STUDIES IN AURICULAR FLUTTER AND FIBRILLATION

by

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PREFACE

Clinical auricular fibrillation has defied a host of investigators to determine the basic etiology, pathophysiology, and successful therapy. Few other clinical conditions have provoked such a variety of theories, explanations or opinions. Little agreement exists between the several serious research teams each of which seems sound in their theory and have a logical experimental approach. A serious omission in the work of most of the investigators is, however, the lack of evidence of correlation of the clinical and laboratory experiments.

In this thesis an analysis has been made of the various physiological phenomenon which seem related to the etiology of the clinical condition. Experiments have then been reviewed, duplicated, altered or devised in an attempt to prove or disprove fundamental concepts. Certain drugs, primarily those containing alkaminoalkyl side chains, were then assayed using all of the methods of establishing experimental auricular fibrillation. Clinical trial of promising drugs has been undertaken to check the validity of experimental methods and to try to find a more satisfactory drug to combat auricular fibrillation in the clinical patient.

I. INTRODUCTION

"Pulsus irregularis, inequalis, deficiens et intermittens" was the descriptive term first applied to auricular fibrillation by Bouilland[1] in 1836 although Bartolommeo Montagna (15th Century) is credited with what may be called the first description of auricular fibrillation and de Senac (1749) is credited with the next known reference which Willius translated as "rebellious palpitations"[2]. Neither Montagna, de Senac, Bouilland, Hoffa and Ludwig[3], nor Nothnagel[4] apparently attached any significance of their observations. Riegel in 1898, by means of a sphygmograph, studied the contour of the pulse pressure changes which occur with this irregular pulse[5]. Wenckebach[6] in 1899 was the first to report a detailed clinical study of this cardiac disorder although Cushny[7], McWilliam[8], Gaskell[9] and Engelmann[10] all contributed findings around this time.

Hering is usually given credit for the first definitive study of the condition and suggesting the modern name "Flimmern der Vorhofe" (fibrillation of the auricle)[11]. Some concept of the nature or locus of the disorder and the relation to the irregular pulse was obtained from studies with frogs and dogs by using faradic stimulation of the auricles. Cushny[7], Rothberger and Winterberg[12], Lewis[13] and McWilliam[8] and others all engaged in these studies in the decade after 1899.

It was not until the advent of the string galvanometer electrocardiograph that the relation between the irregular pulse with cardiac irregularity was possible. To Rothberger and Winterberg[12] we are indebted for this discovery, but it was Lewis[13], who published soon after, to whom we owe most for his emphasis and study of the disorder.

Auricular fibrillation according to White[14] is one of the most common, most interesting and most important cardiac disorders. This condition is third in order of frequency of arrhythmias falling closely behind paroxysmal sinus tachycardia and premature auricular systole. The disorder, while not in itself serious nor debilitating, is disconcerting to those afflicted and may cause or contribute to more severe conditions such as neurocirculatory asthenia, dyspnea, angina, congestive failure, weakness, dizziness or faintness. The most serious of the complications is cardiac insufficiency due to the accompanying tachycardia rather than the arrhythmia itself. Without normal rhythm, cardiac efficiency (cardiac output) may be lowered to a dangerous degree. Auricular fibrillation with severe mitral stenosis is considered a serious problem by some which necessitate immediate treatment. In thyrotoxicosis, auricular fibrillation with cardiac strain due to the increased work load poses an equally grave problem which also should be treated vigorously.

Uncomplicated auricular fibrillation whether of the paroxysmal or permanent type presents a special problem. Should or should not the disorder be treated? This question has never been satisfactorily answered. Individuals have survived 30 years with auricular

fibrillation with little interference of their normal living, but quite often a patient is treated with the complete gamut of anti-fibrillatory drugs in an attempt to arrest the condition which in itself may do no harm. On the other hand, the arrest of long standing auricular fibrillation may do harm if an embolus has formed in the auricle. The possibility of freeing of emboli is an especially grave problem and can result in occlusion of the cerebral, renal, splenic or peripheral arteries with dire consequence. Yet in one study and review(15) the possibility of thrombo-embolic phenomena was felt not to be a contraindication but, on the contrary, a definite indication for therapy. In these patients, auricular fibrillation, with continually forming emboli, presents an especially grave problem which must be treated at once. Tranquilization of the auricle to a normal rhythm may indeed cause dislodgment of some emboli, but the return of the auricles to normal rhythm will prevent or at least hinder the formation of future intra-auricular thrombi.

An experimental study of the auricular arrhythmias for therapeutic purposes has been hampered by lack of a satisfactory animal method by which fibrillation may be produced, or once produced, perpetuated long enough to provide comparative study of "antifibrillatory" drugs. Faradization of an entire animal, or its heart, or the vagus has been available for nearly fifty years as an experimental tool, but the disorder produced by this method is neither certain nor long enough in duration to be of much use. Injection of aconitine intravenously or directly into the myocardium has been used but the method

is rightly criticized as "non-physiological". Auricular crush, forming an artificial infarct, has been the most successful method of inducing fibrillation when such a preparation was stimulated with repetitive electrical stimuli.

The close association of thyrotoxicosis with cardiac irregularities has been known for more than one hundred years. In recent years the autonomic nervous system, especially the parasympathetic, has been implicated in these irregularities. Utilizing this observation and recognizing the failure of the more simple methods to produce experimental auricular fibrillation has led us and others to more complex experiments to mimic this interesting condition. An experimental approach, devised by the author, consisting of long term thyroid extract feeding to produce thyrotoxicosis has been undertaken. Experimental results indicate that thyrotoxicosis produced by such a method mimics strongly the clinical signs of tachycardia, vomiting, diarrhea, excitability and thirst. With longer feeding, additional signs such as dry flaking skin was noted and hair shedding often was marked. Along with the overt symptoms of hyperthyroidism there was also a marked increase in sensitivity to cholinergic drugs induced by the thyrotoxicosis. This hypersensitivity allows easy production of several cardiac arrhythmias; reflex tachycardia and single 2:1 block being the most simple arrhythmias seen in these cases. Other more severe arrhythmias were longer blocks 3:1 to 10:1 or more which are characterized by complete cardiac irregularity. P-R intervals are prolonged, P waves are eventually dropped or appear only occasionally

being superceded by "fragmentation" of P waves which proceeds to variously prolonged episodes of auricular fibrillation.

The cinchona alkaloids, though first used for the treatment of malaria, were observed incidentally to have a sedative action on the heart. Wenckeback(16), then in Vienna in 1914, observed and recorded the first experimental-clinical study of quinine for auricular fibrillation. Wenckeback, however, was dismayed by the poor results from the use of quinine. von Frey(17) in 1918 undertook a systematic study of the cinchona alkaloids and found that quinidine was the most successful therapeutic agent against auricular arrhythmias. Quinidine, although it is a most effective drug, is also dangerous. Idiosyncracy to the drug is not uncommon and a preliminary test dose is often suggested. Reaction to the drug consists of respiratory distress, sometimes with arrest, cyanosis, dizziness, cramps, nausea, vomiting, and cold sweating. A therapeutic danger consists of the possible conversion of auricular fibrillation to flutter, and in this case dangerous ventricular tachycardia often ensues. Fortunately, the simultaneous administration of another drug (digitalis) will prevent excessive speeding of the heart rate. Ventricular standstill is yet another serious danger which occurs due to the profound depression of the S-A and A-V nodes. If some pacemaker does not immediately take over, fatality will result. Ventricular fibrillation also may occur and results from myocardial depression from over-treatment.

Quinacrine, introduced recently as a replacement for quinine in therapy of malaria, has been found to be also of considerable

efficacy in auricular arrhythmias (Gertler)[18]. Of the sixteen patients who failed to respond to quinidine therapy, 50% converted to sinus rhythm by the use of quinacrine. However, in view of some deaths and frequent dangerous symptoms, the conclusion of the authors was that this drug might have some place in therapy but it was dangerous and its general use was not advisable.

Alpha-fagarine is another fairly recently developed drug (De Espanes)[19]. This drug is a natural product closely related to the cryptopine opium alkaloids. The drug has been found reasonably effective against auricular fibrillation and also flutter, but in many cases multifocal ventricular extrasystoles appeared which in a few cases produced fatal ventricular fibrillation (Scherf)[20]. It was felt that the drug was not as effective as quinidine but was more toxic. For this reason the use of this drug has been abandoned.

Sparteine is an old drug and was studied by Cushny in 1895[21]. A later edition of his text (1941) points out that the drug regulates tachycardia and also arrhythmia perpetua (auricular fibrillation). A complex of undesirable side effects consisting of action similar to atropine, curare and nicotine (Go Lu)[22] have precluded the use of this drug to any extent.

Pronestyl, the amide of procaine, initially aroused great hopes for therapy of auricular fibrillation due to its striking depression of ventricular arrhythmias. The action against auricular irregularities has been found to be of no use in these cases.

Diphenhydramine (Benadryl) was noted by McCawley(23) to have a close structural resemblance to Procaine and he predicted a similar but prolonged action due to a more stable chemical linkage. This prediction was proven correct in experimental and limited clinical trial against ventricular arrhythmias. Dick(24) suggested that this drug be tried in auricular arrhythmias which are more common and more of a medical problem.

In addition to the toxic qualities of quinidine, another reason prompts the search for a better drug; it is not uniformly successful. The initial investigations on quinidine by von Frey(17) indicated that 60% of his fibrillating patients had converted to normal sinus rhythm. A compilation by Beckman(25) up to 1928 indicated over-all clinical success of 55% with 415 patients and 15 different investigators. Many of the earlier authors included in the compilation indicated rates of less than 50%, though some reported up to 94% success. Current clinical experience with cases in which quinidine is given to patients in the highest tolerated dosage, indicates successful therapy only in about the same percentage. This rate of success is not exceeded by any other drug. No drug or combination yet discovered will convert more patients than quinidine and unfortunately auricular fibrillation which is resistant to quinidine is frequently resistant to all other current drug therapy.

Clinical confirmation of successful experimental drugs has been disappointing. Only quinidine has been markedly successful in both

the experimental laboratory and the clinical patient, but research must continue to find a more satisfactory agent with none of the undesirable side effects produced by quinidine.

It is the purpose of this research investigation to evaluate all existing animal methods for the study of auricular fibrillation. A further purpose is to devise a new method utilizing the intact animal and to assay pharmacodynamically the efficacy and potency of new drugs. A final purpose will be to correlate experimental success with the result of clinical trial and evaluation with the aim to ascertain the validity of all animal experimental methods and their underlying theories of auricular fibrillation. It is the hope of the author to develop and establish a new useful drug or at the least provide a steppingstone to future investigators who will unravel the mystery of the genesis, perpetuation, but especially the therapy of auricular fibrillation.

II. PART ONE - PHYSIOLOGY OF THE NORMAL HEART AND CARDIAC TISSUE, PATHOLOGY CAUSING AURICULAR ARRHYTHMIAS AND PROPHYLAXIS AND THERAPY OF THESE ARRHYTHMIAS

A. INTRODUCTION

The study of antifibrillatory drugs is complicated by the important consideration that the condition is not only an abnormal state, but also that it has never been observed to occur naturally in animals other than humans. The fact that therapeutic success is measured by the alteration of the abnormal rhythm to normal sinus excitation and rhythm hints at the problem presented in experimental study of these conditions.

To gain an understanding how the various antifibrillatory drugs work or how they affect the various properties of the heart, we must first establish the accepted concepts of the physiological properties of the heart and the properties of cardiac muscle tissue itself before we can hope to understand the cause, consider the probable mechanisms of abnormal rhythm, or hope to treat the abnormal rhythm once it is established.

B. PROPERTIES OF THE NORMAL HEART

The study of the property of automaticity of the heart has occupied the minds of many noted investigators with the production of many elaborate theories but a paucity of information of any value in establishing a mechanism of the normal physiological process of impulse initiation in the heart. With the lack of information on the normal mechanism, the explanations in the case of abnormalities have been even less convincing, more difficult of experimental proof and in many cases impossible of clinical correlation.

Engelmann[10] and Langendorff[26] proposed a periodic variation in excitability to a constant stimulus. Hering[27] believed in a periodic upbuilding and explosion of a stimulus. With the demonstration by Howell and Duke[28] that vagus stimulation caused potassium liberation from the heart, they proposed variable periodic balance of sodium, potassium and calcium in view of their known influences on the heart. Andrus and Carter[29] performed experiments which indicated similarly a possibility of hydrogen ion implication in cardiac automaticity. Many investigators by the use of experiments which are related, although they employ nerve instead of cardiac tissue, have indicated the importance of the potential difference between the inside and outside of a cell and the transference of potassium into the cell and sodium out of a cell during stimulation or activity. At present evidence is accumulating that the difference in concentration of ions inside and outside a cell wall gives rise to a potential difference and that there is a marked change or even

reversal of this potential during stimulation and/or activity. Eccles and Hoff[30] stated that this periodic rise and fall is not necessarily a membrane surface phenomenon but occurs within the protoplasm and wells to the surface at which time it becomes apparent. Harris and Moe[31] observed oscillating potentials in the dog ventricle following anodal or cathodal polarisation. This potential was sub-threshold, but was considered as a possible source of exciting foci. Demoor[32] and Rijlant[33] independently published evidence for a specific hormone or active substance and a similar theory was proposed by Haberlandt[34]. Zwaardemaker[35], with several of his students, designated a hormone-like material, automatinogen, and proposed that it was transformed into automatin by potassium or radio-active emanations. Bozler[36] succeeded in recording from isolated cardiac muscle weak local potentials which are strongest near the origin of (activating) impulses and that a state of increasing negativity precedes the release of impulses.

The relationship of acetylcholine, acting as the neuro-physiological mediator, to the automaticity of the heart remains a mystery mainly due to its complexity of function and action. Potassium ion appears to have a major role in the release, production and possibly the destruction of acetylcholine. The effects of this ion are just now being elucidated and as was suggested by Howell and Duke in 1908 may have a role far more important than acetylcholine.

C. PROPERTIES OF CARDIAC MUSCLE: DEFINITIVE CHARACTERISTICS

The cardiac muscle is a unique transition form between skeletal muscle tissue and nervous tissue. Such being the case, the tissue has its own characteristics which are similar to both other types, but yet different.

Refractoriness is a condition in which a tissue is unresponsive to a stimulus. This condition prevails immediately following a response for varying lengths of time. The duration of time in which a tissue is unresponsive is called the refractory period. There is a period immediately following a response that the tissue is not responsive to stimulus no matter how great the intensity. This is called the absolute refractory period. After this, there occurs a period of time in which the tissue will respond to super-threshold stimuli and becomes less refractory with time until the normal threshold is again reached. This transition period to complete recovery is known as the relative refractory period. Certain investigators use the term effective refractory period because of the difficulties in measuring threshold response.

Conduction of impulse is a phenomenon shown best by nervous tissue but to a much lesser extent by cardiac muscle. The heart contains two specialized conduction systems. The S-A node initiates and conducts impulses along its length. The A-V node transmits the stimulus impulse via the bundle of His throughout the ventricular muscle. In addition to these specialized nerve-like tissues, the

auricle musculature itself and also the ventricular musculature conduct the impulses. Defects in any of the conduction systems can result in various but predictable changes. The emphasis in this thesis will be on the changes in the auricle itself, the sinus nodal tissue, the atrio-ventricular node but especially the auricular musculature.

Rhythmicity of the heart muscle is its most characteristic feature which distinguishes it from other muscle. The basis for cardiac tissue rhythmicity or automaticity is not known although several theories are available as tentative explanations. The establishment of the true reason for automaticity of the heart might well be key to cardiac irregularities and therapy of the disorders.

Irritability and sensitivity are terms used to define the ability of the heart to respond to a stimulus. Stimulatory threshold is a term which quantitates the degree of sensitivity or irritability and is most easily measured by electrical means.

