it was 420 $\pm$ S.E. 9.00/min.

These results show that acetylcholine is not essential for the development and maintenance of auricular flutter.

(ii) Adrenergic influences in auricular flutter

The effect of adrenergic influences was studied by (a) increasing the adrenergic influence through sympathetic stimulation or intravenous administration of adrenaline or noradrenaline, (b) by depletion of cardiac stores of catecholamines by reserpine pre-treatment.

Effect of sympathetic stimulation on auricular flutter

Twentyfour observations were made in 6 dogs. Sympathetic stimulation increased the flutter rate and in 9 experiments fibrillation resulted. The effect disappeared in 30 sec. and sinus rhythm was established in 7 experiments, in the remaining two, flutter at the control rate returned.

The rate increasing effect of sympathetic stimulation was not blocked by atropine sulphate (0.1 mg./kg. i/v.) but fibrillation was not observed after atropine. The increase in flutter rate in different experiments varied from 12 - 114 beats/min.

Effect of adrenaline and noradrenaline on auricular flutter

The effect of adrenaline and noradrenaline on auricular flutter was studied in 5 dogs. 25 observations were made for each drug. Both drugs increased the flutter rate when injected intravenously in dose range of 100 - 250 µg. The increase in rate varied from 50 - 170 beats/min. in different experiments. In 12 experiments (8 adrenaline, 4 noradrenaline) auricular fibrillation resulted and when the drug effect passed off, sinus rhythm was

established in 11 experiments, in the remaining one, flutter at the control rate returned. Both drugs were almost equipotent in their rate increasing effect.

The rate increasing effect of adrenaline and noradrenaline was not blocked by atropine (0.1 mg./kg. i/v.) but fibrillation was not observed after atropine.

Effect of catecholamines depletion on post-stimulatory auricular flutter

Five dogs were treated with reserpine to deplete the cardiac stores of catecholamines. It was not possible to induce auricular flutter in these experiments, electrical stimulation produced short-lived episodes of auricular fibrillation which lasted from a few seconds to a few minutes and then abruptly stopped and sinus rhythm returned. Bilateral vagotomy decreased the duration of auricular fibrillation episodes but flutter could not be induced.

(iii) Effect of cardiac denervation

In 5 experiments, acute denervation of the heart did not affect the production of auricular flutter by electrical stimulation. There was no noticeable effect on the flutter rate or on the duration of the arrhythmia, as compared with the control experiments.

(iv) Effect of focal cooling on post-stimulatory auricular flutter

In 10 experiments, focal cooling of the crushed area promptly arrested the arrhythmia and sinus rhythm returned.

Unlike aconitine-induced auricular flutter, the arrhythmia did not return when the cooling was stopped; sinus rhythm continued. Flutter could be re-induced in all the experiments after electrical stimulation.

(v) Sequential activation of the auricles in auricular flutter and its reversal in consecutive episodes or in the same episode of flutter

The electrodes on the right auricular and left auricular appendages were adjusted in such a way that the sinus impulses (intrinsic deflections) were recorded almost simultaneously at the two electrodes. When post-stimulatory flutter was produced, sequential activation of the two auricles was observed. In some experiments the right auricle was activated earlier than the left auricle, in others, the reverse was true.

Reversal of sequential activation in consecutive episodes of auricular flutter

A total of 232 episodes of flutter were produced in 34 dogs. In 136 episodes, the right auricular activation preceded that of the left auricle; in the remaining 96 episodes, the reverse was true. The difference in the recording of intrinsic deflections in the two auricles varied between 0.016 - 0.024 sec. in different animals, but was remarkably constant in the same animal even when the reversal of sequential activation occurred in consecutive episodes. The occurrence of these two patterns of

sequential activation in any given animal was random and could not be determined in advance. A typical experiment is illustrated in Fig. 42.

This observation can be easily explained on the basis of the circus movement theory (Fig. 45), since the excitation process can travel in a clockwise or anticlockwise direction in the circuit (Lewis, 1920; Lanari et al. 1956).

Reversal of the sequential activation in the same episode of auricular flutter

It has been demonstrated above that once auricular flutter was converted into fibrillation by vagal stimulation or acetylcholine, the arrhythmia terminated abruptly in most of the experiments as the cholinergic influence gradually disappeared. As suggested by Lewis et al. (1921a), this could be due to the extinction of the circus movement under cholinergic influence. However, this hypothesis will not explain those experiments in which flutter returned at the control rate.

A study of the sequential activation phenomenon before and after the acetylcholine-induced auricular fibrillation showed that in 5 experiments, the return of flutter was associated with the reversal of the sequential activation process. A typical experiment is illustrated in Fig. 44. A similar reversal of the sequential activation was also observed in 48 experiments in 14 dogs, following electrically-induced fibrillation. If a single stimulus was

applied to the auricle the flutter was abruptly terminated, but if the electrical stimulation was applied for 10 - 15 sec. (square wave pulses of 1 m. sec. duration; 20 volts; frequency 20/sec.), the flutter was converted into fibrillation. When the stimulation was stopped the arrhythmia terminated abruptly in most of the experiments, but in some, auricular flutter returned. The sequential activation process either remained unchanged or was reversed (Fig. 45). By repeating this process the sequential activation reversal could be demonstrated in all the animals studied. In 6 dogs the reversal could be produced twice in the same episode of auricular flutter, and in one dog it could be produced three times before the arrhythmia terminated abruptly and sinus rhythm returned.

These observations show that the impulses from the fibrillating auricles entering the crushed area can restart the circus movement.

Reversal phenomenon studied in bipolar and unipolar limb leads

A typical experiment is illustrated in Fig. 46. When the right auricle was activated before the left auricle, the flutter waves were positive in leads I, II, III and VF and inverted in leads VR and VL. This pattern was very similar to that obtained with sinus rhythm, but a closer study of the flutter beats revealed some differences in the amplitude and contour of flutter waves, as compared with normal sinus beats. This difference was more marked

in direct leads from the right auricle showing that the impulses were originating outside the sinus node. When the reversal phenomenon occurred in a subsequent episode of flutter, the limb leads also shared in the reversal process. The flutter waves were negative in leads II, III, VF and VL., positive in lead VR., positive, negative or iso-electric in lead I.

These two distinct patterns of flutter waves in limb leads observed in post-stimulatory auricular flutter in these experiments were also noted in the limb lead tracings of clinical auricular flutter published by other workers (Barker, 1952; Goldberger, 1952, Katz & Pick, 1956; Lippman & Massie, 1959). This finding strongly suggests that the mechanism of experimental and clinical flutter may be the same.

(Vi) Timing of the flutter waves around the hypothetical circus pathway in post-stimulatory auricular flutter

The time course of a single flutter wave around the hypothetical circus pathway was studied in 5 dogs. The electrode positions are depicted diagramatically in Fig. 47, with electrocardiographic tracings of a typical experiment. In the presence of normal sinus rhythm the impulse was spreading radially, reaching electrodes 2 & 3 almost simultaneously, and at electrode 4 last of all (excerpt A). The first episode of flutter revealed a clockwise spread of the impulse (excerpt B) and in a subsequent episode of flutter the spread was anticlockwise (excerpt C).

The time required by an impulse to complete one circuit was 0.136 sec. when calculated from the heart rate and 0.128 sec. when calculated from intrinsic deflection at the four electrodes (see arrows in excerpt B & C).

(vii) Role of crushed area in the production of stable auricular flutter

Scherf et al. (1953b) suggested that the post-stimulatory auricular flutter was due to a rapidly discharging ectopic focus. To test this hypothesis, the inter venae-caval bridge was crushed in stages in 14 dogs and the effect of electrical stimulation noted. When the crush was confined to the region near the superior vena cava (see Fig. 1), a part most likely to contain the elements of sinus node, stable auricular flutter could not be produced despite repeated attempts. When the crush was extended towards the inferior vena cava, the duration of flutter episodes increased. The procedure was most effective in producing long-lasting flutter episodes when the crushed area involved the whole of the inter venae-caval bridge.

In another 5 experiments, the sino-auricular node was crushed with a stout haemostat. Nodal rhythm developed in all the experiments. Electrical stimulation failed to induce stable auricular flutter, despite repeated attempts. The inter venae-caval bridge was then crushed, electrical stimulation now produced long-lasting auricular flutter.

(viii) Post-stimulatory auricular flutter and fibrillation in the same animal

In some experiments, electrical stimulation of the auricle after the crush occasionally resulted in the production of coarse auricular fibrillation, which lasted from a few sec. to a few minutes and then stopped abruptly, with the return of sinus rhythm. Subsequent electrical stimulation produced auricular flutter. A comparison of the electrocardiographic tracings of auricular flutter and fibrillation obtained from the same animal, revealed some basic differences between the two rhythms (Fig. 48). In auricular flutter, the amplitude and the form of flutter waves remained remarkably constant in the direct auricular and limb leads. The auricular rate was regular and both auricles showed co-ordinated beating. In auricular fibrillation, however, the rate varied from beat to beat and the two auricles showed little or no co-ordinated beating. The amplitude and form of flutter beats also varied from beat to beat.

These findings demonstrate that in auricular fibrillation the impulse formation is not confined to any single area of the auricular myocardium and it is, therefore, a more or less random activation phenomenon. Fig. 48 also shows that in one episode of flutter the flutter waves were positive in lead II, in a subsequent episode these were negative, but when fibrillation occurred in the same animal these were either positive, negative, intermediate or even iso-electric and their form varied from beat to beat.

(ix) Summary

1. Cholinergic influences increase the flutter rate and frequently flutter is converted into fibrillation. When the cholinergic influence disappears sinus rhythm is established in most of the experiments, but in some, flutter returned. This fibrillatory response is completely blocked by atropine. Transient auricular dissociation is seen after the intravenous injection of acetylcholine but not after the direct intra-ventricular injection or following vagal stimulation.

2. Cholinergic influences are not essential for the development or maintenance of auricular flutter. Atropine or hemicholinium only produce a slight but significant decrease in flutter rate, the arrhythmia is not terminated.

3. Adrenergic influences also increase the flutter rate, occasionally flutter is converted into fibrillation. Atropine antagonises the fibrillatory response, the rate increasing effect is decreased, but not blocked. Following cardiac catecholamines depletion by reserpine, it is not possible to induce stable auricular flutter. Electrical stimulation produces auricular fibrillation instead of flutter in these experiments. Acute denervation of the heart does not affect the production of stable auricular flutter. Focal cooling of the crushed area arrested the flutter permanently.

4. The two auricular appendages beat in phase during sinus rhythm, during auricular flutter they beat out of phase. Sequential activation is seen in that one auricle is excited earlier than the other, this process is frequently reversed in consecutive episodes or in the same episode of flutter following its conversion into fibrillation. The time lag remains remarkably constant during reversal phenomenon in the same animal. Corresponding to the reversal seen in the auricular leads, the limb leads show the reversal of flutter waves. The two patterns of flutter waves seen in the experimental flutter are also encountered in the limb lead tracings of clinical auricular flutter.

