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AN ANALYSIS OF EFFECTS OF PROCAINE AND RELATED SUBSTANCES ON THE DOG'S HEART.

A dissertation submitted to the

Graduate School of Arts and Sciences
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in partial fulfillment of the
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DOCTOR OF PHILOSOPHY

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by

Barbara B. Brown

A.B. Ohio State University 1938

The contribution of many important ideas by Dr. George H. Acheson, as well as his helpful criticism and direction throughout this study are genuinely appreciated. The continued interest and support of Drs. E. F. Van Maanen and M. B. Macht have contributed to the enthusiasm and persistence needed to carry the investigation to its present state. Many thanks are due also to Robert Feldman for his technical assistance and to Clara Sterrett for her efficient secretarial help.

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PROLOGUE

"'Tis not a fib, 'tis fibrillation."
after Shakespeare

Procaine is reputed to be in widespread use in ventricular fibrillation. The rationale for this use is not established. Fundamentally the cardiac use of procaine is related to disturbances of the conducted impulse in the heart. It follows that evaluation of the cardiac action of procaine and related substances is best made by studying its action on both conduction of the impulse and response of the heart to the impulse. The auricle provides a convenient test object; its beat is easily controlled, and its thin myocardium permits easier and less complicated measurements of function than does the ventricle.

The development of new therapeutic agents calls for a systematic pharmacological evaluation. If the evaluation is to have meaning, it should begin with a solid physiological foundation. The study presented here is an attempt in this direction. The objectives are first, the development of methods for the study of cardiac drugs and second, the evaluation of the actions of procaine and some related substances on the heart.

CHAPTER I

The Cardiac Actions of procaine.

History

The changes which occur in cardiac tissue as a result of impulse conduction have received considerable study. The conduction of an impulse through a tissue results in changes in electrical excitability, refractory period, conduction velocity, etc. Events occurring in the auricle also affect the response of the specialized auriculo-ventricular tissue. For the most part these aspects of cardiac function as they change during passage of the impulse or as they are affected by stimulation of the cardiac nerves have been studied as discrete entities. Correlation of the change of any one factor with respect to another has been somewhat difficult since the experimental data have been obtained in many different species of animal and by varied techniques. There has not yet been devised a systematic plan of study whereby the effects of pharmacologically active substances could be compared.

The first report on a cardiac action of procaine was made by Watanabe (1) in 1923. He reported that the local application of procaine to the sinus node of the frog's heart caused auriculo-ventricular dissociation. Shookhoff (2) in 1926 duplicated this result in the dog heart and also stated that the injection of procaine into the jugular vein produced right bundle branch block.

Van Dongen (3) was the first investigator to study extensively certain auricular actions of procaine. He found that procaine raised the threshold of the electrical stimulus required to produce fibrillation and that it prevented the development of heterotopic rhythms

caused by epinephrine in cats and barium chloride in rabbits. Van Dongen (4) has also repeatedly reported that the doses of procaine for these effects were smaller than the doses which decreased conduction velocity or increased refractory period. Unfortunately van Dongen has not presented descriptions of the methods employed for such measurements but has stated he used myographic and electrocardiographic recordings. Interpretation of such recordings is difficult.

Mautz and Beck (5) published several reports in 1936 and 1937 on the topical action of procaine on the dog heart in situ. They also stated that procaine reduced the "irritability" of the heart. Burstein and Marangani (6) in 1940 again demonstrated the local action of procaine.

In 1936 Shen and Simon (7) reported the first studies on the effect of procaine against epinephrine and cyclopropane-epinephrine arrhythmias in animals. Their results demonstrated a protective action for procaine. Mautz and Beck (8) later substantiated their results.

These last pieces of work apparently inspired Burstein and several of his co-workers to continue this line of investigation. They first demonstrated statistically that procaine prevented epinephrine-cyclopropane arrhythmias both experimentally in the dog and in their experiences in the operating room. In 1946 Burstein (9) reported on a series of about 30 patients who had developed acute arrhythmias during intrathoracic operations. After injection of a single dose of 30 to 70 milligrams of procaine, he observed improvement in every case. In some instances "the pulse was restored from zero to normal" (sic). Pulse rate and strength were the criteria used.

On the negative side Stutzman, Orth, et al (10) have reported several times the failure of procaine to protect against cyclopropane-epinephrine induced arrhythmias. In addition they injected procaine after development of the arrhythmia and found it had no action whatsoever. Smith and Ferguson (11) in Toronto also used procaine both before and during the arrhythmias and failed to find a protective action of procaine. They felt that the depression of ventricular muscle, cited as the reason for the reported protective action, was only a transient effect and that the predominant action of procaine is an anti-vagal action resulting in increased heart rate.

In 1942 Hirschfelder and Tamcales (12) issued a preliminary report on the inhibition of auricular fibrillation by procaine in dogs using methods similar to those of van Dongen.

Hazard (13) has reported that in dogs procaine blocked the cardiac slowing caused either by stimulation of the vagus or by the injection of acetylcholine while exerting no effect against the hypotensive response. He further showed that procaine blocked the depressor effects of small doses of nicotine.

Oppenheimer (14) in 1947 described the toxic effects of intravenous procaine on the dog heart. His interpretations were made from electrocardiograms. He reported that "therapeutic" doses usually caused no change in the ekg, heart sounds, or blood pressure. Slightly higher doses generally caused only a decrease in the spike of the R wave. After this, the higher the dose, the wider the QRS complex and the wider the P-R intervals. Doses of 50 to 60 mgm./kgm. produced ventricular tachycardia,

and with slightly higher doses ventricular extrasystoles, flutter, and fibrillation appeared in sequence.

The metabolism of procaine has been studied both in animals and in man. Brodie and his co-workers (15) demonstrated that in normal man procaine is rapidly hydrolyzed to diethylaminoethanol (DEAE) and p-aminobenzoic acid (PABA) after intravenous administration. They found that the urinary excretion of procaine is almost negligible. However, since 70 to 95 per cent of the PABA in the administered procaine was recovered, both free and conjugated, in the urine, it was concluded that this material is largely unaltered in the body. On the other hand, amounts of DEAE equivalent to only 20 to 35 per cent of that in the original procaine were isolated from the urine. When PABA and DEAE were injected as such, the quantitative recovery in the urine was identical to that when they were administered in the esterified form as procaine. It is evident, therefore, that the DEAE product of the hydrolysis of procaine is further metabolized.

Papper (16) has recently reported that DEAE may be somewhat more effective than procaine in reversing epinephrine-cyclopropane arrhythmias in the dog. He reported DEAE to be effective as procaine clinically in the relief of post-operative pain.

The search for more effective substitutes for quinidine has led to the study of local anesthetics. Both van Dongen (17) and Bovet (18) found that several local anesthetics raise the threshold of electrical stimulation required to induce auricular fibrillation. Dawes (19) devised a method for screening compounds for cardiac activity by determining their action on the

isolated rabbit auricle. By the use of myographic recording and electrical stimulation he has reported that many local anesthetics decrease maximal rate.

CHAPTER II

Experimental Procedure

Compounds studied.

It was of interest to compare the cardiac actions of products of the hydrolysis of procaine, namely, diethylaminoethanol (DEAE) and p-aminobenzoic acid (PABA) with those of procaine, particularly since it has been reported that DEAE possesses certain pharmacological properties similar to those of procaine.

A second local anesthetic was made available for the study. This compound is β-diethylaminoethyl 2,4 dichlorobenzoate, and for convenience will be called DCB. This compound appeared interesting, first, because of the different substitutions on the benzoic acid portion of the ester, and second, because it has a low intravenous toxicity. Its products of hydrolysis are DEAE and 2,4-dichlorobenzoic acid. This acid, for convenience called DCBA, was also studied in order to compare it to PABA and to determine its role in the action of the parent compound.

Aqueous solutions of all five compounds were freshly prepared about once a week. The concentrations of the solutions were adjusted so that doses of approximately 1.0 cc. and not more than 3 cc were administered at each injection. Procaine hydrochloride and DCB hydrochloride are water soluble to approximately 30 per cent. PABA and DCBA were neutralized with a molecular equivalent of sodium hydroxide in aqueous solution.

Experimental detail.

The experimental procedures were conducted in dogs, usually of between 16 and 23 kilograms body weight. The dogs were anesthetized by an

intraperitoneal injection of 0.7 cc./kgm. of Dial with urethane solution (Ciba)*. The carotid artery was cannulated for recording of arterial blood pressure and the external jugular vein was isolated for injections of the test compounds. The vagi in the neck were freed for future section and stimulation. The chest was opened under artificial respiration and the chest walls widely retracted. At this point the animal was turned slightly on its left side for freer access to the entire right auricle. The pericardium was then split longitudinally and sutured back over the chest walls to form a cradle for the heart.

Elimination of the sympathetic innervation to the heart was accomplished by removal of both thoracic sympathetic chains including the stellate down to the ganglion of T5. In experiments in which the sympathetics were to be stimulated the chains were freed of all connections except the postganglionic cardiac fibers arising from the stellate ganglion. When the effects of the vagi and sympathetics were eliminated in this manner the heart is referred to as decentralized.

Potential changes in the auricle were recorded by clipping lightly to the auricular muscle pairs of shielded silver electrodes having a small interelectrodal distance (2 to 3 mm.). In most experiments a similar pair of electrodes was placed at the auricular tip and was used as stimulating electrodes. The recording leads were placed at a measurable distance from each other in line with the stimulating electrodes. The ventricular beat was recorded from a lead placed on the ventricular fat, from the apical pericardium, or from the right foreleg and left hindleg. All

*An aqueous solution which contains in each cc.: Diallylbarbituric acid 0.1 gm., Urethane 0.4 gm., and Monoethyl urea 0.4 gm.

recordings were made by means of a three channel ink-writing electroencephalograph.

A Model 3 A or C Grass stimulator giving square waves was employed for stimulation of the auricle. The pulse duration was always 1 millisecond. The frequency of stimuli was varied from 2 to 15 per second and the current strength was varied from 0.5 to 15 volts. The duration of stimulation of the auricle was generally about 20 seconds or until adequate records for analysis could be taken.

The criterion for maximal nerve stimulation was a significant change in ventricular rate while the auricle was being driven. This was accomplished by using the lowest frequency of stimulation which slowed the ventricle sufficiently and a voltage above which no further change could be produced. Maximal stimulation of the cut central end of the vagus was carried out using stimuli of approximately 0.2 or 0.5 msec. at a frequency of 10 to 30 per second and a voltage of 10 to 20.

The sympathetic chain was stimulated by placing the electrodes between the stellate and the ganglion of T2, using a pulse duration of 0.01 msec. and a frequency of 60 per second. Maximal voltage for sympathetic stimulation was generally found to be between 20 and 40 volts.

Experimental sequence.

A procedure composed of two parts was developed during the latter months of the investigation in which several types of experiments were combined. First, the minimal voltage required to drive the auricle at different frequencies was determined. The driving frequency was increased until the maximal rate at which the auricle followed the rhythmic stimuli was established. Particular attention was paid to those frequencies between which the ventricle followed each auricular beat and every second beat.

At each frequency of stimulation the speed of the paper was increased from 15 to 60 mm. per second so that conduction time could be measured. When the effects of nerve stimulation were studied, the nerve was stimulated while driving the auricle at each of the frequencies employed, and measurement was made of their effects on the auricular response and A-V responses. These determinations were then all repeated following injection of the test compound. Drug effects appeared within 60 seconds and were usually maximal 2 to 4 minutes after intravenous injection. Thus in the first part of the experiment information could be obtained on (1) maximal rates, (2) effect of auricular rate on electrical excitability, conduction velocity, and auriculo-ventricular conduction, (3) the effect of nerve stimulation on these factors, and (4) effect of different doses of the drugs under study.

The second part of a typical experiment dealt with auricular flutter. The auricle was crushed and stimulated to induce flutter as described in Chapter III. Dose-response relationships for the different compounds were established by measurement of their effects on both auricular and ventricular rates in flutter. In addition, nerve stimulation was carried out during flutter and drug effects against their actions were determined.

Time course of action of procaine and related substances.

In a number of experiments measurements of effects were made as early as 20 seconds following intravenous injection of the drugs and were continued until return to nearly original conditions occurred. The changes in electrical excitability, maximal rate, A-V conduction, and rate of auricular flutter caused by procaine, DEAE, and DCB frequently appeared within 1 minute. During the period of 2 to 4 minutes after injection the greatest changes were observed with each compound. After this the degree

of change became progressively less over a period varying from 20 to 30 minutes following large doses (8 mgm./kgm.) of procaine or from 5 to 15 minutes following effective doses (32 mgm./kgm.) of DEAE and DCB (8 mgm./kgm.). The actual duration of action was not determined for any compound. Since the greatest effects were obtained during the 2 to 4 minute interval, the different evaluations of drug action in this study were always made during this time period.

Experimental criteria.

The reported results were obtained in animals maintained in comparable and satisfactory conditions during the experiments with regard to level of blood pressure, body temperature, depth of anesthesia, and regulation of respiration.

Rates of injection of the test compounds were also kept comparable. The solutions were generally injected rapidly. Large doses were injected slowly enough to avoid serious falls of blood pressure.

At least three complete experiments per compound were conducted in which evaluation of all of the factors mentioned was made. In most instances considerably more than three experiments per compound were required even if all experiments were successful, mainly because effects of vagal and sympathetic innervation and stimulation could rarely be determined in the same animal. The order of injection of different doses and different compounds was rotated in all experiments of the investigation in order to minimize effects of tachyphylaxis, sensitization, or accumulation.

CHAPTER III

Conduction Velocity in the Auricle.

History

Previous investigators have measured conduction velocity in the dog's auricle from auricular electrograms. Experiments of Lewis (20) indicate that it is about 1000 mm./sec. and tends to decrease as the auricular rate increases. Both Lewis and Rosenblueth and García-Ramos (21) have demonstrated a slowed conduction velocity of about 500 mm./sec. in the auricle fluttering at a rate of 300 to 400 per minute. Limited evidence has indicated that conduction velocity does not change with either vagal or sympathetic stimulation (22, 23).

Methods

The velocity of the auricular conduction wave was determined as follows. Two pairs of recording leads were placed on the right auricle at a measurable distance from each other (usually 2 to 4 cm.) and in line with the stimulating electrodes which were clipped at the auricular tip. The recording field was generally at right angles to the stimulating field. Recordings for conduction velocity were taken only when the auricle was being driven. The time for the impulse to pass from the proximal to the distal pair of electrodes was measured in milliseconds directly from the electrograms and conduction velocity was calculated from this and the distance measured between the leads.

Representative examples of the experiments are presented graphically in figures 1 to 5. The frequency of the electrically drive auricle is plotted directly on the abscissae. Conduction time in msec. is shown on the right ordinates and the left ordinates represent the calculated

conduction velocity in msec. Electrogram measurements could be made to 0.25 mm. which corresponds to 4.1 msec. when the paper speed was 60 mm./sec. This maximal error is indicated in the graphs by the length of the bars.

Results

A. Section and stimulation of nerves.

A typical experiment in which the effect of section of the nerves on conduction velocity was determined is shown in figure 1. Although the graph is not complete in that conduction time was not measured at the highest frequencies following vagotomy, it demonstrates that section of the cardiac nerves exerts practically no influence on auricular conduction. It also shows that while conduction velocity decreases with an increase in auricular rate, the change is gradual and small, particularly at the lower auricular rates. These were the usual findings. In certain animals there was a tendency for conduction velocity to be slower after decentralization but in most experiments the change was insignificant.

Changes in conduction velocity produced by vagal and by sympathetic stimulation are demonstrated in figure 2. Both types of stimulation increase the conduction velocity at all auricular rates. Following vagal stimulation the increase is small at low auricular rates and marked at high rates. Sympathetic stimulation, in the experiment graphed, caused a relatively greater increase in conduction velocity at low rates than at fast auricular rates. Although the number of experiments with sympathetic stimulation in which conduction velocity was calculated was small, conduction velocity was also found to be accelerated at low auricular rates in all these experiments.

Conduction Velocity

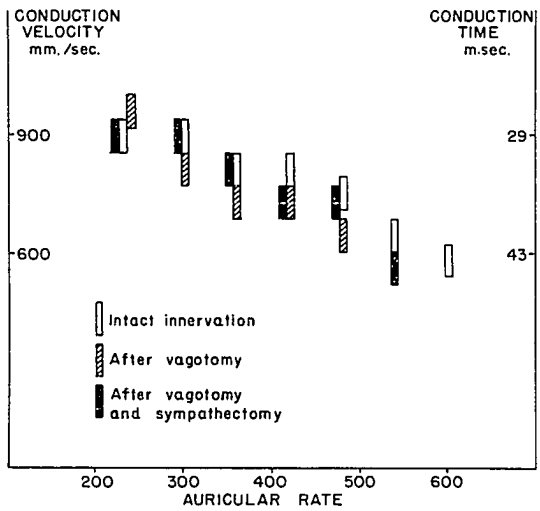
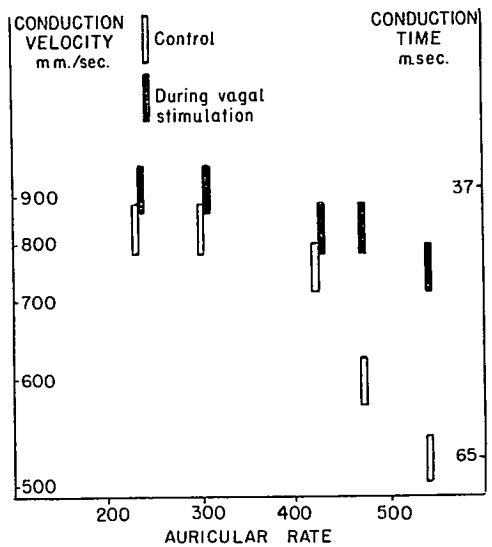


Figure 1

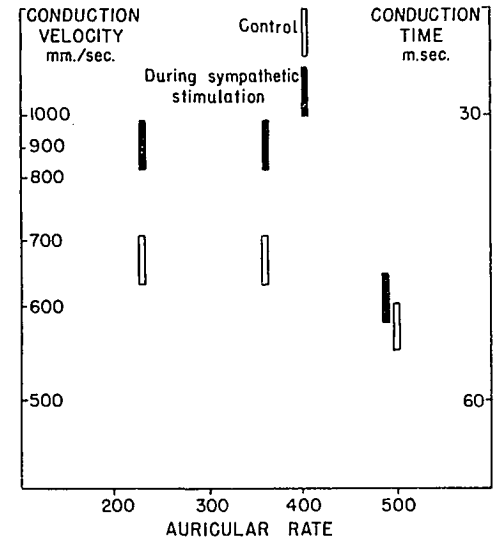
Neither vagotomy nor subsequent sympathectomy changes conduction velocity significantly.



a

Vagal stimulation increases conduction velocity. The effect is more pronounced at high auricular rates.

Figure 2



b

Sympathetic stimulation increases conduction velocity. The effect is more pronounced at low auricular rates.

B. Drugs

Doses of 8 mgm./kgm. of procaine always slowed conduction velocity (table II). Smaller doses also caused slowing but the effect was not marked. Results of a typical experiment are graphed in figure 3. After the injection of procaine conduction velocity falls almost to the lowest levels observed in any experiment thus far performed at low auricular rates, and is slow at all rates.

DEAE in doses of 32 mgm./kgm. slowed conduction velocity in most experiments (table II), but to a much less degree than procaine. The usual effect is shown in figure 4. The effect was usually small but it occurred regularly enough to indicate the direction of DEAE action.

DCB in doses of 8 mgm./kgm. rarely caused a significant change in conduction velocity (table II). The typical effect is graphed in figure 5. A small amount of slowing occurs only at the highest frequencies which the auricle could follow after the injection of DCB.

Discussion.

These studies indicate that conduction velocity can be modified in a variety of ways. It is little affected by tonic activity of the vagal and sympathetic nervous supply to the heart under the conditions of these experiments. Results obtained when these nerves are stimulated, however, suggest that under other conditions tonic activity could increase conduction velocity. The effect of vagal stimulation on conduction velocity is greatest at high auricular rates whereas the effect of sympathetic stimulation is greatest at low rates. One would expect this

Conduction Velocity

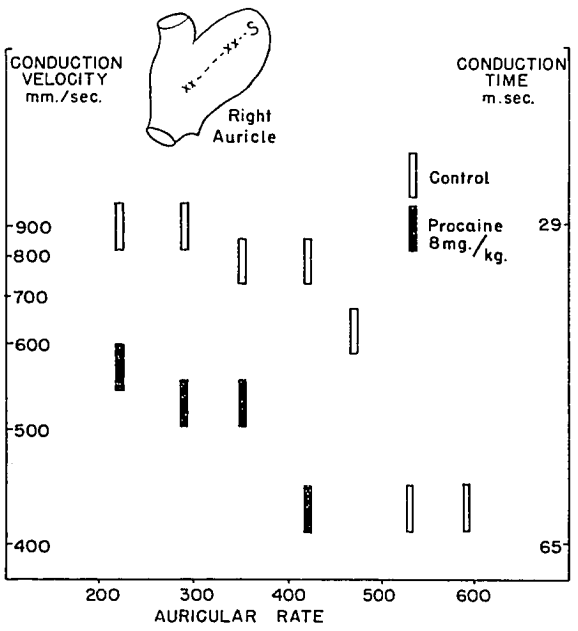


Figure 3

8 mgm./kgm. of procaine markedly reduces conduction velocity at all auricular rates.

Conduction Velocity

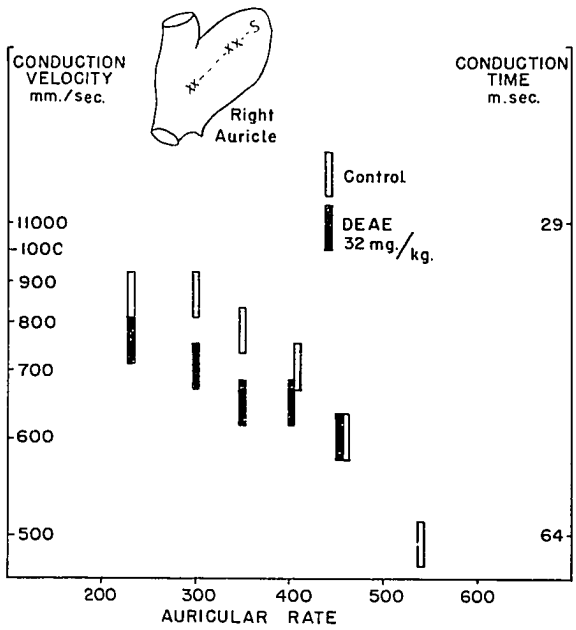


Figure 4

DEAE causes a slight slowing of conduction velocity.