In the cardiac arrhythmias in general and especially the irregularities of the auricle, measurable changes occur in all of the specific physical characteristics of the musculature mentioned above. The relative refractory period is thought to be decreased in auricular fibrillation. With the shortening of refractoriness, the tissue recovers its sensitivity sooner and may respond to stimuli at a faster rate whether these stimuli originate from the sinus node or from a focus independent of the node. The absolute refractory period, however, apparently undergoes no change in auricular fibrillation and similar disorders.

Conduction rate deficiencies appear in conjunction with auricular fibrillation and often immediately preceding experimentally induced episodes of the arrhythmia. The condition appears associated with an increase in vagal tone and this correlation has been used as a basis for testing of drugs for antifibrillatory activity.

The inherent rhythmicity of the heart is disturbed in two ways during auricular fibrillation. There is an inhibition of the S-A nodal pacemaker which may be complete and also there is initiation of abnormal stimuli from ectopic foci. These two effects give rise to characteristic changes of the electrocardiogram; namely absence of P waves (depression of the S-A node) and appearance of U waves ("firing" of the ectopic focus or foci). Normally these "ectopic beats" are not manifest as the auricular muscular threshold is so high that the S-A node is the only focus able to produce threshold stimuli. In the case of suppressed nodal activity along with depressed auricular muscular threshold, the ectopic focus potentials become adequate to propagate limited excitation waves. Indirect evidence has been presented that the above represents the chain of events. Printzmetal et al(37) have shown that the normal P waves produce an intensity of 0.1 to 0.3 millivolts which must be assumed to be the normal threshold. During fibrillation, the fibrillatory waves were less than 0.1 millivolt which substantiates the explanation of lowered auricular muscular threshold causes auricular fibrillation by the "firing" of ectopic foci.

The presence of irritable tissue is necessary for the transmission of the normal waves through the myocardium. Likewise normal or supernormal irritability may be necessary for the initiation and perpetuation of auricular fibrillation. It has been shown that a state of increased irritability has been demonstrated in this irregularity and it is suggested that vagal stimulation is responsible for this increase in auricular irritability. The basic mechanisms upon which auricular arrhythmia depend are decrease in relative refractory period, conduction disturbances, inhibition of the sino-auricular nodal pacemaker, initiation of abnormal ectopic foci and increased myocardial irritability. Any of these changes from normal may indeed be the cause or the effect of the arrhythmia. So far as is known, the above mentioned phenomena are inseparable from the arrhythmia itself and have been used experimentally as objective criteria for assay of antifibrillatory drugs.

D. MECHANISM OF AURICULAR ARRHYTHMIAS

Certain of the cardiac irregularities are sometimes spoken of as chaotic rhythms and chaotic may be aptly used to describe the maze of conflicting viewpoints and theories regarding the mechanisms responsible for the arrhythmias suffered by the heart. There are several theories each of which appears based upon solid theoretical foundation and backed by laboratory experimental results which are readily reproducible but not seen clinically. Few of the major protagonists will accept any part of an explanation not their own. For this thesis, an attempt was made to study exhaustively all possible explanations and experimental procedures with the hope that some "middle road" or combination may provide a plausible answer.

Several theories have been presented to explain the phenomenon we now call auricular fibrillation. It would be somewhat futile to attempt to present all of the explanations regarding this condition. The study of cardiac physiology and arrhythmias has occupied much time and effort by an un-numbered host of investigators. The principally defined and best known theories to explain this condition are presented herewith with no intention, at the present, to favor any one explanation.

The oldest explanation is that offered by Engelmann(10). He explained the condition by the presence of multiple extra-nodal foci in the auricle. Independent rhythms produce incoordinated and rapid

minute contractions of the auricle. Kisch(38) provided some experimental evidence that such was the case by recording local tachysystole by direct auricular electrograms from different points of a heart. This tachysystole was present even in some cases of a non-fibrillating auricle.

A slight modification of this theory is the explanation offered by Rothberger and Winterberg(12). Rapid unifocal tachysystole is the description applied by these investigators. This theory is different in two minor respects from that of Engelmann; a single focus, rapidly firing as opposed to many foci firing at slower, though incoordinated rates. This is also a basis for the unitarian concept; slow discharge from the ectopic focus accounts for premature auricular contractions, as the rate of discharge increases flutter appears and finally fibrillation.

The third and most popular theory has been the concept of a wave of excitation traveling around the tissue ring surrounding the vena cavae of the heart. This is the circus movement theory propounded by Lewis(13). Mayer(39) observed that a stimulus applied to a point on the "rim" of a jelly-fish would travel, ordinarily, in both directions around the rim. Rapid stimulation or a temporary occlusion block of one arm of the ring would frequently produce an excitement wave which would proceed in one direction only and would continue this path for many hours. Mayer later observed the same effect with amphibian hearts. The adaptation of this theory, especially by

Lewis, to explain mammalian and especially human auricular flutter and fibrillation has only recently been seriously challenged after some thirty years of unqualified acceptance.

A somewhat complex theory which appears to have at least an element of the Mayer theory is that of DeBoer(40). This is the concept of fractionated contractions and has also been termed the reentry phenomenon. A description of this concept appears to be a special type of circus, or better, circuitous movement of an excitant wave through the entire auricle or auricles. The circuitously traveling impulse continuously stimulates excitable tissue so that the stimulation and activity is perpetuated. The pathway is guided by the presence of small areas of refractory tissue. Since refractoriness is only temporary, the excitation wave may re-enter the original area under question at some later time.

The old theory of unifocal tachysystole has been re-introduced fairly recently. This is the proposal of Scherf et al(20) and Prinzmetal et al(37). Both of these authors, but Prinzmetal in particular, have shown evidence for a single rapidly discharging abnormal atrial focus. Prinzmetal has cast doubt on the Lewis theory of the circulating excitant wave by cinematophotographic and oscillographic recordings of auricular fibrillation in both experimental animals and man. These pictures have failed to show the circus movement of excitement or contraction. Other theories such as the

"fractionated myocardial contraction" of DeBoer, the "multiple minute re-entry" and "multiple self-sustained microsystole" seem to be modifications or combination of one or more of the main theories.

Kisch(38) aptly states in his review of the mechanics of flutter and fibrillation, "none of the (four) main theories of fibrillation, today still existing have up to date been convincingly proven or disproven. The main feature in the mechanism of fibrillation may be emphasized the asynchronism and the anisorhythmia of quick contractions of the different parts of the heart in fully developed fibrillation".

E. CAUSES OF AURICULAR ARRHYTHMIAS

It can be stated at the outset that the ultimate cause of auricular fibrillation is not known. Many conditions seem to produce a pronounced predisposition to the condition either acting singly or in combination. Mitral stenosis is probably the most frequent concurrent finding with clinical auricular fibrillation. Rheumatic heart disease has been found to be present in many patients. Arteriosclerosis of the coronary vessels also appears to be a common finding as does fibrotic degeneration of the myocardium. Acute infections or toxicity to the myocardium appear to be in a broad group of non-specific causes, these include: diphtheria, scarlet fever, acute rheumatic disease, pneumonia, malaria, large or generalized abscesses, alcohol, nicotine (tobacco), gas poisoning, food poisoning and ether. Hypertension which is a symptom or result of many of the above conditions is quite frequently associated with auricular fibrillation. The hypertension may be a chronic condition which becomes acute due to some other complication or it may be an acute episode caused by exertion or excitement. Thyrotoxicosis is also an important causative factor and may be the only other finding in auricular fibrillation.

Auricular fibrillation may thus be caused by an extended variety of factors. Valvular defects, rheumatic heart disease, coronary arteriosclerosis, myocardial fibrosis, hypertension, acute toxic infections, especially those affecting the myocardium, alcohol, nicotine, gas poisoning, food poisoning and thyrotoxicosis are all

clinical causes of auricular dysrythmias and especially auricular fibrillation. Experimental conditions provoking or predisposing to this condition are cardiac distention, anoxia or lesions of the myocardium, reflex, mechanical, faradic, or electrical stimulation of the auricle. High or low temperatures to the body or heart and administration of a wide variety of drugs such as digitalis, quinidine, aconitine, barium, calcium and potassium and most of the cholinergic drugs represent more definite experimental causes of the condition.

Such a multiplicity of predisposing factors to auricular fibrillation demands an analysis to elucidate a common basis for the disorder. Mitral stenosis, coronary arteriosclerosis, myocardial fibrotic conditions, anemia, anoxia, pneumonia, violent exertion or emotion and abnormal temperatures all strongly suggest ultimate insufficiently of oxygen and nutrition to the myocardium. Distention of the heart likewise suggests poor nutritional state and low oxygenation. The heart strain present in thyrotoxicosis suggests at least two possibilities; first, myocardial overwork with consequent depletion of metabolic stores with inability to supply adequate oxygen to the myocardium due to excessive oxygen demands elsewhere in the body or secondly, toxic effects of thyroid hormone or its metabolic breakdown fragments on the heart.

The effects of bacterial toxins and miscellaneous non-specific drugs such as alcohol present a difficult question for analysis. The best answer available appears to be that the membrane of the tissue

cells is altered, causing them, in effect, to be more irritable, i.e. have a lower threshold of excitability. A more precise answer appears far from possible at the present time.

The study of the effects of the cholinergic drugs, acetylcholine and acetyl-methyl-choline and the acetylcholine esterase-blocking drugs appears to approach the basis of the entire question of cardiac arrhythmias. In certain clinical and experimental conditions, these drugs provoke auricular fibrillation a high percentage of the time. The mechanism is far from clear, but appears inseparable from the cellular membrane and the alterations known to occur at this surface.

The basis of the effect of burns, trauma, malaria, anoxia, and anemia may depend upon changes or alterations of electrolytes in plasma, erythrocytesand muscle tissue. Calcium is known to be low in the overworked heart. Potassium also leaves the heart in the state of exhaustion by fatigue or depletion of metabolic stores.

Whatever the substance provoking auricular arrhythmias may be, and there is no assurance it may be any of the above mentioned materials, it has been given the name "E" (excitatory) factor by Mahum and Hoff. Grant et al(41) believe this factor to be epinephrine on the basis of experiments performed on intact auricles of the hypothermic dog. Part of this thesis will be a review of the more likely substances and conditions which may be the "E" factor.

Myocardial anoxia appears to be one of the more profound factors predisposing to parasympathetic hypersensitivity and the

resulting auricular flutter and fibrillation when parasympathetic drugs are injected. The work of some authors (Smith and Wilson)[42] points out the possibility that anoxia may be the "E" factor of Nahum and Hoff[42].

According to Resnick[44], Vaquez[45] in 1911 was the first to attribute anoxemia as a cause of auricular fibrillation in humans. Vaquez noted auricular fibrillation in patients with myocardial failure but observed that the fibrillation disappeared with circulatory improvement. Cole[46] pointed out that lobar pneumonia quite frequently predisposes to spontaneous auricular fibrillation (3-5 per cent of cases). Resnick reports that other types of pneumococcic infections which do not produce anoxia also do not cause cardiac arrhythmias. Such evidence diminishes the possibility of this bacterial toxin causing the arrhythmias in this particular case.

Resnick performed experiments which varied the amount of oxygen in oxygen-nitrogen mixture. Oxygen saturation of femoral arterial blood was determined. It was found that early and incipient anoxemia predisposed the auricles to fibrillation, but that the late effects were to inhibit fibrillation.

Smith and Wilson[42] performed a different type of experiment - they perfused the coronary arteries with anoxemic blood. They reported the only altered factor was this anoxia, but they reported intermittent spontaneous auricular fibrillation. In addition they reported that the anoxia caused hypersensitivity to parasympathetic agents but

that spontaneous or induced fibrillation was prevented by adequate re-oxygenation of the perfusing blood.

Porter in 1898, presumably working with dogs, was the first to note the effect of anoxemia in producing spontaneous auricular fibrillation(47). He also noted that this fibrillation disappeared when the coronary vessels were perfused with oxygenated blood. Lewis(48) found that paroxysmal auricular tachycardia, a disorder similar to auricular fibrillation, frequently followed experimental ligation of the right coronary artery. DeBoer(49) noted auricular fibrillation after coronary ligation or when the heart was in "a poor metabolic state". Geraudel(50) also mentioned arrhythmias caused by myocardial "anemia" (hypoxia). Master et al(51) suggested that auricular fibrillation after acute coronary thrombosis depended upon altered metabolism, anoxemia and impaired myocardial nutruition.

Prinzmetal(37) has shown that anoxia frequently converts aconitine-induced auricular flutter to fibrillation. Nahum and Hoff(43) found that anoxia favored the production of fibrillation by cholinergic drugs.

Some clinical conditions of anoxia do not produce arrhythmias. Among these is the observation of infrequent clinical correlation of emphysema and certain congenital cardiac disturbances. This may be on the basis of chronicity and that gradually the myocardium has become inured to low oxygen tension.

DeBoer(49) was apparently the first to note that anoxic anemia played a role in fibrillation. He worked with the bled frog's heart

and observed that properly timed stimuli would cause fibrillation. He noted that while the bled heart, which was deficient in nutriment as well as oxygen (and cholinesterase) was prone to fibrillate, the normal heart did not show such a sensitivity.

Anemia has been observed to cause auricular fibrillation in man (Schlicter)(52) and experiments with dogs have been performed which mimic this clinical syndrome (Horlick and Surtshin)(53).

In order to study the possibility of relative or general anemia predisposing to parasympathetic hypersensitivity, Horlick and Surtshin performed several type of experiments to correlate anemia with arrhythmias. This was done by measuring hemoglobin levels during administration of certain hemolytic agents and also by bleeding of controlled quantities from the experimental animals. In all cases, lowered hemoglobin caused an increase in sensitivity to acetylcholine and lowered the dosage of this drug causing secondary block when it was injected intravenously. The authors suggested that the anemia caused relative myocardial anoxia which predisposed to auricular irritability. They also suggested a role of decreased available cholinesterase as a possible mechanism of the hypersensitivity.

Temperature variations from normal, especially that of low temperature or hypothermia have a strong influence to instigate spontaneous auricular fibrillation or predispose the heart so that it is hypersensitive to parasympathetic drugs. These hearts will fibrillate readily when these drugs are administered. Drury in 1925 was apparently the first to demonstrate that cold would have

an important effect upon cardiac physiology(54). He showed that cooling of the auricular musculature prolonged its refractory period. Confusion of the issue is caused by Lewis and Drury(55) who in 1926 cooled the experimentally fibrillating auricle and noted that fibrillation ceased.

Dill and Forbes(56) published the first report of human patients suffering spontaneous auricular fibrillation caused by artificial cooling to 30° C. Talbot(57), Grosse-Brockhoff(58), Alexander(59), Wayburn(60), Graybiel and Dawe(61) have also reported similar observations in man. Most of these authors showed that the cardiac arrhythmia was due to concomitant anoxemia although Grosse-Brockhoff denied this. Hegnauer et al(62) (63) have indicated with rigidly controlled animal experiments it is indeed the tissue hypoxia, as differentiated from hypoxemia, rather than hypothermia which is responsible for the cardiac arrhythmias.

Thyrotoxicosis is a classically recognized factor which causes auricular fibrillation. Parry in 1786 first associated cardiac pathology with hyperthyroidism and many additional clinicians reported intermittently of cardiac arrhythmias associated with thyroid hyperfunction(64). Mobius commenting upon the association of thyroid disease and heart disease stated, "Basedow patients (thyrotoxic) suffer and die through their hearts"(65).

The first modern writer to study auricular fibrillation and its association with thyrotoxicosis was Krumbhaar in 1918(66). Other authors previously reported both conditions, but he was the first to

study critically the intimate association of the two clinical conditions. After this a number of clinical papers appeared corroborating Krumbhaar's finding and broadening medical knowledge concerning this important clinical association.