5. Timing of a single flutter beat around the hypothetical circus pathway showed that in auricular flutter the conduction is uni-directional, in a clockwise or counter-clockwise direction. The auricular cycle calculated from the flutter rate (P' - P' interval) is almost equal to the cycle length calculated from the intrinsic deflections from the four different points on the circus pathway.

6. The extent of the crush is an important factor in the development of stable auricular flutter. Injury to the nodal tissue plays no significant role.

7. Comparison of flutter and fibrillation characteristics in the same animal showed that the rate and form of flutter waves

is constant in flutter and the two auricles show co-ordinated beating. In fibrillation, however, the rate is irregular and the form of ectopic beats varies from beat to beat and two auricles frequently show independent beating with little or no co-ordination at all.

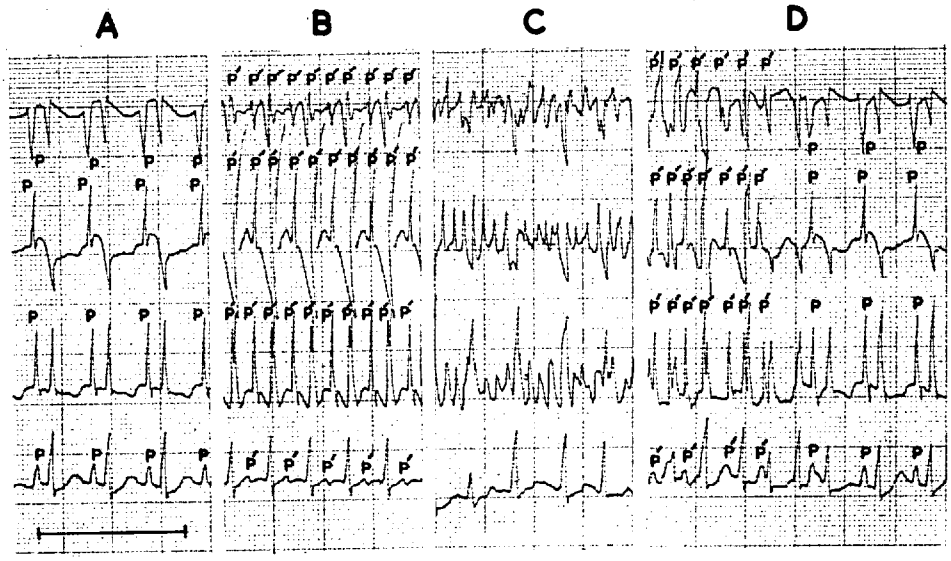


FIG. 36

Fig. 36

Effect of vagal stimulation on post-stimulatory auricular flutter

From top to bottom, electrograms from the region of sinus node, tip of the right auricular appendage, tip of the left auricular appendage, and conventional bipolar lead II.

P = normal sinus beats.

P' = flutter beats, some of the flutter beats are incorporated in the QRS complexes and are not labelled.

(A) Control, heart rate is 150/min.

(B) 20 min. after the production of auricular flutter, the auricular rate is 452/min., with 2:1 A-V block.

(C) Immediately after the stimulation of the right vagus nerve (square wave pulses of 0.5 m. sec. duration; 20 volts; 20/sec.) for 10 sec. Auricular fibrillation is present. Auricular rate varies between 720 - 1260/min. No dissociation is seen. A-V block has been enhanced and is irregular.

(D) 5 sec. after the end of vagal stimulation, auricular flutter has returned but the rate is irregular. Note the abrupt termination of the arrhythmia and return of sinus rhythm.

Time scale = 1 sec.

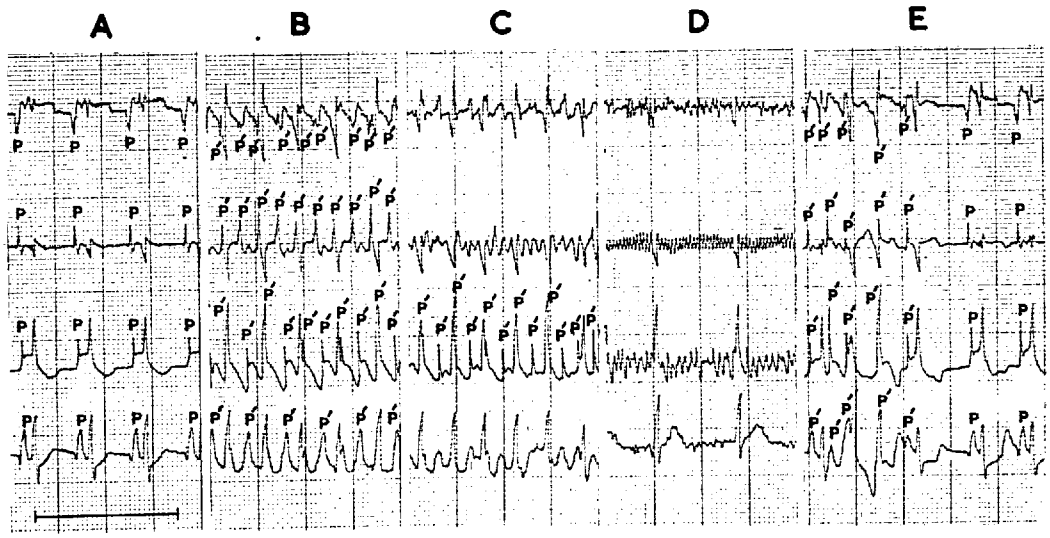


FIG. 37

Fig. 37

Effect of intravenous acetylcholine on post-stimulatory auricular flutter

From top to bottom, electrograms from the region of the sinus node, tip of the right auricular appendage, tip of the left auricular appendage, and conventional bipolar lead II.

P = normal sinus beats.

P′ = flutter beats, some of the flutter beats are incorporated in the QRS complexes and are not labelled.

(A) Control, heart rate is 165/min.

(B) 20 min. after the production of auricular flutter, rate is 450/min., with 2:1 A-V block.

(C) 9 sec. after the intravenous injection of 500 µg. acetylcholine (in 1 ml. of physiological saline, over 5 sec). Note the auricular dissociation, the right auricle is fibrillating (720 - 900/min.) while the left auricle is still fluttering (514/min).

(D) 13 sec. after acetylcholine, both the auricles are now fibrillating, A-V block has been enhanced. The right auricle is fibrillating at a somewhat higher rate than the left auricle.

(E) 34 sec. after acetylcholine injection. The flutter has returned but the rate is irregular. Note the sudden termination of the arrhythmia, and return of sinus rhythm.

Both Fig. 37 and Fig. 38 are from the same animal.

Time scale = 1 sec.

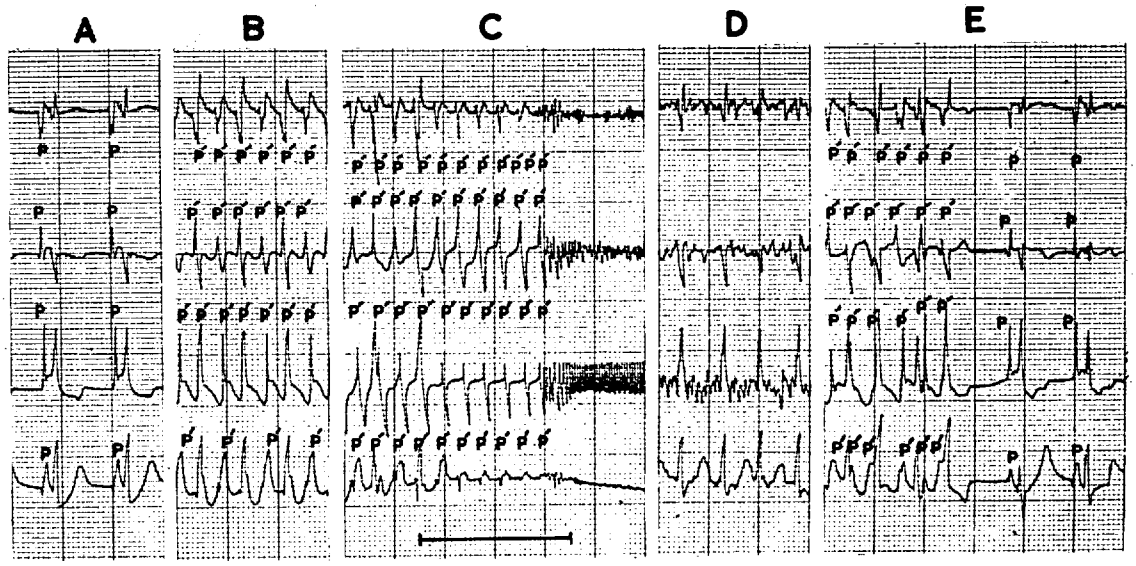


FIG. 38

Fig. 38

Effect of intra-arterial injection of acetylcholine on the post-stimulatory auricular flutter

From top to bottom, electrograms from the region of sinus node, tip of the right auricular appendage, tip of the left auricular appendage, and conventional bipolar lead II.

P = normal sinus beats.

P' = flutter beats, some of the flutter beats are incorporated in the QRS complexes and are not labelled.

(A) Control, heart rate is 162/min.

(B) 20 min. after the production of auricular flutter, auricular rate is 440/min., with 2:1 A-V block.

(C) 2 sec. after the injection of 500 µg. acetylcholine (in 1 ml. of physiological saline, over 5 sec.) directly into the left ventricle. The flutter rate has increased to 452 and later to 610/min. and there is complete A-V block. Fibrillation developed simultaneously in both the auricles and no dissociation is seen. The maximum fibrillation rate reached is 3420/min.

(D) 22 sec. after acetylcholine injection, the fibrillation rate has decreased.

(E) 45 sec. after acetylcholine, auricular flutter has returned but the rate is irregular. Note the abrupt termination of the arrhythmia and return of sinus rhythm in the middle of this excerpt.

Both Fig. 37 and Fig. 38 are recorded from the same animal.

Time scale = 1 sec.