Conduction Velocity

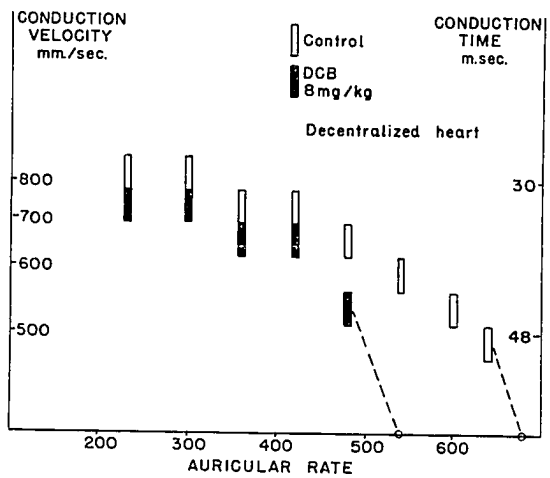


Figure 5

DCB does not change conduction velocity except at the highest frequency of stimulation which the auricle follows.

difference to be evident also in the study of cholinergic and adrenergic compounds. At any auricular rate conduction velocity can be diminished markedly by procaine and somewhat by DEAE whereas DCB decreases conduction velocity only at the maximal rate. These examples show that the study of conduction velocity permits us to differentiate between drugs which in some respects are similar in their cardiac action. This differentiation requires the study of conduction velocity in auricles beating at a range of rates from about 200 to 600 per minute.

Certain influences which produce changes in the velocity of the conducted impulse have been described. The ability of the heart to respond and the conditions under which it can respond will be considered in the following section.

Table I. The effect of procaine, DEAE, and DCB on conduction velocity in decentralized, vagotomized, and innervated hearts.

Compound	Dose mgm./Kgm.	Innervation	Experiments	Conduction Velocity	
				Decreased	Unchanged
			No.	No.	No.
Procaine	8	decentralized	7	7-marked	
		vagotomized	7	7-marked	
		intact	4	4-marked	
DEAE	32	decentralized	4	3-slight	
		vagotomized	4	2-slight	2
		intact	3	2-slight	1
DCB	8	decentralized	2		2
		vagotomized	3	2-slight	1
		intact	3	1-slight	2

CHAPTER IV

Maximal rate and recovery of excitability in the auricle.

Introduction.

When the heart beats, for a short period one is unable to elicit further beats from it. This is called the absolutely refractory period. At its end beats may again be elicited by strong stimuli, and as time goes on by weaker stimuli. This is called the period of relative refractoriness, or, of recovery of excitability. The phases of the cardiac cycle are most conveniently explored by means of electrical shocks. The important variables in such an investigation are (1) interval of the cardiac cycle, (2) strength of stimulus, and (3) duration of stimulus. Refractory period is defined as that interval of the cardiac cycle during which no response can be elicited even with a stimulus strength which approaches infinity. Absolute refractoriness is merely inexcitability. Electrical excitability is defined as the electrical energy required to elicit a response. This must be expressed in terms of strength, duration, and shape of the electrical shock. Relative refractoriness is merely decreased excitability.

The best published studies of the excitability cycle of the mammalian auricle (isolated) are those of Brooks, et al. (24). In cats and guinea pigs they measured the relation of strength of stimulus to the length of shock at different intervals of the cycle and found that the recovery from refractoriness was comprised of intervals of greater and intervals of lesser excitability.

Determinations of refractory period are usually made by introducing a test stimulus between two rhythmic stimuli in various phases of the cardiac cycle (Lewis, 1921), (25). Measurement is made of, first, the

the shortest interval between a rhythmic and a test stimulus, each of which produces a response, and second, the longest interval between these stimuli, the first of which alone produces a response. The intermediate time interval is used to express the length of refractory period. Andrus and Carter (26) used the same method but placed the stimulating and recording electrodes very close together in order to minimize the error due to changes in conduction. The method has been refined by using two test shocks (27). Several rhythmic shocks are given followed by a second test shock which is adjusted as to interval so that the response can be recorded at a distance. The first test shock is then moved through the entire cycle from the rhythmic to the second test shock. The absolutely refractory period is then measured by the earliest shock which, although it produces no conducted disturbance, delays or abolishes the conducted response to a second stimulus which follows.

These methods have been used by many investigators to evaluate the effect of vagal stimulation. Some argument, however, still exists whether vagal stimulation shortens the entire refractory period (28) or shortens the absolute but lengthens the so-called relative refractory period (29). Rosenblueth and García-Ramos (30) have recently estimated effects of vagal stimulation and acetylcholine injection on refractory period by driving the auricle at a rate just faster than it could follow. The application of either influence allowed the auricle to follow each stimulus; this was interpreted to mean shortened refractory period.

The method most generally used for evaluation of electrical excitability is the measurement of chronaxie, i.e., the minimal duration of

electrical stimulation which excites the tissue when the intensity is twice the threshold stimulus for a long shock. In a second method the threshold strength of a shock of convenient duration required to elicit a response is determined. Rosenblueth and Garcia-Ramos (30) have modified the second method by measuring changes in auricular response to vagal stimulation when stimuli just below the threshold value are employed.

Methods

In this study measurements of electrical excitability and absolutely refractory period were made by determining the voltage of a 1 millisecond square wave required to produce a series of conducted responses when the auricle was driven at increasing frequencies. The rate was increased by increments of 15 to 20 per cent and at each interval the minimal voltage was determined at which the auricle followed each stimulus for a period of 20 seconds. The lowest frequencies used were very little above the sinus rate.

Results are present graphically in figures 6 to 13. The auricular frequency is shown on the abscissae expressed as its reciprocal, i.e., the interval between responses in seconds. The ordinates represent a relative voltage scale; the voltage required for excitation at the lowest frequency being taken as one. Upward deviations from the control curve indicate higher thresholds or decreased excitability, and downward deviations indicate lower thresholds or increased excitability. Control curves usually show a plateau at low auricular rates which suggests "resting" excitability while the slope of the curve at faster rates indicates the rate of recovery of excitability. Dotted line extensions from the maximal driving rates

to the next higher frequency (at which the auricle did not follow) and to a voltage of 15 (or 2 to 5 times the threshold at the maximal rate) are used in the graphs to demonstrate differences in length of absolutely refractory period. The difference is indicated by arrows labelled R. Voltage dial settings were found to be accurate to within 0.25 volt. This maximal error is indicated in the graphs by the length of the bars. Less than 2 per cent error was involved in counting the auricular rates from the electrograms.

Results

A. Section and stimulation of nerves.

The effect of section of the vagus and sympathetic innervation to the heart is shown in figure 6. Section of the vagi increases the maximal rate and lowers the curve of thresholds. Subsequent removal of the sympathetic chains results in higher thresholds but no further change in maximal rate.

Typical effects of vagal stimulation are shown in figure 7. The excitability of the auricle is significantly increased, and the maximal rate is also increased (shortened refractory period) as illustrated by the difference between R and R_1. Effects of sympathetic stimulation were not evaluated critically.

Further evidence of a shortened refractory period due to nerve stimulation is shown in figure 8. It can be seen in the upper electrogram that the auricle followed a frequency of stimulation after the beginning vagal stimulation which it could not follow a few seconds before. It is well known that vagal stimulation predisposes the auricle to rapidly repeated response. The electrograms immediately below show the flutter which was frequently induced under these circumstances. The lowest record shows that when the

Maximal Rate and Recovery of Excitability

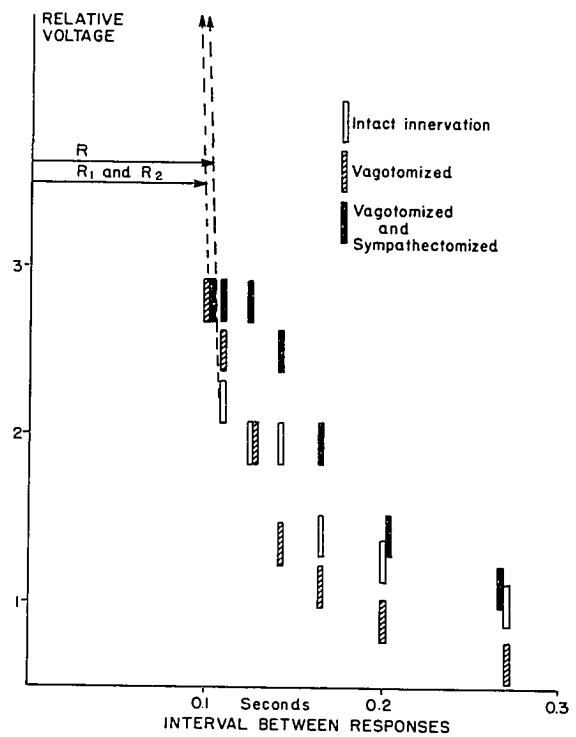


Figure 6

Vagotomy decreases the threshold of excitability and increases maximal rate. Subsequent sympathectomy increases the threshold and has no further effect on maximal rate.

Maximal Rate and Recovery of Excitability

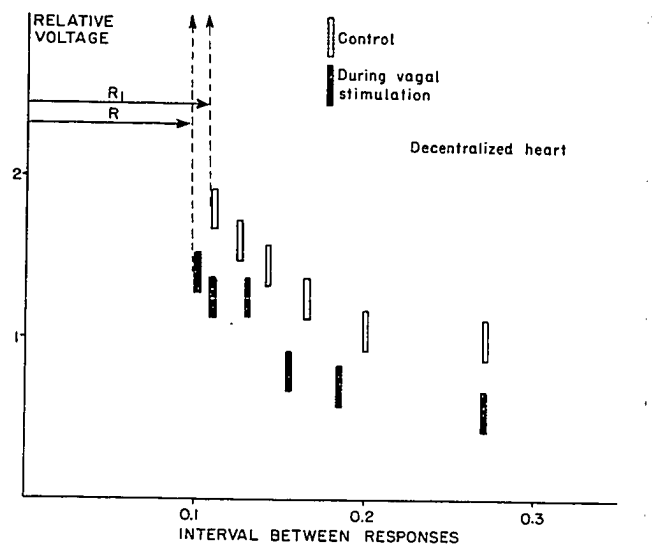


Figure 7

Stimulation of the vagus lowers the threshold of excitability and increases maximal rate.

Maximal Rate

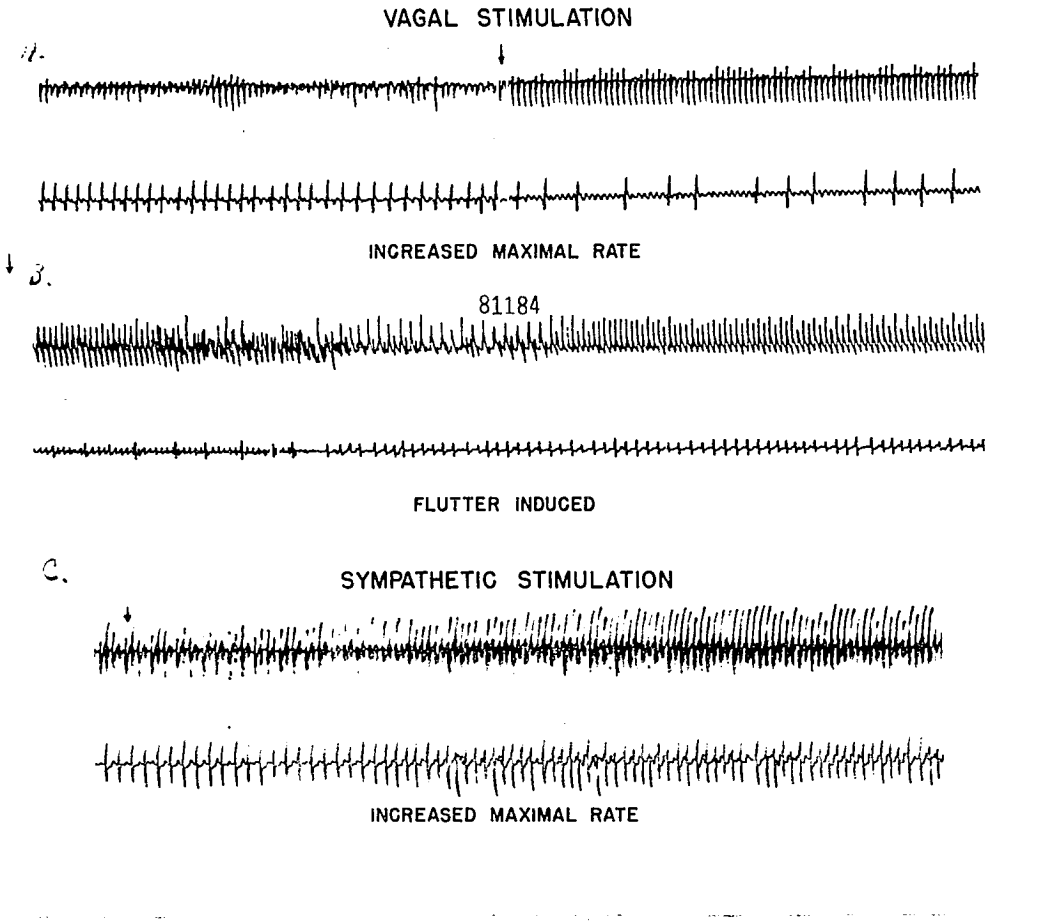


Figure 8

Electrograms recorded from a dog's heart. Upper tracings are from the auricle driven at a rate of 600/min.; lower tracings from the ventricle. Both vagal (A) and sympathetic (C) stimulation, at arrows, increase the maximal rate. Occasionally vagal stimulation (B) induces fibrillation of the auricle.

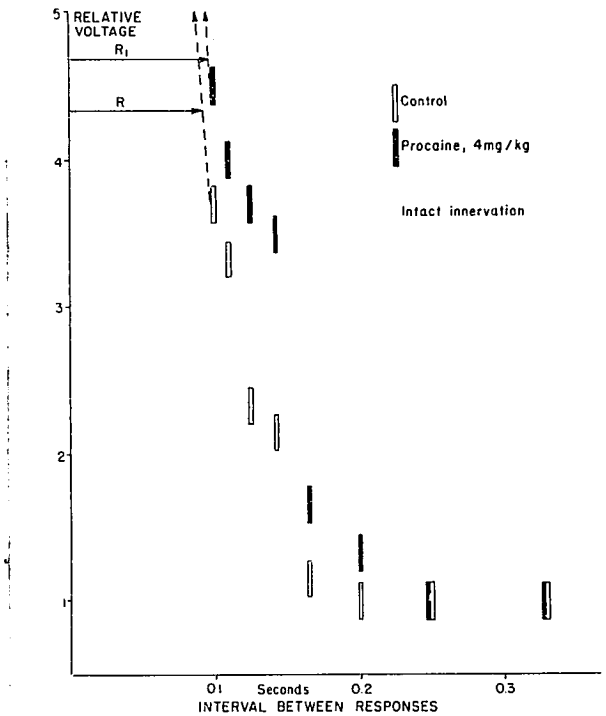
auricle is being driven at a rate which it cannot follow, it begins to follow when the sympathetic chain is stimulated.

Figures 7 and 8 indicate that both vagal and sympathetic stimulation shorten the refractory period as well as increasing excitability throughout the recovery period. It is paradoxical that both section and stimulation of the vagi shorten the refractory period and increase excitability. The same effects are produced by stimulation of the sympathetics. This suggests the hypothesis that the shortened refractory period and increased excitability occurring when the vagi are sectioned may be the result of an increase of sympathetic tone. The reflexes resulting from vagotomy have not been investigated in this study.

B. Drugs

Figures 9 and 10 present typical changes occurring after the intravenous injection of procaine. The effects were similar regardless of whether the heart was innervated, vagotomized, or decentralized. The dose-response relation is apparent; a dose of 4 mgm./kgm. decreased excitability at high auricular frequencies but not at low rates and did not change the maximal rate. A dose of 8 mgm./kgm. always markedly reduced the maximal rate, indicating lengthening of refractory period, as shown by the difference between R and R_1. The 8 mgm./kgm. dose also decreased excitability at high rates but usually not at low rates, suggesting that the recovery of excitability was slow immediately after the refractory period and then became more rapid. Table I shows that at auricular frequencies above 450 per minute procaine in doses of 8 mgm./kgm. always decreased excitability. At low auricular rates procaine increased excitability in 9 out of 19 experiments while in the remaining experiments it was decreased in half and not changed in the rest.

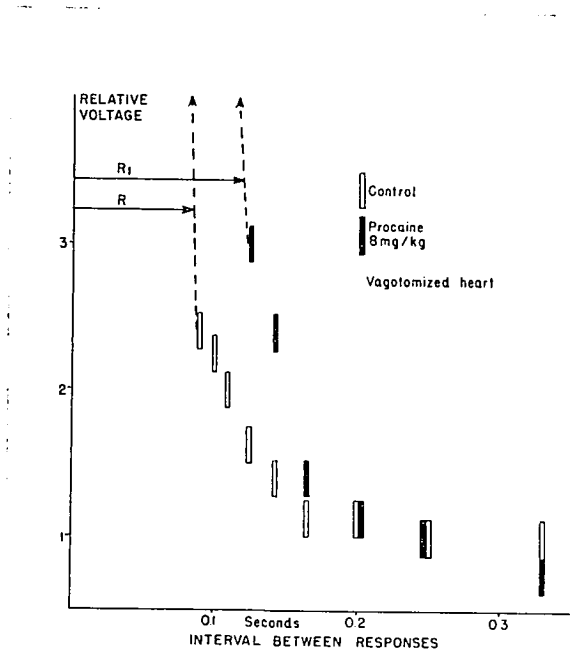
Maximal Rate and Recovery of Excitability



a

4 mgm./kgm. of procaine slows recovery of excitability at high auricular rates but not at low rates and does not decrease the maximal rate in the innervated heart.

Figure 9



b

8 mgm./kgm. of procaine slows recovery of excitability at high auricular rates but not at low rates and decreases maximal rate in the vagotomized heart.

Maximal Rate and Recovery of Excitability

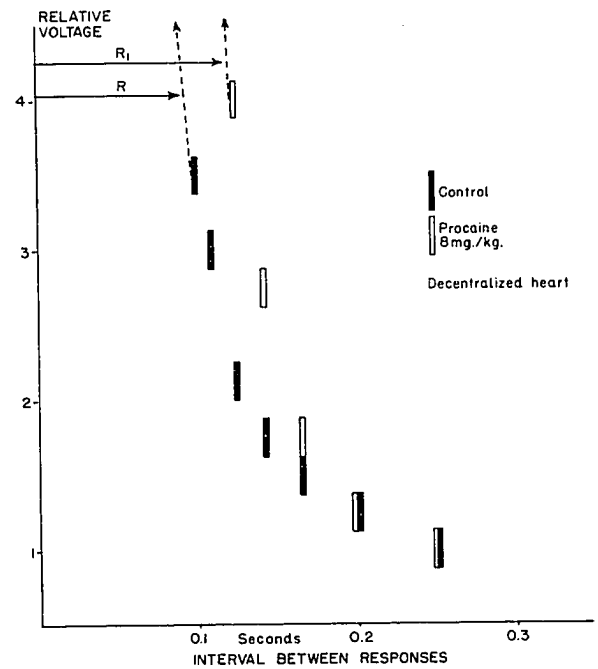


Figure 10

8 mgm./kgm. of procaine decreases the maximal rate, slows recovery of excitability at high auricular rates but not at low rates in the decentralized heart.

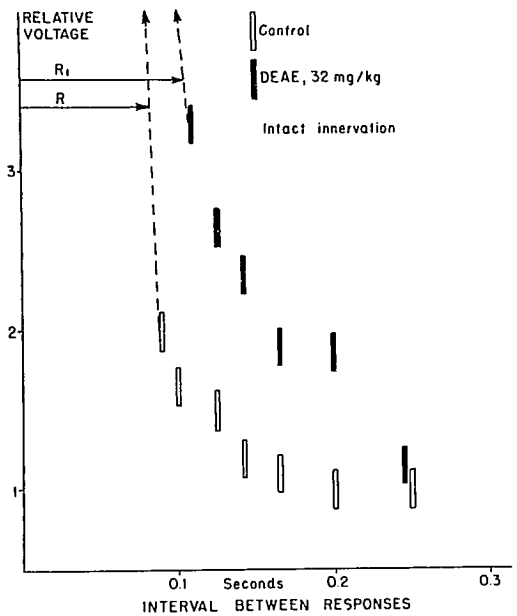
Changes in electrical excitability and maximal rate produced by the injection of 32 mgm./kgm. of DEAE are graphed in figures 11 and 12. Doses of 16 mgm./kgm. caused only small changes. The action of DEAE was not influenced by a change in the innervation to the heart. Doses of 32 mgm./kgm. of DEAE either did not change or significantly increase the threshold of excitability at all auricular rates (Table I). The marked decrease in maximal rate indicates that the refractory period was lengthened.

The effect of DCB on recovery of excitability and maximal rate are demonstrated in figure 13. It was found for this compound also that doses of 4 mgm./kgm. were considerably less effective, and that its action was not affected by state of innervation to the heart. In half the experiments (Table I) DCB in doses of 8 mgm./kgm. caused a significant increase in threshold voltage while in the balance no effect was noted. These doses always markedly decreased the maximal rate.

Discussion.

As the interval between auricular beats is shortened, the electrical energy required to excite the auricle is increased. This proceeds until the auricle can no longer conduct an impulse. When either the vagi or sympathetics are stimulated, the auricle can conduct an impulse at even shorter intervals and less electrical energy is required to excite. When these nerves are sectioned, the auricle is less excitable at all frequencies studied. This suggests that the tonic influence of both nerves tends to keep the auricle more excitable and to decrease the period of inexcitability. The actions of the vagi and sympathetics on these functions of the auricle add to the evidence presented in Chapter III that the sympathetic and

Maximal Rate and Recovery of Excitability



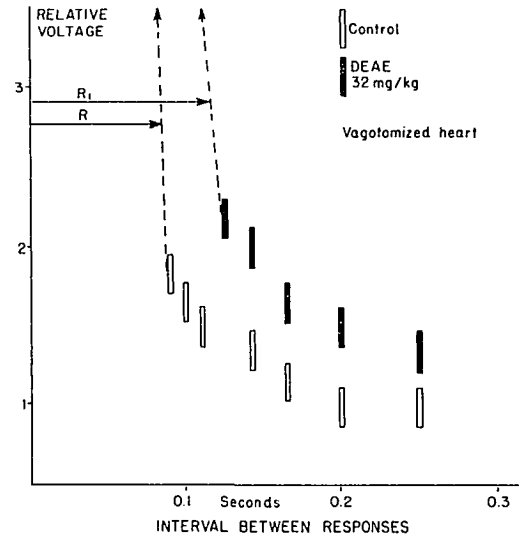


Figure 11

a b

DEAE raises the threshold of excitability and decreases the maximal rate both in an innervated heart and in a vagotomized heart.