Goodpasture in 1921 was the first of a series of experimenters who produced hyperthyroidism by injecting or feeding thyroxine or dessicated thyroid(67). It was the intention of these individuals to produce specific heart lesions or pathologic lesions. No lesions were found definitely attributable to thyroxine or thyroid extracts although evidence is strong that cardiac overwork could have producted the same changes (Menne)(68). The probability of a thyroid toxin was conclusively disproven by McIntyre(69) in 1931 and Markowitz and Yater(70) (71) in 1932 who showed that thyroxine itself stimulates all muscular tissue directly.

The intimate association of cardiac irregularities, hyperthyroidism and parasympathetic drugs was discovered by Nahum and Hoff(43) while they were studying circulation time in hyperthyroid patients. As part of a thesis on mechanism of auricular fibrillation, Weston(72) noted that experimental hyperthyroidism could be produced in the dog and that these dogs were hypersensitive to parasympathetic drugs which were injected intravenously. The observations of Nahum and Hoff and Weston suggested a thorough inquiry of the production of experimental thyrotoxicosis by feeding of thyroid extract to laboratory animals (dogs). It further suggested that this method

might be a useful tool for the production of hypervagotonia or sensitivity to cholinergic drugs and the study of auricular arrhythmias produced by intravenous injection of these drugs. It appeared probable that a method could be devised to screen anti-arrhythmic drugs.

F. CARDIAC PATHOPHYSIOLOGY IN AURICULAR ARRHYTHMIAS

A variety of pathological conditions cause auricular fibrillation. Pure heart pathology such as rheumatic heart lesions including endocarditis, mitral stenosis and other valvular involvements, arteriosclerotic coronary vessels, syphilitic heart conditions including aortitis all are associated with auricular fibrillation. Yet each of these pathological conditions are found without auricular fibrillation being present.

Mitral stenosis with left auricular dilatation is the most common condition associated with auricular fibrillation. Left auricular dilatation especially, but also aortic dilatation and dilatation of the right auricle and great veins cause reflex vagal stimulation. The vagal response releases acetylcholine to the myocardium, lowers the stimulatory threshold of the auricle and simultaneously results in stimulation of the cardio-accelerator nerves, with the release of epinephrine. This epinephrine in conjunction with acetylcholine possibly activates ectopic foci and results in auricular fibrillation. The stellate ganglia mediates this response as has been shown by operations in which this ganglion was removed before, the patient had uncontrollable tachycardia, after the removal, he returned to normal.

Rheumatic fever may sensitize or stimulate nerve endings resulting in a hyperactive vagus. The increase in P-R interval noted in this condition is also produced by vagal stimulation by faradization and also by injection of cholinergic drugs(73).

Coronary disease and infarctions may produce auricular fibrillation by different means. In these conditions, anoxia at the nerve endings may be responsible for the production or potentiation of vagal stimulation. Tachycardia is also a symptom which may be caused by anoxic induced stimulation of sympathetic nerves.

Hypertension with cardiac dilatation and failure produce a condition which is also anoxic in nature. In these cases tachycardia is usually the result and may possibly be explained by reasons given above.

C. THERAPY OF AURICULAR ARRHYTHMIAS

The therapy of auricular fibrillation involves the correction of several simultaneous abnormalities. Some drugs prolong the refractory period and/or conduction time and as a consequence arrest auricular fibrillation. Other drugs shorten the refractory period and conduction time but also neutralize the fibrillation. Another class have neither an effect upon refractory period nor conduction time but neutralizes fibrillation in therapeutic doses (Van Dongen)(74). Several of these "type" drugs have been employed experimentally and clinically with varying success.

Quinidine, the dextro isomer of quinine, remains the drug of choice for uncomplicated auricular fibrillation after forty years of experiment and investigation for a better substitute. Many of the other cinchona alkaloids, synthetic and natural, have been tried on an experimental basis, but none approach the usefulness of this drug. Digitalis preparations are strongly indicated in the patient with the complication of congestive failure. Many cases which included both auricular fibrillation and congestive failure are corrected by the alleviation of the congestive failure through the action of digitalis.

The search for more useful and safe antifibrillatory drugs has produced procaine, procaine amide, quinacrine and many others all of which have been of some clinical use but not great enough to replace quinidine.

For a considerable period of time, it appeared that a criteria for antifibrillatory action was a general antagonism to epinephrine and/or acetylcholine. Experiments reported herein indicate that this is, unfortunately, not the case.

II. MECHANISM OF ACTION OF ANTI-ARRHYTHMIC DRUGS

The multiplicity of causes of auricular arrhythmias necessitates a multiplicity of therapeutic measures and agents for their alleviation. Acute or chronic bacteremias and toxemias must be successfully treated by antibiotics. Anemia must be corrected to provide adequate oxygenation of the myocardium. Thyrotoxicosis must be controlled as a separate entity before any specific cardiac therapy can have other than a transitory effect. Congestive failure, whether it be cause or effect, requires that digitalis must be administered first to induce a more regular, stronger systole but also to prevent cardiac irregularities once quinidine or similar therapy is undertaken. Mechanical defects, if present, must be corrected.

The mechanism of action, the criteria of an anti-arrhythmic drug and the action of quinidine as an antifibrillatory drug are almost synonymous. The drug should lengthen the relative refractory period without producing a supernormally sensitive state. It should prevent or eradicate local blocks and restore or maintain the normal propensity of the myocardium to act as a single unit. It should stimulate or potentiate the nervous system as it pertains to the heart. It should not markedly depress the contractility of the myocardium. It should not slow myocardial electrical conduction (Di Palma and Schultz)(75). The chief difficulty in the action of quinidine is that in therapeutic doses the drug decreases the conduction time. This effect is over-shadowed by desirable results in

all the other important points and quinidine for this reason is still the drug of choice.

Van Dongan[74], after a large series of experiments with many different drugs, proclaimed that the abilities of a drug to suppress heterotropic (ectopically induced) rhythms was a more accurate measurement of antifibrillatory potency. Printzmetal et al[37] and Scherf et al[75] appear to ascribe to this view as correct. There appears to be two possible answers to the therapeutic efficacy of anti-arrhythmic drugs in this case; the drug abolishes the ectopic focus or foci or the exciting factors or, the drug raises the stimulatory threshold of the myocardium so that the focus cannot "fire" or cannot excite the nearby tissue even if it does "fire", a modification of this theory might be that the "firing" rate is slowed so that the normal pacemaker will take over at a slightly more frequent rate.

It has been shown that quinidine will inhibit epinephrine induced tachycardia in the heart-lung preparation of the dog (Krayer)[77]. Diphenhydramine, certain other antihistamines and some other chemically related drugs have been found to depress or inhibit epinephrine induced tachycardia in the isolated rabbit auricle and the same effect may be observed in the intact dog when acetylcholine is injected and epinephrine is released to the heart by the acetylcholine stimulation of the adrenal medulla.

Acetylcholine lowers the stimulatory threshold of auricular tissue but this action is also blocked by quinidine (Starr)[78],

(Lewis)[79], (Weston and McCawley)[80]. Diphenhydramine, atropine, quinacrine, procaine amide, Banthine and meperidine have been suggested or used as antifibrillatory drugs on the basis of their anti-vagal or parasympatholytic action.

It thus appears that a drug must have a three-fold action to be an effective antifibrillatory drug, namely:

(1) It should block or depress the action of the vagus nerve,

(2) It should inhibit the action of epinephrine on the myocardium, and

(3) It should elevate the stimulatory threshold of the cardiac tissue.

It might be said that up to this time no drug has been found which is satisfactory as well as effective in all these respects. Quinidine appears the best after some 40 years of clinical use although the drug has many undesirable side effects. Diphenhydramine appears as a hopeful replacement or adjunct but the use of the drug is hampered by a short duration of action and some minor but distressing side actions. New drugs are constantly appearing and several of these new drugs are herein reported as a comparison to the older standard therapeutic agents.

I. SUMMARY OF PART ONE

1. A review of the normal physiology and properties of the heart, the myocardium and the myocardial "cell" has been discussed with a view of establishing a foundation for consideration of the alterations which occurs, whether they be gross, fine or perhaps obscure, to initiate and perpetuate auricular arrhythmias.

2. The probable and possible mechanisms of initiation and perpetuation of arrhythmia are pointed out, discussed and evaluated. The "Circus Movement" theory is rejected and the theory of focus discharge is fostered as an explanation with reservation that none of the many theories have been adequately proven or disproven.

3. The causes and pathology of the auricular arrhythmias are reviewed and analyzed in an effort to circumscribe the ultimate cause and effect of the abnormalities.

4. The present therapy of auricular arrhythmias is described as being essentially empirical with an empirically used drug as the basic therapeutic agent and the standard for all other comparison.

5. The mechanism of action of drugs used in therapy of auricular arrhythmias is discussed with the hope of establishing criteria for the development of a new synthetic drug which will fulfill the therapeutic requirements on the heart without possessing the liability of undesirable side actions.

III. EXPERIMENTAL METHODS USED TO PRODUCE, ANALYZE, PREVENT AND ARREST AURICULAR ARRHYTHMIAS

A. INTRODUCTION

Many potentially useful methods have been devised for the evaluation of drugs for the therapy of auricular fibrillation. Most of these techniques are derived from observations on clinical patients and attempt to test directly some physiological property of cardiac tissue.

Isolated tissue studies chiefly employ electrical means to quantitate changes in the refractory period and also the alterations in stimulatory threshold in normal, pathological and medically treated preparations. Chemical and mechanical methods of stimulation with isolated tissue have also been studied but these appear to be too difficult of quantitation or too unreliable of execution for experimental drug evaluation.

Methods utilizing the entire animal with open or intact chest are very numerous. The fact that there are several different methods indicates the inadequacy of any one of these methods of the production of auricular dysrhythmia or evaluation of prophylaxis or therapy of the abnormality once it is initiated.

Laboratory methods have, of necessity, followed clinical observation of cardiac abnormality. Most of the factors which produce clinical auricular fibrillation have been adapted for experimental use by various investigators. Thus, anemia, anoxia, hypothermia, hypervolemia, bacterial toxemia and in this study, thyrotoxicosis

have been scrutinized and evaluated for applicability of study. In a different way, other more complex methods have been devised. These methods have employed artificial infarcts produced by a variety of methods. Other methods require injection of various drugs intravenously, intra-arterially, sub-epicardially or into the coronary vessels. Many procedures require combinations of drugs with and without mechanical or electrical stimulation and these may be employed during or after the drug administration. The complexity of most of the intact animal methods will be shown below and it is to be noted that the procedures become chronologically more complicated and require an increasing amount of highly complex equipment.

B. GENERAL EXPERIMENTAL PROCEDURES

The experiments described in this thesis are mainly of three types:

(1) Intact animal without anesthesia,

(2) Intact animal under pentobarbital anesthesia, and

(3) Open chest animal under pentobarbital anesthesia.

A minimum number of experiments were performed without anesthesia as most of the procedures required continuous infusions, intermittent infusions or injections.

Experiments performed on unanesthetized animals required some training of the animals consisting of teaching the animals to lie still upon an operating table while electrocardiographs were recorded. This training was done with dogs carefully selected for mild or quiet disposition. Injections, when necessary, were made via a saphenous vein with a 21 gauge needle. A Sandborn Viso-Cardiette electrocardiograph was used to record cardiac changes. The electrocardiograph was usually allowed to run continuously for a period of about ten seconds before drugs were injected and continuously thereafter until the changes produced by the drug had reverted to normal. In a few cases it was necessary to restrain the animal on its back on stocks and inject via a femoral cannula. In these cases the operated field was heavily anesthetized by injections of a local anesthetic and wet packing applied to the area once the skin was incised.

Operations performed upon intact animals were accomplished using anesthesia produced by pentobarbital (35 mg. per kg.) which was administered intraperitoneally. Frequently this dosage of pentobarbital was insufficient and it was necessary to supplement as necessary with one-half to one grain (0.5 to 1.0 ml.) of the pentobarbital solution. Supplementation was accomplished when possible by intravenous injections, otherwise by intraperitoneal injection.

The open chest procedure was accomplished with the animals with a mechanical respirator connected to a tracheal cannula. Operative procedure for the "open chest" consisted of midline incision the full length of the sternum and careful incision to the cutaneous branches of the internal mammary arteries which were ligated or clamped with hemostatic forceps. The sternum was split longitudinally for its full length to provide adequate exposure of the heart. The heart was on occasion supported in a cradle formed of the split pericardium. Usually, however, this was undesireble as it prevented exposure of the left auricle when the dog was placed in a lateral position. The stimulating electrodes were placed in the right auricular appendage. Gold number 14 fishhooks were used.

C. INDUCTION OF AURICULAR ARRHYTHMIAS BY SYMPATHETIC DRUGS

That sinus tachycardia follows epinephrine injection is well known. It is not so well known that patients with a tendency for paroxysmal auricular fibrillation but with no other evidence of heart disease will develop fibrillation following intravenous epinephrine injection. This fibrillation may last an hour or more (Otto)[81], (Smith and Moody)[82]. These clinical observations, as are many others herein reported, have been adapted for laboratory experiments to study cardiac arrhythmias, their prophylaxis and treatment.

Experiments similar to those of Grant et al[41] were undertaken. These investigators found that epinephrine administered at a rate of 1-4 mcgm. per kg. per min. with concomittant vagal stimulation elicited auricular fibrillation. Epinephrine injected alone (0.05-0.1 mg.) produced auricular fibrillation also, but none was observed with the low rate of continuous infusion. Stimulation of the right vagus was found by them to be six times more effective than stimulation of the left. Other investigators, Rosenblum et al[83] and Aumann and Youmans[84], were able to induce auricular fibrillation by administration of epinephrine alone if the animals were in a hyperthyroid state.

The experiments performed in this study consisted of anesthetizing the animals by the usual procedure, exposing the right vagus for stimulation and injecting the epinephrine via a saphenous or

femoral vein with a syringe and indwelling hypodermic needle or with an intravenous cannula. These injections produced transient (2-3 second) auricular fibrillation following the cessation of vagal stimulation. Because of the very brief arrhythmia, the method was considered to be of little value as an experimental tool.

Nor-epinephrine, presumed by some to be the true neuroeffector hormone, in similar type of experiment produced somewhat longer auricular fibrillation but this type of experiment also was felt to be non-physiological and was abandoned in favor of more promising procedures.

The injection of epinephrine in such doses as 10 mcgm./kg. followed immediately by vagal stimulation (5.4 volts, 1.3 millisecond pulse duration, 3960 per minute for 2 seconds) caused brief auricular flutter and/or fibrillation. This was followed by rapid, irregular ventricular activity. Frequently, larger doses of epinephrine (24-59 mcgm./kg.) or increased vagal stimulation (30-50 volts, 1.3 millisecond, 3960 per minute for 2 seconds) were required to produce this sort of result. The auricular fibrillation produced by this method consisted mainly of a rapid irregular ventricular rate (ca 205 per minute) with slow F waves ca 1200 per minute. Slower auricular fibrillation (80-90 waves per minute) lasted two to three seconds following termination of stimulus.

The injection of nor-epinephrine (Levophed(R)) 24 mcgm. per kg. with right vagal stimulation (50 volts, 1.3 millisecond, 3600 per minute for 2 seconds) produced more prolonged auricular fibrillation

(75 seconds). The character of the arrhythmia produced by this procedure consisted of an initial slow ventricular rate (80-88/min.) increasing to (200-210/min.), then decreasing until normal rhythm was resumed. Occasionally a premature ventricular systole appeared with both types of procedure.

RESULTS AND CONCLUSIONS: INDUCTION OF AURICULAR ARRHYTHMIAS WITH SYMPATHETIC DRUGS

This type of experiment in which the sympathetic drugs were administered alone or with vagal stimulation was felt to be unsatisfactory due to the short duration and lack of predictability of the arrhythmia produced. It was hoped that other procedures might be more advantageous and this type of experiment was abandoned.

