THE CARDIAC TOXICITY OF QUINIDINE

by

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A THESIS

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INTRODUCTION

Uncertainties regarding the toxicity of quinidine undoubtedly contributes to its limited use in medicine. If the fatal reactions encountered during quinidine therapy could be prevented, the drug would be more widely used in the treatment of cardiac arrhythmias. It should be stressed from the outset that disturbances of rate and/or rhythm constitute the only indication for quinidine in cardiac disturbances (14). No satisfactory substitute for quinidine has been discovered, for procaine amide, although safer, cannot restore chronic atrial fibrillation to sinus rhythm and is less certain in its action on other cardiac arrhythmias (6) (16). No new drug to replace quinidine can be expected in the immediate future for no satisfactory technique for producing atrial fibrillation in animals has yet been developed which has clinical validity for the screening of potentially useful antifibrillatory drugs. Thus it was proposed to investigate, in animals, the factors which contributed to the instances of "sudden death" seen in patients receiving quinidine therapy. With a safer quinidine therapy it could be anticipated that a return to a more physiologic sinus rhythm would prevent cardiac cripples and return patients to a happier, more productive life.

Let us consider the need for antiarrhythmic and antifibrillatory therapy. Various authors have reported that between 60 and 90 per cent of persons with congestive heart failure will manifest atrial fibrillation sometime during the course of their disease (1) (20) (31). Congestive heart failure, even now a common disease, can be

expected to increase with the greater longevity of our population. Atrial fibrillation is encountered in nearly 50 per cent of patients who give a history of rheumatic mitral insufficiency (20). Still another source of cardiac arrhythmias is the patients who are candidates for cardiac surgery. Surgical correction of mitral stenosis by commissurotomy commonly leads to the appearance of atrial fibrillation, and when it occurs, prognosis is less optimistic (36). With the advent of extracorporeal circulation, cardiac surgery has become near commonplace. Heart lesions which could not be treated by any means a few years ago are being surgically repaired today with great regularity. We may, however, anticipate the appearance of atrial fibrillation and other arrhythmias following surgical intervention for the correction of these lesions (8) (12).

Until recently, ventricular tachycardia and Adams-Stokes block were the only arrhythmias considered to have a grave prognosis requiring vigorous therapy. (Fatal ventricular fibrillation or prolonged cardiac arrest are, of course, emergencies.) However, recently Prinzmetal, Corday and others have shown that any non-sinus conducted beat decreases the efficiency of the heart (28). For example, supposedly benign atrial fibrillation may result in a 40 per cent decrease in cardiac output; a corresponding reduction in coronary artery flow; and a significant mitral and tricuspid insufficiency or regurgitation (25) (36). Until we understand all of the factors precipitating arrhythmias, we must resort to attempts to restore normal sinus rhythm. The only uniformly effective drug is quinidine.

History:

Quinidine, the dextro-rotatory isomer of quinine, is one of the natural occurring cinchona alkaloids. It was described first by Van Heyninger in 1848 (34), later prepared and named by Pasteur in 1853 (34). When quinine and other cinchona derivatives were used in the treatment of malaria, it was noted that certain malarial patients with atrial fibrillation would lose their arrhythmia while undergoing therapy. The French physician, Jean-Baptiste de Senac, successfully employed quinine in a condition he termed "rebellious palpitation" in 1749 and is perhaps responsible for the earliest recorded reference related to the treatment of atrial fibrillation with cinchona (34). The diagnosis of atrial fibrillation as an irregular irregularity was not known at this time and indeed, was not really established until the development of the electrocardiograph.

Between 1749 and 1914, the year Wenckebach reported his work, an evaluation of quinine therapy in cardiac arrhythmias (34), little or no mention is made of the cinchona alkaloids. Wenckebach observed that if atrial fibrillation was of long standing (that is, "chronic"), his success was less satisfactory than if the arrhythmia was of recent onset (that is, "acute"). Although he was unable to abolish atrial fibrillation in all cases, he made the important observation that in patients which failed to convert to sinus rhythm, quinidine, however, did cause a marked lowering of the often very rapid ventricular rate. Frey, in 1918, as a result of Wenckebach's reports, compared the effectiveness of quinine, cinchonine and quinidine in the treatment of atrial fibrillation (34). His conclusion was that quinidine was the most effective of

these cinchona alkaloids. His work has subsequently been confirmed and the use of quinidine has been extended to embrace other cardiac disorders involving rate and rhythm (16) (34).

Quinidine is a potentially dangerous drug and the possibility of deaths from quinidine is well known. The toxicity of quinidine can be described as belonging to three types:

1. Cinchonism:

This condition affects various body systems and this syndrome can result from the ingestion of salicylates and cinchophen as well as from the cinchona alkaloids. Cinchonism in its mildest form may show only minimal visual disturbance, mild headache, nausea and ringing in the ears. If medication is not stopped or if the patient has ingested a large single dose, the symptoms may be more severe and widespread, i.e., hearing and vision are affected early; there is decreased visual acuity, especially diminished dark adaptation; color perception is also disturbed. The patient is also likely to note constricted visual fields and scotomata. There exists an uncertainty as to whether cinchona exerts its deleterious effect on hearing and vision primarily by involvement of ganglion cells and nerve fibers, or secondarily, through vascular changes in the retina or organ of Corti. Both vascular spasm and nerve degeneration have been observed.

Gastrointestinal symptoms are also frequently seen in cinchonism. Nausea and vomiting as well as abdominal pain may be attributed to the local irritant effect of quinidine. Nausea and vomiting, however, may also be explained on the basis of stimulation of emetic centers of the central nervous system since there is also observed non-

specific central nervous system stimulation from quinidine. With large doses of any of the cinchona alkaloids the signs and symptoms observed include: headache, fever, vomiting, apprehension, excitement, confusion, delirium and syncope.

Respiration is first stimulated, then later depressed; and, indeed, in high dosages the patient may succumb to respiratory arrest. For the most part, the above signs and symptoms are completely reversable when the drug is discontinued. In rare instances some residual damage to optic and/or auditory function may be observed.

2. Quinidine sensitivity:

The allergic manifestations to quinidine include such things as thrombocytopenic purpura (first reported by Phillip Nudelman of Portland, Oregon (26)), early signs and symptoms of which are epistaxis and intra-oral bleeding. Multiple hemorrhagic areas of the skin are visible and there is a decrease in the number of circulating platlets. Asthma may also be seen in hypersensitive individuals following the administration of cinchona. Urticarial rashes occur in susceptible individuals and occasionally edema and collapse are encountered. Photophobia is also manifested in many cases which may aggravate a skin eruption. For the most part, these reactions are quite rare and easily reversable by discontinuing the drug.

3. Quinidine's cardiovascular toxicity:

The cardiovascular toxicity of quinidine can be divided into two main classes: a) shock-like collapse, and b) sudden death. These two classes of quinidine toxicity are the subject of investigation in this paper. In a review article in 1950, Dr. Sokolow estimates the instance of quinidine fatalities as about 1:300 (33).

METHODS AND MATERIALS

Suspicion as to the cause of quinidine's sudden death was directed toward the coexistence of cardiac complications occurring with the cardiac arrhythmia. This appeared to be supported by animal studies where lethal doses of quinidine resulted in "depression" of cardiac function with a shock-like collapse. This phenomenon has been studied by Bellet (1) (2) and may be related to ionic changes, for Wasserman (2) has shown that therapy with sodium lactate is an effective antidote. Large doses of quinidine or the presence of acidosis may contribute to the shock syndrome but this still does not account for the sudden death encountered with usual doses of the drug. Contributing possibly to the quinidine sudden death are the following cardiac complications which accompany cardiac arrhythmias: congestive heart failure, myocardial infarcts and/or coronary insufficiency, valvular defects and disturbances of myocardial conduction (4) (17) (23). The last, disturbances of conduction, was chosen as an initial approach to the quinidine sudden death problem. Various methods of producing conduction disturbance experimentally in animals thus follows. Support for this plan can be found in various extracts of the literature.

DiPalma in 1950 stated that quinidine-induced arrhythmias are caused by a slowing of the conduction of the heart with that heart having an already existing intra-ventricular conduction defect (9). DiPalma is merely repeating earlier clinical impressions for the warning has long existed that quinidine should not be given if it has already caused a 50 per cent prolongation of the ventricular conduction, i.e.

a widening of the QRS wave in the EKG. Dr. Read, in citing a case of fatal ventricular fibrillation following procaine amide therapy, sounded the warning that this drug must also be used with caution in patients with a bundle branch block (29).

As a basis for comparison, the toxicity of quinidine on the normal dog heart is presented. Adult mongrel dogs, anesthetized with 35 mg./kg. of sodium pentobarbital administered intravenously, were used. The drug, as quinidine gluconate, was administered by a slow intravenous drip, the rate of administration being 1 mg./kg./min. In this fashion, a succession of increasing doses was available. Continuous electrocardiograms of several leads were recorded simultaneously using a four channel Sanborn Poly-Viso cardiette (Illustration 1). The 502 Tektronix oscilloscope (Illustration 2) was employed in a like manner and afforded an easy method for continuous monitoring of the experimental preparation. Lead II was recorded in all cases and precordial leads were obtained from both right and left chest as desired. In the text that follows these V leads are identified by the usual clinical designations of V_3R, V_1, or V_6, etc. It must be remembered that since the dog's chest differs considerably from that of man, these identifications are not anatomical but rather represent electrocardiographic pictures typical of those obtained on patients for the appropriate designations.

Figure 1 is a graphic representation of how the empirical dose of 1 mg./kg./min. was selected. It can be seen that at high dosages, i.e. 20 mg./kg./min. the lethal dose is approximately 200 mg. At dosages between 2.5 mg./kg./min. and 0.5 mg./kg./min. the lethal dose remained fairly constant at approximately 115 mg. Below 0.5 mg./kg./min.

Illustration 1 - A Four Channel Sanborn Poly-Viso Cardiette of the type used for simultaneous recording of several leads. The lower channel in some cases was replaced with an amplifier suitable for the recording of arterial and venous pressures.

Illustration 2 - A 502 Tektronix Double Beam Oscilloscope allowed continuous EKG monitoring and afforded a means for viewing and photographing vector resultants of two electrocardiographic leads.

Protocol for
FIGURE 1

This figure demonstrates how the arbitrary rate of administration for quinidine was ascertained. It can be seen that at high rates of administration, found on the left hand portion of the graph, death resulted very quickly. It can also be seen that at very low rates of administration, represented on the right hand portion of the graph, a lethal dose was unnecessarily prolonged or never reached.