Maximal Rate and Recovery of Excitability

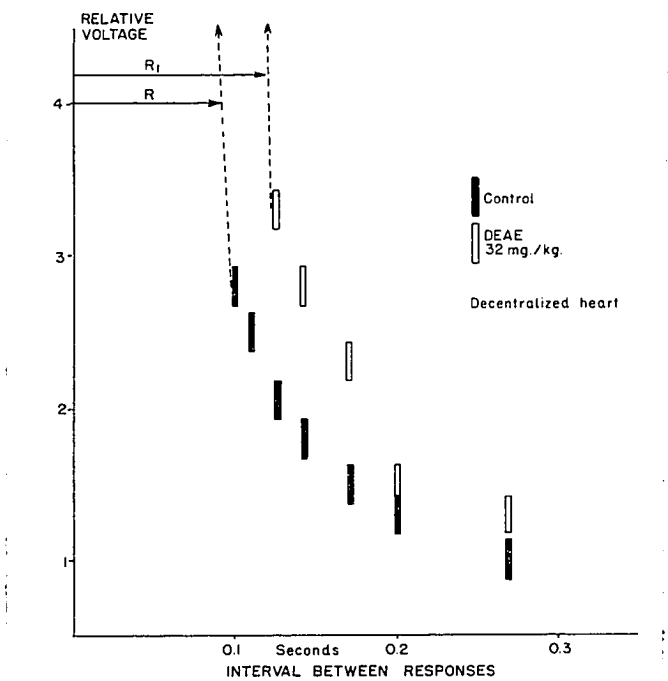
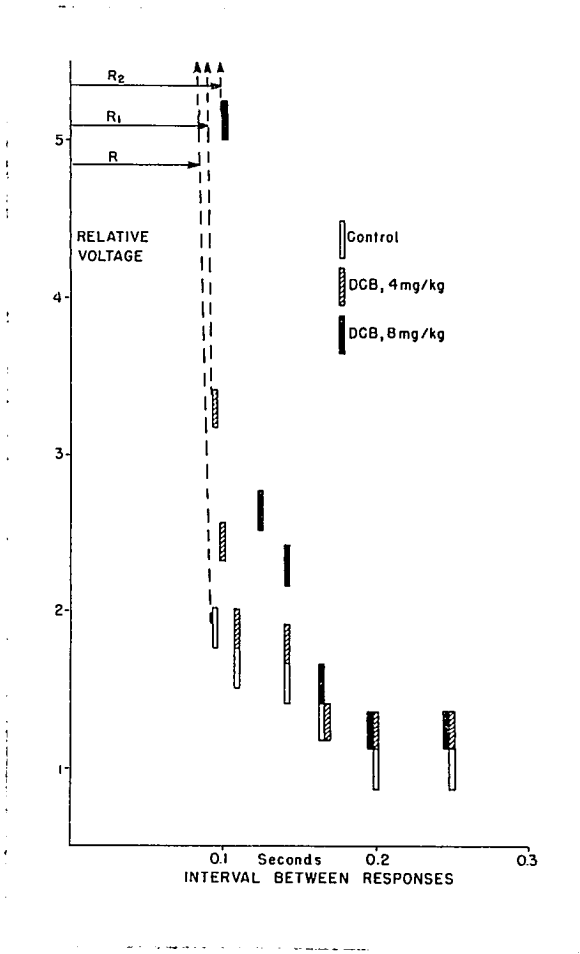


Figure 12

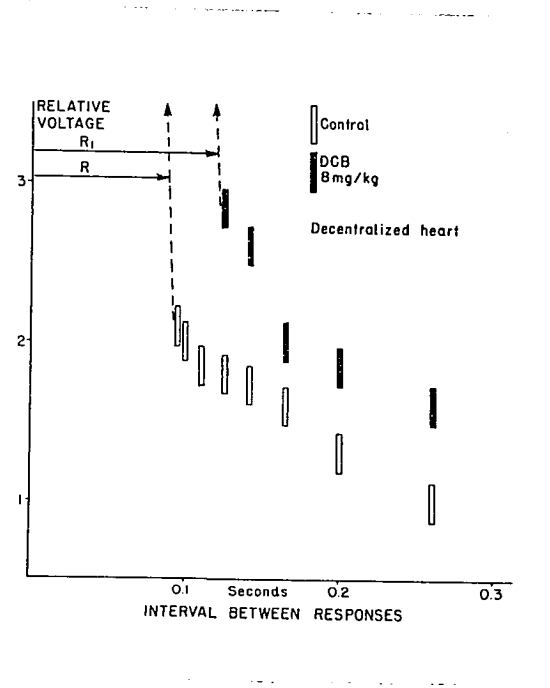
DEAE raises the threshold of excitability and decreases maximal rate in the decentralized heart.

Maximal Rate and Recovery of Excitability



a

4 mgm./kgm. of DCB causes no significant change in maximal rate or excitability. A dose of 8 mgm./kgm. slows the recovery of excitability at high auricular rates but not at low rates and decreases maximal rate.



b

8 mgm./kgm. of DCB raises the threshold of excitability and decreases maximal rate.

Figure 13

parasympathetic divisions of the autonomic nervous system are not always opposite in effect.

All three of the compounds lengthen refractory period. Procaine also slows the rate of recovery of excitability at high auricular rates but not at low rates, while DEAE and DCB decrease excitability during the entire cardiac cycle. These differences demonstrate the importance of determining relative excitability at different intervals during the whole cardiac cycle. By this procedure it is possible to affect the phases of the excitability cycle differentially with different drugs.

This study further demonstrates that the conditions under which the heart responds to an impulse can be changed independently of changes in velocity of the conducted impulse. This is brought out by the actions of DCB which depresses excitability in all phases of the cycle but does not alter conduction velocity.

The investigations so far have dealt with electrical changes in the auricle only. It now becomes important to consider the events occurring when the impulse is conducted from the auricle to the ventricle and various factors modifying these events.

Table II. Effect of procaine, DEAE, and DCB on maximal rate and electrical excitability in decentralized, vagotomized, and innervated hearts.

Compound	Dose mgm./Kgm.	Innervation	Experiments	Maximal Rate		Electrical Excitability			
				Decreased	Unchanged	Increased at high auricular rates	At low auricular rates		
							Increased	Decreased	Unchanged
			No.	No.	No.	No.	No.	No.	No.
Procaine	8	decentralized	8	7		7	5	1	2
		vagotomized		7		7	3	2	2
		intact	4	4		4	1		3
DEAE	16 and 32	decentralized	5	4	1	5	2		3
		vagotomized	4	4		4	2		2
		intact	2	2		2	2		
DCB	8	decentralized	2	2		2	1		1
		vagotomized	3	3		3	1		2
		intact	4	4		4	2		2

CHAPTER V

Auriculo-ventricular Conduction

History.

The term auriculo-ventricular (A-V) conduction includes the entire mechanism concerned in the conduction of an impulse from the auricle to the ventricle. Previous investigators have evaluated changes in A-V conduction in two ways. Usually the interval between auricular systole and ventricular systole or between the auricular and ventricular waves of the electrocardiogram is measured, and lengthening of this period has been interpreted as impairment of A-V conduction. A-V conduction has also been evaluated in terms of the ventricular rate under various conditions during faradically maintained auricular fibrillation (31).

In this study A-V conduction was determined with respect to auricular rate. The ratio of the ventricular rate to the auricular rate, V/A, is determined for different auricular rates over a wide range. Since the auricular rate is controlled, effects on the A-V conducting system can be separated from changes occurring in the auricle.

Methods.

The dog was prepared for electrical recording of the auricular and ventricular impulses as described in Chapter II. The auricle was stimulated at different frequencies from slightly above the spontaneous rate of the heart to frequencies which the auricle could not follow.

The results of these experiments were analyzed as follows. The ratio of the ventricular to the auricular rate, the V/A ratio, was calculated for all auricular frequencies employed. The ratio was then plotted against the auricular rate.

Results.

An example of A-V conduction obtained in a typical experiment is presented in figure 14. Portions of the electrogram from this animal are shown near the points on the curve whose coordinates are derived from them. When the auricle is driven at increasing frequencies, the inability of the ventricle to follow each auricular beat appears at rates between 300 and 360 and becomes progressively more striking at higher rates. In this experiment the ventricle followed each auricular beat up to about 300 per minute. When the auricular frequency was raised to 360 the ventricular rate fell to 290, or a V/A of 0.8. At the next higher auricular frequency tested the V/A fell to approximately 0.6 while at an auricular rate of 600 the ventricular rate was 300, making V/A 0.5. Thus, above a certain auricular rate, A-V conduction decreases roughly in proportion to the increase of auricular rate. This figure also shows the wide range of rates over which V/A ratios of 1.0 and 0.5 prevail. For the most part it is in the range between these two ratios in which changes of A-V conduction can best be demonstrated.

As the V/A decreases from 1.0 to 0.5, there is a progressive increase in the number of dropped ventricular beats. The dropping of beats usually occurs in an irregular sequence as shown in the electrograms in figure 14. This is the result of an interference phenomenon brought into play as the phasic excitatory activity of the auricle is displaced with reference to the phasic recovery of excitability of the A-V node.

A. Section and stimulation of nerves.

Figures 15 and 16 illustrate A-V conduction under different conditions of innervation. Each broken line in the graphs represents results obtained in an individual dog. The experimental groups plotted were chosen from larger groups in order to illustrate the variation from animal to animal.

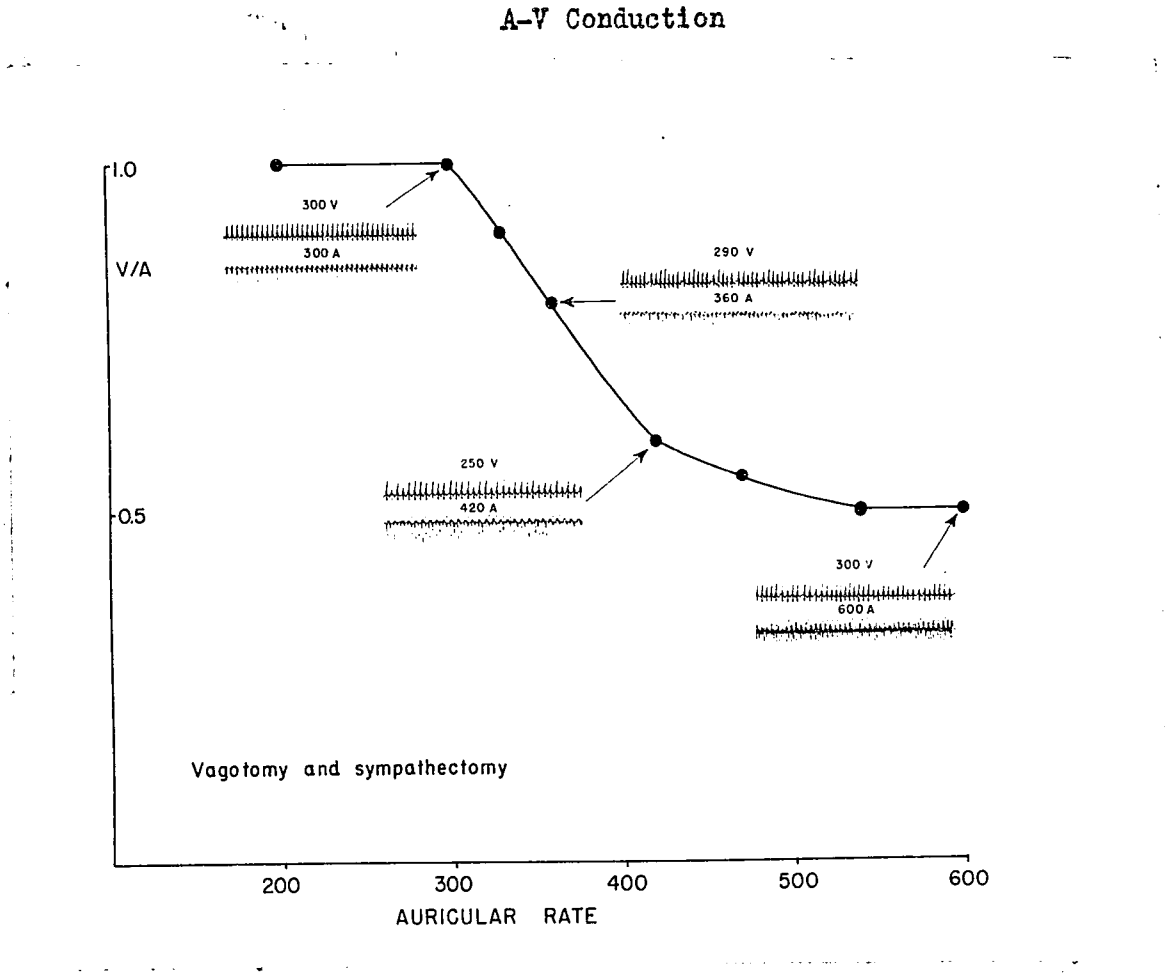


Figure 14

The curve of A-V conduction obtained in a typical experiment. The electrograms indicate the actual ventricular rate and rate of the driven auricle for different points on the curve. $V/A = \frac{\text{ventricular rate}}{\text{auricular rate}}$. Above a certain rate the failure of the ventricle to follow the auricle becomes progressively more pronounced.

A-V Conduction

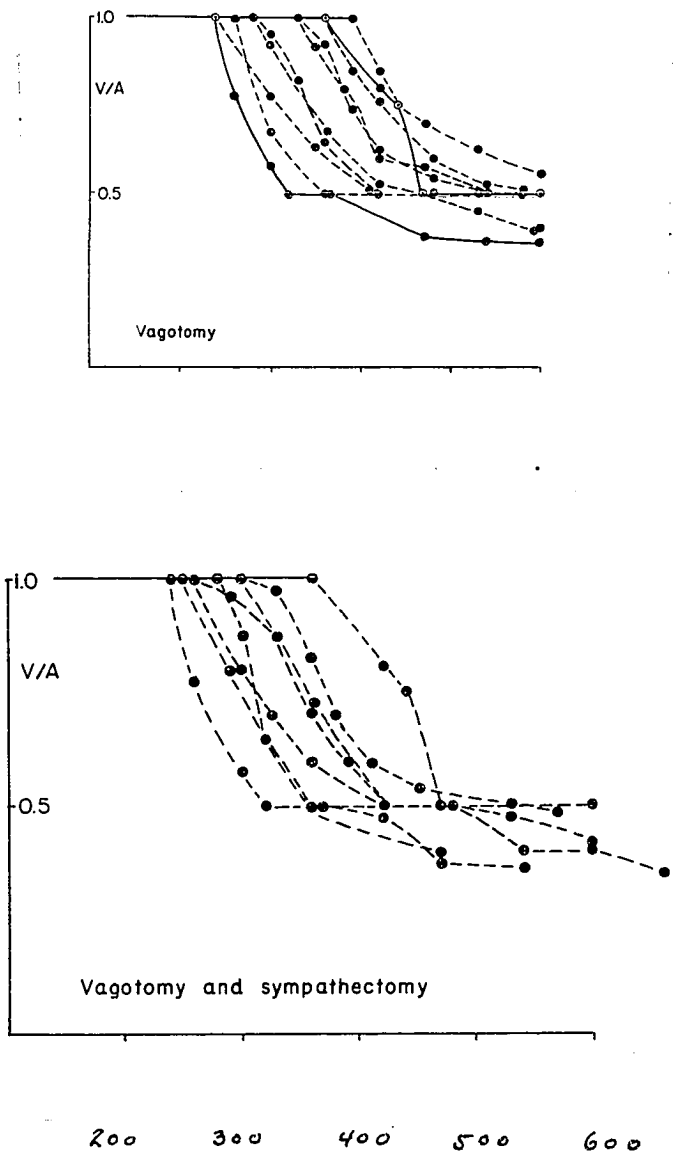


Figure 15

Each broken line represents the curve of A-V conduction for an individual dog and the solid lines show the distribution of curves of A-V conduction obtained in decentralized hearts. Distribution of the curves is similar for decentralized, vagotomized and innervated hearts (see also figure 16).

A-V Conduction

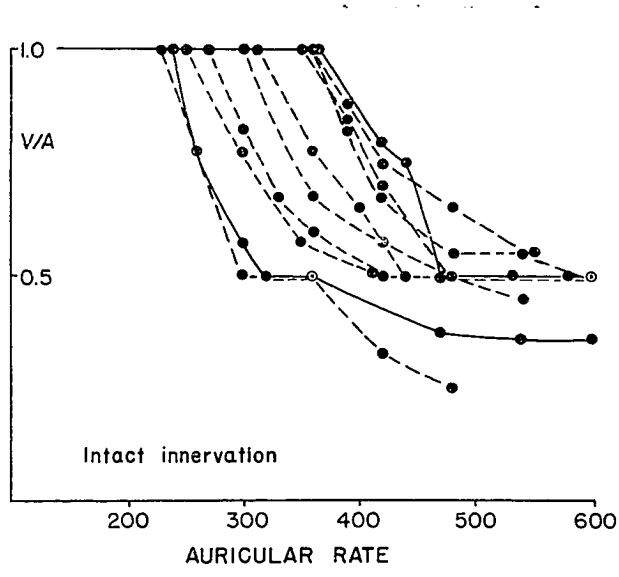


Figure 16

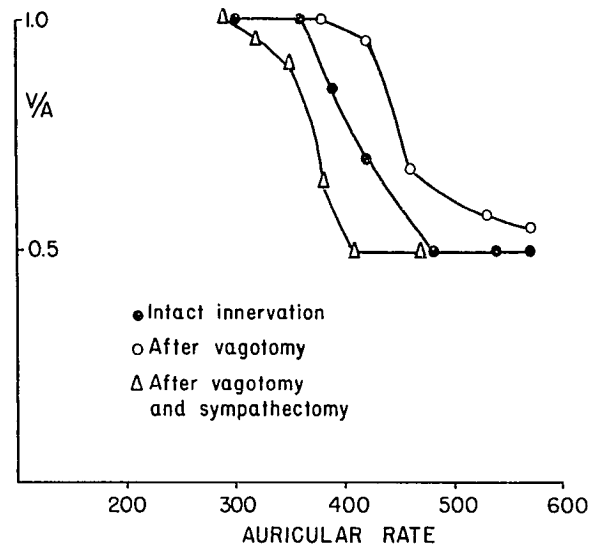
Distribution of curves of A-V conduction in different states of innervation (see figure 15).

The distribution outline found for decentralized hearts (figure 15) is shown by the heavy black lines in the graphs for other conditions of innervation (figures 15, 16). The change in A-V conduction following sympathectomy is plotted for a single experiment (figure 17b). Similar results were obtained in two additional experiments. Almost all experimental results fell within the range for decentralized hearts indicating that distribution of A-V conduction curves is roughly the same for decentralized, vagotomized, and innervated hearts. In individual animals (figure 17a) A-V conduction is slightly improved following simple vagotomy and markedly depressed following sympathectomy with the vagi intact. In the vagotomized heart A-V conduction is impaired following subsequent sympathectomy while in the sympathectomized heart (figure 17b) A-V conduction is enhanced following subsequent vagotomy.

The effect of vagal stimulation and preganglionic stimulation of the sympathetic chain on A-V conduction is graphically represented in figure 18. Vagal stimulation in these experiments was maximal with respect to voltage but the frequency of stimulation was adjusted to yield only a moderate degree of ventricular slowing. The reasons for this selection are, first, that a very slow ventricular rate would impair the circulation significantly, and second, that there is apparently considerable accommodation which occurs during rapid maximal vagal stimulation, and third, strong stimulation of the vagus predisposes to ectopic beats.

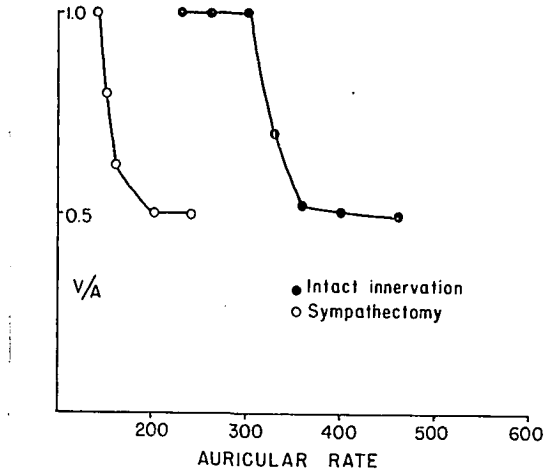
When the sinus node is the pacemaker, depression of A-V conduction is not evident with the rates of vagal stimulation employed. A-V conduction is depressed at auricular rates of approximately 200 to 250 per minute and upward, or about 30 per cent less than the rates at which V/A falls below 1.0 in the absence of vagal stimulation.

A-V Conduction



a

In a typical experiment vagotomy improves A-V conduction and subsequent sympathectomy depresses A-V conduction.



b

In a typical experiment sympathectomy depresses A-V conduction.

Figure 17

A-V Conduction

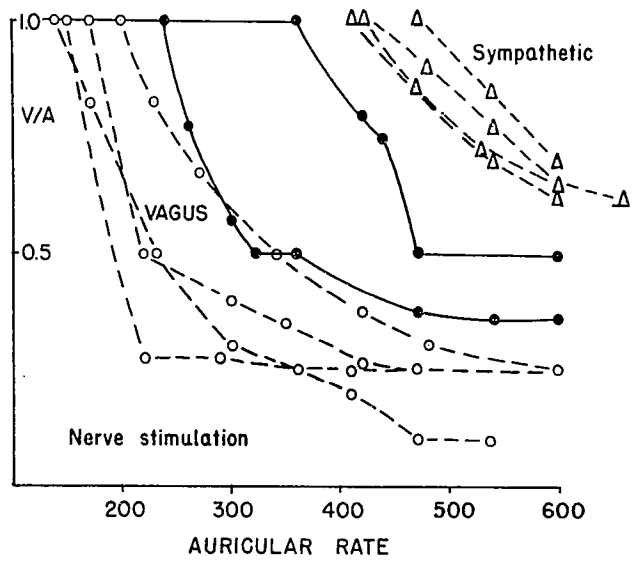


Figure 18

A-V conduction curves during vagal stimulation are depressed.

During sympathetic stimulation the curves are improved.

The curve of A-V conduction during stimulation parallels that obtained before stimulation; however, this figure shows that at the higher auricular rates the V/A ratios fall from a range of 0.5 - 0.3 to 0.25 or lower.

The depression of A-V conduction occurring during vagal stimulation appears within a few seconds and reaches a peak within 5 to 10 seconds. After this there may be some accommodation of the A-V node to the stimulation and the ventricular rate may tend to return toward normal. When stimulation is stopped, A-V conduction returns within 5 seconds to its original value. No overshooting to a more rapid rate has been observed.

As shown in figure 18 the improvement of A-V conduction occurring during preganglionic stimulation of the sympathetic chain is also marked. With the type of stimulation employed the range of auricular rates over which a V/A of 1.0 can be maintained is increased by approximately 25 per cent. The curve of A-V conduction during sympathetic stimulation also parallels that before stimulation and shows that the majority of impulses from the auricle are effective. This suggests a quicker recovery of the A-V node. A V/A of 0.5 is never reached because the auricle cannot be driven at rapid enough rates.