D. INDUCTION OF AURICULAR ARRHYTHMIAS BY VAGAL STIMULATION AND VAGOMIMETIC DRUGS

Electrical stimulation of the vagus nerve produces cardiac arrhythmias in a relatively consistent manner although the arrhythmias are fleeting. Faradization is somewhat more satisfactory as it nearly routinely provokes auricular flutter or fibrillation during stimulation and for a few seconds following the termination of stimulus. The short duration of auricular irregularity has been found, however, to be of little value for the experimental production of flutter or fibrillation and, therefore, of little value for the assay of anti-fibrillatory drugs. Vagal stimulation is useful as a part of other methods as will be shown subsequently. This method, once the basis of action was understood, provided the foundation for a host of other type experiments. These experiments employ the substance released by vagal stimulation - acetylcholine. Vagal stimulation, though in itself of extremely limited usefulness, has provided the means to devise other experiments of far greater utility.

E. INDUCTION OF AURICULAR ARRHYTHMIAS BY PARASYMPATHETIC DRUGS

Acetylcholine was found by Nahum and Hoff[43] to produce disturbances of auricular rhythm and conduction. This has been noted especially in the thyrotoxic human patient. Controlled intravenous injection of carefully graded increments produces successively more serious disturbances until finally, in a susceptible person, a certain dosage will produce an episode of auricular fibrillation lasting for a few to several seconds. Increasing the dose will prolong the episode. The administration of acetylcholinesterase blocking agents will prolong markedly the action of acetylcholine, acetyl-beta-methylcholine and presumably other similar drugs.

The method undertaken in this study employed unselected dogs; the only criteria being apparent good health and weight which exceeded 12 kilograms. Dogs fasted overnight were anesthetized in the usual manner. The animals, when anesthetized, were placed supine upon a flat animal stock with a block under the hips to prevent undue strain of the legs. The animals were secured firmly by 3/16 in. cotton ropes around the wrists and ankles, bits were placed between the teeth and the dog's head sloped downward to promote salivary and mucous drainage out through the mouth. In some animals copious thin saliva or thick mucoid secretions required that an inflatable cuffed Magill endotracheal tube be emplaced to provide adequate airway. The procedure for injection was as follows: The area of the right or left saphenous vein was clipped or shaved for a length of 5 to 10 centi-

meters and width of 3 to 4 centimeters. An area for insertion of a hypodermic needle was selected, a tourniquet was applied around the thigh to cause venous distention and the needle (19-23 gauge, 1-2 in.) which was attached to a three-way syringe stop cock and a 25 ml. syringe was inserted and the tourniquet removed. A special three-way stop-cock was utilized on the hypodermic syringe to enable the indwelling hypodermic needle to remain in place for a long period of time. For this purpose, the syringe was fixed by a burette clamp secured to a ring stand. Injections were made by attaching a small syringe to the third opening on the stop-cock and injecting directly into the animal's vein. The larger reservoir syringe was filled to about 20 ml. with normal saline with 0.25 to 0.5 ml. of Heparin Sodium (1000 units per milliliter) or the same amount of Peritol C(R) (5%) added to prevent the clotting of blood in the syringe and needle. The system was tried frequently to insure a potency of the hypodermic needle and an attempt was made to have the needle always filled with the saline solution containing the anticoagulant to minimize the possibility of injection of "needle clots". The drug injections were made at intervals of about five minutes, shorter when very low doses were employed but longer with the higher doses. This was done in an attempt to eliminate respiratory embarrassment due to the acetylcholine induced bronchiolar constriction and the copious salivation. In the case of prolonged experimental procedures, an

intramuscular injection of penicillin (300,000 units Procaine Penicillin G) was given at the termination of the experiment to prevent respiratory infection, after this the animal was returned to its quarters.

RESULTS AND CONCLUSIONS: INDUCTION OF AURICULAR ARRHYTHMIAS WITH VAGAL STIMULATION OR PARASYMPATHETIC DRUGS

Normal untreated dogs under pentobarbital anesthesia will show a variety of cardiac irregularities when the vagus nerve is stimulated or when parasympathetic drugs are injected intravenously. Progressive increases in dosage will produce the following successive series of irregularities: (1) Tachycardia, which is not the result of the acetylcholine, but probably a reflection of the acetylcholine provoked release of epinephrine from the adrenal glands and other chromaffin tissue. This epinephrine in turn caused cardiac stimulation and tachycardia. Another possibility of the cause of the tachycardia is pulmonary vascular vasodilation or hypotension which in turn provokes reflex tachycardia. (2) Frank bradycardia for one to several beats is the next more severe charge. Extension of interval occurred in all portions of the electrocardiographic complex, but mainly noticeable in the P-R interval and the T-P interval. (3) Single 2:1 atrio-ventricular block was noted as the next most severe sign and variously prolonged A-V blocks up to as many as 38:1 were noticed at higher doses. Irregularities more severe than this were (4) complete heart block - no atrial nor ventricular electrical activity - which occurred in some cases up to 10 seconds. Frequently QRS complexes occurred in these cases at intervals of from 1 to 3 seconds with no P waves but perhaps 6-10 irregularly spaced QRS waves.

The most severe arrhythmia, and the one which was sought, was (6) auricular fibrillation. This result occurred in six of twenty-three normal dogs (26%) with dosages of acetylcholine 1.0 mg. per kg. or less (1.0 mg. per kg. was determined to be the maximum safe dose for intravenous administration and only rarely and with extenuating circumstances was this dosage exceeded). A summary of the table indicating the effects of intravenous acetylcholine indicates that the mean threshold dose to produce fibrillation was 0.3 mg./kg. (range 0.05-0.95 mg./kg.). The mean duration of fibrillation at the minimum dose was observed to be 39.4 seconds (range 12-96 sec.). Although 2:1 block and fibrillation have both been utilized for experimental evaluation of antifibrillatory drugs, in this series no correlation was found between animals manifesting low 2:1 block dose and tendency to auricular fibrillation. The heart rate of the animals, whether anesthetized or not, appeared to have no correlation with fibrillating tendency.

TABLE I

EFFECTS OF ACETYLCHOLINE ON CARDIAC RHYTHM - CONTROL SERIES

Dog Number	Acetylcholine Dose mg./kg. 2:1 Block	Auricular Fibrillation No	Auricular Fibrillation Yes	Duration Auricular Fibrillation sec.	Heart Rate (per min.) Anesthetized	Heart Rate (per min.) Unanesthetized
A-11	0.05	1.0		—	185	112
A-12	0.04	1.0		—	152	96
A-13	0.07		0.95	96	207	120
A-14	0.09	1.0		—	177	96
A-15	0.035	1.0		—	186	80
A-16	0.055	1.0		—	167	96
A-17	0.03	1.0		—	144	108
A-18	0.026	1.0		—	178	75
A-20	0.012		0.08	34	214	—
A-21	0.057	1.0		—	200	88
A-22	0.06	1.0		—	180	—
A-23	0.06		0.2	37	225	—
A-24	0.04	1.0		—	138	—
A-25	0.066		0.09	12	147	97
D-11	0.07	1.0		—	206	—
D-12	0.04	1.0		—	140	—
D-13	0.03	1.0		—	128	—
D-14	0.01		0.05	9	232	—
L-30	0.08	1.0		—	128	—
L-31	0.04		0.2	17	120	—
L-32	0.12	1.0		—	151	—
L-33	0.08	1.0		—	155	—
L-34	0.04		0.12	24	153	—

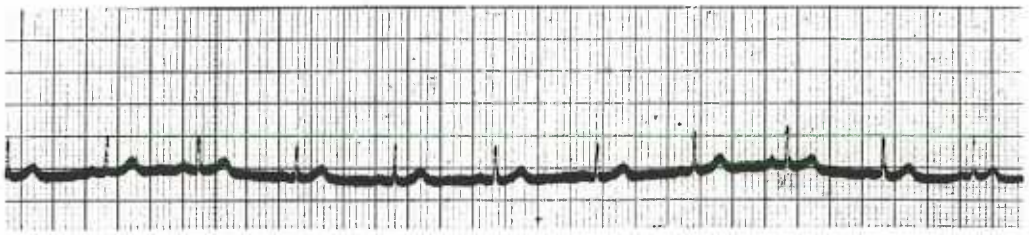
FIGURE I

EFFECTS OF INTRAVENOUS ACETYLCHOLINE

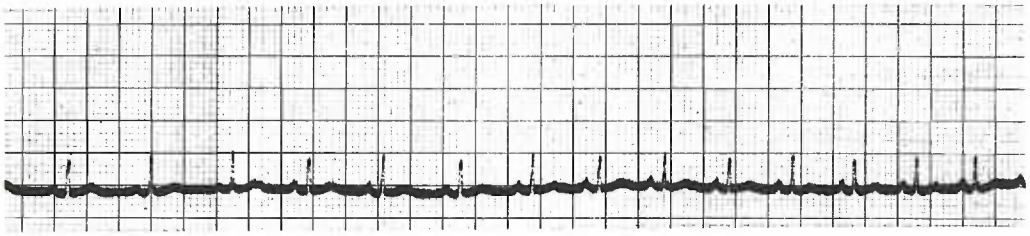
ON NORMAL DOG

1. Normal control: Rate 100
2. Effect of minimal dose: Tachycardia: Rate 150
3. 2:1 atrioventricular block (4 sequences) (0.03 mg. per kg.)
4. Depression of P wave (0.04 mg. per kg.)

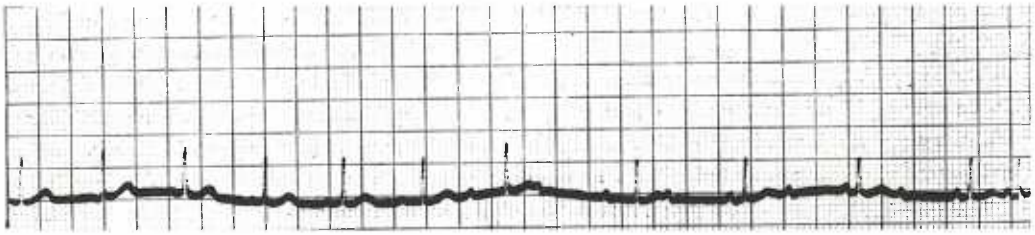
EFFECTS OF INTRAVENOUS ACETYL CHOLINE ON NORMAL DOG



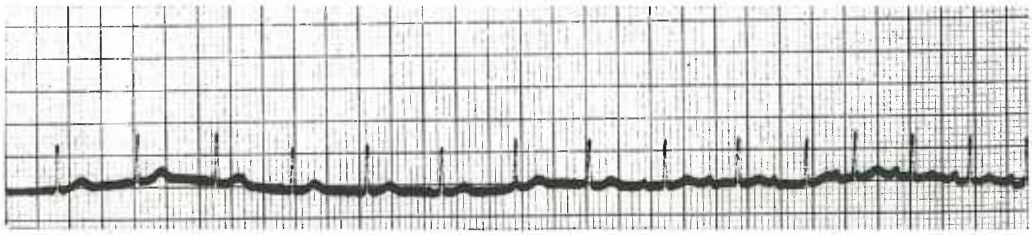
Normal control: Rate 100



Effect of minimal dose: Tachycardia: Rate 150 (0.03 mg. per kg.)



2:1 atrio-ventricular block (4 sequences) (0.03 mg. per kg.)



Depression of P wave (0.04 mg. per kg.)

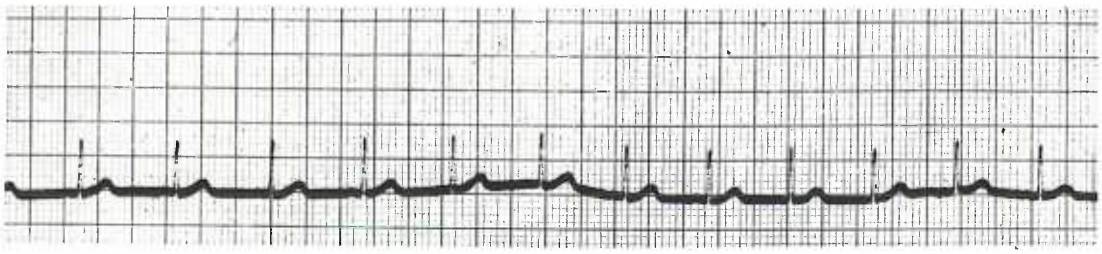
FIGURE II

EFFECTS OF INTRAVENOUS ACETYLCHOLINE

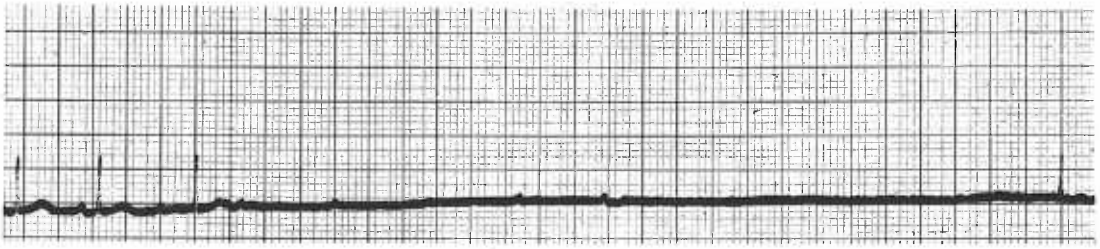
ON NORMAL DOG

(Continued)

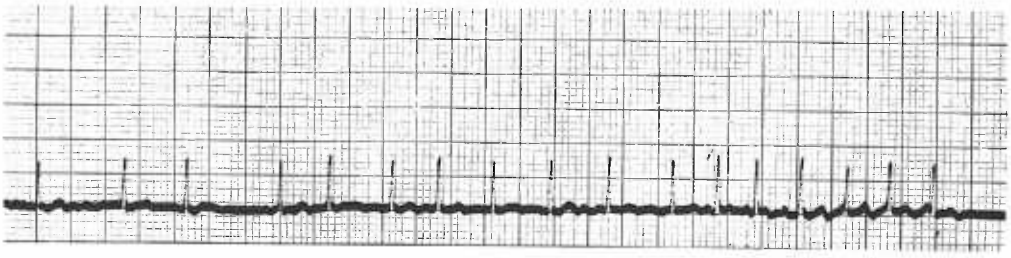
5. Prolonged P wave depression (0.05 mg. per kg.)
6. Acute A-V block with ventricular arrest (0.5 mg. per kg.)
7. Continuation of #6 showing auricular fibrillation
8. Continuation of #7, 10 seconds later showing recovery



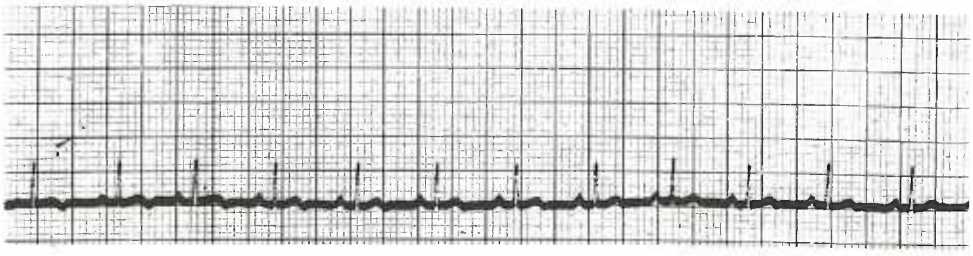
Prolonged P wave depression (0.05 mg. per kg.)



Acute A-V block with ventricular arrest (0.5 mg. per kg.)



Continuation of #6 showing auricular fibrillation.



Continuation of #7, 10 seconds later showing recovery.