LETHAL DOSE (RESPIRATORY ARREST) vs. RATE OF ADMINISTRATION OF QUINIDINE GLUCONATE

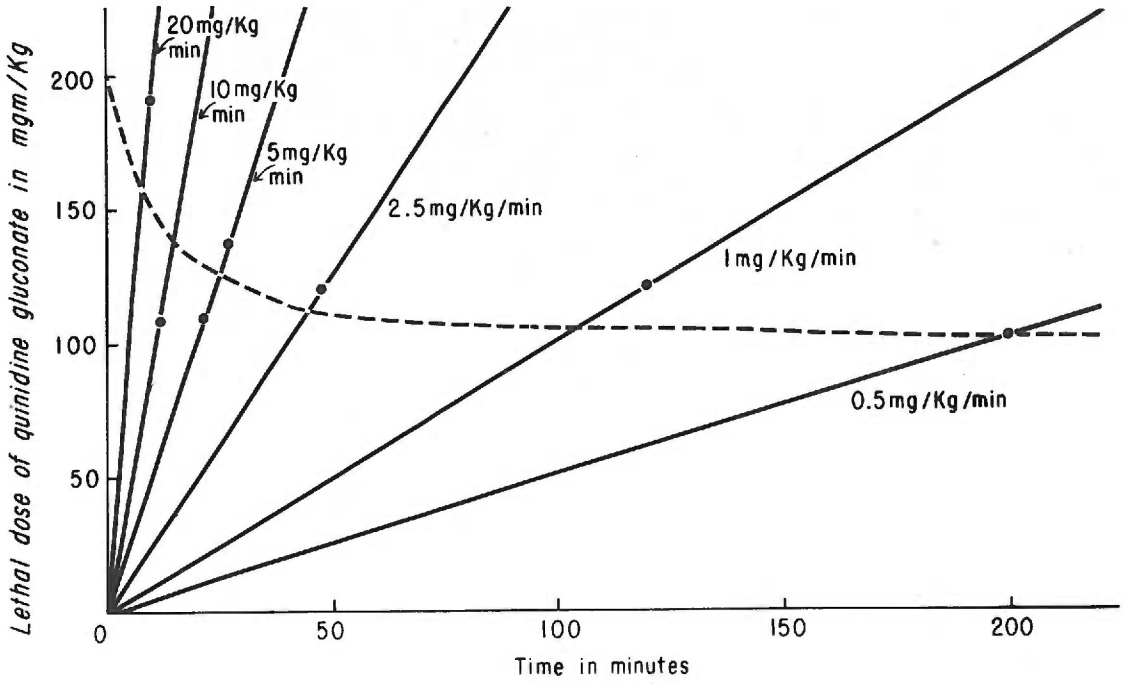


Figure 1

the lethal level was either arrived at very late or, in some cases, not at all. In several instances at the very slow rates of administration, it was suspected that death may have occurred from causes other than the direct effects of quinidine. It was therefore postulated that at the very high rates of administration where a specific level is reached quickly, death is probably due solely to the effects of the drug, but that excess drug has been administered so a true level of toxicity has not been ascertained. At the very slow rates of administration it is possible for the body to metabolize, detoxify and excrete the drug at a rate faster than it is administered, in which case a lethal dose is never reached. 1 mg./kg./min. was therefore selected as a rate which allowed death to occur most likely due to effects of the drug only, and in a reasonable length of time.

Both femoral artery and common iliac vein pressures were available utilizing isometric strain gauge manometers. Although not continuously recorded, sufficient records at appropriate intervals were carried out to establish quinidine's effect on blood pressure. When necessary, respiratory excursions were observed with aid of a strain-gauge tambour connected to a cuffed Magill orotracheal tube. These observations were supplemented by clinical evaluation for such things as: cyanosis, change in response of deep tendon reflexes, general muscle tone, etc.

Electrocardiographic time intervals were measured in the usual clinical manner utilizing magnifying glass and fine calipers. Paper speeds of 50 to 100 mm./sec. facilitated what is believed to be a higher degree of accuracy.

QRS interval broadening was interpreted as directly resulting from quinidine since reports exist showing that the duration of the QRS complex is not altered by a change in heart rate (7) (24). Since both Q-T and P-R intervals widen with a decrease in heart rate, $Q\text{-}T_c$ and $P\text{-}R_c$ intervals were calculated to determine whether changes recorded during the experiments were primary changes from quinidine or were the secondary result of an alteration in heart rate.*

Bazette's (7) formula, $Q\text{-}T_c = \sqrt{\frac{Q\text{-}T}{R\text{-}R}}$, was adopted for the Q-T interval, while Fujiwara's (7) relationship between P-R interval and heart rate was converted algebraically to the following expression:

$$P\text{-}R_c = \frac{1.754\ P\text{-}R}{R\text{-}R^{0.722}}$$

In accordance with accepted electrocardiographic principles, the QRS time interval and the width of the P wave were interpreted as indicating ventricular and atrial depolarization times. Values for ventricular repolarization time were obtained by subtracting the QRS interval from the Q-T interval. The expression "end of S wave to end of T wave (S_eT)" was adopted as a measure of repolarization time. It was assumed, a priori, that this interval would also vary with heart rate. "Correction" was made by dividing the S_eT by a square root function of the R-R interval, as with the $Q\text{-}T_c$.

* The $Q\text{-}T_c$ and $P\text{-}R_c$ intervals represent "corrected" values using an arbitrary heart rate of 60 per minute. Formulae for "corrected" intervals are derived from data using normal human subjects and must be interpreted with caution when applied to the dog. Furthermore, such mathematical relationships were established using heart rates varying from 58 to 130 per minute. In the anesthetized dog the heart rates were between 106 and 216 per minute.

It is not possible to obtain a measure of the true atrial repolarization time during sinus rhythm since the T_a wave is submerged in the QRS complex. Values for P_eR_c (comparable to S_eT_c) were calculated in the hope that they would indicate the direction of quinidine's action on atrial repolarization time. Albers and Urban's (7) equation was transformed mathematically to yield:

$$P_eR_c = P_eR - 0.325\ (1 - R\text{-}R)$$

The time required to inscribe the P wave (atrial depolarization) having been subtracted from the usual P-R interval was used for P_eR. The calculation and interpretation of the various time intervals involved in depolarization vs repolarization will be discussed under Results which is a more appropriate time for this particular factor.

The 502 Tektronix double beam oscilloscope was used on some occasions for continuous monitoring of the electrocardiogram of surgical preparations. Since the output of one amplifier can be imposed on the horizontal plates, a vectorcardiogram was thus available to assist the evaluation of the altered myocardial conduction. Photographs of the vectorcardiographic patterns on the oscilloscope were taken utilizing a Polaroid Land camera and D-3000 film. The standard Wilson electrode placement was chosen arbitrarily for recording the vectorcardiograms (4) (15) (19) (32). Since it did not involve a back electrode, the frontal plane projection vectorcardiogram was found most practical.

Following the establishment of control values of quinidine administration, it was necessary then to obtain appropriate animal preparations with various conduction disturbances. Sir Thomas Lewis in 1915 was apparently the first to attempt the experimental production of

conduction disturbance in the dog heart (22). He cut or clamped the main branches of the bundle of His using a trans-atrial, trans-valvular approach. The procedure, as improved and described in detail by Starzl and Gaertner (35), was employed first in an attempt to produce bilateral bundle branch block. Adult healthy mongrel dogs anesthetized with 30 mg./kg. of sodium pentobarbital administered intravenously were used. The procedure consists of a thoracotomy in the right fourth intercostal space utilizing endotracheal respiratory support, this being necessary once the chest is opened. An occluding ligature is placed about the azygos vein and the pericardium is opened anterior to the phrenic nerve. The atrium was opened longitudinally, utilizing a 2½ to 3 centimeter incision. A temporary occluding ligature of umbilical tape was used on the superior and inferior vena cava which permits a more or less bloodless field. Fine restraining or guy sutures, having been placed at the apicies of the proposed incision, allowed for immobilization of the part while the incision was made. The interior of the atrium could now be viewed under direct vision. A bright head light of the type used by otorhinolaryngologists was found valuable in visualizing the intra-atrial structures through the small incision. A suction tip was necessary to remove residual blood and that draining from the coronary sinus. Under direct vision, an incision is made across the AV junction which lies 5 to 10 mm. anterior to the coronary sinus. The cut was begun at the posterior base of the septal cusp and extended a short distance into the contiguous auricle and ventricle. A successful cut resulted in slow ventricular beat which begins immediately; there is no period of ventricular asystole. Caval-occlusion time was estimated

to be between 50 and 60 seconds. Following the procedure, the caval occlusion is released and blood is allowed to flush the atrium. The atrial incision is then clamped with a Statinsky clamp prior to closure with 4-0 silk suture. The atrium, pericardium, and thoracic wall is then closed by the usual technique.

Pre-surgically, the average heart rates were 150/min. in the thirteen dogs used in this series. Post-surgically, the ventricular rate in the eleven surviving dogs averaged 40/min. The values ranged from 13.6 to 70/min. and those animals with a rate below approximately 35/min. did not survive for extended periods of time. In those animals (two in number) whose idiopathic rate fell below 35, there was noted cardiomegaly with congestive heart failure as a complication of the bundle severance, and the animals succumbed within a few hours. The eleven surviving animals were allowed to recover over a period of weeks and were then given quinidine gluconate by intravenous administration at the rate of 1 mg./kg./min. as described above.

As in the control series, continuous electrocardiographic monitoring was carried out using a paper speed of 50 and 100 mm./sec. Having successfully completed a series of dogs with complete bundle branch block whose response to challenging doses of quinidine could be observed, it was desirable to carry on similar studies in animals with other disturbances of conduction; namely, right and left bundle branch block, each particular condition to exist independent of the other.

Following the blind procedure described by Roberts, Crawford, Abramson, and Cardwell (30), right bundle branch block was attempted. A right thoracotomy was performed using a procedure similar to that

described for complete, bilateral bundle branch block. A cataract knife was inserted through the anterior wall of the right ventricle near its junction with the septum and just below the pulmonary cusps. The knife was aligned parallel to the AV groove and the cutting edge directed against the septum. The knife was then withdrawn so as to transect the bundle on its course toward the anterior papillary muscle.

A similar procedure was followed for left bundle branch block. Beginning with a left sided thoracotomy, the cataract knife was inserted through the outer wall of the left ventricle near its base. The knife was again direct toward the septum. A finger placed in the sulcus between the pulmonary artery and aorta in the outflow tract served as a guide. The tip of the cataract knife was directed to the finger tip, then moved approximately 1 centimeter toward the apex. From this point on the interventricular septum, the knife was then withdrawn, the point being directed against the septum in order that it may transect the left bundle in a manner similar to that described for the production of right bundle branch block. During both surgical procedures the animals were tested to determine whether a successful block had occurred. Using the electrocardiogram a successful procedure was recognized by those criteria that denote right or left bundle branch block respectively. The small stab-like incision in the wall of the ventricle was closed with 4-0 silk suture when necessary to control bleeding; in most cases, however, no such suture was necessary.

This method for the production of right and left bundle branch block was abandoned because it was found to revert in many instances. At times the reversion to normal occurred almost at once; at other times,

within a matter of hours. Repeated sections on the same preparation which had reverted in an attempt to produce a permanent block often led to interventricular septal defects and the resultant death of the animal.

Right and left bundle branch blocks were next produced with the aid of extracorporeal circulation. An arterial and venous pump of the Sigmamotor cam-operated multiple finger type was first used (Illustration 3). Oxygenation was accomplished with a DeWall disposable bag type bubble oxygenator and 100 per cent oxygen administered at approximately 6 liters/min. (Illustration 4). Adult mongrel dogs weighing between 10 and 20 kg. were used. Premedication consisted of morphine, 12 mg. and scopolamine, 0.4 mg. (27). Intravenous sodium thiopental was then employed for anesthesia. Fresh donor blood was obtained from other healthy mongrel dogs utilizing standard heparinized blood collection bottles, the needle being introduced directly into the left ventricle of the donor animals following light anesthesia with pentothal. In no case was the blood collected more than four hours prior to utilization in the surgical preparation. The blood was kept at 39° constant temperature with the aid of a water bath.

The animal's respiration was maintained by use of a standard anesthetic gas machine through a cuffed endotracheal tube. The blood in the bubble oxygenator was maintained at constant temperature by the use of heat lamps controlled by a thermostat introduced directly into the blood column.

A standard right thoracotomy was then effected, and the azygos vein ligated. Occluding tapes were placed around both the inferior and superior vena cavae. Venous catheters were then introduced

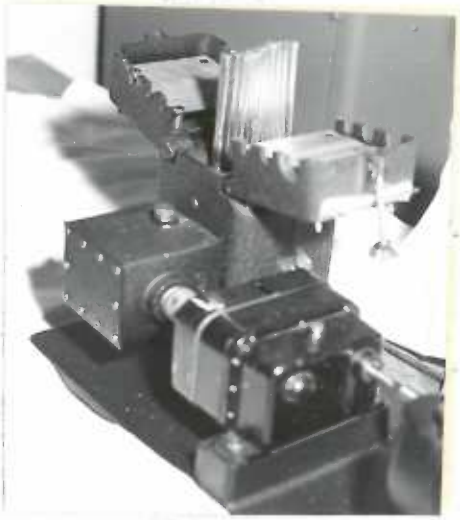


Illustration 3 - Cam-operated Finger Type Sigmamotor Pump of the type employed in the early extracorporeal circulation experiments.