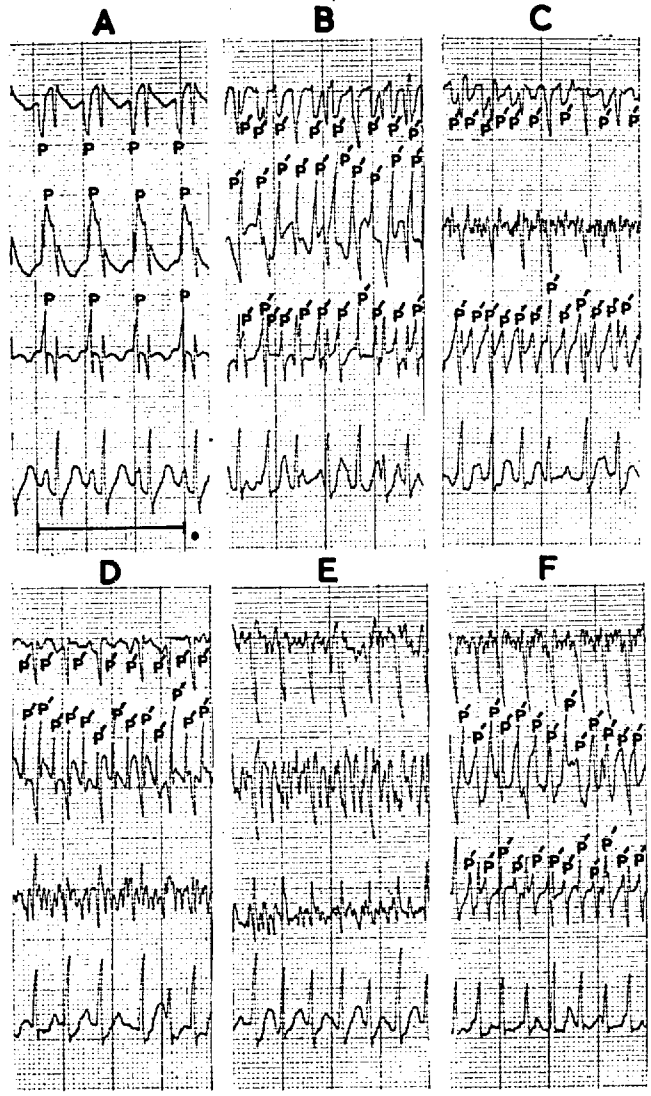


FIG. 39

Fig. 39

Effect of topical application of

acetylcholine on post-stimulatory auricular flutter

From top to bottom, electrograms from the region of the sino-auricular node, tip of the right auricular appendage, tip of the left auricular appendage, and conventional bipolar lead II.

P = normal sinus beats.

P' = flutter beats, some of the flutter beats are incorporated in QRS complexes and are not labelled.

(A) Control, heart rate is 190/min.

(B) 20 min. after the production of auricular flutter, the rate is 454/min.

(C) 15 sec. after the topical application of 5% acetylcholine to the right auricular appendage, note the inter-auricular and intra-auricular dissociation. The right auricular appendage is fibrillating (2160/min), while the electrodes at the sino-auricular node and the left auricle record flutter (572/min). The acetylcholine pledget was removed and within 10 min. flutter at the control rate returned.

(D) 15 sec. after the application of acetylcholine to the left auricle. Note inter-auricular dissociation, the left auricle is fibrillating (1840/min), the right auricle is fluttering (590/min.)

(E) Acetylcholine applied to both the auricles, fibrillation is recorded in both auricles. The acetylcholine pledgets were removed, flutter at the control rate returned in all leads.

(F) 15 sec. after the application of acetylcholine to the crushed area, the sino-auricular electrode has been shifted to the crushed area. Note that the fibrillation is confined to the crushed area (1980/min). The acetylcholine pledget was removed, the fibrillation rate slowed down and then the arrhythmia terminated abruptly and sinus rhythm returned (not shown here).

Time scale = 1 sec.

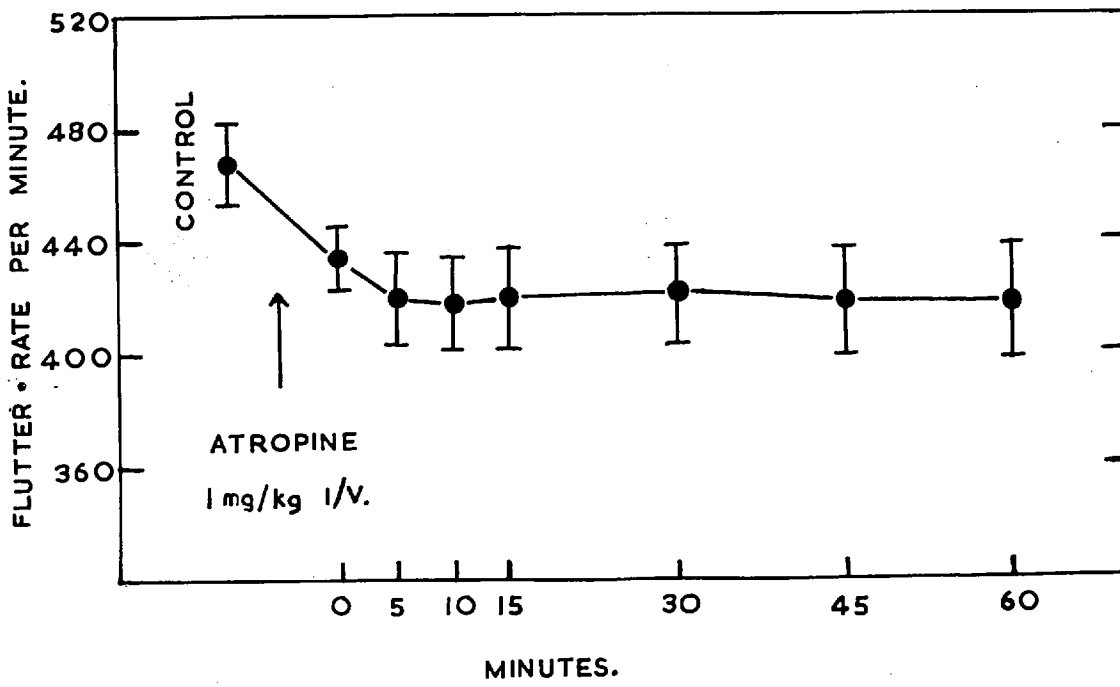

520
480
440
400
360
FLUTTER • RATE PER MINUTE.
CONTROL
ATROPINE
1 mg/kg I/V.
0
5
10
15
30
45
60
MINUTES.

FIG. 40

Fig. 40

Effect of atropine sulphate on
post-stimulatory auricular flutter

Ordinate, flutter rate/min. Abscissa, time interval from the drug injection to the measurement of heart rate. Each point is the mean value $\pm$ S.E. (6 experiments). The peak effect is reached in 5 min.

The drug was injected intravenously, 0.1% solution in physiological saline over a period of 10 min.

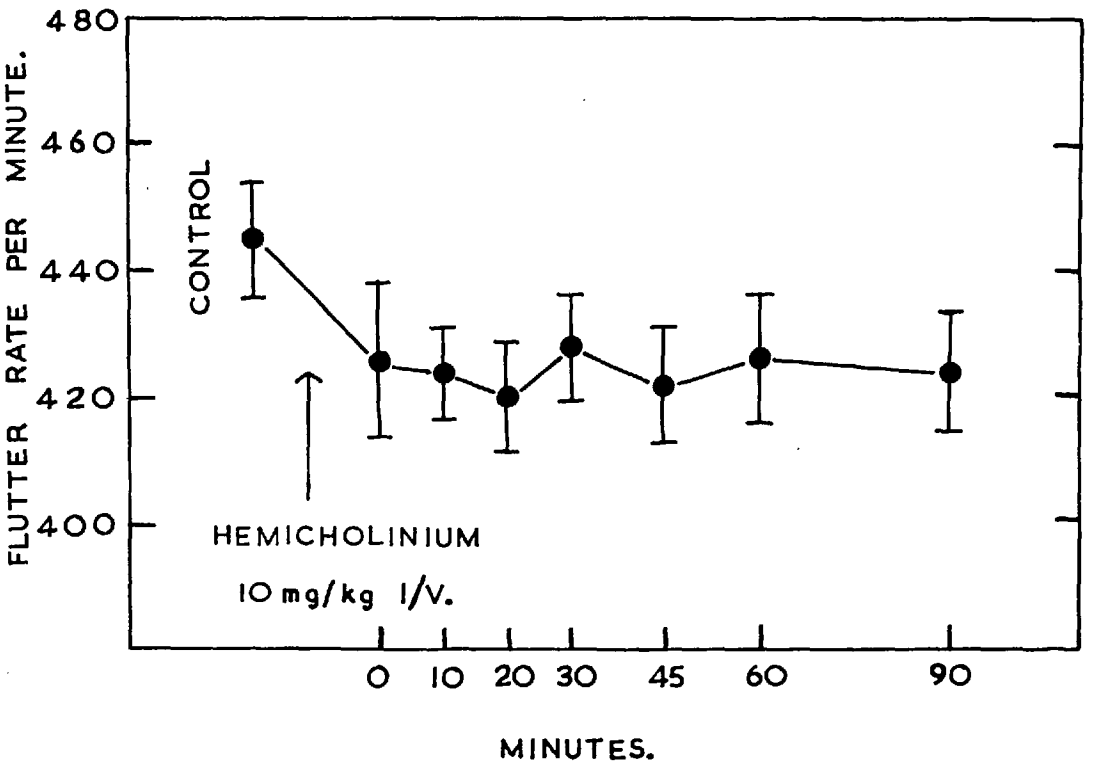

480
460
440
420
400
FLUTTER RATE PER MINUTE.
CONTROL
HEMICHOLINIUM
10 mg/kg I/V.
0
10
20
30
45
60
90
MINUTES.

FIG. 41

Fig. 41

Effect of hemicholinium on the post-stimulatory auricular flutter

Ordinate, flutter rate/min. Abscissa, time interval between the drug injection and measurement of rate. Each point is the mean value ± S.E. (5 experiments). There is a significant decrease in flutter rate, the peak effect is reached in 20 min.

The drug was injected intravenously 0.5% solution in physiological saline, slowly over a period of 10 min.

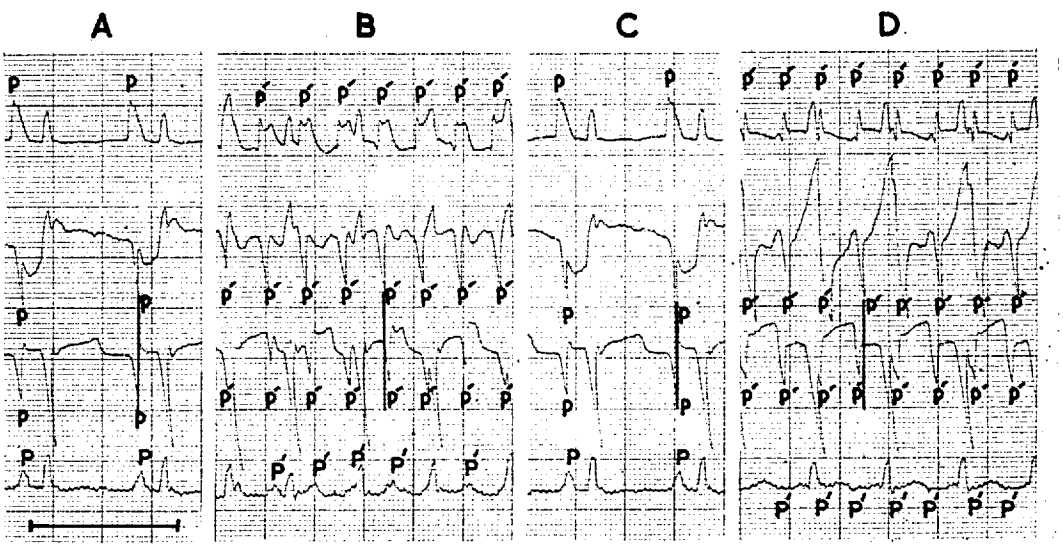


FIG. 42

Fig. 42

Reversal of the sequential activation process in consecutive episodes of auricular flutter

From top to bottom, electrograms from the region of the sino-auricular node, tip of the right auricular appendage, tip of the left auricular appendage, and conventional bipolar lead II.