In one instance stimulation of the sympathetic chain alone without driving the auricle caused the heart rate to increase to 480 per minute with a V/A of 1.0. Since in most experiments the right or left chain was used indiscriminately and the rise of the heart rate was considerably less, it is possible that in this animal the sympathetic fibers of the side used were equally distributed between the sinus and A-V nodes. Generally the rate could be raised to about 350 or 380 by sympathetic stimulation alone, and effects on A-V conduction then demonstrated by driving the heart at greater frequencies. Effects of sympathetic stimulation required

approximately 10 or more seconds to become manifest in the driven auricle as well as in the spontaneously beating auricle. The maximal effect then remained for about the same period after cessation of stimulation. Return to the original heart rate however did not occur for nearly 3 minutes. Residual effects of sympathetic stimulation persisted for as long as 20 minutes following a single effective burst of stimulation since A-V conduction at the various auricular frequencies did not return to pre-stimulation levels for this period of time. In all experiments, therefore, care was taken to wait reasonable periods of time after sympathetic stimulation if other cardiac actions were to be observed.

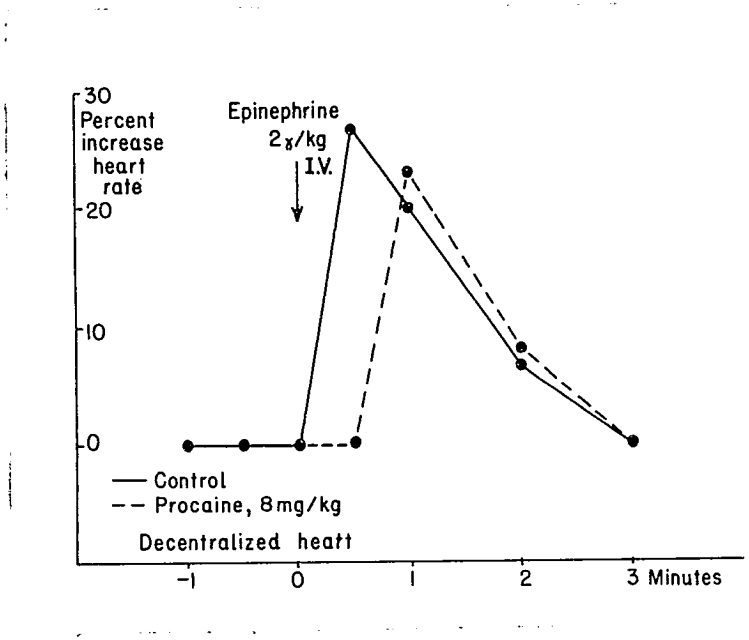
B. Drugs.

1. The response of the heart to an injection of epinephrine is shown in figure 19. When the heart was beating normally, the rate was increased by about 30 per cent (figure 19a). During driving of the auricle at a frequency giving a V/A of about 0.5 the V/A was increased almost to 1.0 (figure 19b).

2. The injection of a large dose of acetylcholine (figure 20), when the heart was beating normally, markedly slowed the ventricular rate but did not change the auricular rate. During driving of the auricle, acetylcholine caused marked A-V block and auricular fibrillation (figure 21).

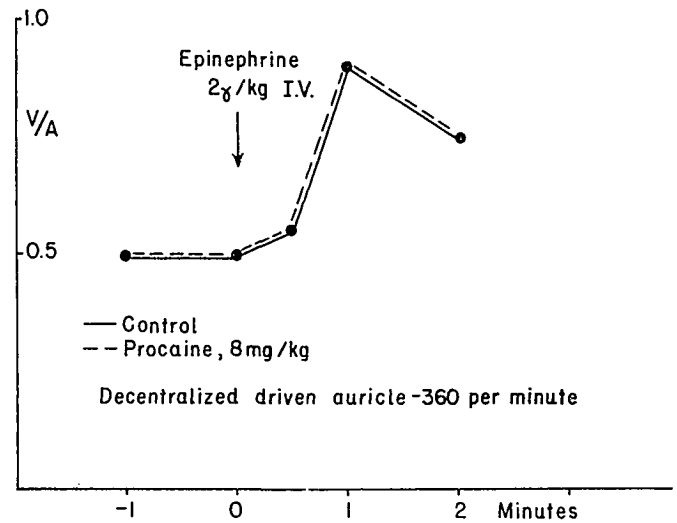
The effects of epinephrine and acetylcholine are comparable to those produced by sympathetic and vagal stimulation.

3. The effects of procaine on A-V conduction in hearts with different states of innervation are shown in figures 22 and 23. Procaine depresses A-V conduction in the decentralized heart. When the innervation is intact



a

Epinephrine increases the spontaneous rate of the heart. 8 mgm./kgm of procaine slightly delays this increase.



b

When the auricle is driven by electric shocks, epinephrine increases the ventricular rate. Procaine does not modify this effect.

Figure 19

A-V Conduction

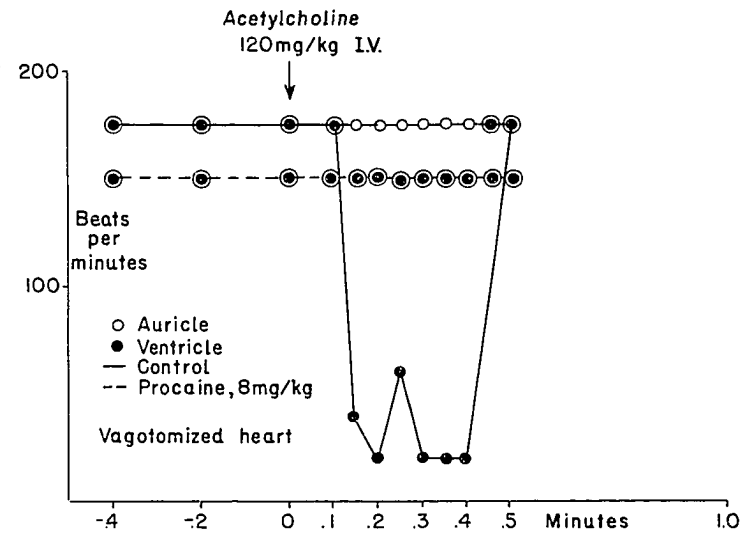


Figure 20

The injection of a large dose of acetylcholine slowed the ventricular rate but not the auricular rate when the heart was beating normally. Procaine completely prevented the ventricular slowing.

A-V Conduction

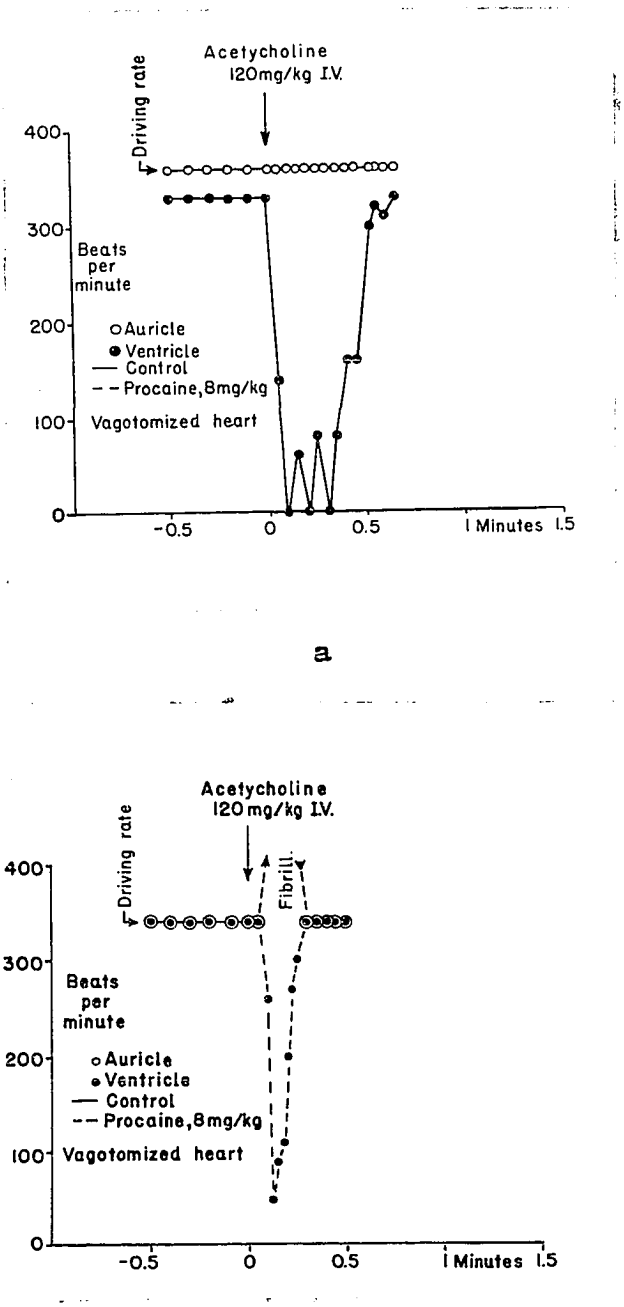
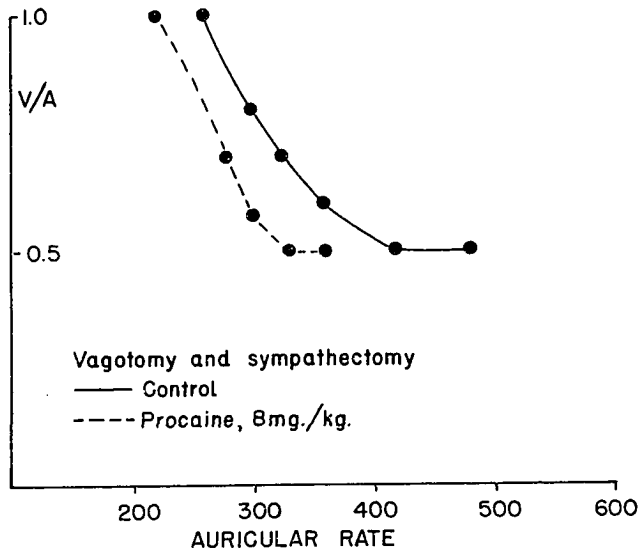


Figure 21

a. The injection of a large dose of acetylcholine markedly reduced the ventricular rate [redacted] when the auricle was being driven by electric shocks.

b. After procaine the injection of acetylcholine caused auricular fibrillation and shortened the period of ventricular slowing.

A-V Conduction



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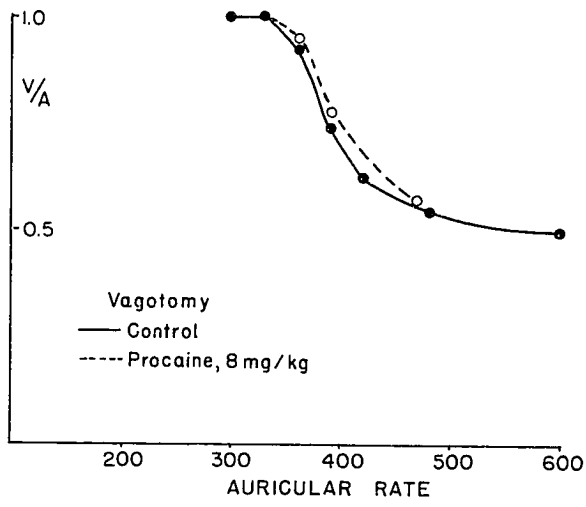
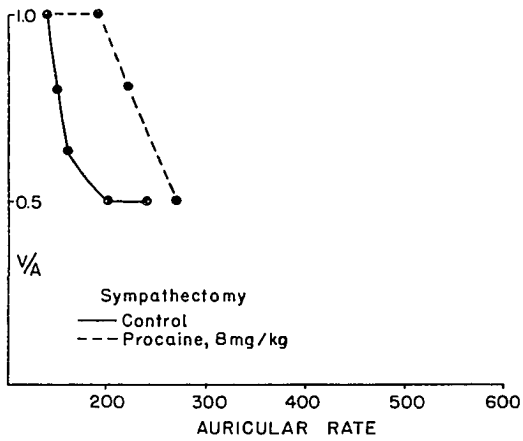


b

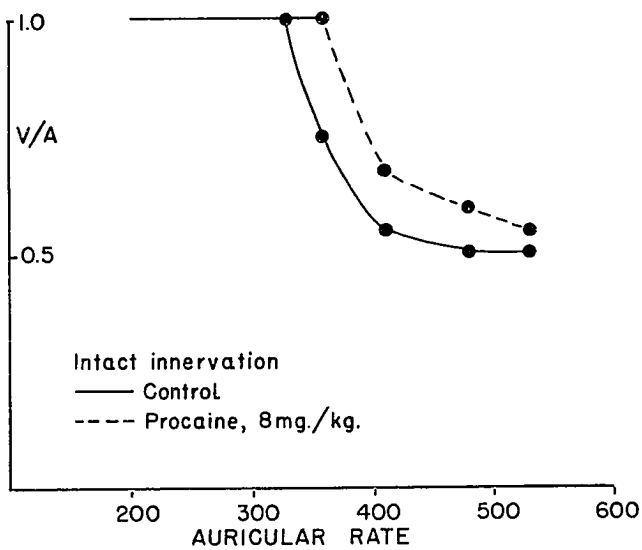
Figure 22

Procaine depresses A-V conduction in decentralized hearts(a) and improves A-V conduction in vagotomized hearts(b).

A-V Conduction



a



b

Figure 23

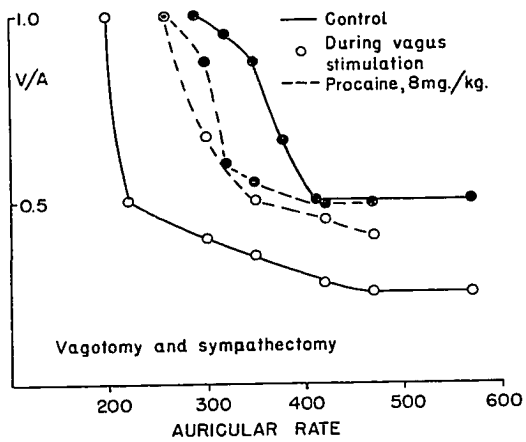
Procaine improves A-V conduction in sympathectomized and in innervated hearts.

or when only the sympathetics are sectioned, procaine improves A-V conduction. After vagotomy procaine slightly improves A-V conduction.

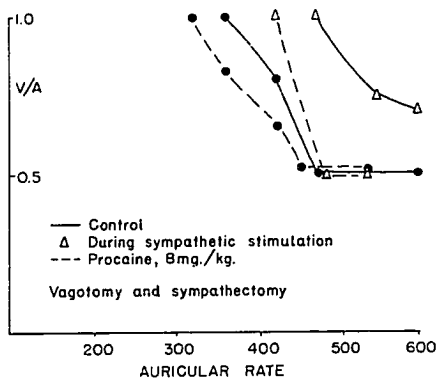
Figure 24 shows the action of procaine on A-V conduction during nerve stimulation. It prevents depression of A-V conduction during vagal stimulation and also prevents the improvement of A-V conduction during sympathetic stimulation. After the injection of procaine A-V conduction was approximately the same with or without vagal stimulation whereas stimulation of the sympathetics after procaine still caused some improvement of A-V conduction.

In the absence of nervous influences, procaine depresses A-V conduction. This can be considered a direct action on the physiological mechanism of A-V conduction. When the vagi are intact, with sympathetics either present or absent, procaine improves A-V conduction. The direct depression of A-V conduction by procaine may be assumed to occur also under these conditions of innervation. The difference between the decentralized and the innervated heart can be attributed to an effect on the innervation, e.g., blocking the vagal action. If the two factors mentioned, that is, direct depression and vagal blocking, were the only ones involved, the impairment of A-V conduction occurring when the innervation is intact would indicate that the direct depression is less important than blocking the vagus. After vagotomy when the sympathetics alone are intact, however, procaine still causes a slight but definite improvement in A-V conduction. But procaine blocks the effects of stimulation of the sympathetic chain, an action which would reinforce the direct action on the A-V mechanism; hence, some excitatory mechanism may be assumed to be at work during the action of procaine. This might, for example, be the reflex activation of the cardiac innervation by the action

A-V Conduction



a



b

Figure 24

Procaine prevents the depression of A-V conduction occurring during vagal stimulation (a) and the improvement of A-V conduction occurring during sympathetic stimulation (b).

of procaine on some other part of the body. Procaine also largely prevents the depression of A-V conduction produced by the injection of acetylcholine (figure 20). Procaine does not prevent the improvement of A-V conduction produced by the injection of epinephrine (figure 19). These facts suggest that the vagal inhibition depends partly upon an anti-acetylcholine action, but that the sympathetic inhibition does not depend upon an anti-epinephrine action.

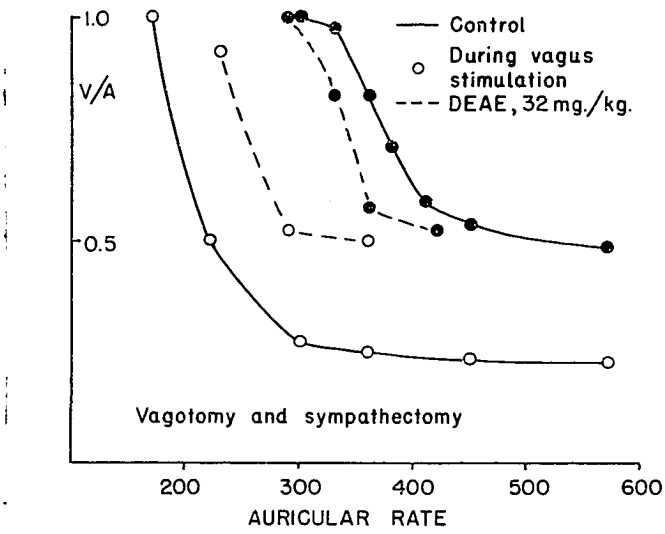
Diethylaminoethanol.

The typical effect of DEAE on A-V conduction is shown in figure 25. Adequate doses always caused a depression of A-V conduction regardless of state of innervation of the heart.

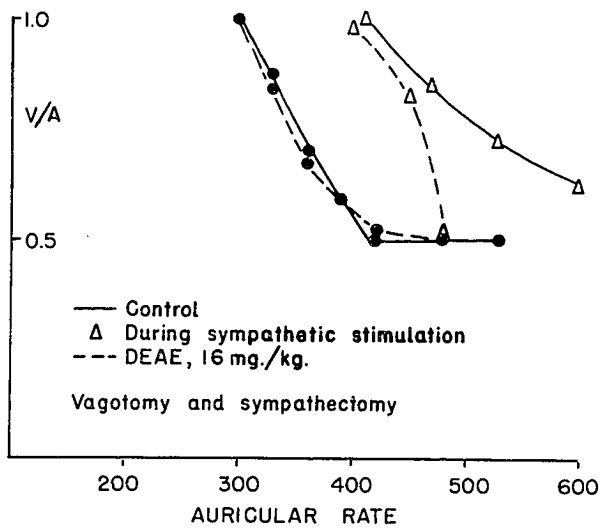
These graphs also demonstrate that DEAE improves A-V conduction depressed by vagal stimulation and depresses the improved A-V conduction caused by sympathetic stimulation. DEAE, like procaine, blocks the effects of vagal stimulation more effectively than those of sympathetic stimulation, but in general the degree of inhibition is less than that produced by procaine. The primary effect of DEAE appears to be directly depressant to A-V conduction because changes in innervation to the heart do not affect its action.

In two out of three experiments DEAE prevented A-V depression produced by the injection of acetylcholine. The duration of this action was less than that of procaine. The actions of procaine and DEAE outlined above suggest that both substances may possess anti-acetylcholine action, in the concentrations used, and thus may antagonize the effects of acetylcholine wherever it occurs.

A-V Conduction



a



b

Figure 25

DEAE depresses A-V conduction. It largely prevents the depression during vagal stimulation and the improvement during sympathetic stimulation.

B-Diethylaminoethyl 2,4-dichlorobenzoate HCl.

DCB depressed A-V conduction in innervated, vagotomized, and decentralized hearts, figure 26. These graphs also demonstrate that DCB has little, if any, blocking action on the effects of either vagal or sympathetic stimulation. Figure 26 shows the small amount of vagal block by DCB in vagotomized or innervated preparations. The action is of short duration.

Table III gives the incidence of change of A-V conduction produced by injection of the three compounds. DEAE and DCB almost invariably depress A-V conduction in the conditions of innervation studied. Procaine always improves A-V conduction when the vagi are intact and depresses it when the heart is decentralized. In the absence of the vagi and in the presence of the sympathetics the results are variable. In two experiments, however, marked improvement of A-V conduction occurred.

Discussion.

Studies on A-V conduction have little meaning unless the time of occurrence of either the phasic excitatory influence of the auricle upon the A-V node or the phasic recovery of excitability of the node is controlled because conduction of the impulse from auricle to ventricle depends upon the temporal relation of these phenomena to each other. When one of these is controlled, the effect of varying its phase on the response of the A-V node to auricular excitation can be determined, and with this information changes in the phasic activity of the other can be evaluated.

A-V conduction can be changed directly by an action on the junctional tissues, or indirectly through the actions of nerves. The potential effect of the innervation is of considerable importance in the regulation

A-V Conduction

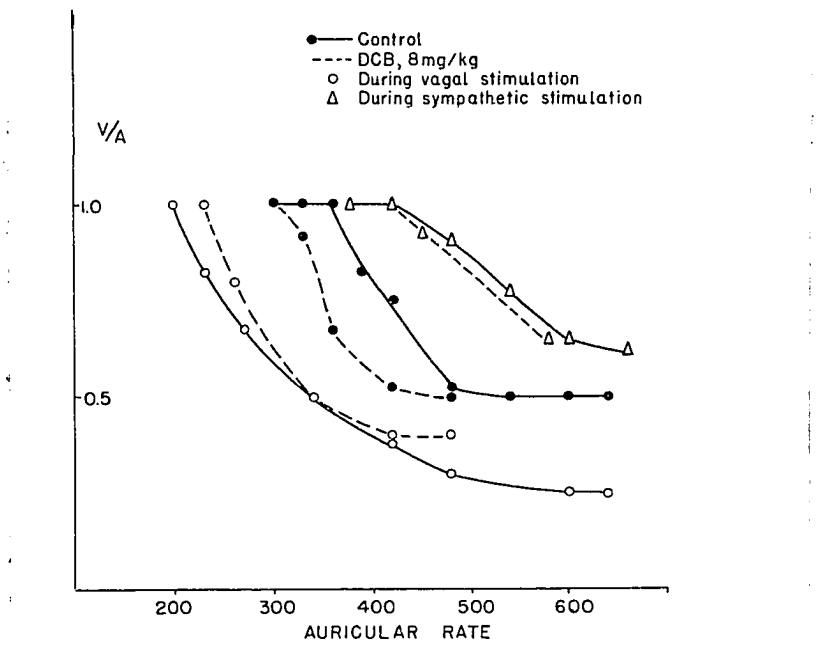


Figure 26

DCB depresses A-V conduction but does not prevent the depression during vagal stimulation or the improvement during sympathetic stimulation.