Illustration 4 - Disposable DeWall Plastic Bag Type Buddle Oxygenator employed in conjunction with the above Sigmamotor pump.

through the right atrial wall into the superior vena cava (Illustrations 5 and 6). These caval catheters were held in position by purse string sutures. At this point in the operation the occluding caval tapes are not compressed and blood is allowed to return to the right atrium around the catheters. Selection of catheter size should be such that there is no undue obstruction to venous return prior to complete by-pass.

The right carotid artery is isolated and cannulated and is utilized for the return of oxygenated blood to the preparation during by-pass (Illustrations 5 and 6). Just prior to cannulation, the animal is heparinized utilizing a dose of 1.5 mg./kg. of heparin. Following the procedure and immediately after removal of the cannulae, twice the dose of heparin, or 3 mg./kg. of protamine sulphate is administered over a five to ten minute period after the method of Paneth, Lillehei et al (27).

With the aid of extracorporeal circulation, either a left or right ventriculotomy could be performed. The septum could be viewed under direct vision and a more precise incision made in the inter-ventricular septum when attempting either right or left bundle branch blocks.

Much difficulty was encountered when using the above described procedure. Although most animals survived the operative procedure itself and were in relative good condition immediately post-operatively, they failed to survive long enough to recover so that they could be given quinidine at a later date.* Among the most prevalent difficulties

* Initial experiments were made using 25 cc./kg./min. blood flow through the extracorporeal circuit. Metabolic acidosis to pH 6.7 was observed. As has so well been documented by others (27), the superiority of the high flow technique is established; subsequent flow rates were maintained at 80 to 100 cc./kg./min.

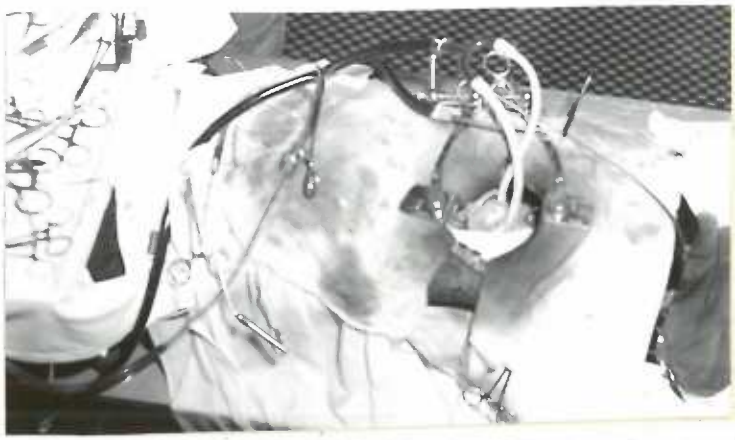


Illustration 5 - Venous return catheters can be seen in place in the right atrium. These catheters are joined at a "Y" junction and are returned via a single tygon tube to the oxygenator. At the extreme right the smaller arterial catheter for the return of oxygenated blood to the appropriate carotid artery.

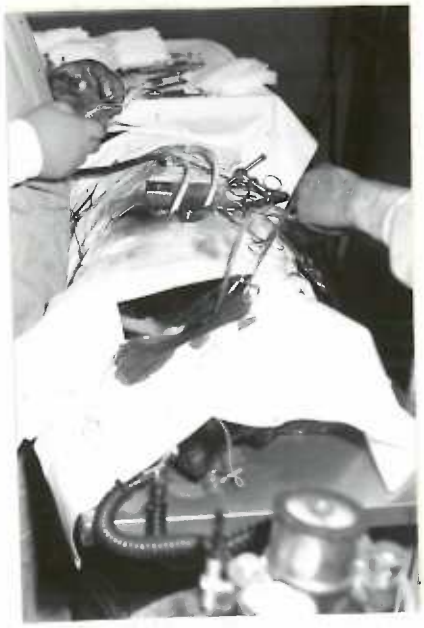


Illustration 6 - A portion of the anesthetic gas machine attached to a cuffed Magill tube is seen in this view. Arterial and venous catheters in place are again visible.

encountered were those concerned with the clotting mechanism and post-operative hemostasis. A number of pathological situations were discovered to exist. It was ascertained by the use of spectrophotometric analysis, using samples of venous blood withdrawn during surgery, that the longer the preparation was carried on extracorporeal by-pass, the greater the hemolysis as evidenced by markedly increasing levels of plasma hemoglobin (3). In all cases at post mortem on these animals, large quantities of unclotted blood were found in the thoracic cavity; indeed, the quantities were more than adequate to account for the marked atalectasis that was evident and easily explained a hypoxic death on the basis of insufficient respiratory exchange.

Selection of the above technique was adopted primarily because of the ease with which aseptic technique could be employed. The DeWall bubble oxygenator being sterile and disposable seemed a wise choice at first. Embolic brain damage due to air, fibrin or antifoam has been described in dogs when these animals have undergone by-pass on a bubble oxygenator of this type (13). Although no brain sections were made on the dogs in this series, there exists a distinct possibility that this could be a contributing factor in the deaths of these animals. For the above listed reasons this technique was abandoned in favor of the following described technique.

Right and left bundle branch blocks were next produced with extracorporeal circulation using the DeBakey rolling pump and Kay-Cross rotating disc oxygenator (Illustrations 7, 8, 9, and 10). Surgical procedure was as described for the Sigmamotor pump. With this preparation, red cell hemolysis was minimal (3), platlet destruction was decreased

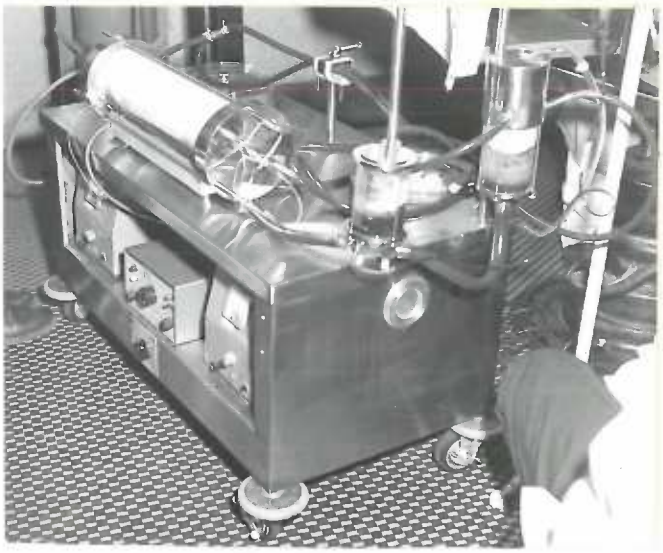


Illustration 7 - The DeBakey Rolling Pump and Kay-Cross Rotating Disc Type Oxygenator.

Illustration 8 - Oxygen Cylinder with flow meter in place for supplying oxygen to the disc oxygenator.

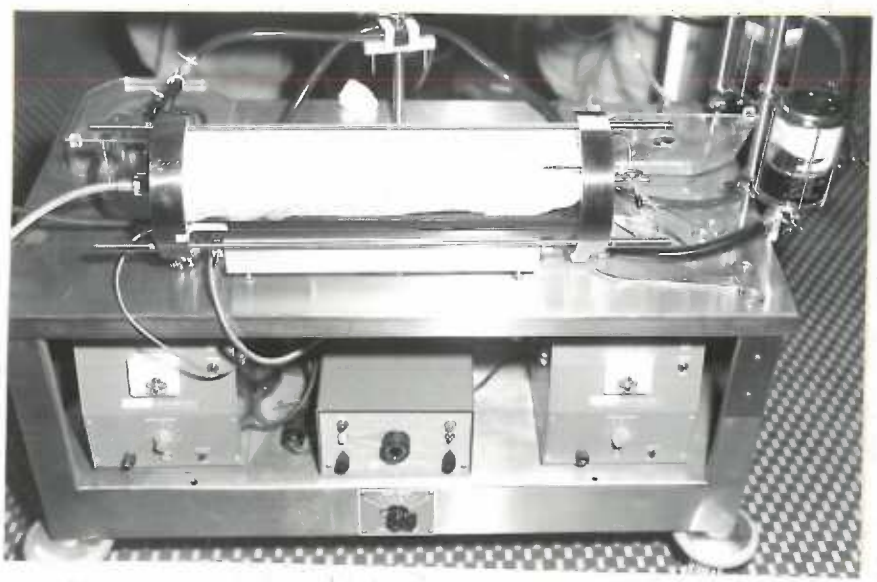


Illustration 9 - DeBakey Rolling Pump and Kay-Cross Rotating Disc Oxygenator. Individual pump speed controls are seen at the bottom left and right and automatic temperature control unit for the oxygenating chamber is seen at the bottom middle.

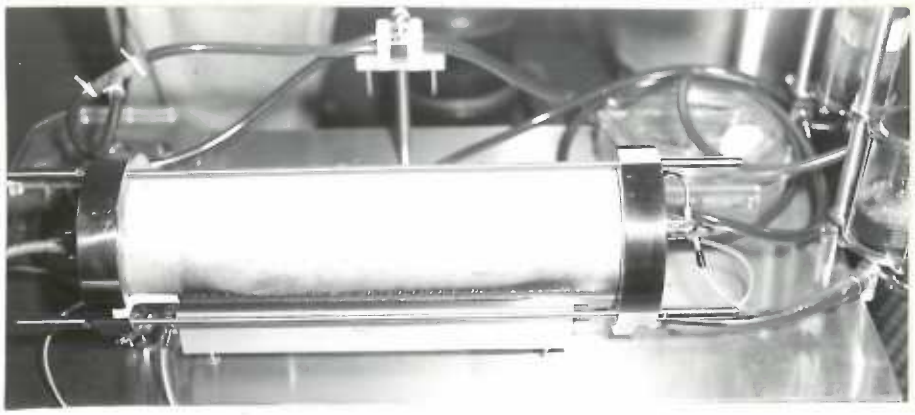


Illustration 10 - The Kay-Cross Rotating Disc Oxygenator resting on the thermostatically controlled heater unit is seen in this view.

and better control of flow rates during perfusion were possible. When cardiac arrest was deemed necessary, either acetyl choline, in an amount of 10 mg./kg. of body weight, was injected into the aorta following aortic clamping (21) or enough solution to produce asystole of a preparation composed of heparinized blood (11). Both right and left bundle branch blocks were produced by an incision into the mid-ventricle and exposure of the septum and a transverse incision could be made under direct vision. As before, a successful bundle branch block was ascertained by interpretation of electrocardiographic changes noted after severance of the bundle, control patterns having been taken just prior to section of the bundle. The animals were closed following by-pass in the usual surgical manner following thoracotomy and allowed to recover.

Having arrived at a value of 1 mg./kg./min. for the rate of administration of quinidine to the various animal preparations, it seemed advisable to correlate the resultant final levels of drug to those seen in man undergoing quinidine therapy. Whenever it has been used clinically, quinidine is rarely given in single doses larger than 1.0 gm. Assuming a weight of 70 kg. this would amount to 14 mg./kg.; accordingly, quinidine given at 10 to 20 mg./kg. to dogs was assumed to represent clinical dosage (5) (19). In dogs 60 mg./kg. could be given without embarrassment to respiration or circulation and was considered to be a maximum safe dose. Quinidine doses greater than 60 mg./kg. caused hypotension and respiratory difficulties; deaths occurred (with 1.0 mg./kg./min.) for quinidine at 90 to 120 mg./kg.