P = normal sinus beats.

P' = flutter beats.

(A) Control, heart rate is 168/min., the thick vertical line shows almost simultaneous activation of the two auricular appendages.

(B) 20 min. after the production of auricular flutter, the rate is 452/min. The thick vertical line shows that the right auricle is now being activated 0.016 sec. earlier than the left auricle. The flutter waves in lead II are all positive.

(C) The flutter was terminated by a brief electrical shock, normal sinus rhythm at the rate of 166/min. returned. The two auricles are once again beating in phase, as shown by the thick vertical line.

(D) 20 min. after the production of a second episode of flutter, the auricular rate is 450/min., the thick vertical line shows that the activation of the right auricle is now following that of the left auricle by 0.016 sec. The flutter waves in lead II are all negative. This is exactly the reverse of what obtains in excerpt B.

Time scale = 0.5 sec.

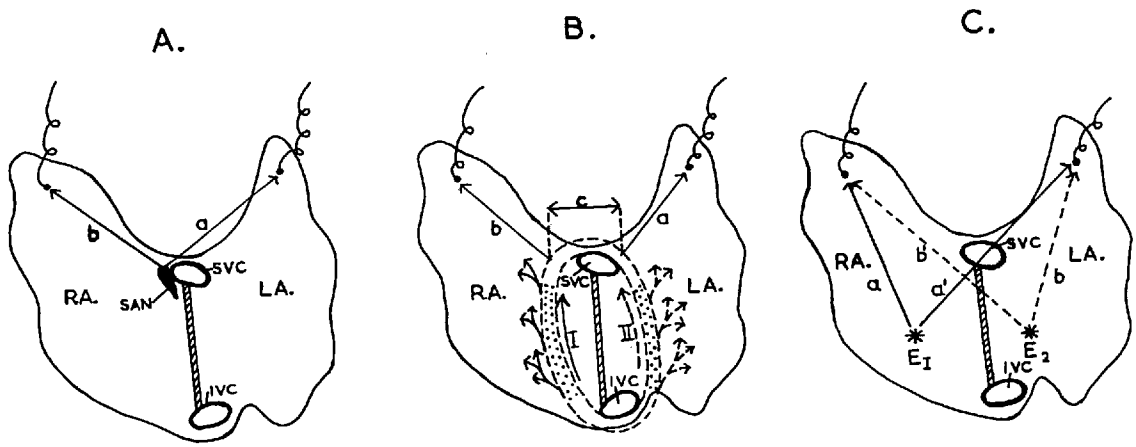


FIG. 43

Fig. 43

Diagrammatic illustration of the sequential activation process in post-stimulatory auricular flutter

(Depicted electrocardiographically in Fig. 42)

R.A. = right auricle. L.A. = left auricle. S.V.C. = superior vena cava. I.V.C. = inferior vena cava. S.A.N. = sino-auricular node.

(A) During normal sinus rhythm. The electrodes on the two auricular appendages are so placed that the sinus impulses reach them at almost the same time.

(B) Explanation of the reversal phenomenon on the basis of circus movement theory.

I. The impulse is circulating in the circuit in a clockwise direction and is reaching the right auricular electrode 0.016 sec. earlier than the left auricular electrode. This is due to the fact that to reach the left auricle the impulse will have to travel a segment of the circuit labelled 'c' (Fig. 42, excerpt B).

II. The reversal has occurred. (Fig. 42, excerpt D). The impulse is now travelling in counterclockwise direction and reaches the left auricular appendage 0.016 sec., earlier than the right auricle. The fixed time lag (0.016 sec.) can be easily explained because now the impulse will have to travel the same segment of the circuit labelled 'c', to reach the right auricle.

(C) Explanation of the reversal process on the basis of the ectopic focus theory. Suppose that E_1 is the site of ectopic focus. The impulse reaches the right auricular appendage 0.016 sec. earlier because the focus is situated nearer to this electrode - i.e. $a < a'$. When the reversal occurred, the impulse is reaching the left auricular appendage 0.016 sec. earlier than the right auricle. To explain this, it will have to be postulated that $b < b'$, and the focus will have to be somewhere in the left auricle, while the electrical stimulation was always being applied to the right auricle. Further to explain the fixed time lag (0.016 sec.) it will have to be presumed that the ectopic focus developed in a definite area E_2, so that $b = a$, and $b' = a'$.

It is, therefore, much easier to explain the reversal phenomenon on the basis of circus wave theory, than on the ectopic focus theory.

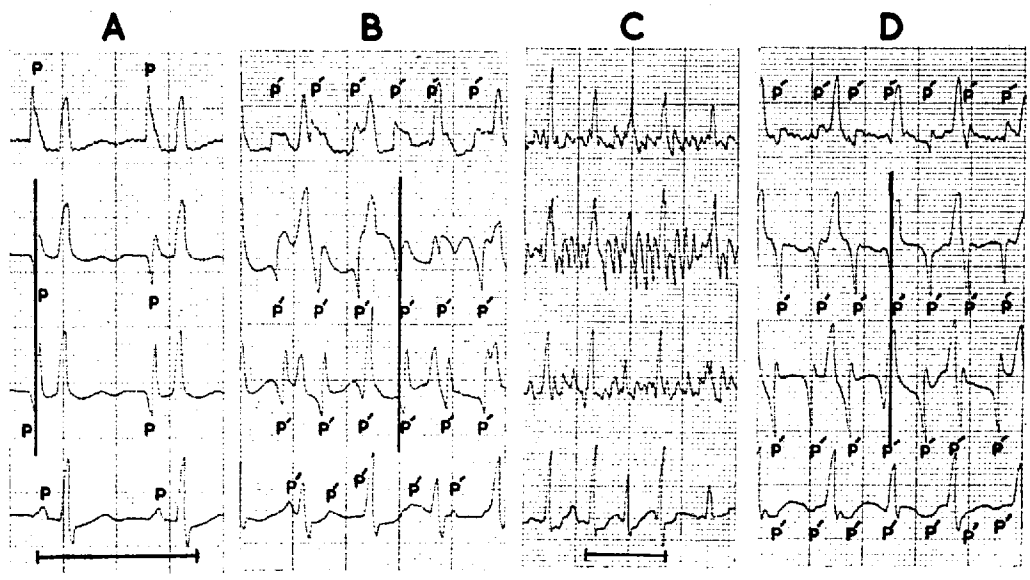


FIG. 44

Fig. 44

Reversal of the sequential activation in the same episode of auricular flutter following acetylcholine-induced fibrillation

From top to bottom electrograms, from the region of the sinus node, tip of the right auricular appendage, tip of the left auricular appendage, and conventional bipolar lead II.

P = normal sinus beats.

P' = flutter beats.

(A) Control, heart rate is 172/min. The thick vertical line shows that the impulse is reaching the two auricular appendages at almost the same time.

(B) 20 min. after the production of auricular flutter, the auricular rate is 510/min. The thick vertical line shows that the impulse is now reaching the right auricular appendage 0.016 sec. earlier than the left auricle. The flutter waves in lead II are positive.

(C) 15 sec. after the intravenous injection of 1.0 mg. acetylcholine, the flutter has been converted into fibrillation.

(D) 1 min. after acetylcholine injection, flutter at the rate of 510/min. has returned but the sequential activation process has been reversed. The thick vertical line shows that the impulse is now reaching the right auricular appendage 0.016 sec. after the left auricle. The flutter beats in lead II are all negative.

Time scale = 0.5 sec.

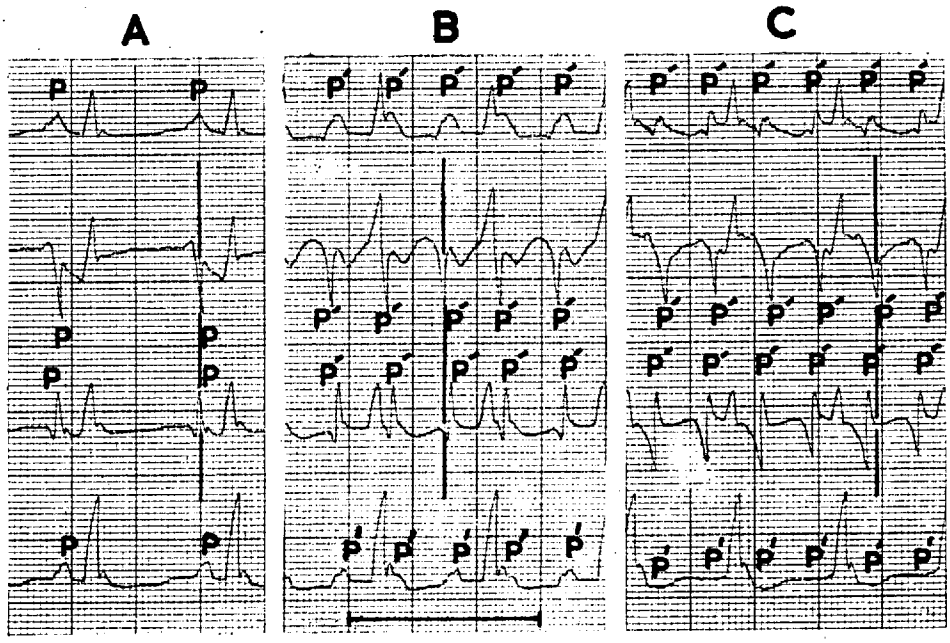


FIG.45

Fig. 45

Reversal of the sequential activation in the same episode of auricular flutter following electrically-induced fibrillation

From top to bottom electrograms, from the region of the sinus node, tip of the right auricular appendage, tip of the left auricular appendage, and conventional bipolar lead II.

P = normal sinus beats.

P' = flutter beats.

(A) Control, heart rate is 165/min. The thick vertical line shows that the impulse is reaching at almost the same time at the right and left auricular appendages.

(B) 20 min. after the production of auricular flutter, the auricular rate is 460/min. The thick vertical line indicates that the impulse is reaching the right auricular appendage 0.02 sec. earlier than the left. Flutter waves in lead II are all positive.

Between B & C, the right auricle was stimulated electrically (square wave pulses of 1 m. sec. duration; 20 volts; 20/sec.) for 10 sec.

(C) recorded 1 min. after the end of electrical stimulation. Flutter rate is 460/min., but the sequential activation has been reversed. The thick vertical line shows that the impulse is now reaching the right auricular appendage 0.02 sec. after the left auricle. The flutter waves in lead II are all negative.

Time scale = 0.5 sec.