Table III. Effect of procaine, DEAE, and DCB on A-V conduction in hearts in different conditions of innervation.

Compound	Dose mgm./Kgm.	Innervation	Experiments	A-V Conduction		
				Improved	Depressed	Unchanged
			No.	No.	No.	No.
Procaine	8	decentralized	8	1	6	1
		vagotomized	5	3	1	1
		sympathectomized	1	1	0	0
		intact	3	3	0	0
DEAE	32	decentralized	5	5	0	0
		vagotomized	4	4	0	0
		intact	2	2	0	0
DCB	8	decentralized	2	2	0	0
		vagotomized	3	2	0	1
		intact	2	2	0	0

of A-V conduction as indicated by the marked changes produced by the stimulation of nerves and the fact that the anti-vagal effect of procaine on A-V conduction is greater than its direct action. The actions of procaine also illustrate the complexity of A-V conduction and that direct and indirect effects of drugs on this system may be completely different.

CHAPTER VI

Auricular Flutter

History.

The term flutter was first used by McWilliam in 1887 (32) to describe an extremely rapid movement of the auricle in response to faradic stimulation. Auricular flutter was not clearly recognized as a distinct condition until it was described for the human auricle by Hertz and Goodhart in 1908 (33). The term was adopted by Jolly and Ritchie in 1910 (34) to mean rapid auricular beating. The term auricular fibrillation is applied to conditions of very rapid and irregular beating.

Rothberger and Winterberg (1909) (35) were the first to examine the fluttering or fibrillating auricle by means of direct leads. They suggested a close interrelation of flutter and fibrillation and that the refractory period was important regarding the behavior of the auricle after stimulation. From subsequent studies they concluded that in fibrillation the muscle fibers contract independently and that this was caused only by agents which increased the excitability of the cardiac musculature. These ideas led to the theory that multiple ectopic foci of stimulus formation had developed.

The demonstration that auricular flutter is probably due to a continuously circulating wave is the end result of observations conducted by Romanes (1876) (36) and Mayer (1908) (37) on the umbrella of jelly-fish and by Mines (1913) (38) on rings of muscle cut from the auricle of fishes. These investigators demonstrated that an induced contraction wave could travel continuously in one direction around such rings of tissue.

Lewis and his co-workers (39), working at the same time as Rothberger

and Winterberg, had attempted to follow the path of the impulse in electrically-induced auricular fibrillation. Fortunately flutter occurred fairly frequently and it was found to be much simpler to follow the excitation wave in this condition. They found they were recording the effects of only one impulse and were able to localize the pathway as being one around the collar of auricular muscle between the atrium (auricular tissue between the 2 vena cavae) and the auricle proper.

Lewis (40) also suggested a very close relationship between flutter and fibrillation. He felt that both conditions were due to a single circulating wave and that the main difference was that in flutter the wave follows a relatively constant anatomical path, whereas in fibrillation this path varies, sometimes considerably, from cycle to cycle. In explaining this similarity Lewis proposed that the main factor affecting the rate is the length of refractory period, which is shorter in fibrillation, and that the regularity or irregularity of transmission of the impulse depends upon the number and size of the refractory barriers. In the case of flutter these barriers are small and such deviations from the straight path as occur are minute, while in fibrillation the barriers are larger and deflect the waves along sinuous paths.

A period of about 25 years has elapsed since the work of Lewis and only recently have further investigations of the phenomena concerned with auricular flutter and fibrillation been conducted, except sporadically by van Dongen.

Since 1938 van Dongen (3, 17) has been accumulating evidence by means

of pharmacological studies to support the theory of Rothberger and Winterberg that fibrillation has its origin in one or more heterotopic centres continuously giving rise to new stimuli with high frequency. His conclusion remains as stated in 1950 that "the complete correlation" between (1) neutralization of fibrillation induced electrically, and (2) suppression of heterotopic rhythms induced by acetylcholine or epinephrine, by different drugs "gives a very strong indication that the origin of fibrillation and flutter lies in one or more ectopic centra, continuously giving rise to a new stimuli." Van Dongen has also concluded that a "general antagonism" with epinephrine and acetylcholine is independent of the anti-fibrillating action of active compounds.

Scherf (41) has recently reported some interesting results of a more physiological analysis of some of the factors he has encountered in auricular fibrillation which may be summarized as follows. By the topical application of aconitine to the auricular tip or to the sinus node he has been able to induce a condition of regular tachycardia of about 300 per minute. Cooling of the treated area interrupts but does not stop the flutter, from which Scherf concluded that rapid impulse formation of this area had been hindered but was still capable of impulse formation since waves resulting from it appear when the tissue again becomes responsive. In addition, Scherf has applied traction or otherwise stretched the auricle, which invariably results in an increased rate of flutter, changing into fibrillation. He feels that this response is analogous to inducing spontaneous rhythmic discharges in nerve or muscle or increasing the rate of an existing stimulus formation (Gaskell) and to that observed in isolated

cardiac tissue (Goldenberg and Rothberger). In these experiments he has determined that stretch does not alter conduction velocity. Thus, if a circus movement were present, the increased rate of flutter and its change into fibrillation would require the assumption of increased speed of the circulating wave. Prinzmetal et al. (42) have demonstrated by means of high speed motion pictures that in the auricular flutter and fibrillation induced by Scherf's methods the contraction waves are initiated at a single ectopic focus and spread over the auricular surface in a non-circus fashion. They report that the contraction waves of auricular extrasystoles, tachycardias, and flutter, and the large waves of auricular fibrillation arising from the site of injection of aconitine are indistinguishable except for their rate and speed of conduction. Above a certain rate of beating the minute waves of fibrillation appear and are superimposed on the large waves.

Rosenblueth and García-Ramos (43) recently have extensively investigated auricular flutter in dogs by inducing a wave to circulate around an artificial obstacle in the auricle. For the obstacle they used a crushed area which in essence prolonged the opening or junction of the inferior vena cava. By means of electrodes placed around the perimeter of the crushed area they were able to demonstrate, more accurately than had Lewis for an uninjured auricle, that in flutter a single excitation wave proceeds around the opening of the cavae with an approximately constant velocity. If the electrodes were placed perpendicular to the perimeter at adistance, the recorded electrograms showed that the impulse reached these electrodes at the time predicted by the assumption that flutter is due to a single impulse traveling continuously and unidirectionally around the obstacle.

It is perhaps Garrey's views on the interpretation of circus contractions, published in a review in 1924 (44) which best express why conflicting views regarding flutter and fibrillation still exist. Employing the fundamental concept of circus motions and taking into consideration possible variations in position, degree, and duration of refractory barriers, and possible differences in excitability and conductivity, Garrey has summarized some of the ways in which circus motions can express themselves. There may be (a) brief, shuttling impulses within the time of a single normal cycle, (b) a simple, single circuit causing an extrasystole superimposed on and continuous with the preceding normal beat, (c) a simple circuit involving the whole structure successively and continuously in its circulating progress, (d) impulses sharply localized and limited to a circumscribed path within a part of the musculature repeating their single course in rhythm, causing a regular coordinate flutter in the rest of the auricle, (e) these latter may cause wild localized fibrillation, (f) wild fibrillation involving the whole auricle; in this the impulse is diverted into different paths, weaving and inter-weaving through the tissue mass. In support of his theories Garrey relied partly on clinical as well as experimental descriptions of localized and generalized fibrillation, and flutter. He felt that an impulse must be already shuttling back and forth since a single impulse may precipitate fibrillation.

The data now available indicate that there are actually two types of experimental auricular flutter. The type which frequently follows rapid faradic stimulation or the local application of agents such as aconitine, methacholine, etc. tends to depend upon one or more ectopic foci of rapid

stimulus-formation resulting in rapid, regular or irregular, sequential or non-sequential contraction waves. The other type of flutter is the one demonstrated to exist in the mammalian auricle by Lewis and Rosenblueth and García-Ramos and employed in the present work. In this type of flutter it can be shown that there are no ectopic foci, and that the contraction wave results from a single impulse continuously circulating around a known barrier.

Methods.

Localized, generalized, or irregular fibrillations are inadequate for several reasons for the quantitative study of the auricular properties concerned and how they can be influenced. First, such arrhythmias are generally transitory and can neither be maintained in a steady state nor can they be accurately duplicated for comparative determinations. Second, the changes involved in such types are rapid and complex and require highly refined techniques for recording and analyzing the phenomena. Third, such types may be induced experimentally only by the application of some noxious agent, i.e. fairly prolonged high frequency stimulation, acetylcholine, methacholine, aconitine, or combinations of these, causing a considerable alteration in excitability.

Auricular flutter as induced by the method of Rosenblueth and García-Ramos was chosen for the experimental study. Rapid and regular contractions involving the entire auricle sequentially at a rate of 2 to 4 times the normal sinus rate can be induced which continue for hours without further stimulation. Further, the conducted wave can be demonstrated to be a single impulse traveling along a circular pathway. The pathway can be localized, conduction velocity calculated, and effects of nerve stimulation

and drug action can be quantitatively and comparatively determined.

The dogs were prepared as described in Chapter II. Flutter was induced around a crushed area on the surface of the right auricle by electrical stimulation at a frequency usually just higher than that which the auricle could follow using a voltage 3 or 4 times that required to excite the auricle.

The auricular surface was crushed by means of a hemostat. Two locations of crush were used. One extended from the superior surface of the inferior vena cava about 1 1/2 cm. caudad to the auricular orifice continuing upward onto the right auricle for several centimeters. This area is similar to that employed by Rosenblueth and García-Ramos. The second type was made across the right auricular surface from the region of the sinus node. The area of either type of crush was extended if difficulty in inducing flutter was encountered, but was generally a crush of about 40 by 4 mm. In most experiments the stimulation was applied near the junction of the superior vena cava and the right auricle.

Instances of flutter which resulted from this experimental procedure were in general of two types apparently differing only in their stability. Some persisted for periods of less than 5 minutes; these could be re-induced repeatedly but the duration of successive episodes was always brief. In this type some instances of flutter showed a gradually decreasing rate while others gradually increased in rate. More frequently the flutter rate was steady until only one or two beats before reversion. Regardless of whether or not such small changes in rate occurred, reversions generally appeared at a certain constant interval from the beginning of the flutter episode.

The behavior of the flutter rate in these episodes suggests that a progressive change occurs. This may be, for example, the result of successive small changes in the path of the impulse which brings it to refractory tissue, or the result of a refractory barrier gradually increasing in size which comes into the path of the impulse. In most experiments flutter usually persisted for longer than 5 minutes. If a flutter persisted for at least 5 minutes, it would almost always persist for hours.

The criteria of flutter suitable for subsequent experimental study were: adequate rate (2 to 4 times the sinus rate), regularity of rate, duration of at least 5 minutes, and failure to revert to sinus rhythm following the injection of 2 cc. of saline.

It was found that a rapid and regular flutter developed in the absence of crush upon stimulation at rates of 9 to 11 per second in 12 of 18 animals, the flutter was frequently stable, but the experiments were not employed in any of the following studies.

Observations incidental to the procedure inducing flutter are briefly as follows. Flutter was difficult to induce in small dogs or in dogs with small hearts, suggesting that in these animals the auricles were not large enough to permit a circus movement. Occasionally with certain sized crushes it was possible to produce a lasting flutter by a single stimulus. If the obstacle was not continuous or of sufficient size, various types of arrhythmias developed upon rapid stimulation. In most experiments this was a generalized fibrillation of short duration. In other experiments flutter was of alternating rhythm, composed of fast and slow components which were separated either by short or long intervals of either rhythm. Frequently this type of flutter could be demonstrated several times in the same heart by stopping

the flutter and re-stimulating, suggesting that alternate pathways are involved. A stable regular flutter could be induced in these hearts either by making the crushed area continuous (by eliminating all normal tissues in the area) or by extending the limits of the crush. If a single excitation wave is assumed to be circulating around the crushed area or around an area adjacent to the crush these results suggest that when the crush is not continuous the impulse at certain times travels through some undamaged non-refractory tissue in the crushed area or is deflected to another path and either long or short pathways can be the site of the circus.

Fibrillating rhythms frequently revert to sinus rhythm, probably because the obstacle is too small and the impulse is more likely to meet refractory tissue. Alternating flutters frequently revert, probably because the impulse meets refractory tissue in changing its course.

Results.

A. Evidence for circus movement of impulse.

Attempts were made to follow the path of the impulse in flutter according to the method described by Rosenblueth and García-Ramos. Several pairs of recording electrodes were placed close to the crush and at several points around its perimeter. Before flutter was initiated a record was taken with the electrodes in place in order to demonstrate that the impulse did not appear at the electrodes in a consecutive pattern. After flutter was established the order of appearance of the impulse at the different electrodes was determined.

It is possible to demonstrate crudely the course of the conduction wave around the obstacle by measuring the conduction time between the different electrodes. The distance between the electrodes was measured in order to calculate conduction velocity.

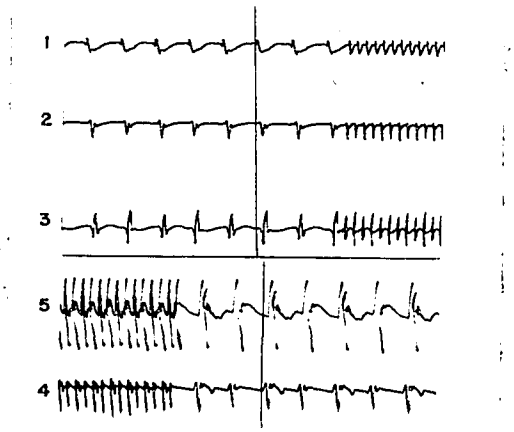
Figures 27, 28, 29, and 30 indicate (1) the position of the electrodes in relation to the auricle and the crush, (2) the actual electrograms recorded from the individual points. Figure 27 also contains a graphic suggestion of the possible path of the impulse considering it in terms of a circle. The area of the crush was also converted to a circular area. This illustration is intended to be a rough description of a process which is complicated by other refractory barriers, anatomical distances, angles and curvatures, and limitations of recording.

Figure 27 demonstrates the type of crush used and flutter obtained by Rosenblueth and Garcia-Ramos. The obstacle extends from a non-conducting portion of the inferior vena cava as determined by the characteristics of the electrograms at that point. The wave appears at electrodes 1 to 5 in successive order. Conduction velocity is similar between each pair of electrodes.

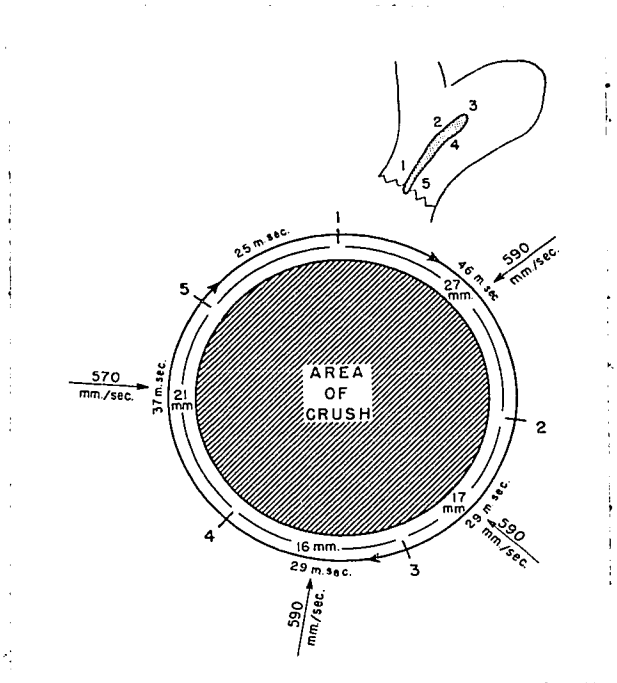
Figure 28 shows a similar experiment in which the impulse circulated around the obstacle in the opposite direction to that shown in Figure 27.

Figure 29 shows the occurrence of alternating slow and fast flutter in the same heart at frequent intervals without reversion to sinus rhythm. One of the possible locations of the fast component is a short cut through the centre of the crush which may not have been entirely damaged. Other possibilities for this path might be around the inferior vena cava or around the opening of the cavae at the auricle. The different locations were not explored sufficiently to determine the exact path of the impulse.

Figure 30 shows flutter when the obstacle was made on the lateral auricular surface from an area midway between the sinus node and the right ventricular orifice toward the tip of the auricle. The electrograms show



a



b

Figure 27

Part (a) shows the electrograms recorded during auricular flutter from pairs of electrodes 1 to 5 placed around a crushed area of the auricle (b). The diagram indicates the area of the crush and path of the impulse considered as a circle. Figures outside the circle are conduction times; those inside the circle are the distances between electrodes. The arrows indicate calculated conduction velocity between each pair of electrodes.

Auricular Flutter

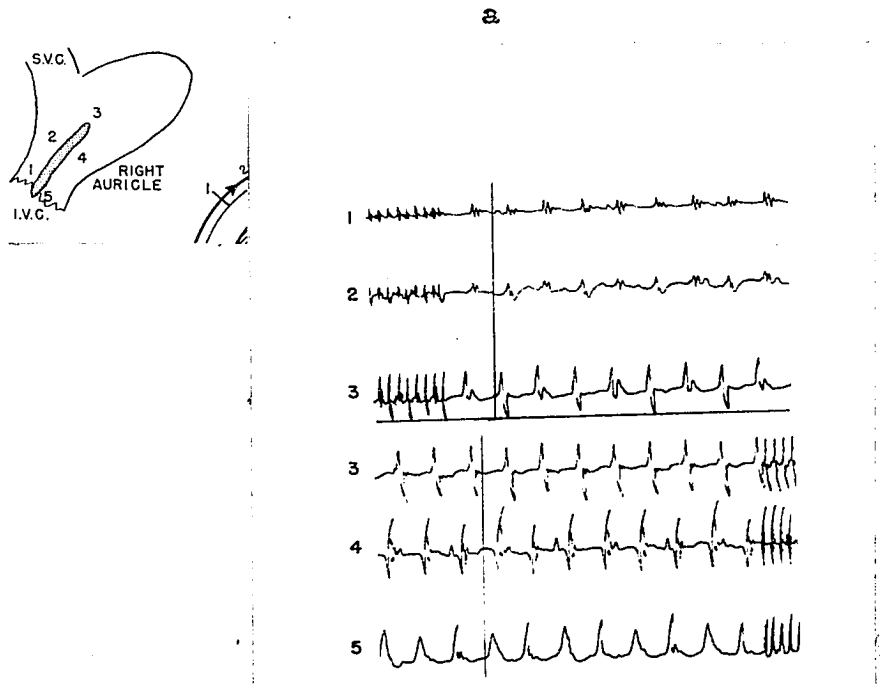


Figure 28

(a) shows the area of a crush in relation to the right auricle and the positions of electrodes 1 to 5 around the perimeter. Part (b) shows the electrograms from the auricle recorded from electrodes 1 to 5 during auricular flutter. The relation of the auricular waves to each other indicates the impulse traveled around the obstacle.

Auricular Flutter

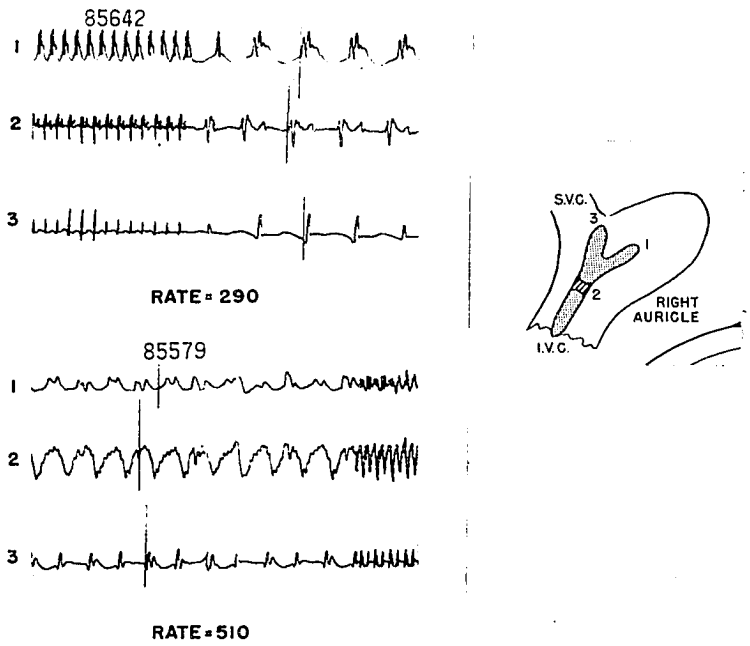


Figure 29

The electrograms show a slow regular flutter (290/min.) and a rapid irregular flutter (510/min.) which occurred in the same heart and alternated for a long period without reversion to sinus rhythm. The position of the crush is shown in the small picture.

Auricular Flutter

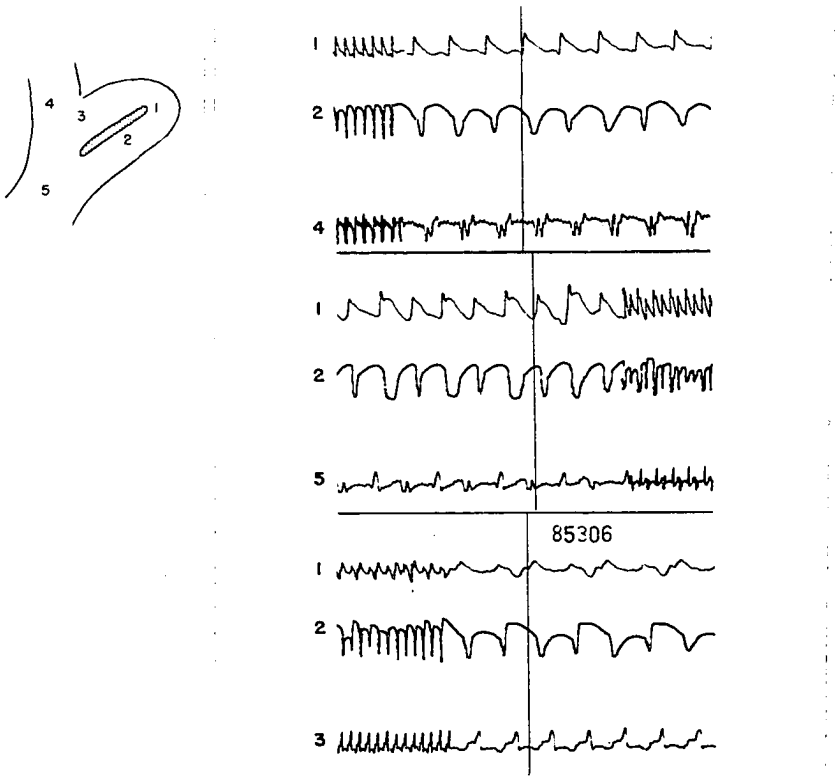


Figure 30

The electrograms indicate the impulse arrives at electrodes 1, 2, and 3 earlier than at electrodes 4 and 5. The path of the impulse may be in the region of the crushed area shown in the small insert.

that the impulse arrives successively at electrodes 1, 2, and 3, and relatively later at electrodes 4 and 5. This indicates that the course of the wave was localized in the body of the auricle nearer to the tip than to the atrium.