RESULTS

Ten healthy adult mongrel dogs of mixed sex and weighing between 10 to 20 kg. comprised the control series. The animals behaved independent of sex when challenged with varying doses of the drug being tested.

In the control series of animals that were administered quinidine gluconate at a rate of 1 mg./kg./min., the following changes were noted: with increasing doses of quinidine there is broadening of the P wave and QRS wave until at 70 mg./kg./min., these waves become quite distorted. A slowing of heart rate is also observed (Figure 2). Respiration should be supported above 70 mg./kg./min. and at doses greater than 120 mg./kg./min., even in the face of supportive respiration, the dog dies of circulatory failure. Respiratory depression in large doses of quinidine is a common effect of this drug (5) (16) (19) (34). In order that the results of increasing doses of the drug might more clearly be observed, the various changes in wave width is plotted on a "dose effect" curve.

Figure 3 shows that with a progressive increase in the dose of quinidine, which is plotted on the abscissa, there is a corresponding progressive percentage increase on the ordinate of QRS and P wave widths. The width of the P wave is taken as a measure of auricular depolarization; the width of the QRS complex as ventricular depolarization; and the width of the qR intervals from precordial leads V_3R and V_5 as the right and left ventricular activation times. The ordinate represents the percentage change of the various wave widths from control values

Protocol for
FIGURE 2

This Figure represents four electrocardiographic records taken from the control series at various dosage levels. It is seen that as the dose is increased there is broadening of the QRS wave and slowing of the heart rate.

EFFECT OF INCREASING DOSES OF QUINIDINE ON THE APPEARANCE OF THE ELECTROCARDIOGRAM

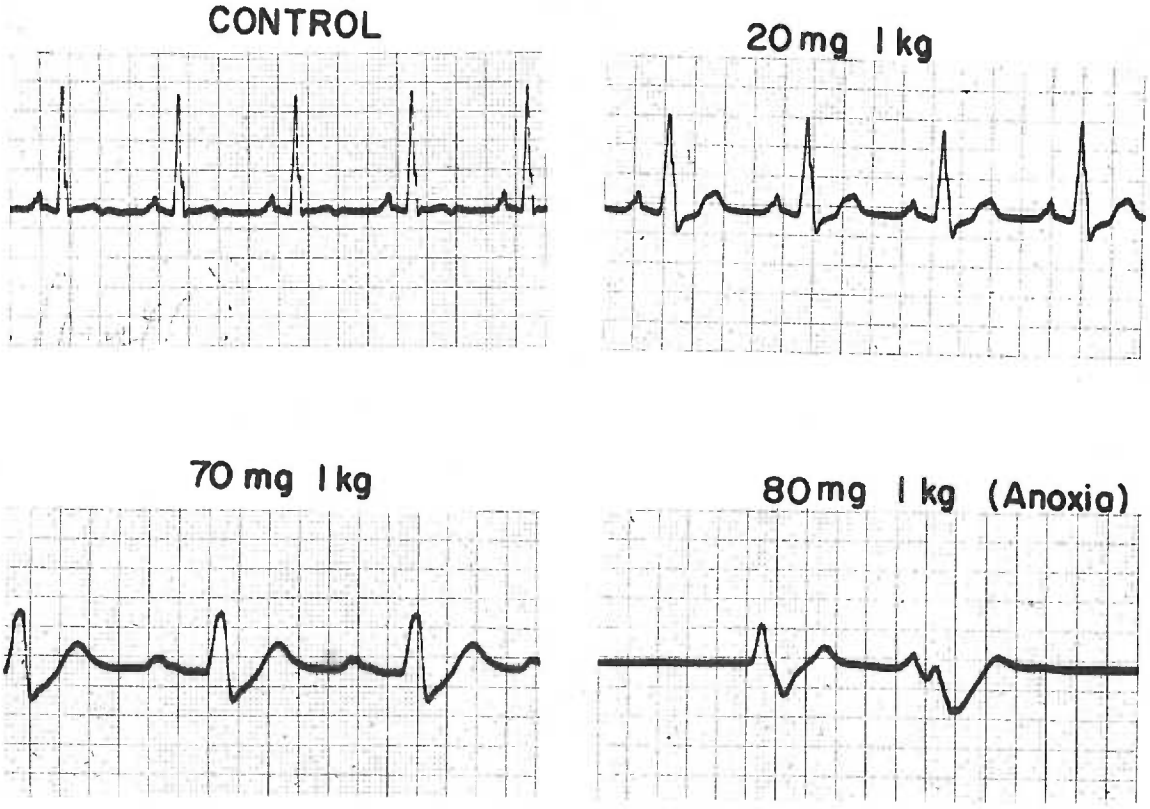


Figure 2

Protocol for
FIGURE 3

Mongrel dogs were anesthetized with pentobarbital sodium 35 mg./kg. Quinidine gluconate was administered via a catheter in a saphenous vein, the tip about 2 centimeters below the vena cava at 1 mg./kg./min.

Intervals and widths of waves were obtained following the criteria of the New York Heart Association. A paper speed of 50 mm./sec., hand lens and fine calipers facilitated the measurements. Each measurement represents the average obtained from three heart beats. As plotted each point represents the mean of 10 experiments. QRS and P wave widths were measured from lead II. In an attempt to determine whether the effect of quinidine was equal on right and left heart the initial phase of ventricular depolarization, Q to peak of R designated as qR, was measured on right and left chest (V_3R and V_6 leads).

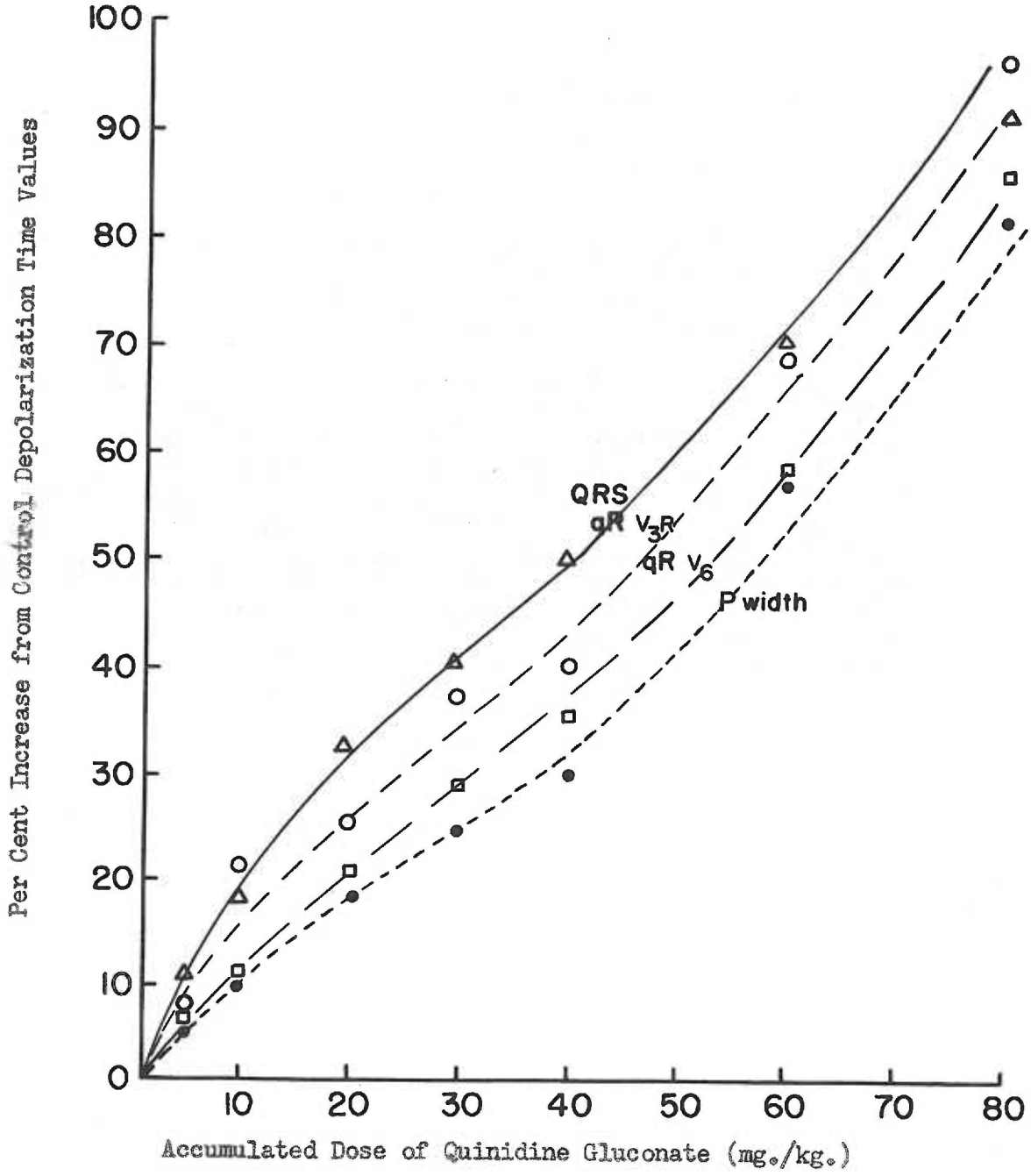

Per Cent Increase from Control Depolarization Time Values
100
90
80
70
60
50
40
30
20
10
0
10
20
30
40
50
60
70
80
Accumulated Dose of Quinidine Gluconate (mg./kg.)
QRS
qR V3R
qR V6
P width

Figure 3

prior to the administration of drug. Each point on the curve represents the mean value obtained from ten dogs.

Only QRS and P wave broadening plus a progressive slowing of rate was noted in the ten dogs in our control series. It should be emphasized that in no case was there any evidence of cardiac arrhythmia in this series. There were, of course, anoxic changes evident in the EKG just prior to death.

Eleven adult mongrel dogs survived the surgical ablation technique of Starzl and Gaertner (35) and comprised our series of complete or bilateral bundle branch block experimental preparations. Following complete recovery these animals were challenged in a manner similar to the control series; that is, quinidine gluconate was administered intravenously at a rate of 1 mg./kg./min. All the animals in this series behaved similarly to those in the non-surgical control series, i.e. there was observed the usual slowing of rate and the further broadening of the P and QRS waves. It will be recalled that this series was comprised of animals whose cardiac status was already much compromised. Heart rates in this series were extremely slow, especially for dogs. These animals tolerated little more slowing of rate before succumbing. At no time, however, prior to death did these animals exhibit any abnormality other than changes in rate and width of P and QRS waves.

Figure 4 is a representative sample of the electrocardiographic recordings of the animals in this series. It will be noted in the Figure that following surgery complete AV dissociation exists, the animal exhibiting an approximate four to one block. Again it should be emphasized that in this symmetrical conduction defect series (both right

Protocol for
FIGURE 4

Transection of right and left bundle.

Time intervals in m/sec.

Dog	Prior to surgery QRS	PR	RR	Following surgery RR	PP	QRS	Remarks
1	51	87	328	3070	364	54	
2	51	89	280	2368	280	54	
3	50	86	408	1790	395	50	
4	50	80	406	1846	400	50	
5	50	80	390	1360	396	50	
6	50	148	532	2360	514	50	initial PR prolonged due morphine sulfate
7	50	90	534	1104	560	50	
8	50	86	400	1280	532	50	
9	42	90	356	1300	322	42	QT = 220
10	53	104	388	1360	406	53	
11	50	87	406	1160	440	50	second cut
12	52	80	340	1170	296	76	
		S	5268	20168	4905		
		M	439	1681	409		
	Mean rate per minute		136	35.6	146		

Quinidine gluconate at 1.0 mg./kg./min.

Time intervals in m/sec.