FIGURE III

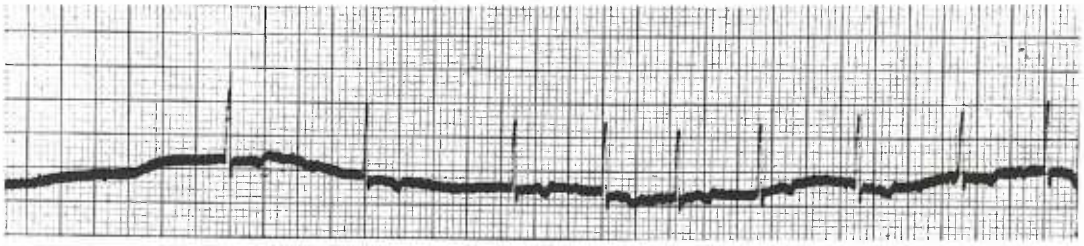
EFFECTS OF INTRAVENOUS ACETYLCHOLINE

ON NORMAL DOG

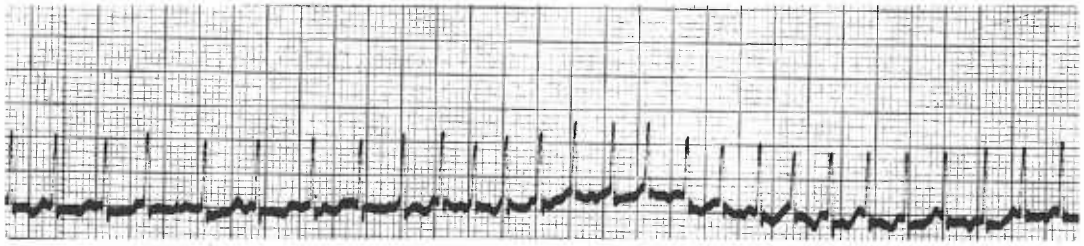
(Continued)

9. Excerpt demonstrating induced fully developed auricular fibrillation (1.0 mg. per kg.)

10. Continuation of #9 demonstrating transition towards normal



Excerpt demonstrating induced fully developed auricular fibrillation (1.0 mg. per kg.)



Continuation of #9 demonstrating transition towards normal

F. SURGICAL AND TRAUMATIC PROCEDURES

1. THE SCHERF ACONITINE INJECTION METHOD

The cardio-stimulatory effect of aconitine (from Aconitum Napellus Linne or Monk's hood) has been known for centuries. Scherf in 1947 published the results of the first controlled experiments in which aconitine was administered for the purpose of provoking arrhythmias(20). Scherf originally found that intravenously injected aconitine would provoke dangerous ventricular dysrhythmias as well as the desired auricular effect. A subsequent report(85) indicated that topical application or auricular sub-epicardial injection would provoke various auricular arrhythmias which were of a satisfactory type and duration to study and evaluate drugs. At the same time this procedure does not provoke ventricular disturbances which would interfere.

The usual operative procedure to perform this experiment was followed. Our original experiments included careful midline incision of the pericardium and suspension of the heart by means of a cradle made of the pericardium sutured to the margins of the split sternum. It was found that such suspension produced torsion of the heart and distortion of the electrocardiogram. When the distortion was discovered, the procedure of suspension was discontinued and the heart was allowed to settle freely.

Aconitine solutions (0.05 ml. of 0.05% in benzene) were injected sub-epicardially into the auricular myocardium with a 28 or 30 gauge hypodermic needle while the electrocardiogram was being recorded.

RESULTS AND CONCLUSIONS: THE SCHERF ACONITINE INJECTION METHOD

Within 2-3 minutes following the sub-epicardial injection of aconitine, a rapid auricular arrhythmia develops. Usually a gradually developing auricular tachycardia proceeds into a 2:1 flutter with a ventricular rate of 240-290 per minute. On other occasions a rapid ventricular rate (260-390 per minute) occurred with supra-ventricular tachycardia or 1:1 flutter. Grossly irregular ventricular activity was also observed. By experimentation it was found that reasonably persistent auricular fibrillation could be produced for evaluation of antifibrillatory drugs. This auricular fibrillation was characterized by irregular R-R intervals and ventricular rates of 240 to 324 per minute.

Three animals, in which satisfactory auricular fibrillation had been produced, were treated with intravenous Banthine bromide(R) (methantheline bromide). Doses of 2.0 to 3.7 mg. per kg. were injected intravenously. Conversion of the fibrillation to normal was noted in from 15 to 114 seconds after injection. The ventricular rates after conversion had slowed to rates of 220 to 264 per minute. In one instance fibrillation was replaced by a transitory supra-ventricular tachycardia (330 per minute) which lasted 240 seconds before conversion to a normal sinus rhythm.

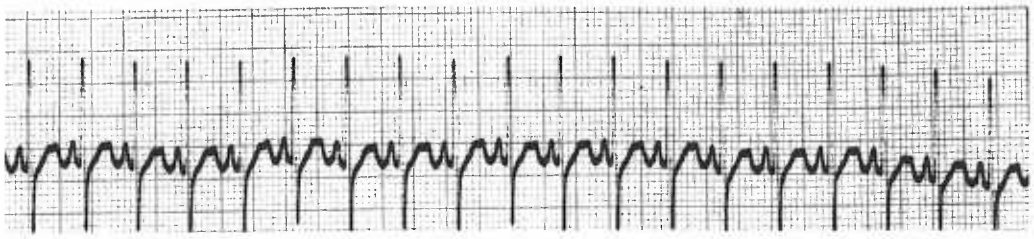
In some experiments, aconitine (0.05 ml. of 0.05%) was injected intravenously via the saphenous or femoral vein at 5 minute intervals.

FIGURE IV

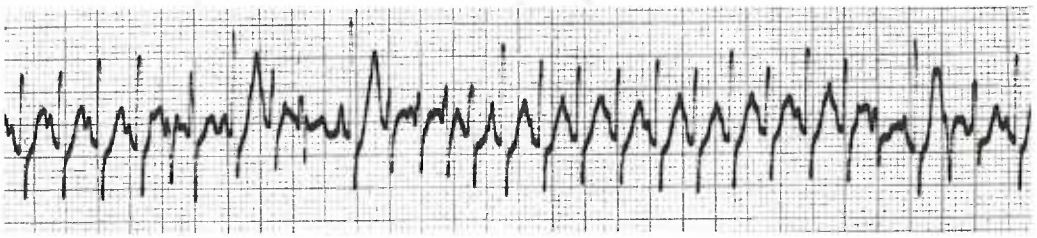
SCHERF ACONITINE INJECTION PROCEDURE

1. Normal control: Rate 180
2. 45 seconds after aconitine injection (0.05 ml. 0.05% in benzene), demonstration of onset of arrhythmia
3. 60 seconds after aconitine injection. Rapid impure flutter.

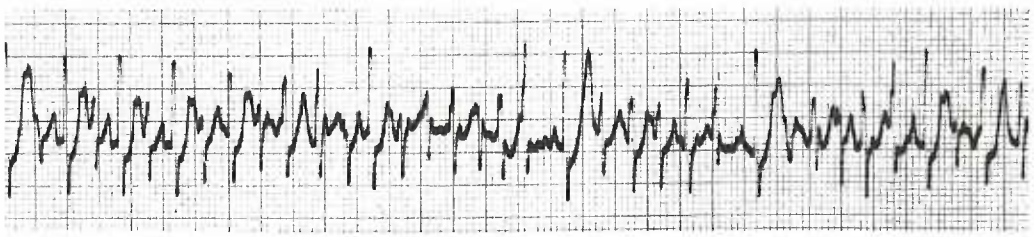
SCHERF ACONITINE INJECTION PROCEDURE



Normal control: Rate 180



45 seconds after aconitine injection (0.05 ml. 0.05% in benzene), demonstration of onset of arrhythmia.



60 seconds after aconitine injection. Rapid impure flutter,

Following several injections (6 to 8) persistent ventricular tachycardia appeared (200-260 per minute). In these cases the lead II electrocardiogram showed upright and/or inverted QRS with slurred or notched QR with the T wave opposite in deflection to the QRS.

Benadryl (diphenhydramine) was administered (10 mg. per kg.) in an attempt to convert a case of ventricular tachycardia with a changing pacemaker which was produced by intravenous aconitine injection. Benadryl converted this ventricular arrhythmia to an impure auricular flutter and later restored a normal rhythm. The normal rhythm was only temporary under the influence of the Benadryl, and the ventricular tachycardia later returned.

In our hands the arrhythmias produced by aconitine were not predictable in time of onset, duration, nor the type of arrhythmia produced. It was felt that this type of experiment was useful only to demonstrate a method for experimental production of arrhythmias and not a useful tool for the study of prophylaxis and therapy of the auricular arrhythmias.

2. THE ROSENBLEUTH AND GARCIA-RAMOS ATRIAL CRUSH PROCEDURE

The method used for this series of experiments was a modification of the method of Rosenbleuth and Garcia-Ramos[86] necessitated by some slight but inconsequential dissimilarity of equipment. Our method was as follows: Dogs were anesthetized and prepared by the usual open chest procedure. To produce the infarct, the entire heart was rotated *in situ* from right to left by hand as gently as possible and a crush was made in the now visible right atrium at the bridge between the venae cava with the aid of a small forceps for holding while one or two large curved intestinal forceps were clamped in place. The optimum size crush appeared to be 1.5 cm. by 4-5 cm. with the long axis aligned slightly from the direction of the two venae caval orifices so that a portion of the right atria was crushed. The large curved forceps were allowed to remain in place from 10 to 20 minutes and supplementary crushes were made when necessary to assure traumatization of the area to form an artificial infarct. Perforation of the cardiac wall was avoided. When the crushing forceps were removed, fishhook (No. 14) stimulating electrodes were implaced at random in the auricular appendage with, however, the following restrictions: The atrial margins, the auriculoventricular margin and the sino-auricular margins were avoided at least 1 cm. It was found that more consistent and reproducible results were obtained when the stimulating electrodes were at least 1 cm. apart.

The stimulator used for the majority of the experiments was a Techtronix 160-161-162 series stimulator producing a square wave impulse and the parameters of stimulation were 300 to 6000 stimuli per minute, 10 to 50 volts, 1 millisecond pulse width, 10 to 30 seconds of stimulation. The most satisfactory procedure to produce auricular flutter or fibrillation was found to be the following: Start at the lower voltages and frequencies and increase either or both step wise until a "permanent" arrhythmia was established. Once an arrhythmia was "permanently" established (10-20 minutes) experimental drugs were injected in an attempt to arrest the arrhythmia.

RESULTS AND CONCLUSIONS: ROSENBLEUTH AND GARCIA-RAMOS METHOD

Cardiac arrhythmias consisting of auricular fibrillation or various grades of flutter were established in about one-half the animals following the procedure described by Rosenbleuth and Garcia-Ramos[86]. Most of our failures were our first experiments and were attributed to the following causes: (1) Too small or too young an animal and (2) too small a heart on an otherwise large dog. Several applications of the stimulus were usually found to be necessary to produce a "workable" arrhythmic heart. Initial stimuli at lower rates and voltages would produce moderate irregularities for a few seconds, but repetitive application, allowing a few minutes between each successive stimulation would finally result in an arrhythmia lasting ten minutes or more. This was our minimum criteria of established arrhythmia. Once arrhythmia had been established for such a period or longer, various drugs were administered in attempts to arrest the chaotic heart rhythm and re-establish normal sinus rhythm. Quinidine was used as a standard drug. Benthine(R), Benadryl(R) and S-135 were tested in an attempt to establish regimen for the treatment of clinical patients. We were able to confirm the report of Brown that quinidine in doses of 4-16 mg. per kg. arrested this type of arrhythmia. The larger doses of quinidine were toxic to the heart and shortly after conversion to normal sinus rhythm, death ensued[88].

TABLE II

INDUCTION OF AURICULAR ARRHYTHMIAS
ROSENBLEUTH AND GARCIA-RAMOS TECHNIQUE

Dog Number	Inciting Stimulus: Volts	Pulse Width Milliseconds	Stimulatory Rate	Stimulus Duration Seconds	Type of Arrhythmia Obtained	Duration of Arrhythmia Seconds	Remarks
2	50	1	3000	20	Fib.	3+20*	M.
4	35	1	2400	10	2:1 Fl.	9+23+11	
5	30	1	3000	20	2:1 Fl.	18+2	
7	20	1	3000	20	Imp. Fl.	10+1	
11	50	1	3000	20	Fib.-Fail.		M. - V.S.
12	20	1	3000	20	Imp. Fl.	120	
14	50	1	1200	20	1:1 Fl.	65+6	
15	30	1	1200	20	Fib.-R.	68+10	
16	30	1	1200	20	1:1 Fl.	20+2	
17					1:1 Fl.		M.
	25	1	2400	20	$\bar{\beta}$ Banthine	10+50	
18	30	1	600	10	1:1 Fl.	12+1	
20	40	1	600	20	1:1 Fl.	22+5+16+39+69	M.
83 min. $\bar{\beta}$ drug	50	1	6000	10	1:1 Fl.	4 Spont.	
	50	1	6000	10	2:1 Fl.	16+6	

(An explanation of the above abbreviations and symbol are presented on the next page.)

ABBREVIATIONS AND SYMBOL USED IN TABLE II:

* First number refers to duration of arrhythmia before drug was administered. Other numbers refer to time required for drug to arrest arrhythmia.

M. = Arrhythmia induced mechanically

Imp. = Impure (Indefinite 1:1 - 2:1 - 3:1)

Fl. = Auricular flutter

Fib. = Auricular fibrillation

Spont. = Spontaneous (Arrhythmia or conversion)

V.S. = Vagi severed

Fail. = Failure, usually auricular arrhythmia could not be permanently induced by stimulation

R. = Rapid (uncountable)

TABLE III

EFFECT OF ANTI-ARRHYTHMIC DRUGS ON
EXPERIMENTALLY INDUCED ARRHYTHMIAS

Dog Number	Type of Arrhythmia	Drug Tested	Dose mg./kg.	F Rate	V Rate	Conversion Time in Minutes	Rate $\bar{p}$ Conversion
2	Fib.	Q.	11	460	160	31	100
4	2:1 Fl.	Ban.	3	290	190	N.E.	N.E.
			+6	290	190	34	140
5	2:1 Fl.	Ban.	6	440	220	2	140
7	Imp. Fl.	Ban.	4	900	120	1 temp.	170
	Imp. Fl.	Ban.	+8			N.E.	N.E.
11	Fib.	Ban.	2	600	120	1 temp.	160
12	Imp. Fl.	Ban.	2	560	240	N.E.	N.E.
		Ban.	+4	560	240	N.E.	N.E.
		Ban.	+8	560	240	N.E.	N.E.
		Q.	4	560	240	N.E.	N.E.
14	1:1 Fl.	Ban.	2	240	240	2 temp.	190
		Ban.	+4	240	240	1.5 temp.	195
		Bd.	2	240	240	6	176
15	Fib.	Ban.	2	240	240		
		Ban.	+2	240	240		
		Ban.	+4	240	240	Temp. Fib. to Imp.	2:1
		Ban.	+6	192	192	2	
16	1:1 Fl.	Ban.	2	250	250	N.E.	N.E.
		Ban.	4	250	250	2	160
17	1:1 Fl.	Ban.	2	250	250	39	180
*18	Imp. Fl.	Bd.	2	450	300	1	180
	1:1 Fl.	S-135	1	300	300	5	*
20	Imp. Fl.	Bd.	1	330	330	N.E.	N.E.
		Bd.	+1	330	330	N.E.	N.E.
		Bd.	+2	330	330	N.E.	N.E.
		Bd.	+4	330	330	69	150
	Imp. Fl.			480	240	Spont.	140
		Q.	4	480	240	6	130

(An explanation of the above abbreviations and symbols are presented on the next page.)

ABBREVIATIONS AND SYMBOLS USED IN TABLE III:

* 18 - Electrocardiograph stylus burned out: Conversion in about 5 minutes after S-135 administration.

Fib. = Auricular fibrillation

Fl. = Flutter

Imp. = Impure or mixed

Q. = Quinidine Lactate

Ban. = Banthine Bromide

Bd. = Benadryl Hydrochloride

Temp. = Temporary

N.E. = No effect of drug

In the course of these experiments, three apparently different types of auricular arrhythmia were noted. The most frequently obtained "permanent" arrhythmia by this procedure was auricular flutter. This irregularity was in some cases pure, with a regular ratio of "f" waves and ventricular complexes, and in other cases impure, in which no regularity of ratio between "f" waves and QRS complexes was obtained.