Figure 27 is one example of a demonstrated circus movement. The same phenomenon was observed in additional experiments. In other experiments the circus nature was demonstrated only partially and in still others no attempt was made to explore the path of the impulse. It is assumed, however, based on the results obtained when the movement was studied and on incidental observations, that the circus phenomenon was present in all flutter preparations employed in this study.

The velocity of the conducted impulse during auricular flutter was found to be between about 500 and 600 mm./sec. in all experiments, as illustrated in figure 27. This velocity of conduction is similar to that occurring in the electrically driven auricle when the rate of stimulation approximated that of flutter (Chapter III, figures 2, 3). As has been noted, Lewis and Rosenblueth and García-Ramos also found the same range of conduction velocity for flutter.

The effect of a crushed area of the auricle on maximal rate and excitability was determined in order to learn whether the crush employed in the procedure to induce flutter might complicate the actions of the drugs. Figure 31 demonstrates that essentially no change occurred in this experiment although the decrease in maximal rate indicates a slight lengthening of refractory period. In some experiments the threshold of excitability was slightly increased. Local changes in excitability occurring close to

Auricular Flutter

Maximal Rate and Recovery of Excitability

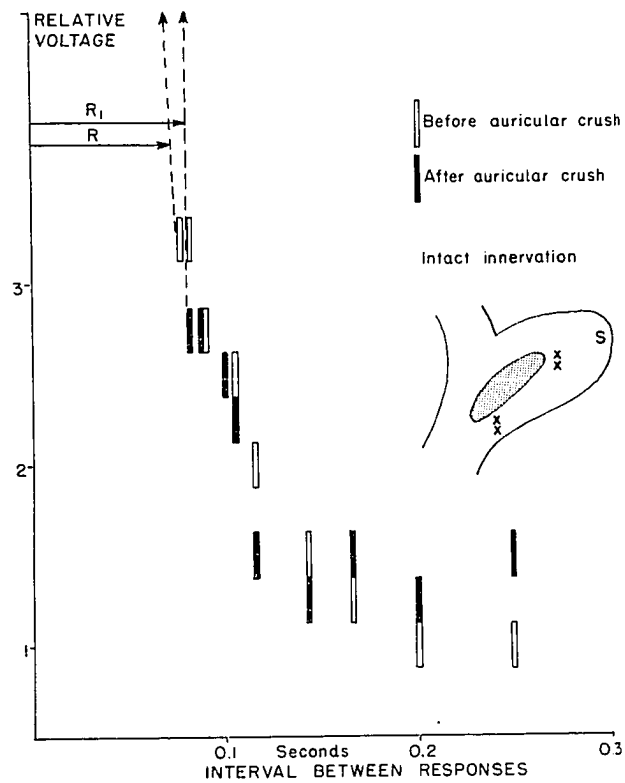


Figure 31

A crushed area of the right auricular wall produces no significant change in maximal rate or excitability.

the crushed area may have been greater than the changes recorded at the location of the electrodes.

B. Section and stimulation of nerves.

Figure 32 summarizes the relation of V/A to auricular rate in over 40 experiments with auricular flutter. It shows that flutter rates tend to be higher when the innervation to the heart is intact than when the heart is decentralized.

It is known that vagal or sympathetic stimulation during flutter increases the rate. Typical effects of vagal stimulation are shown in figures 33 and 40. Figure 34 shows the usual effect of sympathetic stimulation. The increase in rate of flutter during stimulation of either nerve averaged about 5 per cent under the conditions of these experiments. Since both vagal and sympathetic stimulation increase the rate of flutter, the effect of their tonic discharge may account for the tendency toward higher flutter rates when innervation is intact.

C. Drugs.

1. The effects of the injection of acetylcholine and of epinephrine on the auricular rate in flutter are shown in figures 35 and 36. Both substances increase the rate. Acetylcholine always caused the flutter to change to a fibrillation which reached a rate of 2000 or more per minute within a few seconds, usually followed by reversion to sinus rhythm. This wild activity probably represents the type of fibrillation induced by acetylcholine in the experiments reported by van Dongen. Epinephrine increased the rate from 5 to 25 per cent but did not affect the regularity of the beat and rarely caused reversions. These results are similar to those reported by Rosenblueth and García-Ramos (43) and by Acheson et al. (45).

Auricular Flutter

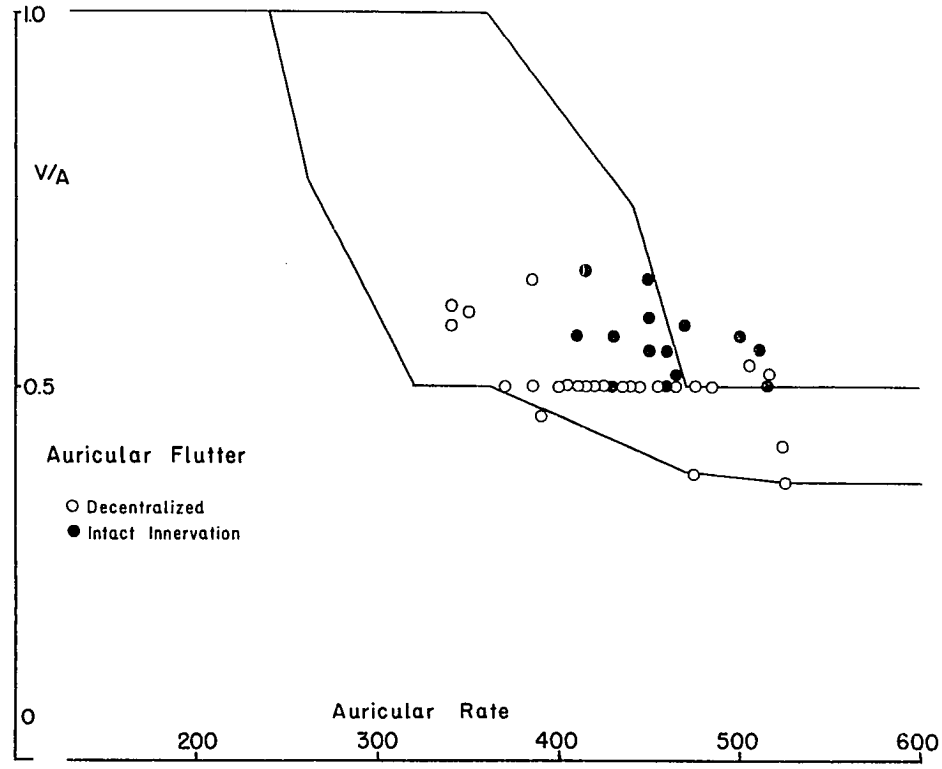


Figure 32

Auricular rates in flutter appear to be higher in innervated than in decentralized hearts. The V/A shows A-V conduction is also somewhat better in innervated hearts. The V/A in auricular flutter is similar to that obtained with the electrically driven auricle.

Auricular Flutter

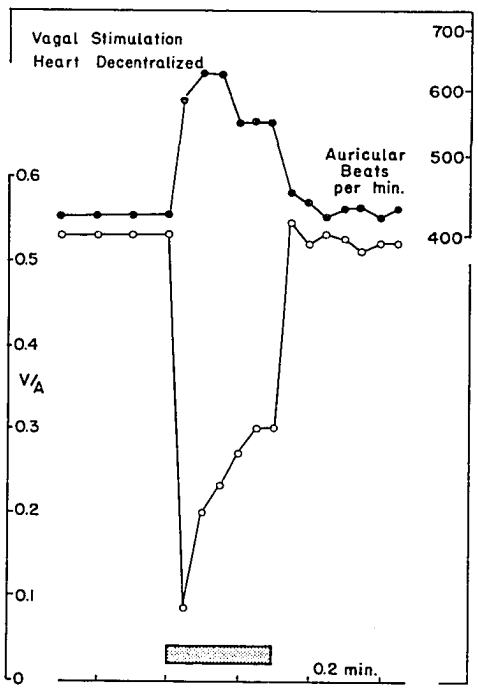


Figure 33

During auricular flutter vagal stimulation causes increased rate of flutter (top line) and fall of $V/_A$ (bottom line).

Auricular Flutter

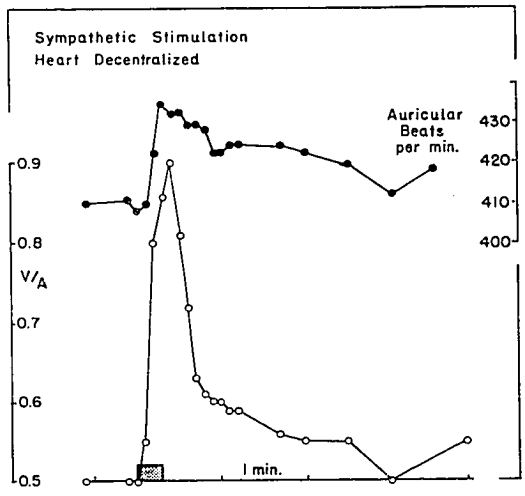


Figure 34

During auricular flutter sympathetic stimulation increases the rate of flutter (top line) and increases V/A (bottom line).

Auricular Flutter

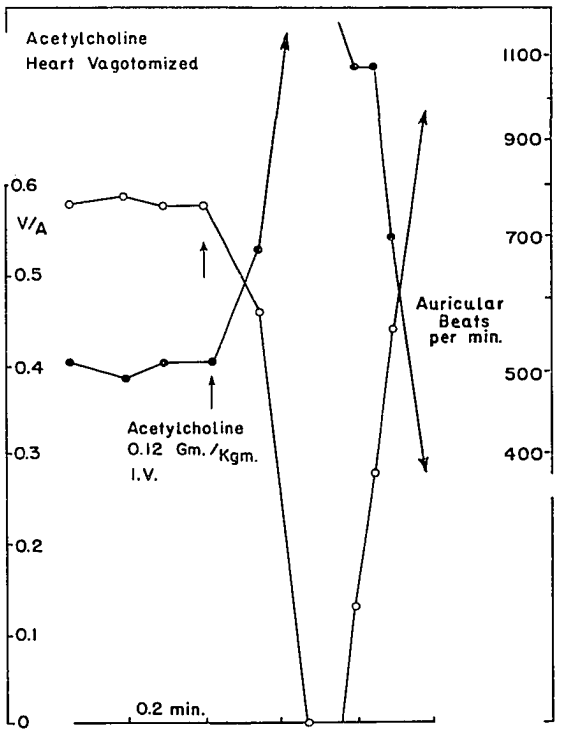


Figure 35

During auricular flutter the injection of acetylcholine changes flutter into fibrillation and decreases V/A.

Auricular Flutter

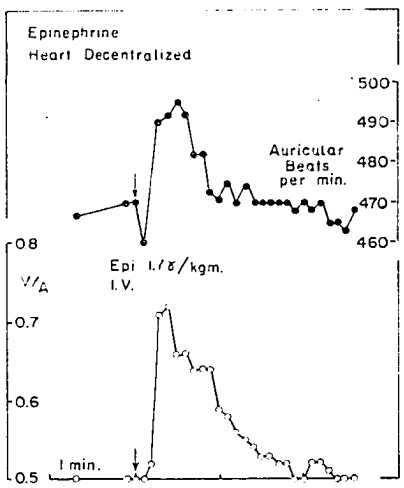


Figure 36

During auricular flutter the injection of epinephrine increases the rate of flutter and increases V/A.

2. Results of experiments using procaine are summarized in figures 37 to 41. Typical effects of various doses of procaine on flutter rates when innervation was intact are shown in figure 37. Doses as small as 0.5 mgm./kgm. are effective in slowing the auricular rate. The fall of auricular rate is accompanied by an increase of the ventricular rate. The duration of the effect is relatively brief and almost full recovery to the initial flutter rate occurs within a few minutes. In the vagotomized heart the auricular effect is similar but the ventricular rate remains essentially unchanged (figure 38). When the heart is decentralized (figure 39), the auricular slowing is less than when the innervation is intact but the ventricular rate is slowed also.

Figure 40 presents a summary of the effects of various doses of procaine on auricular and ventricular rates for both innervated and denervated hearts. The per cent of auricular slowing is increased as the dose is increased. For all comparable doses the reduction of flutter rate in the decentralized heart is significantly less than in the innervated heart. The ventricular rate is frequently slowed in decentralized hearts, while it is almost always increased when the innervation is intact.

The injection of procaine prevents the effects of vagal stimulation during flutter (figure 41). During the time that the auricle is slowed by procaine, vagal stimulation no longer increases the auricular rate. Procaine also markedly reduces the amount of ventricular slowing produced by vagal stimulation.

3. The effects of various doses of DEAE on auricular flutter in innervated, vagotomized, and decentralized hearts is shown in figures 42 and 43. Doses of 32 mgm./kgm. cause slowing of both auricular and ventricular rates regardless of state of innervation. Smaller doses are almost ineffective.

Auricular Flutter

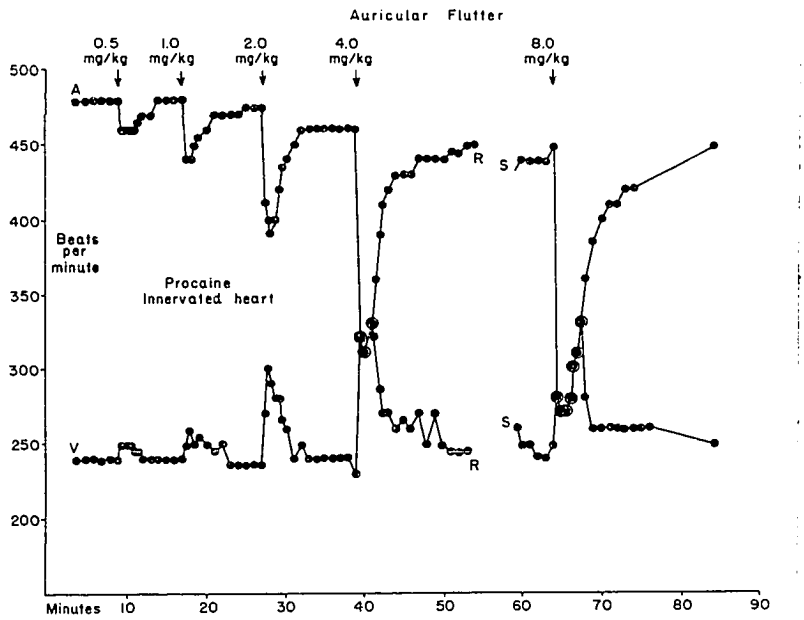


Figure 37

Increasing doses of procaine cause an increased slowing of auricular rate and an increased ventricular rate in the innervated heart.

Auricular Flutter

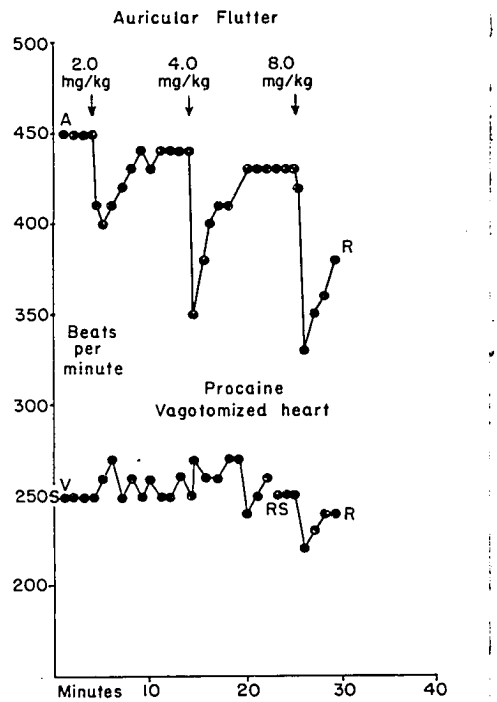


Figure 38

When the heart is vagotomized procaine slows the rate of auricular flutter but has little effect on the ventricular rate.

Auricular Flutter

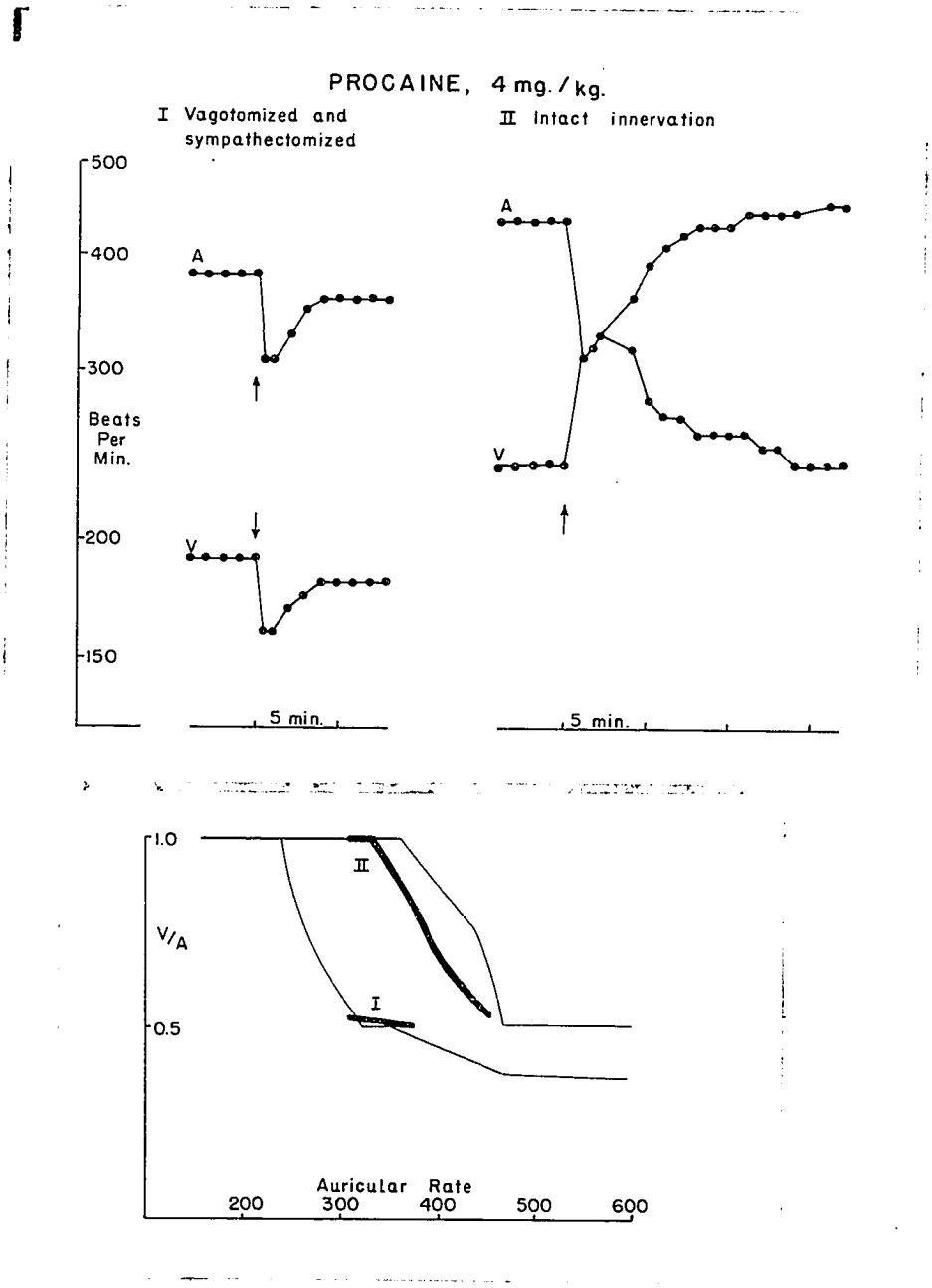
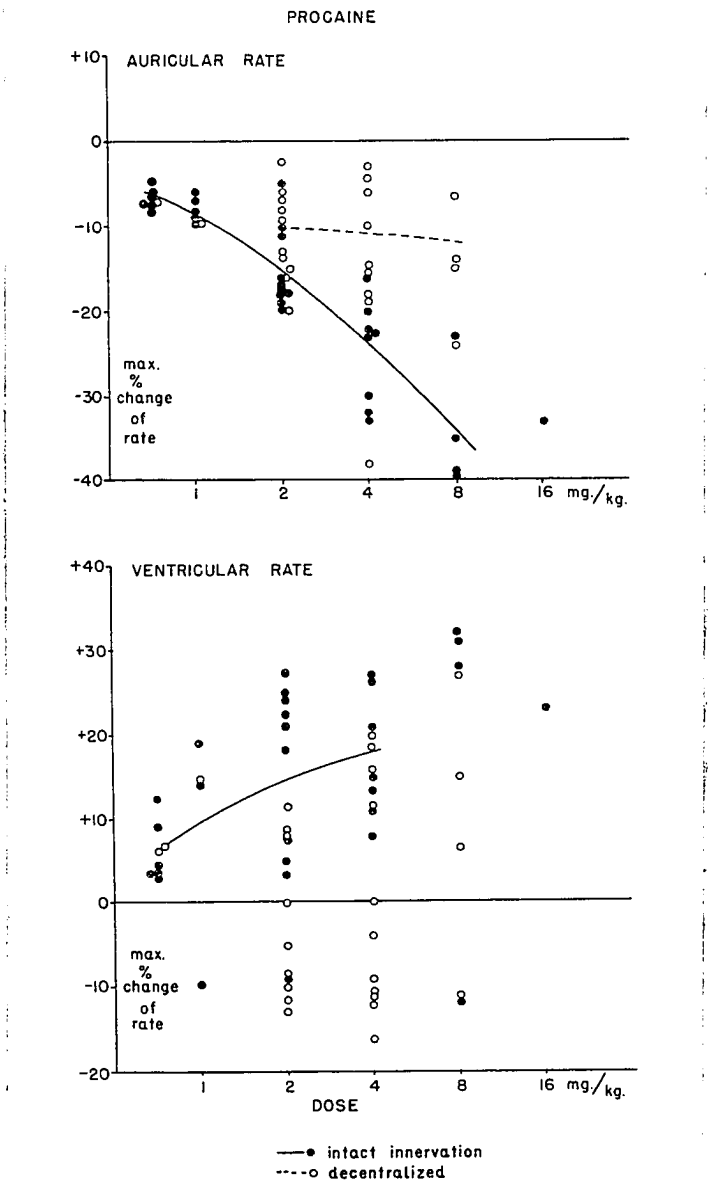


Figure ~~40~~ 39

During auricular flutter procaine causes greater slowing of auricular rate in innervated than in decentralized hearts. It increases the ventricular rate when innervation is intact but slows it when the heart is decentralized. A-V conduction during recovery from the maximal effect falls within the distribution range obtained with electrically driven auricles.