	PP	RR	
Control	283	1200	
10 mg./kg./min.	320	1220	no tachycardia
40 mg./kg./min.	504	1830	

ELECTROCARDIOGRAPHIC CHANGES RESULTING FROM SEVERING BOTH LEFT AND RIGHT BUNDLES

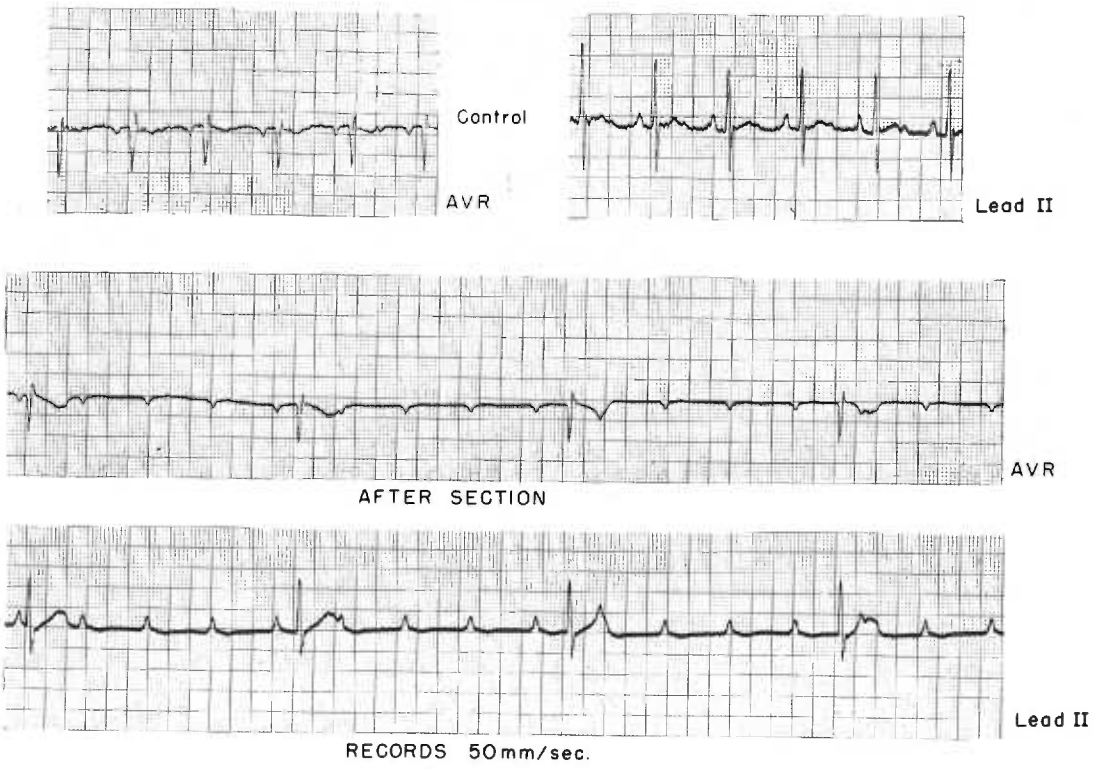


Figure 4

and left bundle branch block), no arrhythmia other than slowing was elicited when quinidine was administered in clinical and higher doses (10-20 mg./kg.) As mentioned previously, these animals tolerated very little more slowing of heart rate and so succumbed at much lower doses than did the control series. No dog in this series was even able to tolerate what we had previously determined to be the maximum safe dose, namely 60 mg./kg.

In the right and left bundle branch block series respectively, the following sequence was noted: when the animals were administered quinidine gluconate at a rate of 1 mg./kg./min., a tachycardia appeared with dosage levels of approximately 10-20 mg./kg./min. This corresponds quite closely to the therapeutic dosage levels commonly employed in human patients undergoing quinidine therapy where 800 to 1200 mg. comprises a maximum single dose for a 70 kg. man (5) (19). Following the onset of the tachycardia, cardiac output is decreased and an immediate shock-like sequence ensued not unlike that seen in rapid ventricular tachycardia and/or ventricular fibrillation and the animals expired.

Ten dogs survived the procedure described for the production of right bundle branch block and were allowed to recover. Following recovery, these animals were challenged with intravenous quinidine gluconate administered in the previously described manner of 1 mg./kg./min. All the dogs in this series resulted from the latter procedure described in the section on Methods and Materials. Although several survivors were obtained using the blind stab technique first mentioned, it was deemed advisable not to include these animals in the same series as

those obtained following extracorporeal circulation utilizing the DeBakey pump and disc oxygenator.

Figure 5 illustrates a representative control electrocardiogram of right bundle branch block taken from the above mentioned series. Figures 6 and 7, also selected from this series, represent typical right bundle branch block AVR and AVF patterns: before operation, following section of the bundle, and after the administration of quinidine. It is noted in the two typical examples selected (Figures 6 and 7) that when quinidine was administered to these animals with previously prepared right bundle branch block, that a tachycardia resulted at dosages near the usual therapeutic level. It was similarly observed that all the animals in this series, possessing an asymmetrical conduction disturbance, namely, right bundle branch block, developed a rapid tachycardia resulting in the near immediate death of the animal and again at dosages commonly encountered in clinical practice, recalling that 14 mg./kg. is an approximate average single dose in human subjects.

Five dogs comprised the series of surgically induced left bundle branch block. All of these animals were prepared in the manner similar to that described for the right bundle branch block series utilizing extracorporeal circulation with the DeBakey rolling pump and disc oxygenator. Figures 8 and 9 illustrate typical electrocardiographic patterns selected from this series. It can be noted, as in the former series, that when these animals were challenged with intravenous quinidine at a rate of 1 mg./kg./min., a rapid tachycardia again resulted at near clinical dosage levels—certainly far below the 60 mg./kg. previously ascertained as the maximum safe dose. All animals in the series behaved similarly and death resulted shortly after the onset of the tachycardia.

Protocol for
FIGURE 5

Figure 5 illustrates the various unipolar lead patterns seen in a surgically induced septal type right bundle branch block.

Protocol for
FIGURE 6

Right bundle branch block (septal) Heart rate as RR in m/sec.

Dose of Quinidine mg./kg. Pretreatment	Dog II		Dog VI		Normal conduction Average of 10 dogs	
	RR	% rate	RR	% rate	RR	% rate
Control	394	100	503	100	382	100
10	436	91	496	101	326	117
20	365	108	234	215	414	92
30	282	140	shock	death	522	73
40	260	152			566	67
50	246	161			582	65
60	265	149			618	62
1 hour later	340	116			-	-

Sample records of two types of response to quinidine. Dogs anesthetized with pentobarbital sodium 35 mg./kg. Electrocardiogram speed 50 mm./sec. Quinidine administered at 1.0 mg./kg./min.