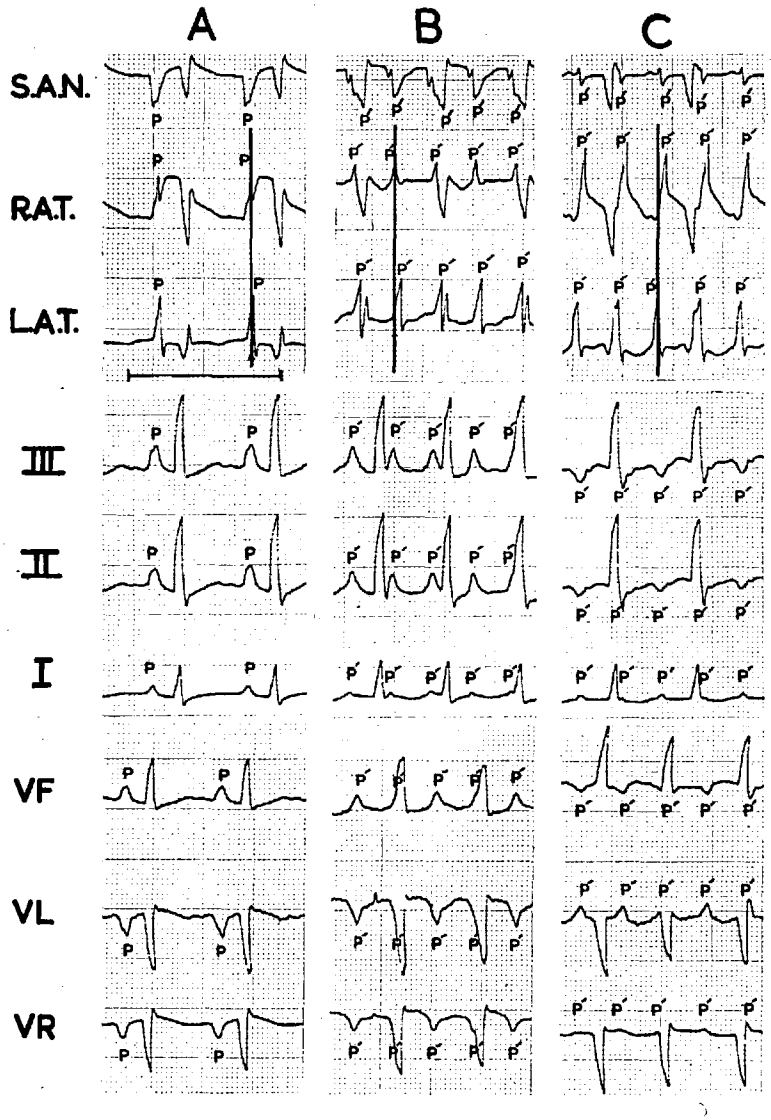


FIG. 46

Fig. 46

Reversal of sequential activation process studied in the direct auricular leads, unipolar and bipolar limb leads in the same animal

SAN = direct lead from sino-auricular node.

RAT = direct lead from right auricular appendage.

LAT = direct lead from left auricular appendage.

P = sinus beats.

P' = flutter beats.

(A) normal sinus rhythm. The thick vertical line shows that the two auricles are beating in phase. P waves are positive in bipolar leads and in VF, negative in VR and VL.

(B) 20 min. after the production of post-stimulatory auricular flutter. The thick vertical line shows that the activation of the right auricle is preceding that of the left auricle by 0.024 sec. Limb leads show a change in the amplitude and form of flutter beats but their direction remains the same as in excerpt A.

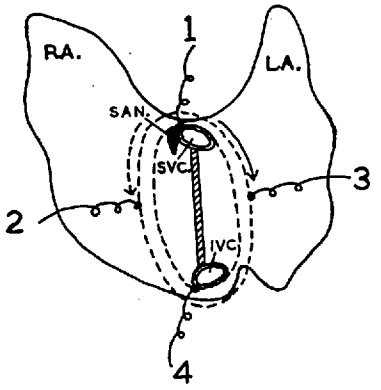
(C) electrical stimulation was applied to right auricle for 10 sec. the arrhythmia did not terminate, flutter at the rate of 454/min. returned but reversal phenomenon has taken place. The thick vertical line shows that the activation of the right auricle is now following that of the left auricle by precisely 0.024 sec. (reverse of excerpt B). Flutter waves are positive in lead I, VR, VL, and negative in Lead II, III and VF. The configuration and direction of the QRS complexes remain unchanged in all the three excerpts.

Time scale = 1 sec.

A:- 1→2&3→4.

B:- 1→3→4→2.

C:- 1→2→4→3.



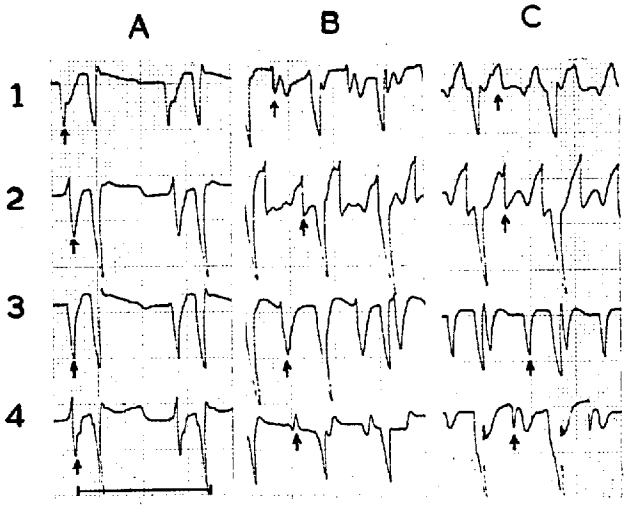


FIG. 47

Fig. 47

Timing of the excitation process around the hypothetical circus pathway in post-stimulatory auricular flutter

Direct electrograms recorded from four points on the hypothetical circus path, as shown in the diagram. The intrinsic deflections of a single flutter beat are marked with arrows in each excerpt. Electrode No. 1 was used as a reference point.

(A) Control, shows the radial spread of impulses from the region of sinus node.

(B) during an episode of flutter, the impulse spread is unidirectional, in a clockwise direction.

(C) reversal of the impulse propagation was induced electrically. The spread is still unidirectional but the direction is counterclockwise.

The time required by an impulse to complete one circuit (P' - P' interval) in any of the leads is 136 m. sec., while the time calculated from the intrinsic deflections in different leads is 128 m. sec.

Time scale = 0.5 sec.

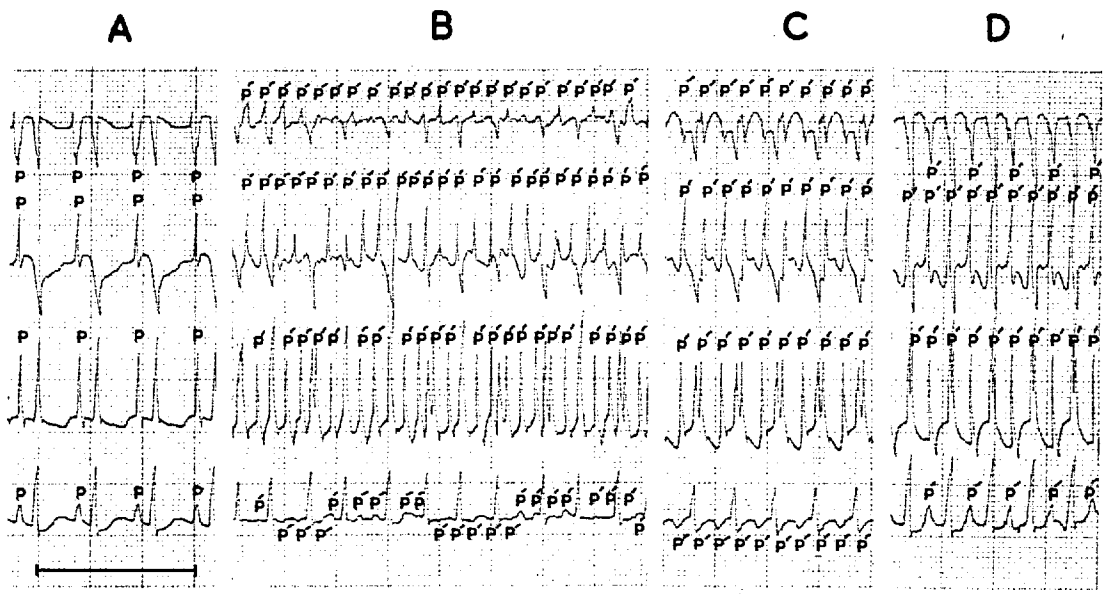


FIG. 48

Fig. 48

Post-stimulatory auricular flutter and fibrillation in the same animal

From top to bottom, electrograms from the region of the sino-auricular node, tip of the right auricular appendage, tip of the left auricular appendage, and conventional bipolar lead II.

P = sinus beats.

P' = flutter beats or fibrillation beats. Some of the P' waves are incorporated in the QRS complexes and are not labelled.

(A) Control, heart rate is 165/min.

(B) Immediately after the electrical stimulation, coarse auricular fibrillation is present. The rate is irregular and varies between 540 - 720/min. The auricular complexes vary in amplitude and form. The P' waves in lead II are positive, negative, biphasic or isoelectric. The arrhythmia terminated spontaneously after 28 sec. and sinus rhythm was re-established (Not shown).

(C) 5 min. after electrical stimulation, auricular rate is 440/min. The left auricle is being activated earlier than the right auricle. All the P' waves in lead II are negative.

(D) the flutter was terminated by a brief shock (not shown here) and re-induced by electrical stimulation 10 min. later. The flutter rate is 440/min. The right auricle is being activated before the left auricle (reverse of excerpt C). All the P' waves are positive in lead II.

Note that the flutter beats in excerpts C and D are all of the same form and amplitude and the two auricles show co-ordinated beating.

Time scale = 1 sec.

VI. D I S C U S S I O N

The experiments reported above were performed to investigate the controversial problem of mechanism of auricular flutter and fibrillation, in the dog.

I. Acetylcholine-induced auricular fibrillation

Scherf et al. (1950b) stated that acetylcholine-induced fibrillation was due to the development of rapidly discharging ectopic foci, in the sino-auricular and auriculo-ventricular nodes. They showed that focal cooling of one of the nodes failed to arrest the fibrillation, but cooling of both the nodes was successful in arresting the arrhythmia. Their findings are, however, open to another explanation. It is only to be expected that the effect of cooling must spread for some distance around the thermode and by cooling both the nodes, the effective cooling must have spread to a large part of the auricles, and so the arrhythmia was arrested. It is important to point out here that these workers failed to arrest fibrillation by cooling both the nodes in 3 dogs, all weighing over 18.[illegible] kg. It, therefore, seems that the mass of auricular tissue plays an important part in determining the outcome of cooling experiments. Again, West & Cox (1960) and Klein & Holland (1960) showed that in acetylcholine-induced fibrillation in isolated rabbit auricles, the sinus node continued to beat slowly and independently. Nelson & Smith (1960) showed the same phenomenon in the frog's heart during

acetylcholine-induced fibrillation. These findings do not agree with the hypothesis of Scherf et al. (1950b).