Auricular Flutter



40
Figure ~~39~~

Increasing doses of procaine cause increasing slowing of the auricular rate (~~lower~~ upper graph) in both innervated and decentralized hearts and increasing ventricular rates (~~lower~~ graph) in innervated hearts and generally decreasing ventricular rates in decentralized hearts.

Auricular Flutter

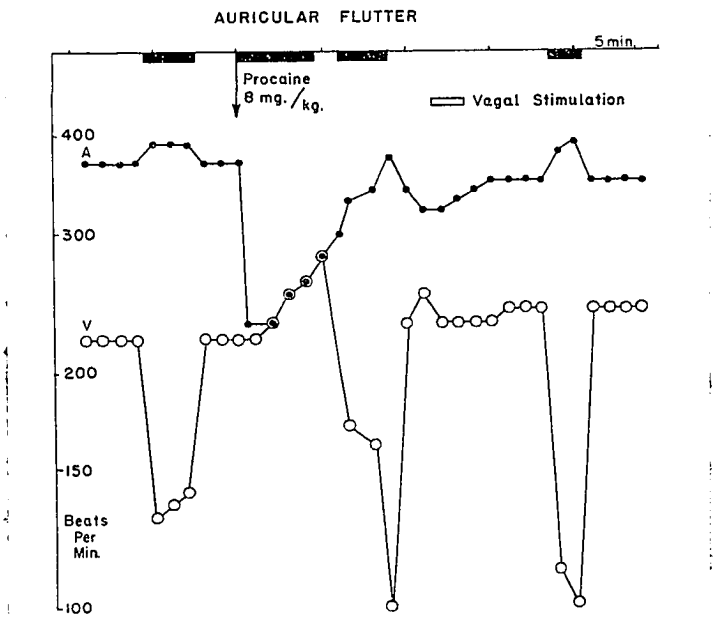


Figure 41

During vagal stimulation the rate of auricular flutter is increased and the ventricular rate is slowed. When the auricular rate is slowed by procaine, vagal stimulation does not change the rate and the ventricular slowing is reduced and even rises.

Figure 44 is a summary of the effects of various doses of DEAE on auricular and ventricular rates in both innervated and decentralized hearts. The per cent slowing of auricular rate increased as the dose is increased and is greater at all comparable doses when the innervation is intact than in the decentralized heart. Since doses of 64 mgm./kgm. or more were generally lethal, the effectiveness of DEAE never reaches that of procaine. DEAE usually slows the ventricular rate and when the heart is decentralized the per cent of ventricular slowing is usually greater than that of the auricle. DEAE occasionally causes an increase in ventricular rate. This occurred frequently when reversion followed in a few seconds, and also when DEAE caused rapid death of the dog.

4. Results of experiments with DCB are presented in figures 45, 46, and 47 in the same manner as those for the preceding compounds. DCB slows the auricular rate (figures 45 and 47) but the effect is small and reversions occur frequently, so that maximal effects could not be determined. DCB always causes a simultaneous slowing of the ventricular rate regardless of the innervation. In terms of percentage the ventricular slowing is usually about the same as the auricular slowing. DCB also slows a dose-response relationship (figure 46); this is nearly the same for both innervated and decentralized hearts.

5. The influence of injections of p-aminobenzoic acid on auricular flutter in an innervated heart is shown in figure 48. Since no cardiac effects were noted in these experiments no further studies of this compound were made.

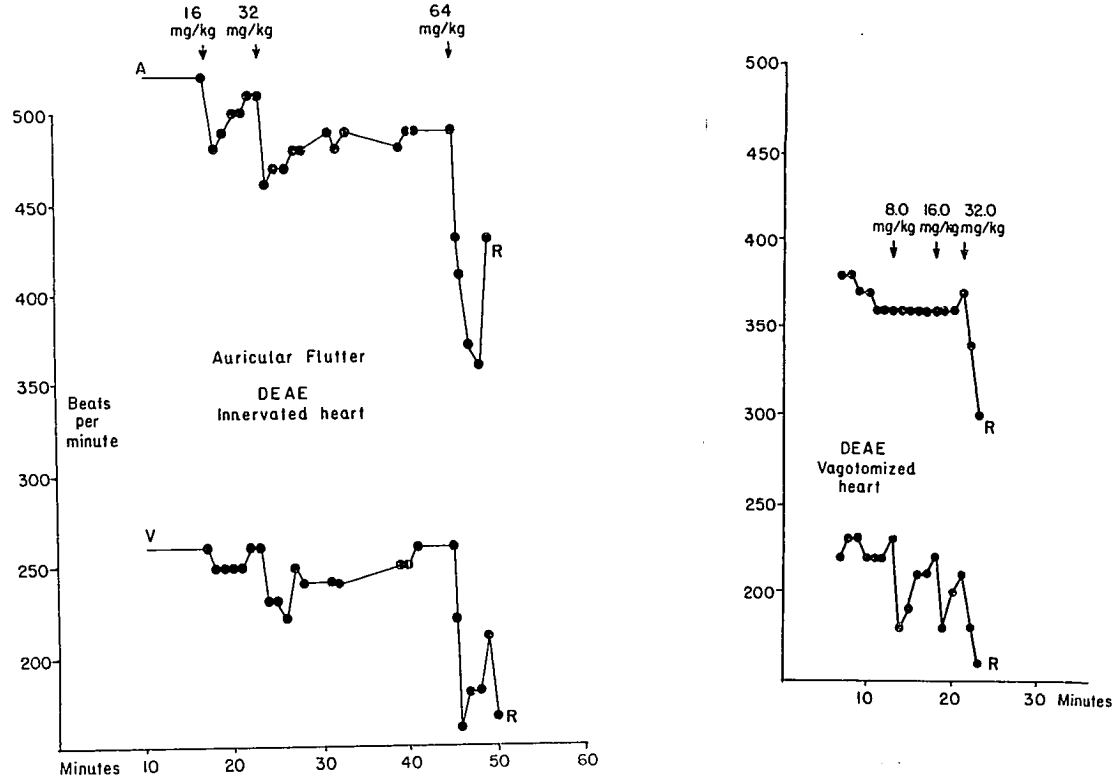


Figure 42

DEAE slows both auricular and ventricular rates in auricular flutter in innervated and vagotomized hearts.

Auricular Flutter

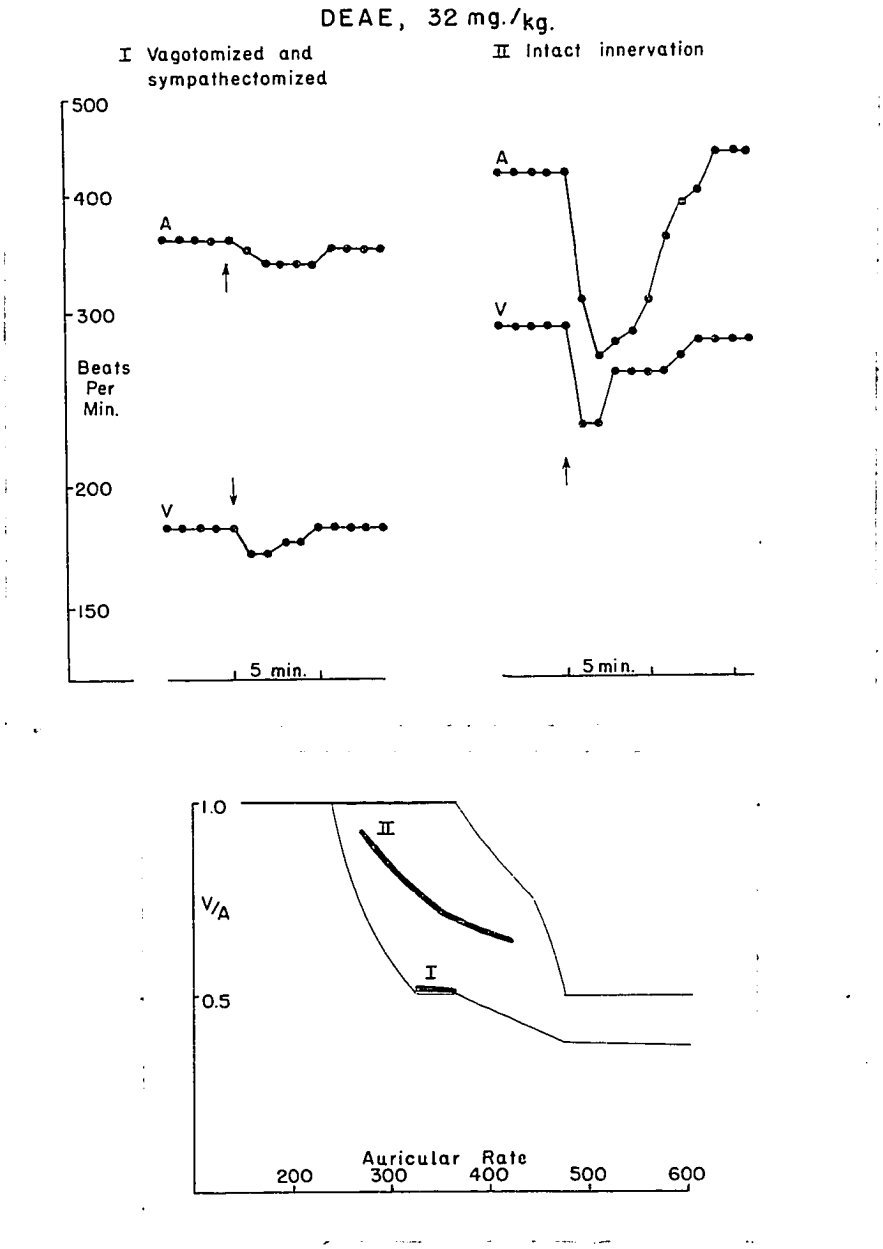


Figure 43

DEAE slows both auricular and ventricular rates in flutter. Its action is greater in innervated than in decentralized hearts. The curves of A-V conduction during recovery from the maximal effect indicate a possible depression of A-V conduction.

Auricular Flutter

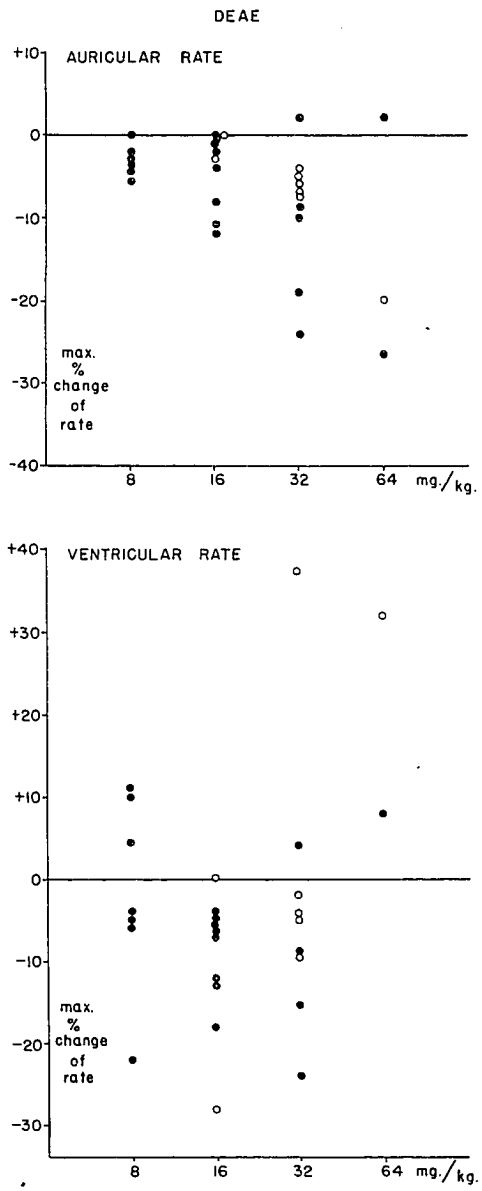


Figure 44

During auricular flutter the injection of increasing doses of DEAE causes an increased slowing of auricular and ventricular rates in both innervated and decentralized hearts.

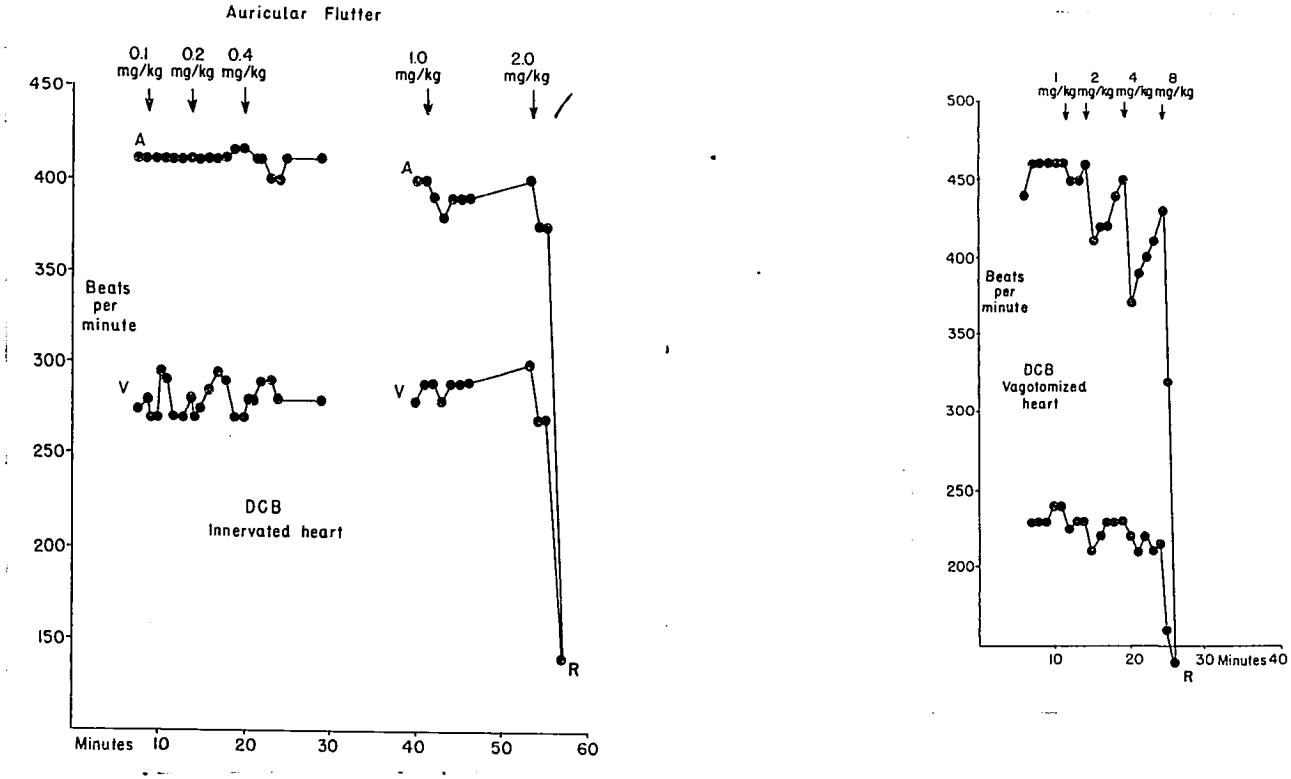
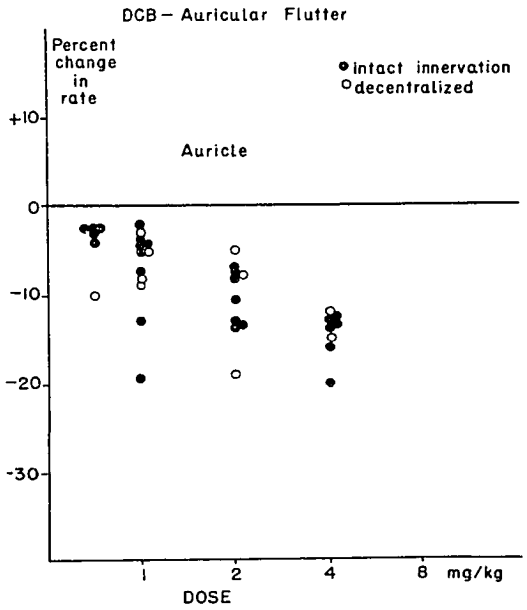


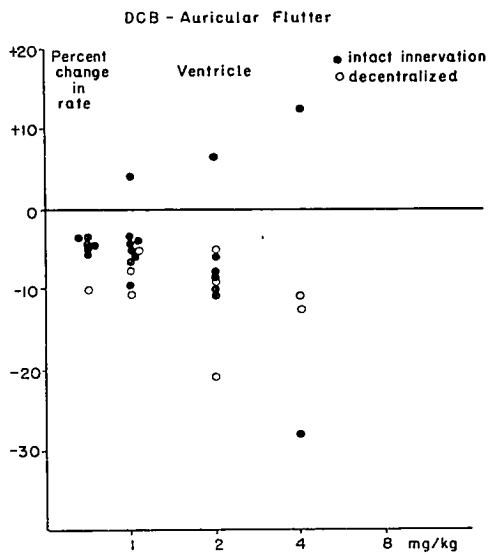
Figure 45

a b

DCB slows both auricular and ventricular rates in flutter and frequently causes reversions to sinus rhythm.



a

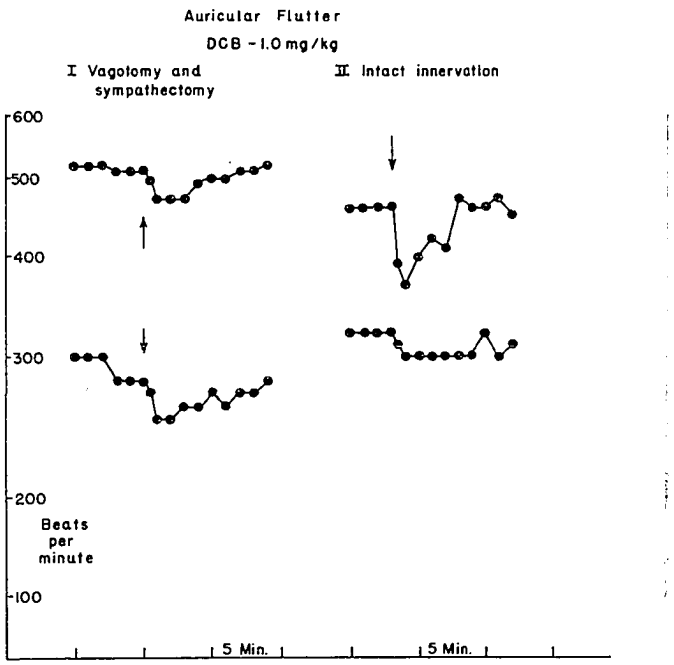


b

Figure 46

Increasing doses of DCB cause increased slowing of both auricular and ventricular rates. Occasionally the ventricular rate is increased. The effects are similar for both innervated and decentralized hearts.

Auricular Flutter



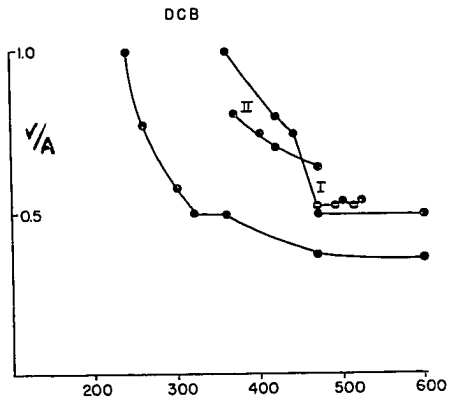


Figure 47

DCB slows auricular and ventricular rates in flutter in both innervated and decentralized hearts. The curves of A-V conduction during recovery from maximal effects do not indicate the depression of A-V conduction which DCB produces in experiments with the driven auricle.

Auricular Flutter

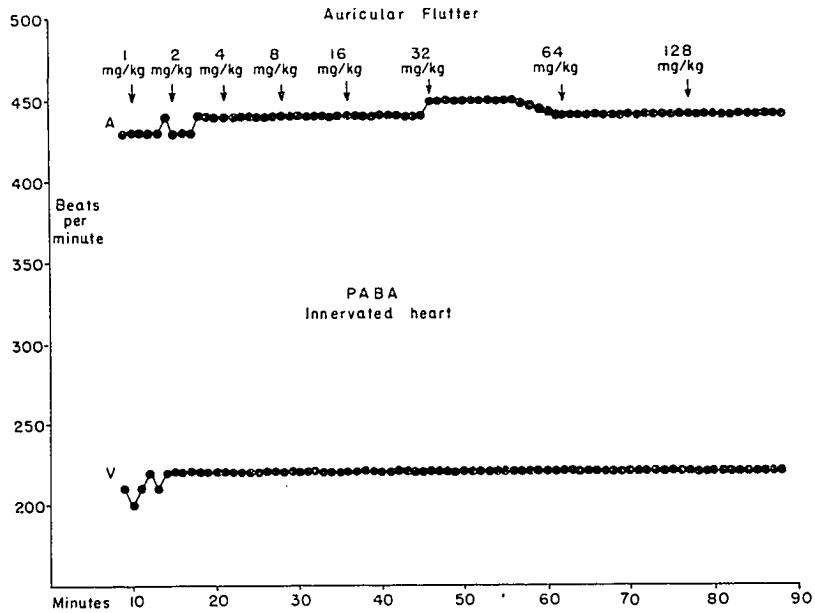


Figure 4g

PABA has no effect on rate of flutter

in doses as high as 128 mgm./kgm.

6. The effect of various doses of 2,4-dichlorobenzoic acid are shown in figure 49. It does not cause slowing of the flutter rate but frequently increases the ventricular rate. The lethal dose of this compound for dogs was lower than that of p-aminobenzoic acid. Since it did not change the auricular rate in flutter, it was not studied further.

D. A-V conduction in flutter.

The effects of nerve stimulation and drugs upon A-V conduction during auricular flutter are difficult to interpret because the auricular rate usually changes at the same time.

Figure 32 shows the relation of V/A to auricular rates during flutter in hearts with intact innervation and in decentralized hearts. V/A at any particular auricular rate is similar to the V/A at similar rates in the electrically driven heart, although in some instances V/A is somewhat higher. The graph shows that A-V conduction is better when innervation to the heart is intact. Since vagal stimulation depresses and sympathetic stimulation improves A-V conduction, this suggests that in these hearts sympathetic tone was greather than vagal tone.