UNIPOLAR RECORDS OF SURGICALLY INDUCED RIGHT BUNDLE BRANCH BLOCK

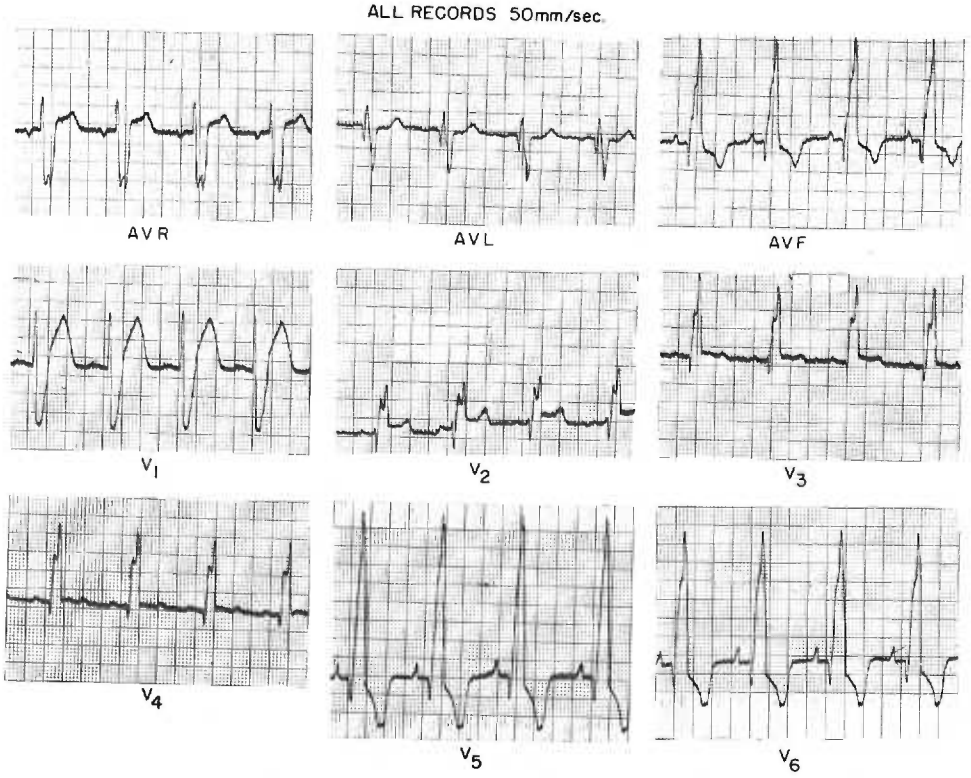


Figure 5

QUINIDINE TACHYCARDIA IN RIGHT BUNDLE BRANCH BLOCK

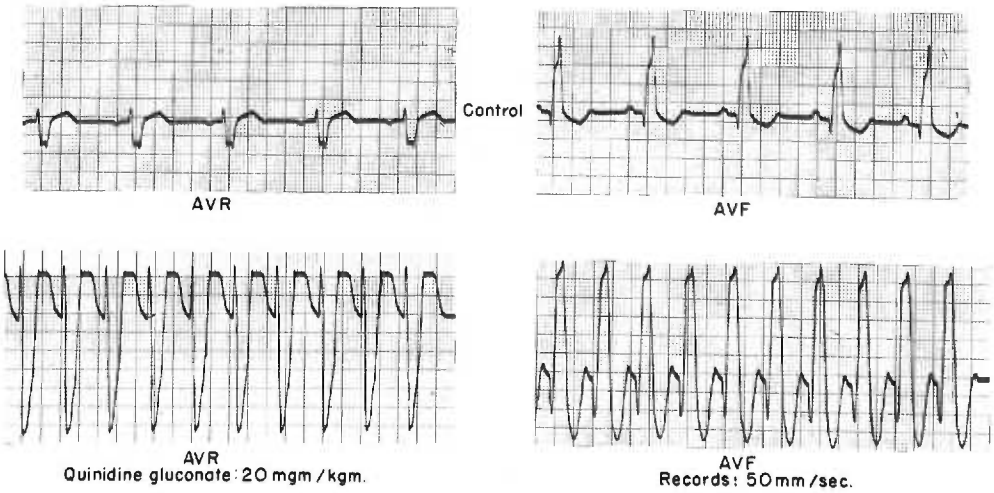


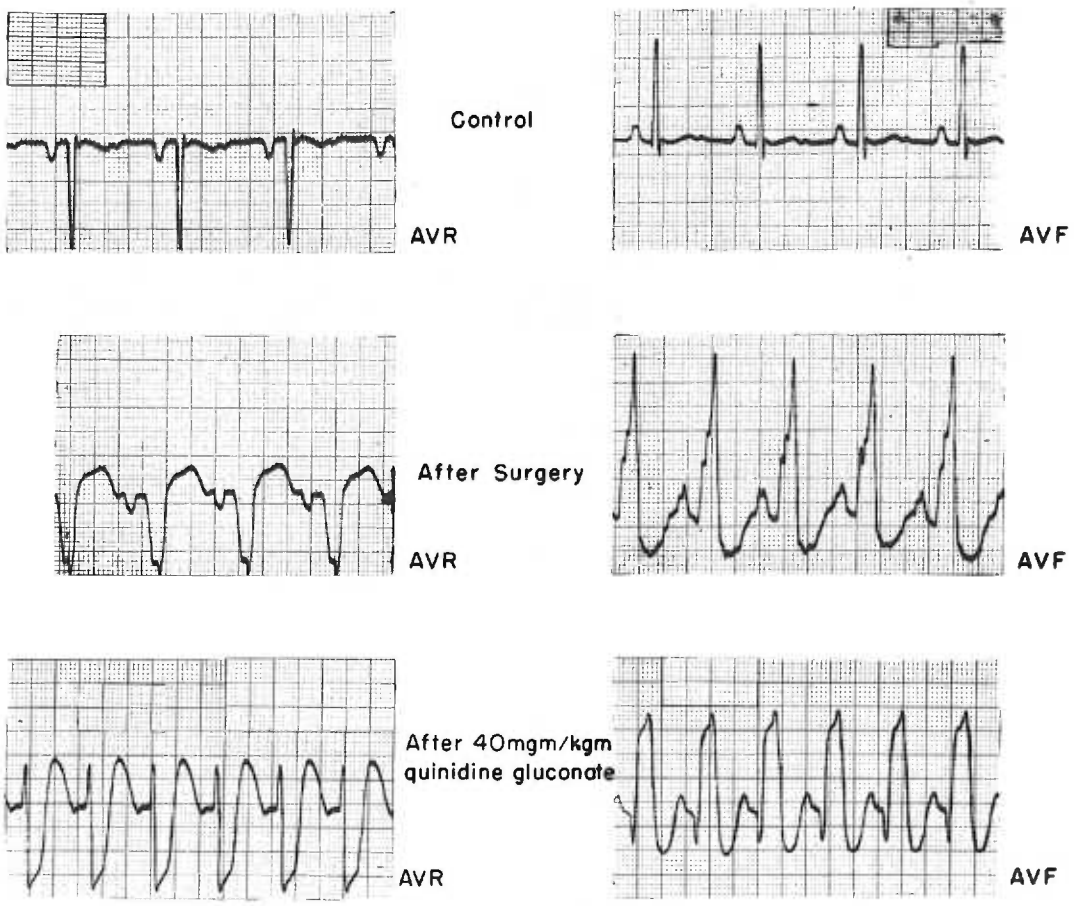
Figure 6

Protocol for
FIGURE 7

Figure 7 is another example of the electrocardiographic patterns obtained with quinidine following surgical section of the right bundle.

The protocol for Figure 6 would likewise apply to this Figure.

ELECTROCARDIOGRAPHIC CHANGES RESULTING FROM QUINIDINE ADMINISTERED TO A DOG WITH SURGICALLY INDUCED RIGHT BUNDLE BRANCH BLOCK



ALL RECORDS 50mm/sec.

Figure 7

Protocol for
FIGURES 8 and 9

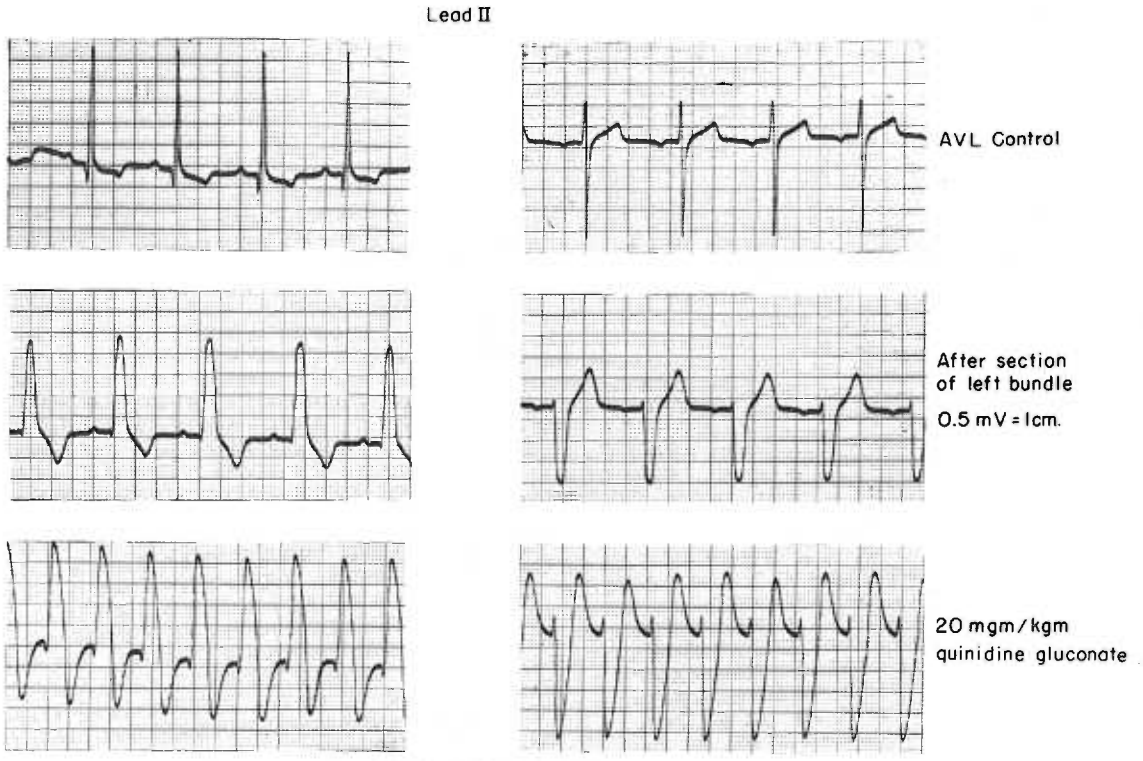
Left bundle branch block (septal)

	QRS	PR	RR	Heart rate per minute
Pre-surgical control	54	98	406	146
Post-surgical control	103	104	427	140
Quinidine 20 mg./kg.	110	-	236	254

Time intervals in m/sec.

Sample experiment in response of left bundle branch block dogs to quinidine. Dogs anesthetized with pentobarbital sodium 35 mg./kg. Electrocardiographic records taken at 50 mm./sec. Quinidine gluconate administered at 1.0 mg./kg./min.

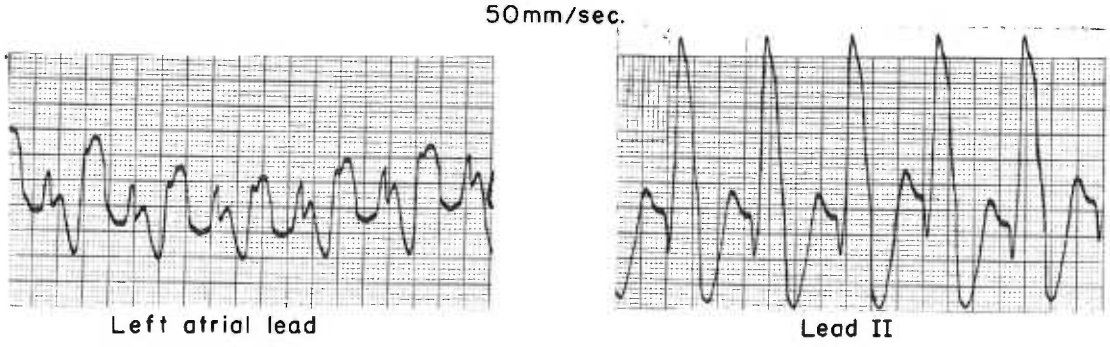
EFFECT OF QUINIDINE ON EKG OF A DOG WITH SURGICALLY PRODUCED LEFT BUNDLE BRANCH BLOCK



All records 50mm/sec.

Figure 8

TACHYCARDIA PRODUCED BY QUINIDINE IN A DOG WITH LEFT BUNDLE BRANCH BLOCK



Dose of quinidine gluconate: 18 mgm/kgm.

Figure 9

On casual inspection the arrhythmia observed in either right or left bundle branch block preparations challenged with quinidine resembles that of ventricular tachycardia and indeed, references to the production of ventricular tachycardia in patients following the administration of quinidine has been reported in the literature (7). The experimental arrhythmia was regular, showed no ventricular capture beats and had a broad QRS wave. The suggestion of an occasional P wave superimposed on this tachycardiac rhythm (Figure 9 left atrial lead), however, suggested the possibility that it was, in fact, a supra-ventricular tachycardia. Further evidence was needed to substantiate this suspicion and, therefore, in a dog with a previously prepared right bundle branch block, the chest was exposed and an electrode was applied directly to the atrium itself so that an exaggeration of the P waves could be obtained. Quinidine was administered in the usual fashion. Figure 10 demonstrates the electrocardiographic pattern of such a preparation. Note that a paper speed of 100 mm./sec. was also used to further facilitate interpretation. Upon administration of the dog the usual tachycardiac arrhythmia resulted as in all previous preparations with asymmetric conduction defects. It was also noted P waves were present and had the same rate as that of the ventricles; thus demonstrating that the rhythm was not that of a ventricular tachycardia but rather a supra-ventricular tachycardia.

The classic supra-ventricular tachycardia does not exhibit a prolonged or broadened QRS wave. Supra-ventricular tachycardia in the presence of a bundle branch block, however, would have a broad QRS wave. In addition, quinidine also widens the QRS wave and might easily account for the record having the appearance of a ventricular tachycardia.

Protocol for
FIGURE 10

This is the record of a dog operated on eleven weeks previously. At that time a septal type right bundle branch block was effected. The animal was allowed to recover. Just prior to the making of this record the dog was anesthetized with thiopental and a thoracotomy in the right 6th intercostal space performed. A direct atrial electrode was put in place and the electrocardiographic record taken at 100 mm./sec. while quinidine gluconate was administered at 1.0 mg./kg./min. Heart rate prior to the administration of quinidine was 130/min. and at 30.0 mg./kg./min. the rate was 180/min.

REVISION added subsequent to the oral examination for the Master of Science degree - 10 May, 1960:

Differentiation between supra-ventricular tachycardia and ventricular tachycardia is a difficult decision. In both arrhythmias a tachycardia is required. In ventricular tachycardia the QRS is widened (greater than 0.12 sec. in man); the T wave is often continuing and opposite to the QRS; the P wave occurs at an independent and slower rate than the ventricular complexes. In supra-ventricular tachycardia the QRS is not widened and P waves occur with the same frequency as the ventricular complexes.

In the records of Figure 10 the following points are pertinent:

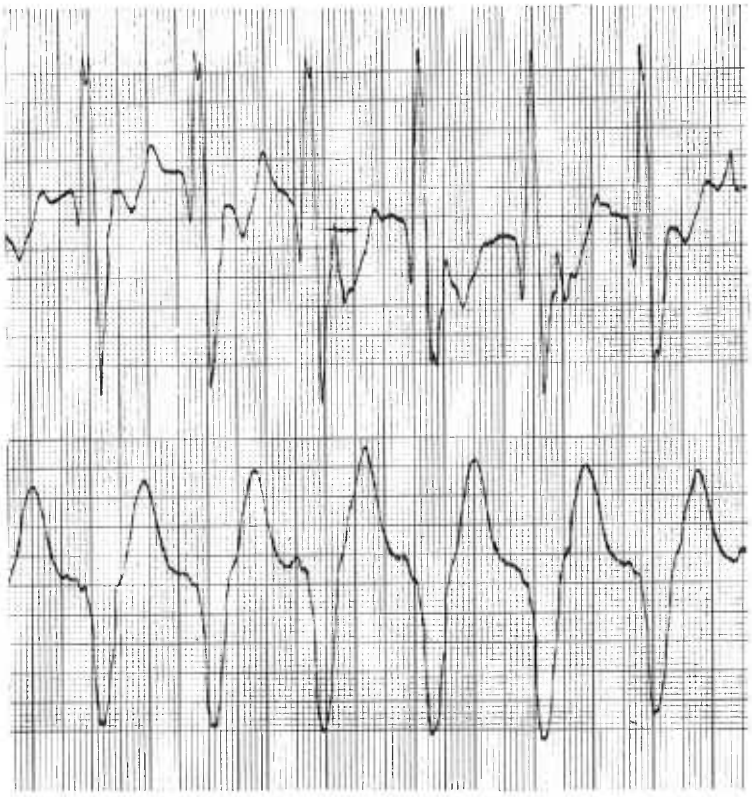
The QRS width is 0.07 sec. whereas the normal dog QRS width is 0.04/0.05 sec. This prolongation at first suggesting ventricular tachycardia may well be due to prolongation of the QRS complex by the bundle branch block plus this effect due to quinidine.