Further, Moe & Albidskov (1959) showed that auricular fibrillation could persist as a self-sustaining rhythm independent of the focal discharge, in the presence of adequate cholinergic influence. They produced fibrillation by the topical application of aconitine to the right auricular appendage, and clamped off the treated area during vagal stimulation; the fibrillation continued in the body of the auricle for the duration of vagal stimulation, but terminated abruptly soon after the stimulation of the vagus was discontinued. This finding, however, did not exclude the possibility of ectopic foci developing in the nodal tissues under cholinergic influence, as suggested by Scherf et al. (1950b).

In the present study, it has been demonstrated that nodal tissues are not essential for the maintenance of fibrillation, since this arrhythmia persisted in the acetylcholine-treated area when it was clamped off, while sinus rhythm returned in the body of the auricle (Fig. 6). Also, it was possible to induce fibrillation in the functionally isolated right auricular appendage, by focal application of methacholine and electrical stimulation, while sinus rhythm persisted in the body of the auricle. By focal cooling of the sinus node, the auriculoventricular node was also seen to beat at a slower rate (Fig. 7).

Burn et al. (1955a) advocated a method for the production of auricular fibrillation in the heart-lung preparation (HLP) of the dog, by continuous infusion of acetylcholine and electrical stimulation of the auricles. They claim that this is the best method of producing fibrillation (Burn et al. 1956; Burn, 1957a, b; 1959, 1960). The method obviously has certain definite limitations, viz., (a) clinical fibrillation occurs in the intact heart and so the results obtained in the HLP would need to be treated with reservation; the different effects of digitalis on flutter in the denervated and the innervated heart is a suitable example in this context (Farah & Loomis, 1950), (b) the mechanical efficiency of the heart in the HLP is known to decrease the very moment it is isolated from the rest of the circulation (Starling, 1918), (c) the preparation is not suitable for studying quinidine-like activity of drugs, since the important variables of distribution, metabolism and excretion of drugs would not be evaluated in the HLP and both the intensity and duration of action would tend to be exaggerated.

In the present study, fibrillation was produced by continuous infusion of acetylcholine and gently stroking the auricle with a blunt instrument, in the intact heart (Fig. 3). The preparation has all the advantages of the HLP method and is free from the above mentioned disadvantages. The fibrillation continues for the duration of the infusion, and can be re-induced with equal facility. Denervation of the preparation, if desired, can be achieved

by bilateral vagotomy and removal of sympathetic ganglia (1-5th thoracic) on both sides.

Burn et al. (1957) also studied the acetylcholine-adrenaline interaction in the HLP of the dog. They concluded that simultaneous infusion of adrenaline antagonised the fibrillatory activity of acetylcholine. The findings obtained in the present study, do not agree with their results. Both adrenaline and noradrenaline were found to produce short runs of fibrillation in most of the experiments, in a few, flutter developed and continued for the duration of infusion; and their effects were synergistic with the fibrillatory activity of acetylcholine. The antagonism mentioned by Burn et al. was not observed. This discrepancy in results could be due to the intact innervation of the heart in these experiments. These findings are, however, in agreement with the observations of Grant et al. (1949), who showed that adrenaline produced fibrillation more consistantly during vagal stimulation.

There is evidence that both acetylcholine and adrenaline may be involved in inciting fibrillation in man. Vagal hyperactivity has been implicated in auricular fibrillation associated with thyrotoxicosis (Nahum & Hoff, 1935). rheumatic heart disease (Altschule, 1938, 1945), and myocardial infarction (Kleiner & Altschule, 1942). The occurrence of high degree of correlation between partial heart block and fibrillation in these cases, strongly points to vagal involvement. In several cases, fibrillation was

abolished by atropine (Bruen, 1937; Keith, 1938; Kleiner & Altschule, 1942). Smith & Moody (1923), stressed the importance of adrenaline in auricular fibrillation, they found that adrenaline injection frequently precipitated fibrillation in elderly patients. Otto(1927) also noted auricular fibrillation following intravenous injection of adrenaline in man.

The mechanism of the fibrillatory activity of acetylcholine appears to be a shortening of the refractory period (DiPalma & Mascatello, 1951; DeElio, 1947; Burgen & Terroux, 1953; Hoffmann & Suckling, 1953), and accelerated conduction (Prinzmetal et al. 1952; Burn, 1954). Under normal circumstances, the conduction velocity is decreased as the auricular rate is increased (Rijlant, 1946), and acetylcholine by accelerating conduction would allow the auricles to be driven at higher rates. The nodal tissues play no part in the maintenance of fibrillation, since auricular tissue devoid of nodal areas, can be made to fibrillate. Also the occurrence of localized fibrillation, under focal cholinergic influence (Fig. 2), can be explained on the basis of shortened refractory period. In the untreated area, the refractory period imposes a limit to the maximal response rate. In the treated area, acetylcholine shortened the refractory period and so the auricular muscle was able to sustain higher rate of beating. Further, from the experiments of Hoff & Geddes (1955), it appears that a beating auricle is essential for the genesis of fibrillation, since this arrhythmia never occurred during methacholine

induced cardiac arrest. Fibrillation was always preceded by a normal sinus impulse. This is highly suggestive of a re-entry mechanism developing in the treated area. The non-uniform effect of cholinergic influences on auricular refractory period, observed by Alessi et al. (1958) would also support this possibility.

II. Aconitine-induced auricular flutter and fibrillation

The mechanism of aconitine-induced auricular flutter and fibrillation in the dog has been extensively studied (Scherf et al. 1948, 1953a, b; Brown & Acheson, 1952; Prinzmetal et al.,1952; Kimura et al.,1954; Lanari et al.,1956). All these workers agree that this arrhythmia is due to focal discharge, and that impulses spread out from the focus in a radial direction. The cooling and clamping experiments of Scherf et al. (1948), the high speed cinematography and direct auricular lead studies of Prinzmetal et al. (1952), are fully consistant with the focal origin of this arrhythmia. Unfortunately, these experiments reveal nothing about the mechanism of impulse formation within the ectopic focus. These workers, however, suggested that the mechanism of impulse formation in the aconitinised tissue was repetitive discharge from a single cell. This conclusion was based mainly on the findings obtained in the nervous tissue, and the similarities of nervous and cardiac tissues were stressed in great details, with no mention at all about their dissimilarities.

It must be pointed out here that the radial spread of impulses cannot be explained on the basis of circus movement theory as

outlined by Lewis (1918, 1925), but as pointed out by DiPalma & Schultz (1950), Dawes (1952), and Tenney & Wedd (1953, 1954), the arrhythmia could be due to localized circus movement in the aconitine treated area. Such a localized circus movement would behave as a rapidly discharging focus in the cooling and clamping experiments, and the impulses would spread from this focus in a radial fashion. No experimental evidence is available in the literature to prove or to disprove this possibility. Theoretically, it is not difficult to comprehend how aconitine could create conditions suitable for the establishment of a localized circus movement.

The crucial requirement for re-entry to occur is that some fibres are able to conduct at a time when others are not. Now the auricular myocardium is a syncytium and conduction can occur practically in all directions. Again, aconitine is known to produce a shortening of refractory period (Tenney & Wedd, 1953; Dawes & Vane, 1956), and to prolong conduction time(Tenney & Wedd, 1954; Yelnowsky & Clark, 1960). The diffusion of aconitine around the central spot, where it was initially applied would affect a block of tissue, roughly circular in shape, in which the drug effect would decrease from centre to periphery. This would result in local areas of profound assymetry in terms of tissue function (refractory period, conduction velocity and excitability). Sinus impulses entering this area would no longer produce uniform depolarization, and this would favour re-entry. Thus it is possible that a single impulse could travel around a centrally non-

functioning area and send out impulses in a radial fashion, so that the whole area would appear as a rapidly discharging focus. It would be difficult to recognise such a mechanism in either high speed films or in cooling and clamping experiments.

Evidence against repetitive focal discharge from a single cell.

Repetitive discharges have been demonstrated to occur in the cardiac muscle, under certain experimental conditions. Brooks et al. (1955) produced them by applying an extra stimulus during the vulnerable phase of the preceding beat, in the dog's heart, while Dawes & Vane(1951a) produced them in the isolated guinea-pig auricles in the same manner.

In the present study, aconitine produced flutter in the normally beating heart, without the application of any extra stimulus. Under these circumstances, how could the repetitive discharge begin? It is possible that a premature systole originating in the aconitinised tissue could act as the extra stimulus. If this be so, then the flutter is atleast started by re-entry mechanism and is perpetuated by repetitive discharge. Dawes & Vane (1951a) worked on the mechanism of repetitive discharge, and concluded that it originated in a single cell, but later they studied the problem by multipoint recordings and concluded that a re-entry mechanism was involved (Dawes, 1952). Also, there is evidence that the repetitive discharges in the cerebral cortex may be due to re-entrant excitation in the neurone circuits, and the close analogy of the network of cortical cells, dendrites, and axons and the branching syncytium of the cardiac muscle has been stressed (Burns, 1950,

1951). The occurrence of uni-directional conduction in the relatively refractory nerve has also been demonstrated (Rosenblueth et al. (1949).

Aconitine is also known to produce negative after-potentials (Graham & Gasser, 1931; Seegers, 1941, 1942), and attempts have been made to explain the phenomenon of repetitive discharge on this basis. These potentials are oscillatory in character and once they reach the threshold value, repetitive firing takes place (Aravantaki, 1940). Brooks et al. (1951) suggested that the supernormal phase of excitability in the cardiac cycle could be due to these negative after-potentials, while Goldenberg & Rothberger (1953) showed that the appearance of premature systoles in early diastole could be related to the supernormal phase of excitability, during negative after-potentials. It is, however, difficult to comprehend how such a mechanism could produce single premature systoles. A premature systole has a short refractory period (DeBoer, 1918, 1920; DiPalma, 1955), and it would be expected that the subsequent oscillatory potentials should also elicit contractions, as seen in Aravantaki's experiments on nerve (Aravantaki, (1940). Also, the premature systoles produced by aconitine occur in late diastole, a little before the next sinus beat. Again, veratrine is known to produce negative after-potentials more than any other drug but did not elicit premature systoles with fixed coupling (Scherf et al. 1952). The explanation of DiPalma & Schultz (1950), to account for the occurrence of supernormal phase of excitability near the end of relative

refractory period seems to be more plausible. They believe that this is the period in the cardiac cycle in which a local state of inequality of recovery of heart muscle exists most frequently. In other words , it is that period in cardiac cycle where a local block exists due to delayed recovery of certain areas and re-entry in cardiac muscle exhibiting local blocks is an obvious possibility. Further, it is possible that negative after-potentials are mere electrical correlates of unequal recovery in the aconitinised tissue, and as suggested by Brooks et al. (1951), it is not unreasonable to assume that an excitatory process persisting in a tissue manifesting oscillatory potentials is more likely to be disorganised, than an excitatory process developing in a tissue of uniformly changing excitability. Any influence which tends to disorganise the orderly sequence of excitatory process would tend to permit re-entry, because of syncytial nature of the myocardium.