The most common flutter observed was an impure type which appeared in general to be a combination of 1:1 and 2:1. The ventricular rate in these cases was often above 300 for considerable periods of time and the "f" waves were interspersed at seemingly uneven or random intervals between the QRS complexes. The next most common flutter seen was 1:1 in which case the T and P waves were apparently synchronous or nearly so. This arrhythmia was characterized by an auricular and ventricular rate of 250 to 300 per minute. The least common flutter seen was a pure 2:1 rhythm. In these cases the ventricular rates were slower, about 200 per minute and the "f" waves were quite regular.

An examination of the results obtained from the administration of drugs to arrest the induced arrhythmias indicates some noteworthy and unusual observations and some previously unreported findings:
(1) Auricular fibrillation appears to be the easiest arrhythmia to convert to normal. In this case both quinidine and Banthine converted the arrhythmia. Quinidine afforded a permanent and Banthine temporary conversion. Benadryl has been previously shown to arrest and prevent auricular fibrillation in the dog(72). (2) The pure flutters were

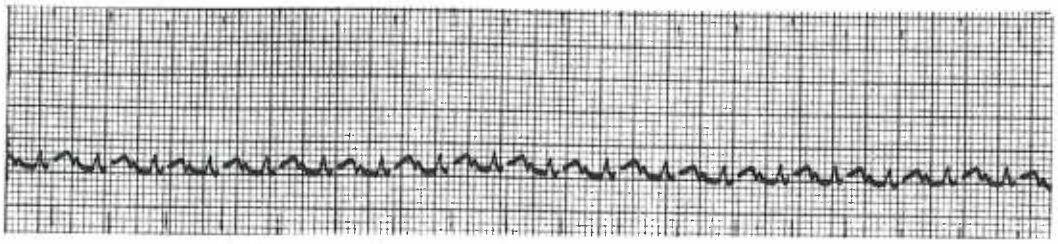
FIGURE V

ROSENBLEUTH AND GARCIA-RAMOS AURICULAR

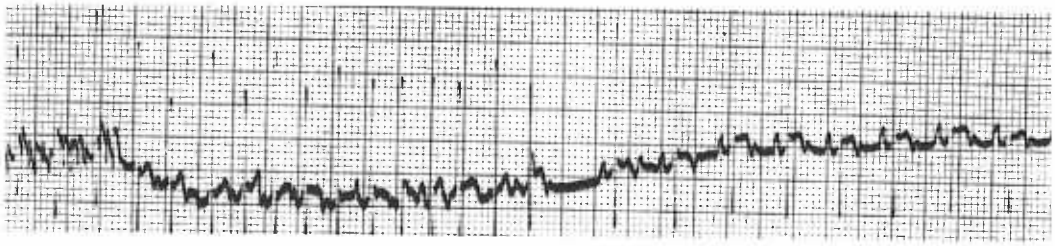
CRUSH TECHNIQUE

1. Normal control: ("Open chest") Rate 180
2. Excerpt demonstrating (a) stimulus (1200 per min., 50 volts, 1 millisec. pulse, 20 second duration), (b) "Nach Flimmern" or post stimulatory flutter and (c) spontaneous conversion to normal.
3. Excerpt demonstrating stimulation and "permanent" 1:1 flutter (Rate 270)
4. 2 minutes after 4 mg. per kg. Banthine demonstrating arrest of arrhythmia and conversion to normal (rate 160)

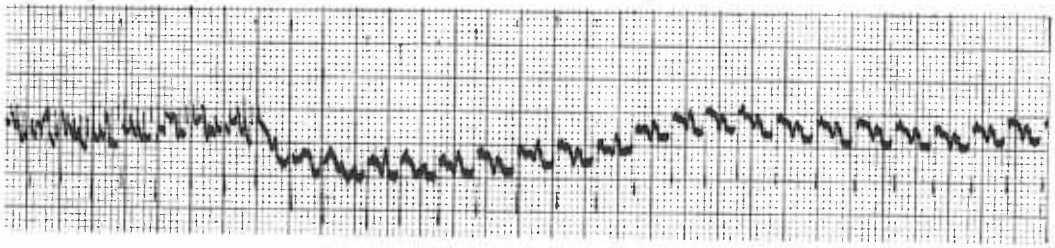
ROSENBLEUTH AND GARCIA-RAMOS AURICULAR CRUSH TECHNIQUE



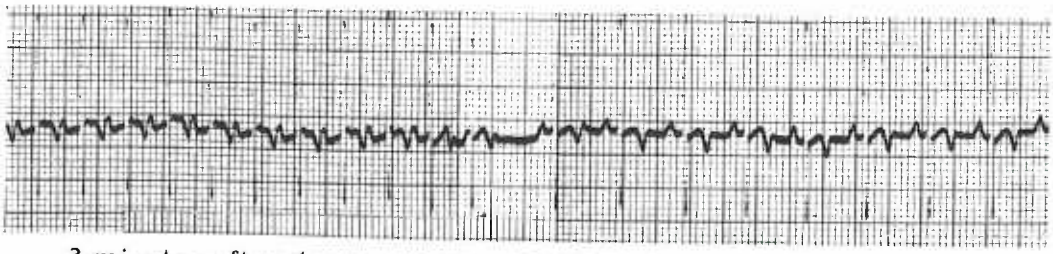
Normal control: ("Open chest") Rate 180



Excerpt demonstrating (a) stimulus, (1200 per min., 50 volts, 1 millisec. pulse, 20 second duration), (b) "Nach Flimmern" or post stimulatory flutter and (c) spontaneous conversion to normal.



Excerpt demonstrating stimulation and "permanent" 1:1 flutter (Rate 270)



2 minutes after 4 mg. per kg. Banthine demonstrating arrest of arrhythmia and conversion to normal (Rate 160)

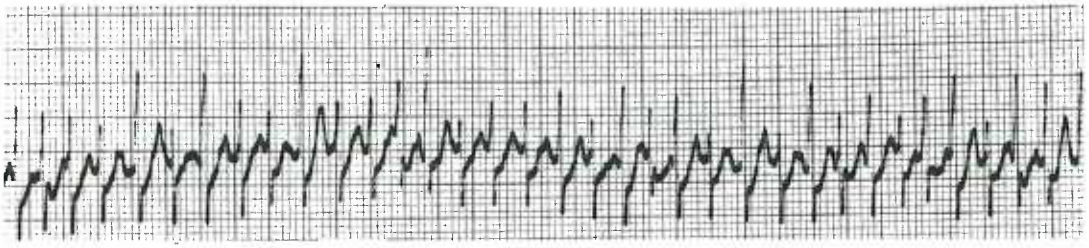
FIGURE VI

ROSENBLUTH AND GARCIA-RAMOS AURICULAR

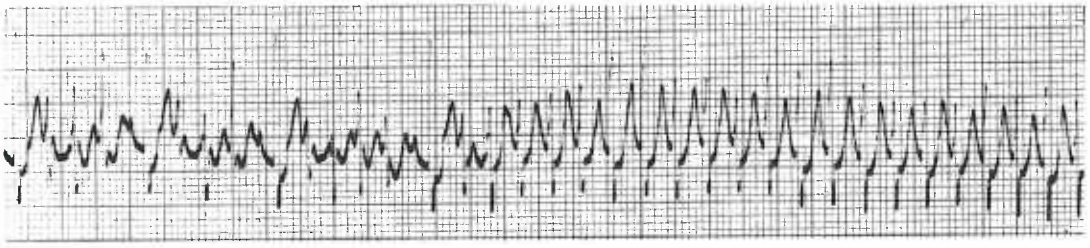
CRUSH TECHNIQUE

(Continued)

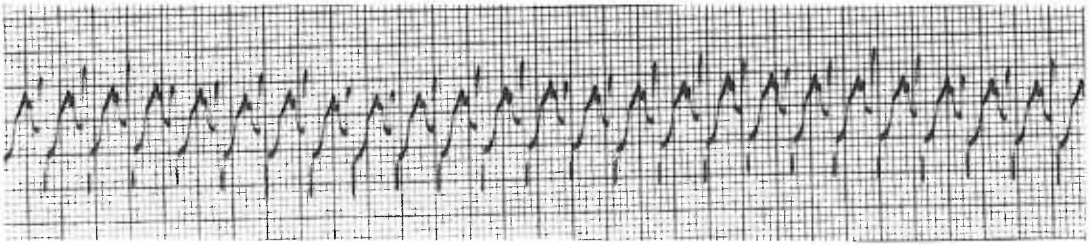
5. 8 minutes later, 1:1 flutter.
6. Conversion of impure flutter to 1:1 flutter by Banthine, 2 mg. per kg.
7. Conversion of 1:1 flutter towards normal by additional Banthine, 4 mg. per kg.



8 minutes later, 1:1 flutter.



Conversion of impure flutter to 1:1 flutter by Banthine, 2 mg. per kg.



Conversion of 1:1 flutter towards normal by additional Banthine, 4 mg. per kg.

converted in a high percentage of cases (7 of 9) by all of the drugs tested. In this series, Banthine was used most, but observations were also obtained with Benadryl and S-135. (3) It was noted that Banthine usually produced only a temporary arrest of an arrhythmia. (4) Benadryl and S-135 produced relatively permanent conversions. (5) An unusual finding is the previously unreported resistance of impure flutter to the several drugs used. Banthine, quinidine and Benadryl seem to have little effect upon this arrhythmia. (6) An additional observation is believed especially noteworthy. Originally, the criteria for a permanent arrhythmia was a duration of about 10 minutes. Late in the investigation it was observed that even the experimental failures (those experiments in which a permanent arrhythmia could not be provoked) provided information which may prove of future value although these observations may only be considered to be preliminary at this time. Stimulation of the heart at high rates (above 600 per minute) provokes, nearly uniformly, a temporary arrhythmia which has been previously described as "nach flimmern" (after fibrillation). A review of the electrocardiograms obtained in this series indicates that this phenomenon is a quite common result and occurs more often than any other arrhythmia. A further preliminary observation is that all of the drugs tested seem to effectively decrease the intensity, duration or prevent the appearance of this "after fibrillation". The significance of these observations cannot be adequately discussed at this time.

G. PRODUCTION OF EXPERIMENTAL THYROTOXICOSIS AND INFLUENCE OF PARASYMPATHETIC DRUGS

The evidence that thyrotoxicosis and the concomittant heart strain predisposes to cardiac arrhythmias encouraged a detailed examination to see if the production of the experimental condition might mimic that of the clinical patient.

Unselected adult dogs of either sex weighing at least 25 lbs. (12 kg.) were placed in individual cages and observed for about a week. During this time, at least one control electrocardiograph was taken and one experiment was run to find the sensitivity to acetylcholine while the animals were under pentobarbital anesthesia as described previously. If the animal was found to be normal, i.e. with no natural arrhythmia, it was placed immediately upon a normal diet consisting of kibbled dog biscuits plus a small amount of horse meat. To this was added at feeding, thyroid extract powder (U.S.P., 1 gram). After the thyroid extract regime was started, the animals were examined daily for overt evidence of thyrotoxicosis. In addition, the animals were tested regularly for change of sensitivity to parasympathetic drugs. For this purpose the animals were studied as outlined in the previous section. This procedure allowed each animal to serve as his own control for normal electrocardiographic study, the influence of injected parasympathetic drugs and also the effect of thyroid extract administration and injected parasympathetic drugs.

RESULTS AND CONCLUSIONS: EXPERIMENTAL THYROTOXICOSIS AND PARASYMPATHETIC DRUGS

Thyrotoxicosis, induced by feeding of large amounts of thyroid extract powder in the diet, produced most of the typical clinical signs and symptoms of the condition. The animals became more alert and sometimes irritable. Diarrhea was a frequent sign. The mean apical heart rate (unanesthetized) increased from 95.8 per minute (range 75-120) to 160.6 per minute (range 144-188). Increased thirst was evident. Anorexia, vomiting, and retching were all frequently noted and weight loss was usual. Long continued administration of thyroid extract powder finally produced a condition which might be considered a refractory state to the administered drug. This refractoriness appeared usually about the third or fourth week of administration. Usually after this time, the only sign of thyrotoxicosis was an increased heart rate.

Before and at periodic intervals during the time the animals were administered thyroid extract; they were selected for experiments to ascertain any change in sensitivity to injected acetylcholine. The procedure used was as outlined previously for the intact anesthetized animal. In the normal animal not fed thyroid, the incidence of fibrillation was 26% (6 of 23) but in this experimental series it was 85% (11 of 13). The period of greatest sensitivity was found to be between the sixth to 24th day of thyroid administration and it was noted that dogs fibrillating after this period had also done so before the administration of thyroid extract.

TABLE IV

EFFECT OF ACETYLCHOLINE ON AURICULAR RHYTHM IN THYROID-FED DOGS

Dog Number	Days on Thyroid	Dose of Acetylcholine Producing Fibrillation mg./kg.	Duration Fibrillation Seconds
A-13	6	0.42	48
L 34R1	7	0.4	33
L 33R1	8	< 1.0	-
L 32R1	9	< 1.0	-
L 30R1	10	0.6	37
L 31R1	10	0.6	7
L 34R2	15	0.3	30
W 3A	16	0.1	29
W 1A	16	0.5	34
W 2A	16	0.1	19
L-14	17	0.04	13
L 30R2	17	0.6	37
L 31R2	18	< 1.0	-
L-12	19	0.15	21
L-13	20	0.32	24
W 3AR1	21	0.2	20
L 33R2	22	< 1.0	-
L 34R3	22	0.16	18
W 2AR1	22	0.1	25
L 32R2	23	0.6	21
A-18	25	< 1.0	-
L 31R3	25	< 1.0	-
L 32R3	27	< 1.0	-
L-19	28	< 1.0	-

TABLE IV (cont.)

Dog Number	Days on Thyroid	Dose of Acetylcholine Producing Fibrillation mg./kg.	Duration Fibrillation Seconds
L 17R1	30	< 1.0	-
W 3AR2	30	0.31	14
L 33R3	30	< 1.0	-
W 1AR1	30	< 1.0	-
L 34R4	30	0.3	24
L 15R1	31	< 1.0	-
L-20	32	< 1.0	-
L 31R4	32	1.0	32
L 12R1	33	< 1.0	-
L 13R1	33	0.6	37
L-21	37	< 1.0	-
W 3AR3	37	0.31	24
L-18	38	< 1.0	-
L 34R5	39	0.3	35
L 32R5	40	< 1.0	-
L 14R1	40	0.3	10
A 15R1	41	< 1.0	-
L 34R6	43	0.3	30
L-11	43	< 1.0	-
L 32R5	44	< 1.0	-
L 31R6	46	< 1.0	-
L 13R2	48	< 1.0	-
L 34R7	50	0.6	51
L 32R6	52	< 1.0	-

TABLE IV (cont.)

Dog Number	Days on Thyroid	Dose of Acetylcholine Producing Fibrillation mg./kg.	Duration Fibrillation Seconds
A-14	53	< 1.0	-
L 31R6A	55	0.6	21
L 32R7	60	< 1.0	-
L 34R8	60	0.08	12
L 31R7	60	0.3	30
L 34R9	67	0.6	60
L 32R8	67	< 1.0	-
L 31R9	71	0.6	36
L 34R10	73	0.16	39
A-12	75	0.5	21
L 31R10	146	0.64	45+
L 34R11	148	0.16	27
L 34R12	154	0.14	24
L 34R13	183	0.12	24+
L34R14	204	0.08	27
L 31R11	273	0.32	21
L 34R15	280	0.08	15
L 31R12	286	0.50	160
L 31R13	441	0.70	57
L 31R14	497	0.16	7
L 31R15	505	< 1.0	-
L 31R16	531	0.32	42

No alteration in the 2:1 atrio-ventricular block dose was noted in this series. The mean pre-thyroid 2:1 block dose being 0.050$\frac{1}{4}$ ± 0.025 mg. per kg. of acetylcholine and in this experimental series it was 0.0$\frac{1}{4}$82 ± 0.038 mg. per kg. The mean dose of acetylcholine provoking fibrillation in the control and experimental series was not altered significantly being 0.3 mg. per kg. (range 0.05-0.95) in the control series, and 0.32$\frac{1}{4}$ mg. per kg. (range 0.0$\frac{1}{4}$-0.6) in the thyrotoxic series. The mean duration of fibrillation in the controls was 39.$\frac{1}{4}$ sec. (range 12-96 sec.) and the experimental series it was 2$\frac{1}{4}$ sec. (range 7-37 sec.).