The role of innervation on A-V conduction during auricular flutter is the same as in the electrically driven auricle. While vagal stimulation and sympathetic stimulation have the same effects on the auricle, their effects on A-V conduction are opposite. As in the electrically driven auricle vagal stimulation impairs A-V conduction, whereas sympathetic stimulation enhances it. The difference of effect is found as between acetylcholine and epinephrine. The changes of V/A in these conditions are plotted in figures 33, 34, 35, and 36. The changes of V/A shown in these four are

Auricular Flutter

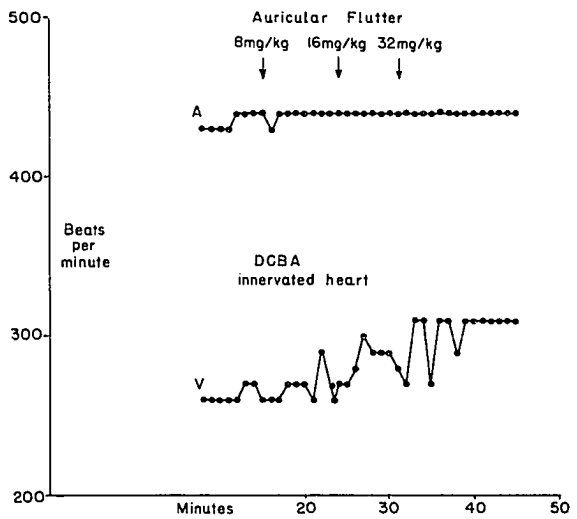


Figure 49

DCBA has no effect on rate of flutter. It frequently causes an increase in ventricular rate.

dramatic, but the effect upon A-V conduction cannot clearly be separated from the effects of change of auricular rate.

Figures 39, 43 and 47 show in the upper graphs the typical slowing of auricular and ventricular rates in flutter in innervated and decentralized hearts produced by procaine, DEAE, and DCB. In the lower graphs, the relation of V/A to auricular rate during recovery from the maximal slowing is plotted for each of the compounds. The curve of V/A with respect to auricular rate for each compound in either state of innervation falls within the normal distribution curve and cannot be distinguished from changes in auricular rate alone. In the case of DEAE, the curve of A-V conduction when innervation is intact is similar to that of procaine; the former, however, slows both auricular and ventricular rates whereas the latter increases the ventricular rate as the auricle is slowed. In experiments with the electrically driven auricle these compounds can be demonstrated to have opposite effects on A-V conduction when innervation is intact. The above disparities demonstrate that determinations of A-V conduction during auricular flutter are misleading and complicated by the change in auricular rate, which, as described in Chapter V, exerts its own influence on the A-V conducting mechanism. For this reason controlled conditions of either auricle or A-V mechanism are essential to determinations of A-V conduction.

Discussion.

The condition necessary for the continuous passage of an impulse around a fixed obstacle is that a gap of excitable tissue must be present between the head of the impulse and its tail. Judging from studies in the driven auricle the smaller the gap, the smaller should be the conduction velocity.

In auricular flutter conduction velocity is indeed slow, about one-half of the rate found when the auricle is beating slowly, and similar to that occurring at the same auricular rate in the electrically driven auricle. So long as the path of the circus is fixed, the rate of recurrence of the beat at a given spot will be proportional to the average conduction velocity around the whole path. Agencies which change the recovery of the mechanisms underlying conduction velocity in the driven auricle should be expected to affect the rate of flutter in a corresponding direction, i.e., if the recovery is accelerated, the rate of flutter should also be accelerated and vice versa. Physiological evidences of this relationship are seen in the effects of vagal and sympathetic stimulation, both of which increase conduction velocity and increase the rate of flutter.

The actions of the drugs studied also evidence this relationship. Procaine, DEAE, and DCB all slow the rate of flutter. The effect of procaine is the greatest and that of DCB the least. The slowing is evident with smaller doses than are required to slow conduction velocity in the driven auricle. This difference probably depends upon a difference of sensitivity in the two conditions. Changes as low as 2 per cent in rate of flutter can be detected while changes in conduction velocity in the driven auricle can be detected only to within 20 per cent. Because of this limitation in the latter condition, a small amount of slowing which may have been produced by DCB was not observed. That DCB does posses some action, however, can be seen when it slows the auricular rate in flutter.

The change in ventricular rate during flutter caused by the three compounds is just what would have been expected from their actions on A-V conduction with the electrically driven auricle.

All three compounds can also prevent the auricular response at some critical point to the circus wave, thus causing reversion to sinus rhythm, presumably by shortening the gap between the head and the tail of the circulating impulse. This might occur as a result of lengthening the refractory period or increasing the conduction velocity. None of the compounds increase conduction velocity, but all three lengthen the refractory period, approximately to the same degree. The frequency of reversions occurring following the injection of various doses of the three compounds is given in table IV. Reversions occur more frequently when either DCB or DEAE are injected than when procaine is injected. The number of reversions for comparable doses in the different states of innervation are approximately the same for DEAE and for DCB. Reversions are much less frequent following the injection of procaine and occur more often in the decentralized than in the innervated heart.

The reversions caused by DEAE and by DCB probably are the result of a relatively greater effect of lengthening refractory period than of slowing conduction velocity. The gap between the head and the tail of the circus is thus shortened and finally closed. Procaine, in contrast, both lengthens refractory period and slows conduction velocity considerably, the latter effect being relatively greater. In this event the gap tends to remain about the same or may even be lengthened, so that the head of the conduction wave, traveling slowly, rarely meets its tail (refractory tissue) and hence reversions rarely occur.

If lengthening the refractory period caused a decrease in the recovery of the mechanism underlying conduction velocity, the auricular rate would slow progressively and reversions would not occur. Since reversions do

occur, the important conclusion can be reached that changes in refractory period do not necessarily affect the course of recovery of conduction velocity.

Table IV. Incidence of reversions from flutter to sinus rhythm occurring following the injection of procaine, DEAE, and DCB in decentralized, vagotomized, and innervated hearts.

PROCAINE

	DECENTRALIZED HEARTS		VAGOTOMIZED HEARTS		INNERVATED HEARTS	
DOSE Mgm./Kgm.	No. Injections in Flutter	Percent Reversions	No. Injections in Flutter	Percent Reversions	No. Injections in Flutter	Percent Reversions
0.5	1	0	-		6	0
1.0	2	0	2	0	8	12.5
2	10	60	2	0	12	33
4	11	66	3	0	9	0
8	2	100	4	25	5	40
16	-		-		1	0

DEAE

8	-		3	0	5	0
16	2	0	4	25	9	44
32	5	60	4	25	5	40
64	1	100	1	100	1	100

DCB

0.5	1	0	-		7	14
1.0	4	0	1	0	9	22
2	3	66	1	0	9	55
4	3	100	1	0	4	75
8	-		1	100	1	100

CHAPTER VII

Miscellaneous Observations

Effects on S-A node.

The injection of 8 mgm./kgm. of procaine usually increases the sinus rate approximately 8 per cent. This occurs more frequently in innervated than in decentralized hearts.

Doses of 32 mgm./kgm. of DEAE or of 8 mgm./kgm. of DCB usually slowed the sinus rate by about 8 per cent.

Blood pressure and evidences of toxicity.

Toxicity of the compounds studied was estimated roughly from the degree of their depressor action. Large doses (16 mgm./kgm. of procaine or DCB or 64 mgm./kgm. of DEAE) caused a fall of blood pressure to zero within a few minutes. In a small number of experiments smaller doses of DEAE or DCBA caused death by cardiac failure. In general the fall of blood pressure increased as the dose was increased for all compounds.

Doses of 64 mgm./kgm. of DEAE were fatal to about 50 per cent of the dogs when innervation to the heart was intact. In dogs with decentralized hearts doses of 32 mgm./kgm. were lethal to 3 of 5 animals. The hearts stopped suddenly and dilatation occurred soon after the DEAE injection. The depressor response to this and smaller doses of DEAE was always more severe when the heart was decentralized. Changes in innervation to the heart did not appear to alter the blood pressure responses to either procaine or DCB.

During auricular flutter the effect of comparable doses of procaine on blood pressure was less marked when the heart was decentralized than when innervation was intact. This probably results from the improved A-V conduction occurring in innervated hearts after the injection of procaine

which results in a ventricular beat so rapid as to allow little time for filling of the ventricular cavity and hence producing smaller cardiac output.

Spike Potential.

The changes in potential which occur in the tissue beneath a pair of electrodes during the passage of an impulse have been recorded in these experiments by means of an ink-writing oscillograph. The height of the recorded potential is a measure of the potential difference between the poles of the electrodes.

No critical measurements of spike potential were made because of the mechanical limitations of the ink-writing system. It was observed incidentally in certain experiments that procaine reduced the height of the auricular spike potential. Two examples are given in figure 50. The upper electrogram was recorded during auricular flutter and the lower electrogram was recorded during spontaneous beating of the heart. DEAE and DCB did not change the height of the auricular spike potential.

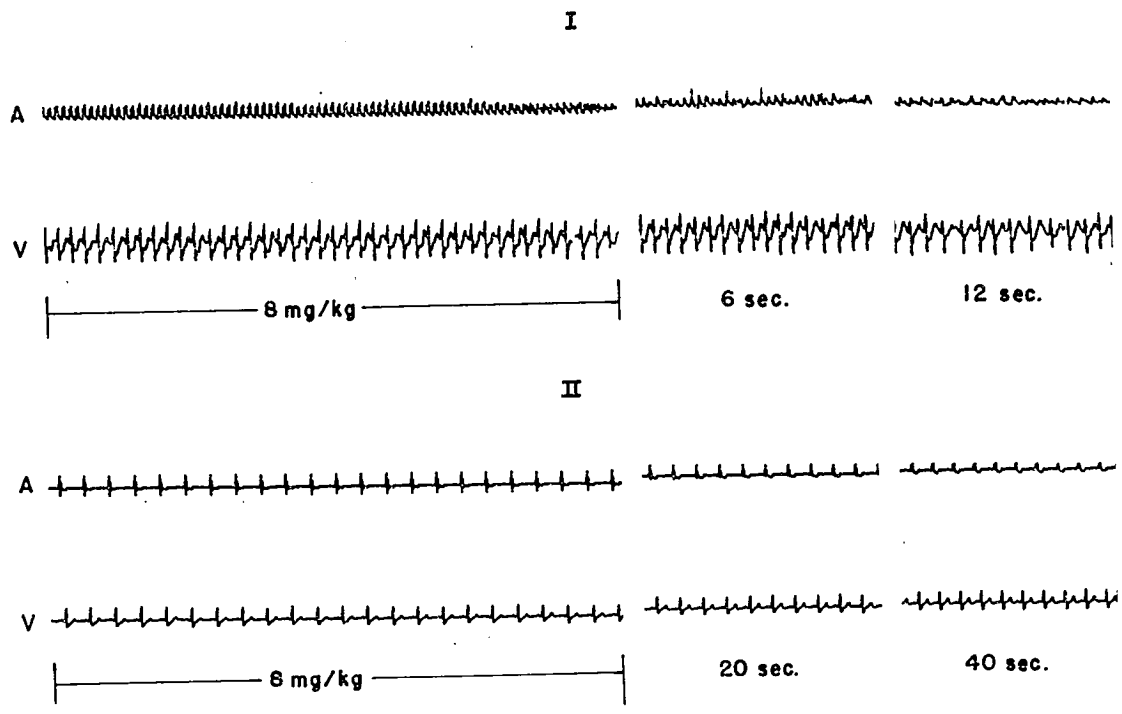


Figure 50

The electrograms show the decrease in height of spike potential following the injection of procaine in auricular flutter (I) and when the heart was beating slowly (II).

Conclusions

1. Section of both the vagal and sympathetic innervation to the heart results in decreased excitability of the auricle, no change in conduction velocity, and an impairment of A-V conduction. Section of the vagi only results in increased excitability and shortens the refractory period.

2. Stimulation of either the vagi or the sympathetics has the same effects on the auricle; it increases conduction velocity, increases excitability, shortens the refractory period, and increases the rate of flutter. On auriculo-ventricular conduction, however, stimulation of the two innervations has opposite effects; the vagi impair, the sympathetics improve.

3. Auricular flutter induced around an obstacle by rapid stimulation is due to a single impulse circulating continuously around the obstacle.

4. Procaine lengthens the refractory period, decreases excitability at high auricular rates but not at low rates, and markedly slows conduction velocity. It improves auriculo-ventricular conduction when the vagi are intact but impairs auriculo-ventricular conduction when the heart is decentralized. In auricular flutter procaine slows the auricular rate and increases the ventricular rate when innervation to the heart is intact, but slows both auricular and ventricular rates when the vagi and sympathetics are sectioned. Reversion from flutter to sinus rate occurs infrequently following procaine injection especially when the cardiac innervation is intact. Assuming a circus movement of the impulse, the slowing of the rate of flutter by procaine is probably due to slowed conduction. The infrequency of reversion is attributed to a relatively greater slowing of conduction

velocity than lengthening of refractory period. Procaine blocks the effects of vagal stimulation on the auricle and of vagal and sympathetic stimulation on auriculo-ventricular conduction. The action of procaine on auriculo-ventricular conduction in the innervated heart appears to be of at least two types, directly depressant and anti-vagal.

5. Diethylaminoethanol (DEAE), the alcoholic moiety of both esters used, lengthens the refractory period of the auricle, decreases excitability throughout the cardiac cycle, slows conduction velocity but to a much less degree than procaine, and depresses auriculo-ventricular conduction in innervated, vagotomized, and decentralized hearts. DEAE also blocks the effects of both vagal and sympathetic stimulation on A-V conduction, but less effectively than procaine. In auricular flutter this compound slows both auricular and ventricular rates regardless of innervation to the heart. Reversion to sinus rhythm occurs frequently following its injection, presumably because it lengthens the refractory period relatively more than it decreases conduction velocity. The toxicity of this compound is greater for decentralized than for innervated hearts.

6. B-diethylaminoethyl, 2,4-dichlorobenzoate (DCB) lengthens the refractory period of the auricle and decreases excitability throughout the cardiac cycle, but does not affect conduction velocity. It depresses auriculo-ventricular conduction in innervated, vagotomized, and decentralized hearts. DCB does not influence the effect of either vagal or sympathetic stimulation on A-V conduction. In auricular flutter this compound slows both the auricular and ventricular rates but less effectively than procaine. Reversion to sinus rhythm is frequent. It is proposed that

reversion occurs because refractory period is sufficiently lengthened without change of conduction velocity.

7. The acid moieties of the esters used, p-aminobenzoic acid and 2,4-dichlorobenzoic acid, injected as sodium salts, do not affect the rate of flutter even in the highest tolerated doses. They were not studied further.

8. The refractory period, electrical excitability, and conduction velocity of the dog's auricle can be varied independently of each other by means of changing the innervation and the use of drugs with selective actions.

Epilogue

The characterization of drug action in auricular flutter is important because it may be of immediate practical use. Such studies, however, yield data which are inadequate for an analysis of drug action and which may even be misleading. The major difficulty is that changes due to drug administration cannot be deduced from the changes in auricular rate. Experiments in which the auricular rate was controlled demonstrated that auricular refractory period, excitability, and conduction velocity, and A-V conduction changed with the rate. When these changes are related to auricular rate, standard curves can be constructed by which the effects of nerve stimulation, drug action, etc., can be compared. Further, by manipulation of the innervation and the selective actions of certain drugs, the above mentioned characteristics of the auricle as well as A-V conduction can be dissociated from each other, and the role of the individual variables in the whole complex of auricular function can be determined. Studies of the type under consideration are important not only in the study of drug action but also in expanding the knowledge regarding the basic phenomena of the heart beat.

Bibliography

1. Watanabe, M., Folia japon, 1923.

2. Shookhoff, C., The action of procaine and cocaine on the mammalian heart, Ztschr. f. d. ges. exper. Med., 49; 110, 1926.

3. van Dongen, K., The action of novocaine on fibrillation of the heart. Arch. internat. de pharmacodyn. et therap. 60; 207, 1938.

4. van Dongen, K., The action of novocaine on auricular fibrillation. Arch. internat. de pharmacodyn. et therap., 54; 252, 1936.

5. Mautz, F.R., Reduction of cardiac irritability by the epicardial and systemic administration of drugs as a protection in cardiac surgery. J. Thoracic Surg., 5; 612, 1936.

6. Marangani, B. A., Burstein, C. L., and Rovenstine, E. A., Protecting action of chemicals related to procaine on ventricular fibrillation during cyclopropane anesthesia, Proc. Soc. Exper. Biol. & Med., 44; 594, 1940.

7. Shen, T.C.R. and Simon, M.A., Protecting action of novocaine upon chloroform-adrenalin ventricular fibrillation. Arch. internat. de pharmacodyn. et therap., 59; 68, 1938.

8. Beck, C.S. and Mautz, F.R., Control of the heart beat by the surgeon, with special reference to ventricular fibrillation occurring during operation. Ann. Surg., 106; 525, 1937.

9. Burstein, C., Treatment of acute arrhythmias during anesthesia by intravenous procaine. Anesthesiol., 7; 113, 1946.

10. Stutzman, J.W., Allen, C. R., and Orth, O.S., Failure of procaine to reverse cyclopropane-epinephrine ventricular fibrillation. Anesthesiol., 6; 57, 1945.

11. Smith, C. and Ferguson, J.K.W., Effect of procaine on the response of the heart to epinephrine during cyclopropane anesthesia. Proc. Soc. Exper. Biol. & Med., 72; 161, 1949.

12. Hirschfelder, A.D. and Tamcales, G., Inhibition of experimental auricular fibrillation by procaine. Proc. Soc. Exper. Biol. & Med., 50; 272, 1942.

13. Hazárd, R., Corteggiani, E., and Cheymol, J., Effets parasympatholytiques de la novocaine, de la Butelline, et de l'atropine sur les actions cardiaques et tensionelles du vague et de l'ácetylcholine. Compt. rend. Soc. biol., 140; 83, 1946.

14. Oppenheimer, M.J., Effect of intravenous procaine on the heart. Am. J. Physiol., 155; P 457, 1948.

15. Brodie, B.B., Lief, P.A., and Poet, R., Fate of procaine in man following its intravenous administration, and methods for the estimation of procaine and diethylaminoethanol. J. Pharmacol. & Exper. Therap., 94; 359, 1948.

16. Papper, E. M., Brodie, B.B., Lief, P. A., and Rovenstine, E. A., Studies on the pharmacological properties of procaine and diethylaminoethanol. N. Y. State J. Med., 48; 1711, 1948.

17. van Dongen, K., and Taal, A., Remarks on the mechanism of heart fibrillation. Arch. internat. de pharmacodyn. et therap., 81; 129, 1950.

18. Trefouël, J., Strickler, H., and Bovet, D., Activité comparée d'une nouvelle série de dérivés de l'aminoethoxydiphenyle sur le coeur. Compt. red. soc. biol., 130; 27, 1939.

19. Dawes, G.S., Synthetic substitutes for quinidine. Brit. J. Pharmacol., 1; 90, 1946.

20. Lewis, T., The law of cardiac muscle with special reference to conduction in the mammalian heart. Quart. J. Med., 14; 339, 1921.

21. García-Ramos, J. and Rosenblueth, A., Acetilcholina y potasio en auricula. Arch. inst. cardiol. mex., 17; 384, 1947.

22. Lewis, T., Drury, A.N., and Bulger, H.A., Effect of vagus upon the rate of transmission of the excitation wave in the dog's auricle. J. Physiol., 54; 99, 1920.

23. Izquierdo, J.J., The influence of sympathetic stimulation upon intra-auricular block in the mammalian heart. Am. J. Physiol., 91; 696, 1930.

24. Brooks, C. McC., et al., Excitability of mammalian heart during the cardiac cycle: the auricle. Federation Proc., 9; 18, 1950.

25. Lewis, T., Drury, A.N., and Bulger, H. A., Observations on flutter and fibrillation, VI. Refractory period and conduction velocity. Heart, 8; 83, 1921.

26. Andrus, E. C. and Carter, E. P., The refractory period of the normally-beating dog's auricle: with a note on the occurrence of auricular fibrillation following a single stimulus. J. Exper. Med., 51; 357, 1930.

27. Love, W.S., Quinidine and strophanthin on the refractory period of the tortoise ventricle. Heart, 13; 87, 1926.

28. Drury, A.N. and Regnier, M., Observations upon conduction in the mammalian heart. Auricular conduction. Heart, 14; 263, 1924.

29. Gilson, A. S., Determinations of refractory period in the turtle heart. Am. J. Physiol., 112; 610, 1935.

30. García-Ramos, J. and Rosenblueth, A., Acetilcholina and potasio en auricula. Arch. inst. cardiol. mex. 17; 384, 1947.

31. Carlen, S.A. and Katz, L.N., The ventricular rate in faradically maintained auricular fibrillation; an index of A-V conductivity. Am. J. Physiol. 127; 272, 1939.

32. McWilliam, J.A., Fibrillar contraction of the heart. J. Physiol., 8; 296, 1887.

33. Hertz, A.F. and Goodhart, G. W., The speed-limit of the human heart. Quart. J. Med., 2; 213, 1908-9.

34. Jolly, W.A. and Ritchie, W.T., Auricular flutter and fibrillation. Heart, 2; 171, 1910-11.

35. Rothberger, C.J. and Winterberg, H., Über das elektrokardiogramm bei flimmern der Vorhäfe. Archiv. f. d. ges Physiol., 131; 387, 1910.

36. Romanes, G. J., Preliminary observations on the locomotor system of medusae. Phil. Trans., Roy. Soc., CLXVI; 269, 1876.

37. Mayer, A. J. Rhythmical pulsation in scyphomedusae. Papers from the Tortugas Laboratory, Washington 1; 115, 1908.

38. Mines, G. R. On circulating excitations in heart muscle and their possible relation to tachycardia and fibrillation. Trans. Roy. Soc. of Canada, 8; 43, 1914.

39. Lewis, T., Feil, H.S., and Stroud, W.D. Observations upon flutter and fibrillation. Part II, the nature of auricular flutter. Heart 7; 191, 1918-20.

40. Lewis, T., Oliver Sharpey lectures on the nature of flutter and fibrillation of the auricles. Brit. Med. J. 1; 551, 1921.

41. Sherf, D and Terranova, R., Mechanism of auricular flutter and fibrillation. Am. J. Physiol. 159; 137, 1949.

42. Prinzmetal, M., et al., private communication.

43. Rosenblueth, A. and García-Ramos, J., Estudio sobre el flutter y la fibrilacion. Arch. inst. cardiol. mex., 17; 441, 1947.

44. Garrey, W.E., Auricular fibrillation. Physiol. Rev., 4; 215, 1924.

45. Acheson, G.H., Farah, A., and French, G. N., Some effects of dibenzyl-β-chlorethylamine (Dibenamine) on the mammalian heart. J. Pharmacol. & Exper. Therap. 97; 455, 1949.