Another factor worth consideration in the causation of repetitive discharges, is the role of eddy currents. This factor has been stressed by Brooks et al. (1955). When an action potential encounter a block (injured area), eddy currents flow and partially depolarise the membrane distal to the block. This concept is very attractive and will explain why aconitine does not produce flutter in quiescent auricle. It is possible that eddy currents set up in the area injured by aconitine, maintain the muscle in a heterogenous state of excitability by producing partial depolarisations. Sinus impulses

entering this area will no longer produce uniform depolarisation, and this would permit re-entry to develop.

Evidence in favour of re-entry mechanism.

According to Mines (1913), the development of re-entrant excitation requires a short refractory period and prolonged conduction time. Aconitine is known to produce both these effects on the auricle (Tenney & Wedd, 1953, 1954; Dawes & Vane, 1956; Yelnowsky & Clark, 1960). In the present study, aconitine has been shown to produce tissue injury (Fig. 12), and the initiation of flutter has been shown to depend on the entry of sinus impulses into the aconitinised tissue. Also, the similarity of the form of premature systoles and of flutter beats and the irregularly irregular rate at the start of the arrhythmia has been stressed. All these findings fit in well with the re-entry concept.

The premature systoles with fixed coupling preceed the aconitine-induced flutter, in most of the experiments (Fig. 8- 11). This could be due to the development of local blocks in the aconitinised tissue. It is therefore, the local blocks which preceed the development of premature systoles and flutter. Fig. 12 shows that monophasic action potentials developed several seconds before the premature systoles appeared. These premature systoles with fixed coupling are believed by some workers to originate by re-entry mechanism (Schmitt & Erlanger, 1928; DiPalma & Schultz, 1950; Barker, 1952; Langendorff et al. 1955; Katz & Pick, 1956), while others (Scherf & Boyd, 1953; Scherf & Schott, 1953, 1959; Scherf, 1959) believe that they are due to repetitive

discharge. The irregularly irregular rate of the arrhythmia in early stages, and during recovery from focal cooling (Fig. 8- 11), would support the re-entry mechanism, since both repetitive discharges (Dawes & Vane, 1951a; Brooks et al. 1955) and negative after-potentials (Aravataki, 1940) are known for their clock-like regularity of rate. The increase of flutter rate under cholinergic influence would also favour re-entry mechanism, as discussed below.

Role of nodal tissues.

Yelnowsky & Clark (1960) could not induce flutter with aconitine in the quiescent left rabbit auricle. They concluded that the arrhythmia was due to stimulation of sinoauricular node by aconitine. Findings obtained in the present study, donot support this possibility, since flutter persisted in the aconitine-treated area when it was isolated from the nodal tissues by a clamp. The genesis of the arrhythmia has been shown to be dependent upon the entry of sinus impulses into the aconitinised tissue (Fig. 13- 15), and this would explain the inability of these workers to produce flutter in the quiescent auricle.

Role of cholinergic influences.

Scherf et al. (1953b, 1955) showed that aconitine did not induce flutter in the atropinised dogs. The findings obtained in the present study show that aconitine regularly produced flutter after atropine, and that this flutter can be distinguished from the atropine-induced sinus tachycardia, by the contour of flutter beats in the direct auricular leads but not in limb leads and in clamping experiments (Fig.

22 - 26). Similar results were obtained when acetylcholine synthesis was blocked by hemicholinium (Fig. 27). The inability of Scherf et al. to demonstrate the slow rate flutter after atropine could be due to the fact that they did not record direct auricular leads. As shown in Fig. 23, the flutter waves in lead II are positive and cannot be distinguished from sinus beats, but the difference is very obvious in direct auricular leads recorded from aconitine-treated area. These findings show that acetylcholine is not essential for initiation or maintenance of flutter. It does, however, play a part in determining the rate of ectopic rhythm. The demonstration of antiacetylcholine action of aconitine in isolated guinea-pig auricles and ileum (Fig. 29), also suggests that acetylcholine may not be concerned in the development of flutter, in fact, the reverse may be true.

These results do not support the hypothesis of Torchiana & Angelakos (1961), that acetylcholine may be concerned in the development of all types of auricular arrhythmias.

The conversion of flutter into fibrillation by vagal stimulation in the dog has been described by Brown & Acheson (1952), Scherf et al. (1953a) and Lanari et al. (1956). The present experiments confirm the fibrillatory activity of acetylcholine. The fact that fibrillation was never observed in the atropinised dogs , and that atropine converted fibrillation into flutter lends further support to this view. This fibrillatory activity of acetylcholine appears to be due to its effect on refractory period. By decreasing refractory period

of the auricle (Samojloff, 1914; Lewis et al. 1920a; Andrus & Carter, 1930; DeElio, 1947; Burgen & Terroux, 1953), acetylcholine determines the rate of localised circus movement. Also the effect of acetylcholine on refractory period is known to be non-uniform (Alessi et al. 1958), and the presence of an adequate amount of acetylcholine, will tend to throw adjacent fibres out of phase, making an orderly spread of impulses impossible, and end-result is fibrillation. Thus the reduction of refractory period appears to be the most important factor to account for the fibrillatory activity of acetylcholine. This is in agreement with the hypothesis of Burn (1957a,b)and Moe & Albidskov (1958).

Prinzmetal et al. (1952) suggested that auricular tachycardia, flutter and fibrillation were all due to single ectopic focus, and that the rate of discharge determined the type of arrhythmia developed. The occurrence of localised fibrillation (Fig. 19) showed that mechanism of flutter and fibrillation was not the same, since it was possible to induce localised fibrillation in left auricle, while the right auricle containing the ectopic focus continued to flutter. The same objection also applies to the hypothesis of Scherf et al. (1953b) that fibrillation was due to the development of ectopic foci in nodal tissues. Thus the shortening of refractory period by acetylcholine, permitting re-entrant excitation, appears to be most plausible of all explanations to account for the phenomenon of localised fibrillation.

Further, acetylcholine exerted different effects on sinus rhythm and on flutter (Fig. 20, 21). The flutter was converted into fibrillation, while the sinus rhythm was inhibited. This finding also suggests that the mechanism of impulse formation in the sinus node and aconitine-induced ectopic focus is not the same. Proponents of ectopic focus theory do not provide an adequate explanation for the increased flutter rate under cholinergic influence (Scherf, 1947; Scherf et al. 1953a) and they concede that this fact can be better explained on the basis of circus movement theory. However, Scherf et al. (1953a, b), suggested that acetylcholine inhibited slower rhythms (sinus rhythm) and stimulated the faster ones (auricular flutter). The results obtained in this study, do not support this hypothesis (Fig. 21). Another possibility considered by Scherf et al. (1950a) was that the stimulus formation was rhythmic in sinus node and this was inhibited by acetylcholine. Stimulant effect of acetylcholine on flutter may be due to a continuous stimulus in the aconitine-treated area. Unfortunately, they did not state, what form of continuous stimulus it could be. Such a continuous stimulus could be a re-entrant excitation, or even a small circus movement, as shown in the present study.

This being so, the only difference between the mechanism of impulse formation in aconitine-induced and post-stimulatory flutter is that the former is due to localised circus movement, while the latter is due to classical circus movement. This would explain why both respond to cholinergic influences by an increase of rate, a fact which supporters of the ectopic focus theory find difficult to explain.

Role of adrenergic influences

The increase in flutter rate following sympathetic stimulation is partly due to reflex increase in vagal tone. Atropine only partially antagonised the rate increasing effect, but prevented the development of fibrillation. This is in agreement with observations of Scherf (1949). Similar results were obtained with adrenaline and noradrenaline (Fig. 28). The rate of sinus rhythm as well as of flutter was increased. This is in contrast to the differential effect of acetylcholine discussed above. Atropine completely blocked the fibrillatory activity of adrenaline and noradrenaline, but the rate increasing effect was only partially antagonised.

The increase of flutter rate could be due to a shortening of refractory period and accelerated conduction (Brooks et al. 1955). The fall in rate, after the initial increase, could be due to the rebound phenomenon, i.e. the refractory period transiently increasing above the control value as the adrenergic effect disappeared; the secondary rise being due to disappearance of this rebound. As no decrease in flutter rate was observed after noradrenaline, it could be that the rebound is more marked after adrenaline than noradrenaline. Another reason for this discrepancy may be that noradrenaline is known to act on alpha receptors (excitatory) only, while adrenaline acts on both alpha and beta (inhibitory) receptors.

Depletion of cardiac stores of adrenaline and noradrenaline

by reserpine pretreatment, enhanced the fibrillatory activity of aconitine, and fibrillation lasting for over one hour was produced in all the experiments. This could be due to the unopposed cholinergic influence. Malhotra & Das (1962) showed that acetylcholine content of the auricles was increased by as much as 50 per cent, following catecholamines depletion by reserpine, in the dog.

Acute denervation of the heart did not affect the intensity or duration of aconitine-induced flutter. This could be due to the fact that cardiac stores of acetylcholine and catecholamines remained intact.

Dual effect of aconitine.

Aconitine per se produced a cholinergic effect which was blocked by atropine, and it produced a competitive blockade of acetycholine responses, in isolated guinea-pig auricles and ileum preparations. It must be pointed out here that experiments on isolated tissues were done to study the autonomic effects of aconitine . Guinea-pig ileum was used because, it was not possible to study the effect of large doses of aconitine on the auricles, due to the rapid development of ectopic rhythm. Also care must be exercised in the application of findings obtained in the gut, to the heart. In the present study, however, some generalisations about the mode of action of aconitine on the heart can be made, since there are no drugs known which exert a selective acetylcholine-like or antiacetylcholine action on the gut but not on the heart.

Acetylcholine is known to shorten the refractory period and to increase conduction velocity. Diffusion of aconitine around the central spot where it was initially applied would affect an area, roughly circular

in shape, in which drug effect would decrease from centre to periphery. In the centre, the antiacetylcholine effect of aconitine would produce a lengthening of the refractory period and decreased conduction velocity, while at the periphery cholinergic influence of aconitine would produce a shortening of refractory period and accelerated conduction. The effect on tissues between centre and the periphery would be a mixture of these effects. Thus aconitine would create all the conditions known to favour re-entrant excitation, in the treated area. The acetylcholine-like action of aconitine is not essential for the production of flutter, since atropine does not terminate the arrhythmia. This will, however, explain the occurrence of slower flutter rates after atropine. The shortening of refractory period and accelerated conduction at the periphery of the treated area will be antagonised by atropine, and this will slow the flutter rate.