The success of this experiment in providing an animal preparation for the study of auricular arrhythmias appears to mark a great advance in this type of work. The procedure of induction of the hyperthyroid state mimics a well known clinical syndrome, thyrotoxicosis. This condition, once induced, predisposes the experimental animal to the arrhythmic state which is prolonged to a degree of experimental usefulness for the evaluation of drugs to combat the clinical conditions. The procedures for inducing and testing are not grossly traumatic and it appears that such experiments could be repeated on the same animal weekly or oftener with a trained unanesthetized dog. The ultimate cost does not seem great as the animals can be re-used many times then still be useable for other procedures.

When another research group undertook a similar type of study using acetylcholine to provoke arrhythmias in thyrotoxic dogs, results comparable to those reported here were not observed(59).

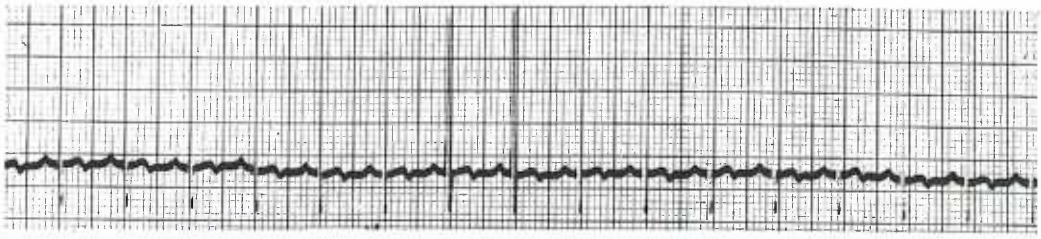
FIGURE VII

EFFECT OF INTRAVENOUS ACETYLCHOLINE

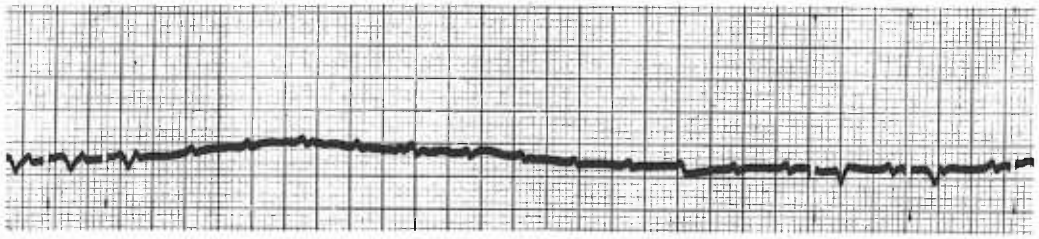
ON THYROID DOG

1. Control: Before "thyroid" administration. Rate 150
2. Effect of 0.6 mg. per kg., before "thyroid" administration.
3. Control: 23 days "on thyroid". Rate 170
4. Effect of 0.6 mg. per kg., 23 days on "thyroid"

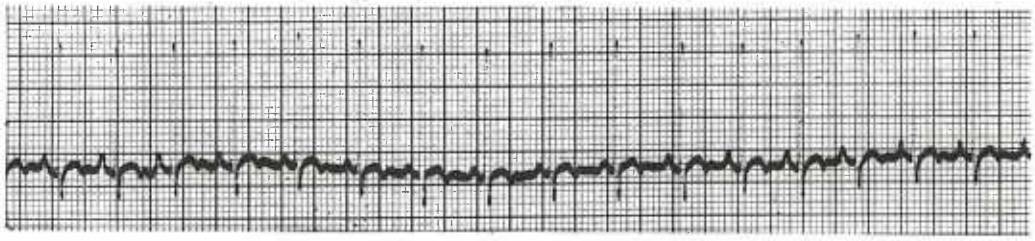
EFFECT OF INTRAVENOUS ACETYL CHOLINE ON THYROTOXIC DOG



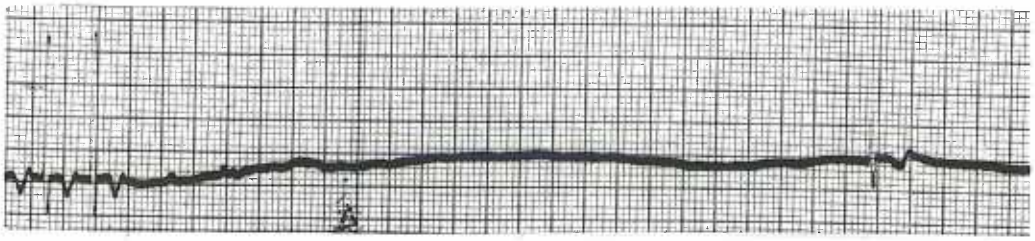
Control: Before "thyroid" administration. Rate 150



Effect of 0.6 mg. per kg., before "thyroid" administration.



Control: 23 days "on thyroid". Rate 170



Effect of 0.6 mg. per kg., 23 days on "thyroid"

FIGURE VIII

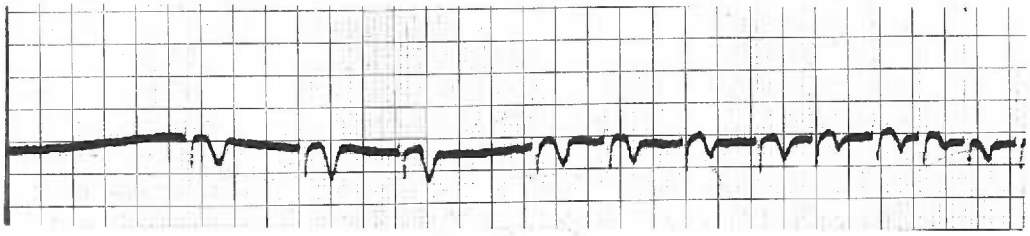
EFFECT OF INTRAVENOUS ACETYLCHOLINE

ON THYROID DOG

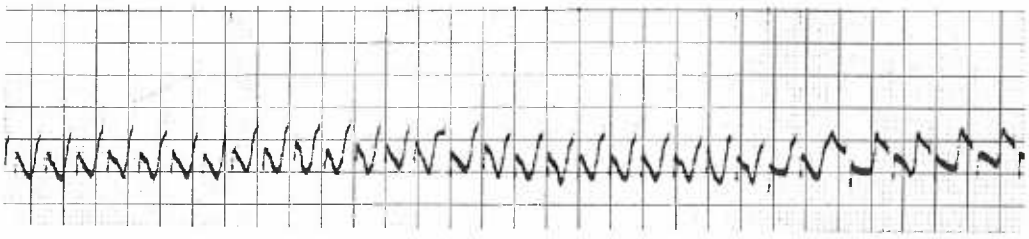
(Continued)

5. Continuation of #4

6. Continuation of #5 but 30 seconds later showing transition towards normal.



Continuation of #4



Continuation of #5 but 30 seconds later showing transition towards normal.

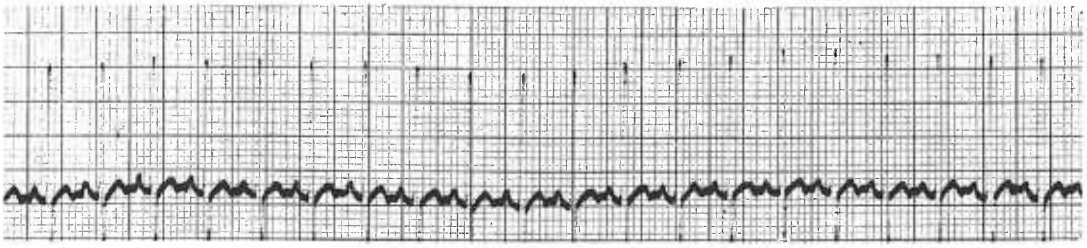
FIGURE IX

EFFECT OF INTRAVENOUS ACETYLCHOLINE

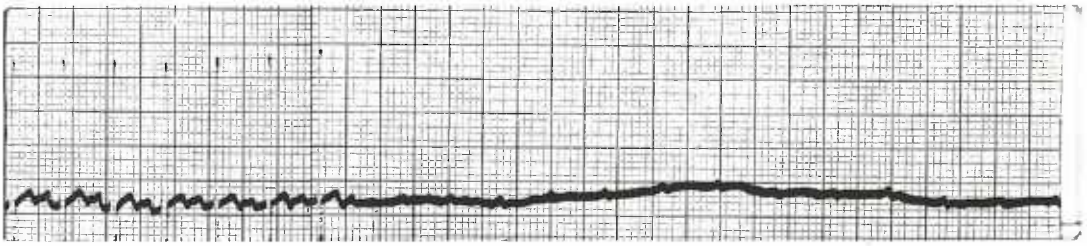
ON THYROID DOG

(Continued)

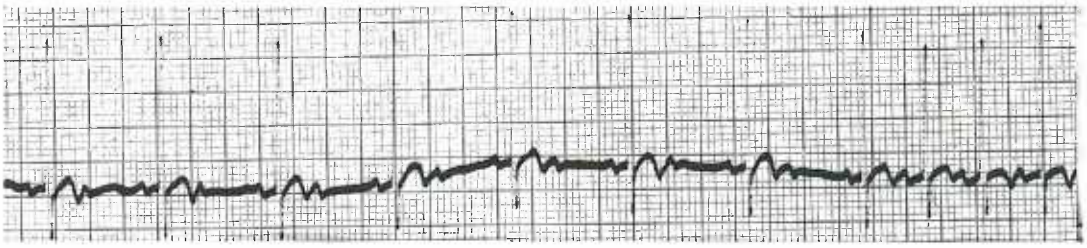
7. Control: 27 days "on thyroid"
8. Effect of 1.0 mg. per kg., 27 days "on thyroid"
9. Continuation of #8 but 15 seconds later (No fibrillation! - Transition towards normal)



Control: 27 days "on thyroid"



Effect of 1.0 mg. per kg., 27 days "on thyroid"



Continuation of #8 but 15 seconds later (No fibrillation! - Transition towards normal)

This group reported an increased tendency to auricular fibrillation with acetylcholine injection in only one animal of 15 tested. They did, however, report fibrillation in three animals during the control period which corresponds to our findings. One of these animals fibrillated also after thyroxine administration with acetylcholine.

An analysis of the failure of this group is relatively simple in view of these experimental results: (1) Their thyroid extract feeding continued for about 28 days, but the animals were tested for fibrillation on the tenth and seventeenth day and sometimes later. In view of the results herein reported this is the period in which the animals are no longer sensitive or decreasing in sensitivity to injected acetylcholine. (2) The doses of acetylcholine administered were in most cases far less than the doses used in this series. It is felt, with considerable assurance, that if the doses of acetylcholine had been raised, more fibrillation would have ensued regardless of the fact that the animals were tested at the later period of decreasing sensitivity to acetylcholine. The findings herein reported deny the contention of Surtshin and Ruckmagel(89) that no increased sensitivity to acetylcholine is present in experimental canine thyrotoxicosis.

H. DESTRUCTION OF THYROID GLAND

An explanation was sought for the observations that thyroid extract administration results in an increased incidence of acetylcholine induced auricular fibrillation for only a limited period of time. There is a possibility that as a result of the administration of thyroid substance the thyroid gland produces some factor or effect that prevents the appearance of true chronic thyrotoxicosis. To evaluate this possibility the thyroid gland was removed completely so that it could not counteract the exogenous thyroid substance. The objective of these experiments was to provide a continuing state of severe thyrotoxicosis by feeding large doses of thyroid. It was considered possible that in severe experimental thyrotoxicosis the acetylcholine might provoke lasting auricular fibrillation instead of the brief paroxysmal form.

In a limited series of dogs surgical removal of the thyroid was found unsatisfactory for our purposes. Immediate postoperative mortality was higher than desired because of the extensive exploration in an attempt to remove all thyroid tissue. (In non-malignant individuals thyroid tissues have been found in sublingual, subclavicular and substernal area.) Moreover, some dogs died in tetany because of trauma or loss of parathyroid tissue.

The action of radioactive iodine in causing destruction of thyroid tissue was studied. Because of the expense of the isotope this experiment was limited to five dogs. Radioactive iodide $_{129}I^{131}$ having

a half life of 8 days and emitting beta rays with an upper energy limit of 690,000 electron volt, (the majority of the beta rays have energies of 250,000 e.v.); weak gamma rays also are released(90). Each dog received an intravenous dose of 1.0 millicurie per kg. $Na_{129}I^{131}$. The animals did not show symptoms of rapidly progressive hypothyroidism and myxedema due, it is believed, to the meat diet and kibbled biscuit diet which contained significant amounts of thyroid hormones. Up to 28 weeks, however, some clinical signs of myxedema were found. At that time in two animals injection of a tracer dose (1.0 microcurie per kg.) of $Na_{129}I^{131}$ indicated less than 3% uptake of the isotope in the thyroid area. This rate of uptake was evaluated as being due to incomplete shielding of the Geiger-Muller counter tube and reflects general body iodide: Thus complete destruction of the thyroid gland was believed obtained. This was confirmed in two animals who died of intercurrent infection or anesthesia. Histologic examination revealed no functioning thyroid tissue. After testing for 2:1 block and fibrillation, as described elsewhere, the animals were placed on a diet supplemented with 3.0 gm. thyroid extract powder (U.S.P. XIV).

Change in sensitivity to injected acetylcholine in producing auricular fibrillation was evaluated frequently and in the usual manner. Heart block (2:1) and fibrillation thresholds were obtained where possible, in the control, myxedematous, and thyrotoxic periods.

Case histories of the five dogs in which radio-iodide was injected are presented in the appendix.

I. DISCUSSION OF EXPERIMENTAL RESULTS

Experimental methods for the laboratory study of auricular arrhythmias were very carefully selected after a thorough analysis of work done by the instigators of the methods or by later workers who applied these methods or modifications on extended experimental trial. Injection or infusion of epinephrine by itself appears to produce auricular fibrillation in a high percentage of patients having a tendency for paroxysmal auricular tachycardia. Such experimental procedures have not produced similar arrhythmias in the experimental animal. But, with concomittant vagal stimulation or if the experimental animal is hyperthyroid, auricular fibrillation or the other less severe arrhythmias may be provoked.

Vagal stimulation by electrical means was devised as a refinement of accidental electrocution, which is observed to provoke marked cardiac arrhythmia. This stimulation is usually consistent in its effect, but the arrhythmia produced is transitory and for this reason the method has not been utilised to any great extent. The intravenous injection of various of the parasympathetic drugs such as acetylcholine, acetyl-beta-methylcholine and physostigmine has been found to be much simpler of execution that the complex surgery of isolation of the vagus and implantation of stimulatory electrodes. Moreover, vagal stimulation, to be effective, requires current densities far greater than the physiological range. Injection techniques have been utilised on one animal as many as twenty times utilising "cut down" procedures in many cases to insure intravenous injection with a "permanently"

implaced indwelling hypodermic needle or polyethylene intravenous catheter. Injections can be made at will over a period of many hours without fear of severe trauma at the site nor damage distant due to emboli. The procedure of intravenous injection of parasympathetic drugs is admirably simple, but with the normal animal only a small percentage will "fibrillate". An increase in the percentage of fibrillators occurs with various experimental procedures. The production of anemia by bleeding, administration of hemolytic agents and hemoglobin binding agents has been found to be a partial answer to the problem but not a satisfactory one. Anoxia which may be concomittant with anemia or may be induced by entirely different proceduzes has been found by some to be an improvement but these more complex methods are entirely too cumbersome. The employment of surgical techniques wherein the heart is exposed is a method which has proved to be satisfactory in some respects although the presently available methods leave much to be desired. Surgical proceedings are time consuming, require in addition highly complex equipment, are expensive and a preparation may only be used once for an extremely limited number of drug trials.