If it is assumed that the negative deflection following the QRS complex (in the upper record) are the T waves, then one may assume the upright wave which follows is a P wave. This apparently has a relatively constant P-R interval with the expected time interval for the tachycardia, hence the interpretation of supra-ventricular tachycardia.

If, however, the P waves as recorded in a direct atrial lead should have a sharp contour, then the small sharp waves of the fourth, fifth and sixth complex would indicate P wave activity. If so, they occur after a QRS and cannot then initiate the "supra-ventricular" tachycardia. It may be objected that if these be P waves, they occur at the same frequency as the ventricular complex (at least in the three complexes where they are visible) and thus cannot indicate ventricular tachycardia.

It is thus admitted that in the records presented for Figure 10 the differential interpretation of supra-ventricular vs. ventricular tachycardia cannot be made. Additional study of unpublished records is necessary.

DEMONSTRATION THAT QUINIDINE'S TACHYCARDIA IN RIGHT BUNDLE BRANCH BLOCK IS SUPRAVENTRICULAR



PAPER SPEED 100 mm/sec.
Quinidine gluconate: 30 mgm/kgm.

Figure 10

It has already been shown in the previous section that quinidine's broadening of the QRS and P waves is independent of heart rate (24). It was next ascertained that the action of quinidine was apparently primarily a retardation of the rate of depolarization of the heart (Figure 11). QT and PR intervals are used to indicate the time required for total depolarization and repolarization. Since the T_a wave of auricular repolarization is buried in the QRS wave, the time of total electrical activity of the atria is longer than the PR interval. These time intervals of the electrocardiogram were measured in the control unoperated dogs given quinidine. It is known that both the PR time interval and QT interval vary with the heart rate. Progressively increasing doses of quinidine cause, first, a transitory tachycardia, and then, there is significant slowing of heart rate. When the QT interval is calculated as a corrected QT_c some of the apparent widening of QT interval is the result of heart rate. However, the PR_c interval is still widened by quinidine. This broadening action of the QT_c, however, appears largely related to the depolarization phase. When the QRS is subtracted from the total QT interval, the remainder, described as end of S to end of T corrected (S_eT_c), reflects the repolarization phase according to some investigators (7). The S_eT_c is not significantly altered by increasing doses of quinidine. In a similar fashion, the indirectly derived atrial repolarization phase as well as time (P_eR_c) is not significantly widened indicating that quinidine has very little effect on atrial repolarization.

Protocol for
FIGURE 11

Mongrel dogs were anesthetized with pentobarbital sodium 35 mg./kg. Quinidine gluconate was administered via a catheter in a saphenous vein, the tip about 2 centimeters below the vena cava at 1 mg./kg./min.

Intervals and widths of waves were obtained following the criteria of the New York Heart Association. A paper speed of 50 mm./sec., hand lens and fine calipers facilitated the measurements. Each measurement represents the average obtai ned from three heart beats. As plotted each point represents the mean of 10 experiments.

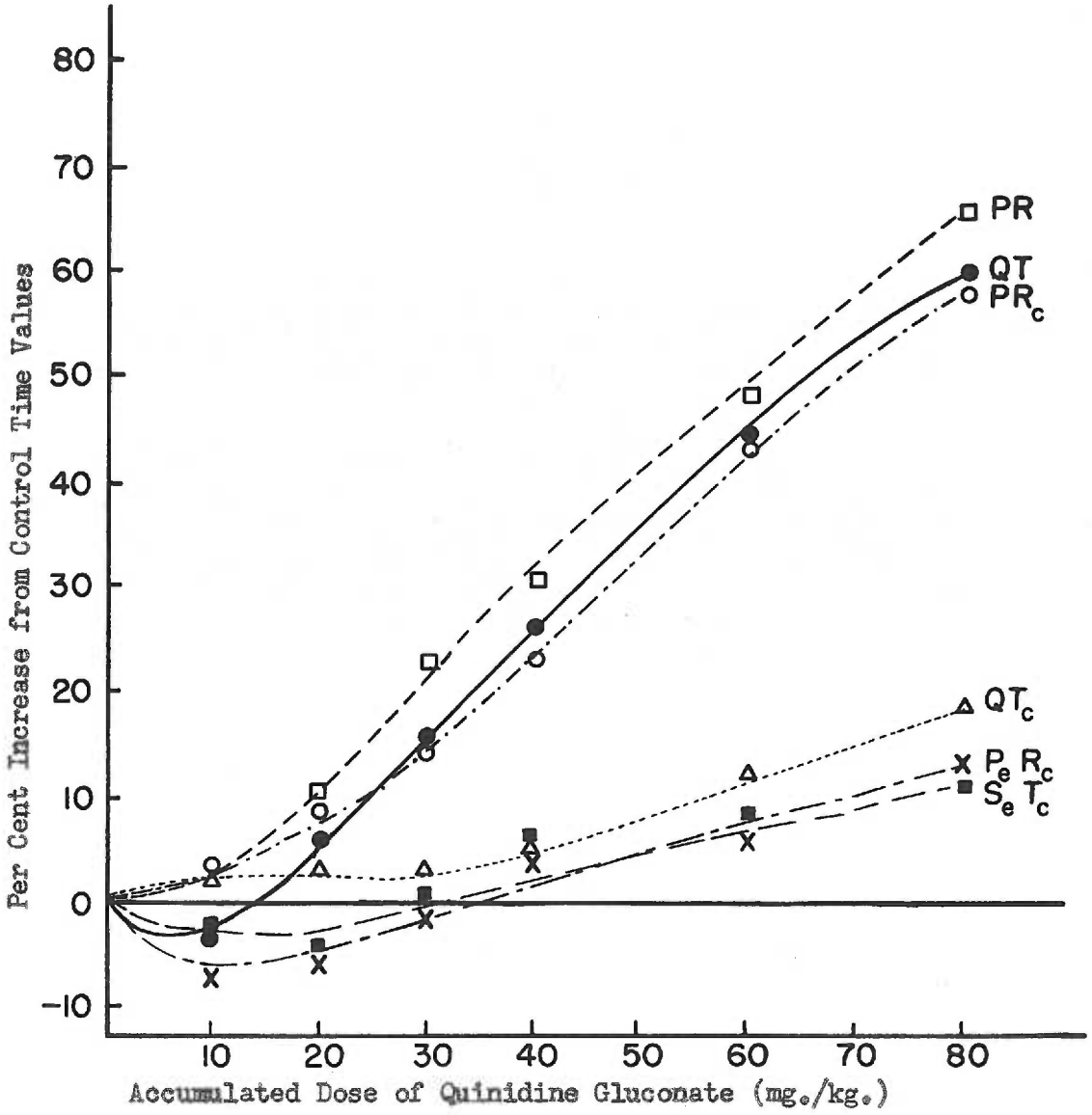

80
70
60
50
40
30
20
10
0
-10
Per Cent Increase from Control Time Values
10
20
30
40
50
60
70
80
Accumulated Dose of Quinidine Gluconate (mg./kg.)
PR
QT
PRc
QTc
Pe Rc
Se Tc

Figure 11

In reviewing the classic papers of Robert Grant in the American Journal of Medicine on the electrocardiographic diagnosis of right and left bundle branch block (10) (18), it was observed that the experimentally produced right bundle branch block differed from that of the usual clinical picture. Dr. Grant comments that only about 3 per cent of the right bundle branch blocks seen in patients have an EKG picture which resembles that which can be produced experimentally by surgical section in the dog. He attributes the clinical right bundle branch block of this pattern to the presence of an infarct in the septum. This particular pattern is characterized by a dominant S wave in lead AVR with secondary R' waves and S' waves and a dominant upright wave in lead AVF with an absent S wave. The more common clinical type has an EKG pattern characterized by a predominant R wave in lead AVR and a W shaped wave in lead AVF. Fortunately a dog was obtained with a spontaneous right bundle branch block which showed this picture of the more common clinical right bundle branch block (Figure 12). With this type of right bundle branch block, quinidine also produced, in the usual therapeutic dose levels, a supra-ventricular tachycardia. This picture was mimicked in animals by making an elliptical incision in the right ventricle near the apex and extending essentially from anterior septum to posterior septum, but not involving the septum itself. This second type of surgically-induced right bundle branch block is described as the peripheral lesion or the surgically-induced Type 2. Figure 12 demonstrates that surgically-induced Type 2 has at least the upright and broadened R wave and there is a W pattern, although small, in lead AVF as described by Grant (10) (17) (18). With this Type 2

Protocol for
FIGURE 12

Figure 12 illustrates the various types of bundle branch block described more fully in the text. The top graphs show the patterns obtained in one animal that was found to have a spontaneous right bundle branch block. The middle graphs show typical examples of the patterns obtained in those animals operated and a septal type right bundle branch block produced. The bottom graphs illustrate typical patterns obtained when the surgical right bundle branch block was of the peripheral type.