Thus the principal action of aconitine in producing flutter appears to be tissue depolarization, as seen from the development of monophasic action-potentials (Fig. 12). The most probable site of action of aconitine is acetylcholine receptors. Eddy currents emanating from the injured area (depolarised region), may be playing a part in maintaining the surrounding tissue in a heterogenous state of polarisation. Sinus impulses entering this area will no longer produce uniform depolarization, and this will favour re-entrant excitation. The cholinergic effect of aconitine determines the rate of re-entry or of localised circus movement.

III. Post-stimulatory auricular flutter and fibrillation

Recently the mechanism of post-stimulatory auricular flutter and fibrillation has been studied by several workers. Strong experimental evidence in support of circus movement theory has been presented by Rosenblueth & Garcia Ramos (1947a, b), Selfridge (1948), Brown & Acheson (1952), Kimura et al. (1954) and Lanari et al. (1956). On the other hand, Scherf et al. (1948, 1953a, b), Prinzmetal et al. (1952) and Puech (1956) have advanced convincing evidence in support of ectopic focus theory. The experiments discussed below were undertaken in an attempt to clarify the situation.

Reversal of sequential activation.

The phenomenon of sequential activation of the two auricles was first described by Lanari et al. (1956). They explained the reversal process in consecutive episodes of flutter on the basis of circus movement theory. These workers, however, did not study the timing of the intrinsic deflections before and after the reversal phenomenon. The findings obtained in the present study support and extend their observations. It has been demonstrated that the time lag between the activation of the two auricular appendages, before and after the reversal of sequential activation in consecutive episodes of flutter in the same animal remains remarkably constant (Fig. 42). Also a reversal of sequential activation in the same episode of flutter, following its conversion into fibrillation by acetylcholine or electrical stimulation has been demonstrated (Fig. 44, 45). These findings can be best

explained on the basis of circus movement theory, than the ectopic focus theory. As depicted in Fig. 43, the reversal of sequential activation and the fixed time lag can not be explained on the basis of ectopic focus theory. It is difficult to comprehend, how in one episode of flutter the activation of one auricle precedes that of the other, and in a subsequent episode or in the same episode of flutter following acetylcholine or electrically-induced fibrillation, the reverse holds true. To explain this on the basis of the ectopic focus theory, it must be assumed that ectopic focus some time developed in the right auricle and at others in the left. Further, to account for the fixed time lag before and after the reversal process, an unlikely presumption must be made, that such an ectopic focus always developed in two identically situated areas of the two auricles (Fig. 43, sites E_1 & E_2). Both these findings, however, can be easily explained on the basis of circus movement theory, since the excitation process can travel in the circuit in a clockwise or counter-clockwise direction.

The simultaneous recording of direct auricular and bipolar and unipolar limb leads, showed that the limb leads also exhibit the reversal process. Two distinct patterns of flutter waves were seen, depending upon whether the activation of right auricle preceded or followed that of the left auricle (Fig. 46). These two patterns of flutter waves have also been noted in the limb lead tracings of clinical flutter published by other workers (Barker, 1952; Goldberger, 1952; Katz & Pick, 1956; Lipman & Massie, 1959). It is, therefore,

suggested that limb lead tracings of clinical cases of flutter, having repeated attacks, should be studied for the reversal of flutter waves. If one pattern of flutter waves is found to change into the other, that would be a convincing evidence in support of circus movement theory, in clinical auricular flutter.

Timing of single flutter beat around the circus pathway.

Timing of intrinsic deflections around the hypothetical circus pathway, has clearly shown the unidirectional spread of impulses , in post-stimulatory flutter (Fig. 47). The impulse circulated in the circuit in a clockwise or counter-clockwise direction. Lewis et al. (1920a) also studied the time course of excitation process in flutter, but they could not explore the left auricle and presumed that impulse returned in the left auricle towards the inferior vena cava. In this study, the cycle length of flutter calculated from auricular rate (P - P' interval)and that from the intrinsic deflections in four leads located on the circus pathway, were found to be equal. This finding and the unidirectional spread of impulses cannot be explained on the basis of ectopic focus theory. The evidence presented above, therefore, conclusively shows that post-stimulatory flutter is due to circus movement mechanism. Evidence in support of circus movement mechanism in some cases of clinical auricular flutter has been presented by some workers (Lewis et al. 1921b; Decherd et al. 1945; Grishman et al. 1950; Wenger & Hoffmann Credner, 1952), but other workers do not agree with their interpretations (Groedel & Miller, 1950; Prinzmetal et al. 1952; Scherf & Schott, 1953; Puech, 1956).

Role of cholinergic factors.

The increase in flutter rate and its conversion into fibrillation, under cholinergic influence was first studied by Rothberger & Winterberg (1910), Robinson (1913) and Lewis et al. (1921a). Lewis et al. (1921a) offered two explanations for this phenomenon. Firstly, a shortening of refractory period would lead to disappearance of islands of refractory tissue , making the central wave to pursue its path in a less sinuous way and, therefore, with an increased speed. Secondly, under vagal stimulation the central wave would follow an even shorter path around the venae cavae. When the cholinergic influence was stronger, the central wave would break up and fibrillation would occur. They also explained the abrupt termination of flutter in some cases, during vagal stimulation; the refractory period was shortened so much that the central wave met refractory tissue and was abolished.

In the present study, abrupt termination of flutter under vagal stimulation was not observed. Unless vagal stimulation converted flutter into fibrillation, the flutter was never terminated. This could be due to the some what different technique employed in these experiments. The flutter persisted for hours in these control experiments, but in those of Lewis's its duration varied from a few seconds to a few minutes, and could not be predicted in advance. It is, therefore, possible that some of the effect seen in their experiments, under vagal stimulation , could be due to spontaneous

reversion of flutter. Once the flutter was converted into fibrillation it usually terminated abruptly. Similar results were obtained when flutter was converted into fibrillation, by acetylcholine or electrical stimulation. This finding can be explained on the basis of breaking up of the central wave, under cholinergic influence. On the basis of these findings it is suggested that acetylcholine may prove useful in the treatment of clinical auricular flutter. Vagal stimulation is known to increase the rate of clinical flutter, and to convert it into fibrillation (Wilson, 1924; Bussan et al. 1957). Schoolman et al. (1960) tried acetylcholine in 14 cases of auricular flutter in man. Sinus rhythm returned only in two cases. However, they did not report, whether the flutter was ever converted into fibrillation by acetylcholine. This study has demonstrated that unless acetylcholine converted flutter into fibrillation, the arrhythmia always returned. It is important, therefore, that the dose of acetylcholine used in clinical cases should be large enough to convert flutter into fibrillation.

The hypothesis that the central wave breaks up under strong cholinergic influence, would not explain the return of flutter in some of the experiments, when the cholinergic influence disappeared. Theoretically, it is possible that impulses from the fibrillating auricles entering the crushed area, recovering from cholinergic influence may restart circus movement. The reversal of sequential activation in the same episode of flutter, following its conversion into fibrillation by acetylcholine or electrical stimulation, has provided the experimental

evidence in support of this possibility. The response of clinical auricular flutter to digitalis therapy, presents a similar problem. Digitalis by virtue of its vagomimetic effect converts flutter into fibrillation and when the drug is withdrawn, sinus rhythm returns in some cases, while in others flutter returns (Goodman & Gilman, 1955). On the basis of the above mentioned evidence it is suggested that the limb lead tracings of patients in whom flutter returns, should be studied for reversal of flutter waves.

This fibrillatory activity of acetylcholine is due to its effect on refractory period. The non-uniform effect of acetylcholine on refractory period (Alessi et al. 1958) would break up the central wave and result in fibrillation. This will also explain the occurrence of localised fibrillation, under focal cholinergic influence. The shortening of refractory period in the treated area would permit re-entry and fibrillation, while the rest of the auricle would not respond to rates higher than 600/ min., due to the long refractory period.

The results obtained with atropine and hemicholinium demonstrate that cholinergic influences are not essential for the development and perpetuation of auricular flutter. Available evidence suggests that this may be true for clinical flutter as well. Jolly & Ritchie (1910) and Wedd (1924) showed that following atropine administration in clinical flutter, the only effect observed was a slight decrease in rate; the flutter did not terminate.

Role of adrenergic influences.

The increase in flutter rate following sympathetic

stimulation is partly due to reflex increase in vagal tone. Atropine only partially antagonises the rate increasing effect, but prevented the development of fibrillation. Similar results were obtained after intravenous injection of adrenaline and noradrenaline.

Both adrenaline and noradrenaline are known to shorten refractory period and to increase conduction velocity (Brooks et al. 1955). This would account for the increase in flutter rate. This evidence that adrenaline shortens the refractory period is, however, conflicting. Webb & Hollander (1956) and Furchgott et al. (1960) showed that it prolonged the duration of action potential, while Brooks et al. (1955) and Toda (1960) showed that the duration of action potential was shortened by adrenaline.

The failure of long-lasting flutter to develop after the depletion of cardiac stores of catecholamines by reserpine, could be due to unopposed vagal effect. Malhotra & Das (1962) showed that cardiac acetylcholine content was markedly increased, following reserpine treatment in the dog. This could be the reason for the development of fibrillatory episodes instead of flutter, after electrical stimulation.

Possibility of ectopic foci developing in crushed area.

Scherf et al. (1953b) suggested that post-stimulatory auricular flutter could be due to the development of ectopic foci in the crushed tissue. They believe that crushed area contained elements of sinus node, and injured nodal tissue would act as ectopic focus. The experiments involving the crushing of the whole of the sinus node, and the crushing of inter-venae caval bridge in stages done in the present

study show that the most vital factor is the extent of crushed area, and not injury to the nodal tissues.

Post-stimulatory auricular flutter versus fibrillation

The occassional occurrence of transient episodes of fibrillation (Fig. 48)may be due to shortening of refractory period by stimulation of vagal nerve endings, as suggested by Lewis & Cotton (1921). Lewis et al. (1921 c,d) observed that like flutter, fibrillation was also due to circus movement. The rate was faster and uneven in fibrillation, because the path was shorter and more sinuous. Scherf et al. (1953a,b) believe that fibrillation was due to ectopic foci in nodal tissues, while Prinzmetal et al. (1952) maintain that both flutter and fibrillation were due to single rapidly discharging ectopic focus. In the present study, a comparison of flutter and fibrillation characteristics, in the same animal, suggests that the mechanism of flutter and fibrillation is not the same. Also the occurrence of localised fibrillation under cholinergic influence, is difficult to explain on the basis of any of the above mentioned hypotheses. This shows that the cause of fibrillation is to be found in the treated area.

The phenomenon of fibrillation is, therefore, better explainable on the basis of mutiple re-entries, than on circus movement theory as outlined by Lewis or mutiple ectopic foci theory. This is in agreement with the hypothesis of Moe & Albidskov (1959).

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2. A study on the mechanism of cardiac arrhythmias, veratrine response and antiveratrinic action as a common property of antiarrhythmic drugs (1960). Arch. int. Pharmacodyn, 124, 386.

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