The utilization of the observation of intimate correlation between thyrotoxicosis and heart disease has provided what appears to be the closest approach to clinical auricular fibrillation yet devised. The method seems to provide experimental animals at a cost which is not prohibitive in that the animals may be used over and over again for a period of several weeks. The animals were usually anesthetized in

the experiments herein reported, but it is probable that with trained animals this might not be necessary. It is highly possible that an animal once thyrotoxic and sensitive to parasympathetic drugs might be used one whole working day with varying doses of drug being tested, be allowed to recover 3 to 4 days and another drug be tested. In our hands the method was used as developmental procedure and in several cases mortality occurred through oversight. This could probably have been avoided by proper attention in recovery rooms and by use of analeptics in heavily pentobarbitalised dogs. Marked success with several drugs and experimental correlation with quinidine, a known antifibrillatory drug, encouraged us to try a cautious clinical trial of these drugs in selected patients with auricular fibrillation.

J. SUMMARY OF PART TWO

1. All of the known feasible methods of production of auricular arrhythmias are reviewed, repeated and critically analyzed for their utilization.

2. Some experimental methods have been altered in view of modified concepts of physiology or pharmacological action of new drugs.

3. Auricular arrhythmias of all types from simple tachycardia to "permanent" auricular fibrillation have been produced in several different species of animals by a variety of techniques.

4. Quinidine has been found to be nearly routinely effective in the arrest of all types of experimental arrhythmia whether they be artificially induced or occur "spontaneously" after experimental stimulation.

5. A new method has been established for the production of experimental thyrotoxicosis with concomitant hypervagotonia and cardiac sensitivity to injected parasympathetic drugs. Auricular arrhythmias have been induced in these experimental animals in a high and workable percentage of animals.

6. Several new drugs have been studied in the experimental laboratory in an attempt to find a successful replacement for quinidine.

IV. CLINICAL CORRELATION*

On the basis of well established pharmacological action and successful laboratory experimentation to evaluate a series of compounds as antifibrillatory drugs, two were selected for a limited trial on patients with auricular fibrillation. These drugs were Benadryl and Banthine. The patients were unselected but were consecutive cases of auricular fibrillation in which quinidine would ordinarily be administered. In the case of therapeutic failure with one of the new drugs, quinidine was administered three or four days later. No patients with uncontrolled thyrotoxicosis were utilized in this series, and all patients were adequately digitalized. All patients were hospitalized.

Benadryl was administered to 15 patients. Nine patients converted to a normal sinus rhythm. Of the six therapeutic failures, one converted with a combination of Benadryl plus quinidine. Five others were given quinidine alone; of this group three converted. Two patients were not benefited by either drug.

Benadryl hydrochloride solution (10 mg. per ml.) was administered by the intravenous route. In most instances the contents of one vial (10 ml.) was diluted with 20 cc. of pyrogen-free normal sterile saline and injected over a ten minute period of time. A similar amount had also been added to 250 cc. of 5% glucose and administered by drip over a thirty minute period of time. Five patients converted to normal

*Information provided through the courtesy of Dr. H. Lenox H. Dick.

sinus rhythm after a single 100 mg. dose of Benadryl. The others responded only to 200-300 mg. dose. One patient developed sufficient undesirable side actions to necessitate cessation of Benadryl administration after 100 mg. had been given. The maximum dose administered to any patient during a course of therapy was 400 mg. of Benadryl. Those patients, who continued in auricular fibrillation, were given 300-400 mg. of Benadryl which was considered a maximum tolerable dose. Following conversion of the arrhythmia, Benadryl was administered by mouth successfully as a maintenance dose for several months in two patients.

Several actions of Benadryl which appeared during its trial in auricular fibrillation may be contrasted with those of quinidine. There was no severe hypotension produced by Benadryl such as that seen when quinidine gluconate is given intravenously. Rather, Benadryl, in the doses that were given, caused an increase in systolic and diastolic pressures of 20-30 mm. Hg. This effect lasted for 1-2 hours. Like quinidine, Benadryl causes an increase in ventricular rate, presumably by vagolytic action. The pulse rate during fibrillation speeded from 10-40 beats/min. and this increase appeared whether or not the patient had been adequately digitalized. The ventricular rates, after Benadryl caused conversion to normal sinus rhythm, were within normal values. Unlike quinidine, Benadryl caused no increase in the QRS interval or ST depression - a clear indication for a lack of any deleterious slowing of myocardial conduction. Benadryl, however, did decrease the QT interval indicating a slightly more rapid

ventricular repolarization. The mean QT interval, before Benadryl, was 0.33 sec. (range 0.28-0.42 sec.), and the QT interval during the peak of the Benadryl effect was 0.31 sec. (range 0.24-0.38 sec.).

Benadryl, injected intravenously, caused drowsiness and other unusual nervous system reactions; blurring of vision, supra-orbital headache and dryness of the mouth were also observed. These symptoms alone are not considered a mandatory indication for stopping Benadryl medication. Muscular irritability, manifested as tremors or twitching, respiratory changes (rapid, shallow breathing) may appear after 200-400 mg. of Benadryl have been injected. These signs are indications of potentially dangerous overdosage. Animal experiments indicate, if Benadryl administration is continued, that muscular tremors, fibrillating, fasciculation and finally convulsions with respiratory arrest will ensue. The convulsions have been reported to respond to phenobarbital and in experimental animals are prevented by pentobarbital anesthesia but respiratory stimulants are of no value in the experimental animal and artificial respiration is necessary in event of this type of accident.

Benadryl administered to anesthetized dogs by intravenous drip until death occurred did not reveal any significant warning signs that were observable in the electrocardiogram. When patients were placed on a maintenance dose of Benadryl, the drowsiness effect produced by the drug usually wore off in a week or two. It is to be noted that central nervous system changes precede any other side effect by this drug.

Benadryl has proven to be an effective agent in restoring normal sinus rhythm in patients with auricular fibrillation. It does not equal the efficacy of quinidine as it was used during this investigation. Benadryl, however, does have certain apparent advantages. It does not slow myocardial conduction, it does not lower blood pressure and may be used with somewhat greater assurance in the elderly patient whose fibrillation accompanies major cardiovascular pathology. In the aged patient with cerebral arteriosclerosis, Benadryl does appear to cause temporary psychotic episodes which would limit its use.

Banthine bromide was given intravenously to 11 patients who had sustained atrial fibrillation. The duration of the fibrillation when known was 1 day to 5 years. Banthine administered intravenously was not able to convert the fibrillation to normal sinus rhythm in any of these patients. All patients had been digitalised. Eleven of these patients were later given quinidine therapy and 5 converted to normal sinus rhythm.

Banthine bromide (100-400 mg.) was diluted with pyrogen-free normal sterile saline and injected slowly intravenously. There were no significant changes in blood pressure or characteristics of the electrocardiogram. In one patient the drug produced an abolition of ventricular premature systoles. The drug caused sinus tachycardia (average increase of 60 beats/min.) that is expected of a vagolytic agent. This dose of Banthine was judged adequate by virtue of its effect of increasing the pulse rate and also because carotid sinus

massage failed to cause any change in heart rate, indicating an effective paralysis of the vagus by Banthine. In 5 patients the dose of Banthine was increased to 400 mg. but even this very high dose failed to alter fibrillation.

There was a moderate increase in heart rate presumably due to its vagolytic action. A few patients complained of dryness of the mouth and blurred vision.

Benadryl, though it is not as effective as quinidine for the correction of auricular arrhythmias, offers some advantages for the treatment of selected clinical patients. Benadryl does not slow myocardial conduction, it does not lower blood pressure and within a wide therapeutic dosage range the drug does not appear to be highly toxic to the myocardium. Sedation produced by the drug is seemingly a real advantage but higher doses appear to cause psychotic episodes. The side effects produced by Benadryl appear to be well characterized as the drug has been used in therapy for other purposes. Attention to the signs and symptoms of the patient will give adequate warning of potential overdosage.

Banthine, though it proved highly effective in the experimental animal, was a failure when used to arrest auricular fibrillation in the clinical patient. An analysis of this failure is somewhat difficult but it probably indicates that the vagus and acetylcholine is not so strongly implicated as was formerly assumed(72). Many other anti-vagal drugs such as atropine have been tried(76). It has been found in regard to atropine that comparatively massive doses are

necessary in the dog and that such doses would produce extremely undesirable side effects in the human. It is possible that some atropine-like drug with a relatively specific action on the heart may be of some use, but in view of the lack of effect of Banthine as mentioned above, this is for the present unlikely.

1. After extensive experimental and literature research, two drugs which appeared promising for the arrest of clinical auricular arrhythmias were selected for trial on hospitalized patients.

2. The two drugs, Benadryl and Banthine, were administered intravenously with careful observation during and immediately after administration.

3. The drugs were administered slowly and in amounts which either arrested the arrhythmia or such side effects occurred which precluded further administration.

4. Benadryl converted auricular fibrillation in nine of fifteen patients with dose of 200 to 300 mg. although many (5) converted with 100 mg.

5. The maximum dose of Benadryl administered was 400 mg. This was considered to be the maximum tolerable dose.

6. Banthine proved to be a failure for the correction of clinical auricular fibrillation in 5 patients to whom the drug was administered.

7. Benadryl is felt to be a useful addition to the armentarium of the physician for therapy of auricular arrhythmias.

8. Banthine itself does not appear useful but some chemical modification of this drug or a pharmacodynamically similar drug offers a continuing hope for more satisfactory treatment of auricular arrhythmias.

PREFACE TO BIBLIOGRAPHY

The references on auricular arrhythmias number in the thousands. For this reason, reviews, original observations and key articles have been utilized whenever it was practical to do so.

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APPENDIX

CASE HISTORIES

The progress of five animals used was quite varied after the injection of the radio-iodide. Dog No. 1 was a 4 month old female mongrel terrier. The drug, $_{129}I^{131}$ 1.0 millicurie/kg., was administered I.V. during pentobarbital anesthesia. A mild diarrhea occurred three or four days after the procedure, but the animal was eating well. The diarrhea condition was ascribed to rich diet (½ lb. meat per day) or the rough kibbled biscuits which the dog "wolfed down" with little water. On the eleventh post-injection day, the animal was found lying prostrate in its cage unconscious or nearly so with evidence of marked diarrhea. The animal was "glassy eyed" and "shivering" although the room temperature was mild (June 19, 1953). The muscles were twitching spasmodically and respiration was irregular. Fifty milliliters of milk were warmed and administered by stomach tube. The animal died the next day. The symptoms of this animal before death indicated tetany due to parathyroid insult at the time of radio-iodide injection. A similar condition was observed in a dog in which the thyroid was removed surgically. The surgically operated animal, however, survived and at the time of crisis it was felt that this dog would also - for this reason blood studies were not attempted as it was felt that they would add further insult to the already critical state. The eleven day time lag was considered remarkable as the parathyroid crisis delay in human cases and the surgically treated animals have been observed

to be about 36 hours for the onset of difficulty with the crisis past in the third or fourth postoperative day.

The second dog to receive radio-iodide was an old (13 years) castrate dachshund weighing 10 kg. This animal had large tumor masses in the upper sternal region and also lower on the thorax. The animal was chosen because it was felt an older animal might be more likely to demonstrate cardiac arrhythmias as a result of the experiment. The animal became weaker and weaker as the experiment progressed and finally could neither get up nor eat. The animal was in obvious pain from the infirmaties of age and was sacrificed with a high dose of pentobarbital. A histological examination of the thyroid gland post-mortem indicated the animal to be athyroid, but this fact was not felt to have influenced the animal's debilitation.

The third dog was a (2-3 years) male black cocker-type mongrel weighing, at the time of radio-iodide injection, 14 kilograms. The animal was in good physical condition. About 6 months following radio-iodide therapy, this animal was considered to be myxedematous. The trunk became barrel shaped and the tissue covering the ribs was spongy to digital pressure, though pitting was not observed. The animal was dull in appearance and action and although the weight had increased, the legs had become "spindly". The hair had become sparse and a scaly dandruff was observed to be generalized. At the 20th week following thyroid destruction, a test procedure was undertaken to ascertain the sensitivity of the animal to intravenously injected acetylcholine. The animal was observed to be sensitive to low doses

which produced prolonged respiratory block along with extended atrio-ventricular impulse interruption for prolonged periods. A dosage of 0.16 mg. per kg. produced respiratory block and embarrassment for a four minute period. It was felt that further increase in dosage would be dangerous. The animal, upon recuperation, was fed 1 gm. of thyroid extract powder with its food every day for 15 days. On the sixteenth day, the animal was showing marked change of its myxedematous state towards normal. At this time an experiment was undertaken to determine the cardiac changes produced by this dosage of thyroid extract in the athyroid dog. The animal was more tolerant to intravenously injected acetylcholine than it had been in the myxedematous state. This was evident in both the respiratory and cardiac systems. A dose of 1.0 mg. per kg. produced intermittent atrioventricular block for 27 seconds which was not considered remarkable or dangerous. When attention was redirected from the electrocardiograph to the animal, it was observed that respiration had ceased entirely. Artificial respiration and administration of analeptic drugs failed to resuscitate the animal. The death was attributed to myocardial anoxia due to the increased oxygen demand by the extra cardiac tissues as a result of the thyroid extract feeding and that the cardio-respiratory system had not recovered sufficiently from the compound insult of bronchiolar as well as general myxedema followed by the over-stimulation of excess dosage of thyroid hormone.

Dog number four was a tan toy collie 9 kg. female. It was given radio-iodide July 27, 1953, and then was observed daily for any changes

attributable to the radio-iodide or the operation (pentobarbital anesthesia and intraperitoneal iodide injection). After about 28 weeks no myxedematous condition had appeared. This seems remarkable as human patients show this sign usually within three months. Other investigators have noted this apparent species variation and have attributed the resistance to low thyroid hormone requirement of canines and necessary amounts for maintenance being present in the usually high animal protein food intake. This dog was placed upon a kibbled herbivorous animal diet eight weeks postoperatively with the hope that a diet containing minimal animal protein might hasten the appearance of myxedema. Such was not the case. On the 28th week, radio-iodide uptake studies were performed on this animal according to the technique mentioned above. Uptake was calculated as 3% compared to 12% in a normal dog when both tests were run simultaneously. This was felt to indicate that the animal was functionally athyroid. Utilizing this result as criteria that the animal was athyroid, the animal was tested for sensitivity to intravenously intravenously injected acetylcholine two times 8 days apart. Both times the animal was found to be more sensitive than the usual animal. Thyroid extract feeding was nevertheless instituted immediately and any changes indicating hypervagotonia or increased cardiac susceptibility to injected acetylcholine were observed by the aid of an electrocardiograph taken during operative procedures. The fibrillatory dose with

thyroid extract feeding decreased from 0.07 mg. per kg. average of two experiments to a low of 0.02 mg. per kg. after 4 weeks feeding of thyroid extract.

Dog number five was a black 14 kg. mongrel shepard female and was administered radio-iodide July 27, 1953. At 28 weeks, despite a diet consisting of herbivorous animal kibble the last 2 months, no myxedema appeared. A tracer dose of radio-iodide was injected during the 28th week and the uptake study indicated 2% uptake compared with 12% with a control normal run simultaneously. It was felt that 2% represented inadequate shielding of the Geiger-Muller tube and that the animal was athyroid. Three gm. per day thyroid extract was incorporated in the daily diet immediately. Before thyroid feeding this animal would not fibrillate with an intravenous dose of acetylcholine of 1.0 mg. per kg. With thyroid feeding sensitivity increased so that fibrillation on two occasions after 31 days on this diet was produced with 0.02 mg. per kg.