VARIOUS TYPES OF RIGHT BUNDLE BRANCH BLOCK

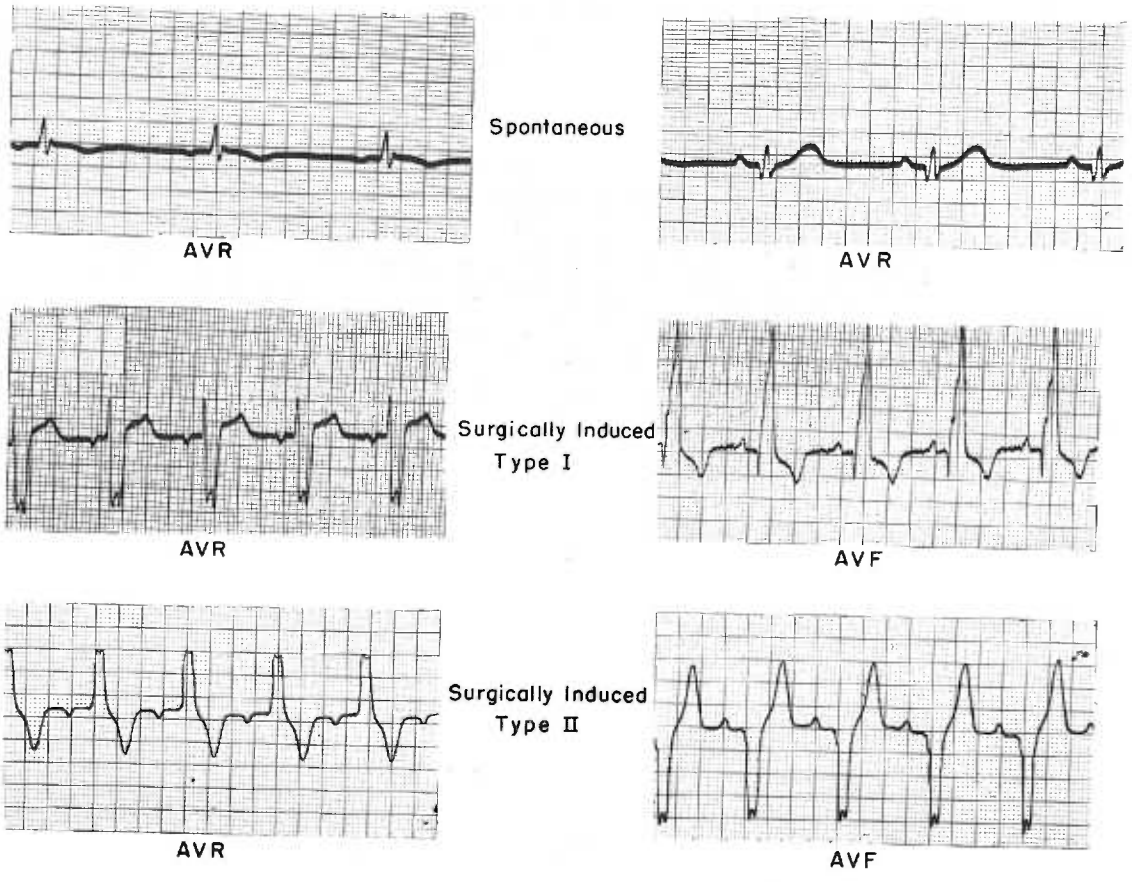


Figure 12

surgical lesion of the right bundle branch, quinidine in the usual clinical dose produced the supra-ventricular tachycardia. Dr. Grant explains the more common clinical right bundle branch block as being due to an infarct in the right coronary artery such that its distribution affects the right conduction bundle as it enters the major portion of the right ventricle itself after having left the septum. Preliminary attempts in animals to produce this more common clinical right bundle branch block by ligating the right coronary artery were unsuccessful due to death of the animals in acute right ventricular failure. It was thought that the ligations were being placed too high on the right coronary artery and the instantaneous massive right ventricular infarct probably accounted for these rapid deaths. Recently, more distal ligations of the right coronary have been effected and a pattern more nearly resembling the criteria of Dr. Grant's common clinical type right bundle branch block have been obtained. At the time of this writing there has not been sufficient time to allow surgical recovery of these animals and subsequent challenging with quinidine.

Observing that quinidine produced no tachycardia in normal animals or animals with a symmetrical conduction defect, i.e. complete bundle branch block, it was desirable to further analyze the postulate made by various investigators who have also reported that quinidine produces in itself in high doses a bundle branch block pattern which may be of the right or left variety rather than a completely symmetrical type. Continuous monitoring of our control preparations with the Tektronix 502 double beam oscilloscope recording vectorcardiographic patterns failed to show any axis deviation with increasing

doses of quinidine, i.e. no asymmetry in the "block pattern". Figure 13 illustrates the vectorcardiographic patterns of a control preparation at various increasing doses of quinidine. Likewise, it will be noted that right and left heart patterns of the various precordial leads fail to suggest either right or left bundle branch block.

No significant change in arterial blood pressure is noted with increasing doses of quinidine in the normal animal and in those with symmetrical conduction defects. Indeed, the maximal safe dose of 60 mg./kg. must be exceeded before a significant measureable change is noted. At dosage levels of 80 mg./kg. (approximately five times the average single clinical dose) a slight decrease in both systolic and diastolic femoral artery pressures was noted.

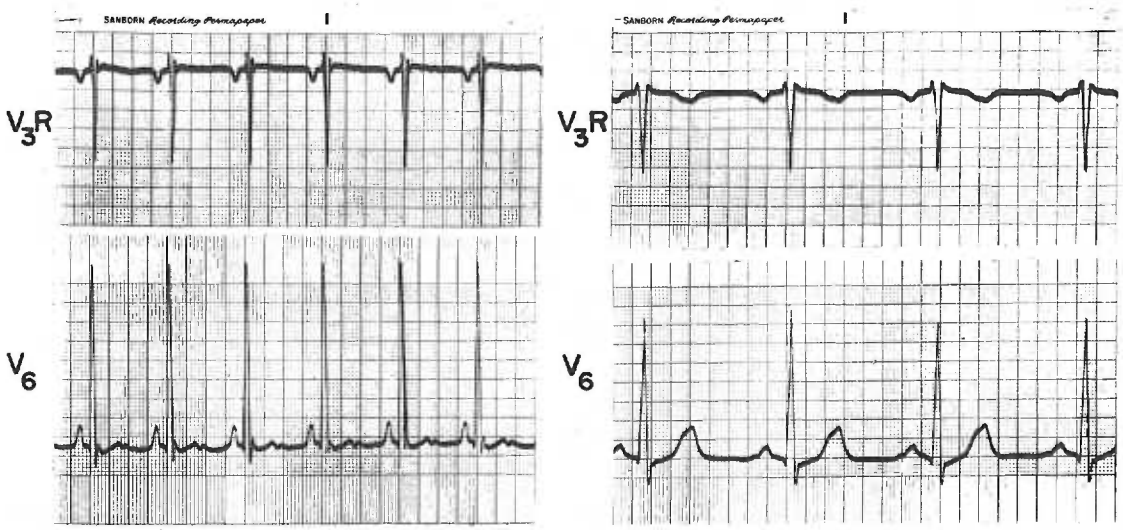
Protocol for
FIGURE 13

Figure 13 illustrates simultaneously recorded right and left precordial leads, namely V_3R and V_6, under normal control conditions and after the administration of 80 mg./kg. of quinidine gluconate.

The resultant vectorcardiograms are also included. These figures attempt to illustrate that although there are electrocardiographic changes consistent with slowing of conduction following the administration of quinidine, this slowing is symmetrical involving both right and left bundle branch pathways. Note that there is no significant shift of the electrical axis as illustrated in the two vectorcardiograms.

Refer to text for further discussion.

Precordial lead electrocardiogram



Control

80 mg. per kg. Quinidine

Vectorcardiogram

Control

QRS $s\hat{E}+44$

80 mg. per kg. Quinidine

QRS $s\hat{E}+42$

Figure 13

DISCUSSION

Quinidine, when administered intravenously in steadily increasing doses to normal dogs or dogs with complete bundle branch block, fails to provoke a tachycardia. It appears that in the absence of an asymmetrical conduction defect that the lethal dose of quinidine is much higher than when such a conduction defect is present. Admittedly, the intravenous route of administration for quinidine is not commonplace and indeed, the dangers that may occur with such therapy are well known. This method of administration did, however, have certain definite advantages. It eliminated any question as to the quantity of drug absorbed, which is always of concern when medications are given orally. It also afforded in a sense an infinite number of separate experiments since every increase in dosage encountered by the slow intravenous drip method is a new experiment. Much variation is encountered in all biological preparations. When many animals in a series are compared one to the other as to their response to a stimuli, small individual differences inadvertently influence the results adversely. In support of the method used in these experiments, each animal acted as his own control over a range of increasing doses.

It appears to have been shown rather conclusively that under these experimental conditions at least, a tachycardic rhythm is produced in a dog with a surgically produced asymmetrical conduction defect. One case of a spontaneous asymmetrical conduction defect responded similarly. That this tachycardia is supra-ventricular rather

than ventricular in origin has also been demonstrated. The fact remains, however, that even though the above points have been clearly shown, the type lesion responsible for these experimental results is not the one most commonly encountered in clinical practice, and quinidine sudden death from the more common pathology will continue unless a readily recognizable contraindication to its use is realized. Whether all peripheral bundle branch block will react as the more proximal type cannot be implied for certain.

The accurate diagnosis as to whether right or left bundle branch block exists in a patient may, in fact, at times be extremely difficult. The presence of myocardial infarcts that do not directly involve the regular conduction pathways may complicate interpretation of electrocardiograms by affecting the electrical activity of contractile tissue. Bundle branch block may be associated with a number of conditions, namely: coronary artery disease; hypertensive and valvular heart disease; myocarditis; congenital heart disease; and pulmonary embolism. Bundle branch block may also develop in a heart which is clinically normal and may be recognized only by electrocardiographic diagnosis. Prognosis or status of cardiac function, however, should not be ascertained solely on interpretation of the electrocardiograph.

Incomplete right or left bundle branch block designates a condition similar to the complete type with less broadening of the QRS complex. Incomplete right or left bundle branch block is difficult to differentiate from right or left ventricular hypertrophy. Incomplete right bundle branch block has been observed as a transient phenomenon in right ventricular strain due to pulmonary embolism, in acute myo-

cardial infarction, during febrile disease and in the presence of congenital heart disease. It is conceivable that a quinidine sudden death could occur as the result of incomplete bundle branch block produced by a febrile reaction. The situation being transient in nature would naturally have been absent on electrocardiographs prior to the onset of fever.

Valvular abnormalities, both stenosis and insufficiency, lead to dilatation and hypertrophy of the various heart chambers and subsequent disturbances of conduction. Prior to the studies done as outlined in this paper, attempts were made surgically to alter valvular function in the dog heart and thus produce a more chronic, more slowly developing conduction disturbance. Preliminary experiments were unsuccessful. With the aid of extracorporeal circulation this approach is now more feasible and should be further investigated. If successful, it promises to produce a more physiologic condition and more closely resemble that seen in human patients with cardiac disease and conduction disturbance.

The criteria for designating right bundle branch block varies from author to author. Generally accepted, however, is broadening of the QRS complex to 0.12 seconds or more resulting from delay of the stimulus in arriving at the right ventricular wall. Ventricular activation time is increased from approximately 0.025 seconds to as high as 0.1 seconds over the right precordial leads. Because of delayed conduction time in the right ventricle there is noted an R' wave of greater amplitude than the R wave. This results because the late occurring potential of the right ventricle is unopposed by the earlier

occurring potential of the left ventricle. This phenomenon is best observed in right precordial leads.

Many patients receiving quinidine are also receiving other drugs, most commonly digitalis and diuretics. It is well known that digitalis in excessive doses may lead to AV block, auriculoventricular dissociation, ventricular tachycardia and other arrhythmias. A change in myocardial irritability may also result. Various ion concentrations affect cardiac irritability and indeed, the calcium, potassium and magnesium serum levels when disrupted alter greatly the response of the heart to drug therapy. The electrolytic imbalance and subsequent effect of low serum potassium levels was rapidly recognized with the advent of chlorthiazide and hydrochlorthiazide therapy as a diuretic in cardiac patients. Further investigation into this and other biochemical lesions may be very revealing.

It is readily appreciated that many things may complicate quinidine therapy in the cardiac patient. It is realized that only one aspect of myocardial conduction has been presented and that under conditions which were otherwise perfectly normal. Much work is left to be done in this area and it is hoped that other investigations will be undertaken in the future.

SUMMARY

The results of these experiments demonstrate that tachycardia, reduced cardiac output and rapid ensuing death does not follow administration of either therapeutic or toxic doses of quinidine to experimental animals with no conduction defects. Similarly, animals surgically prepared with complete bilateral bundle branch block, i.e. a symmetrical conduction defect, failed to develop tachycardia. In these two situations two phenomena were observed: 1.) a progressive slowing of heart rate directly related to increasing levels of quinidine until death resulted from respiratory arrest and/or circulatory collapse at dosage of approximately 120 mg./kg./min., a level 8 to 10 times that normally employed in therapeutic use; and 2.) a progressive broadening of the P and QRS waves also related to increasing dosage. It was also demonstrated that this P and QRS wave broadening was primarily due to the action of quinidine on the depolarization mechanism rather than that of repolarization. Vectorcardiographic analysis demonstrates that the "block pattern" produced by quinidine is symmetrical; no shift of axis is noted despite a change in the overall configuration of the patterns. In those animals with an asymmetrical conduction defect, i.e. right or left bundle branch block independent of the other, quinidine in near therapeutic levels produces a rapid supra-ventricular tachycardia, decreased cardiac output and sudden death. In an effort to correlate the cause of quinidine sudden deaths in this immediate area with our recent experimental findings, seven Portland hospitals' medical record libraries were searched for the past

few years for instances of quinidine sudden death. Six such patients have been located. In four of the six, there was clear evidence of a right or left bundle branch pattern and in three, the width of the QRS wave was sufficiently broad to make the diagnosis of incomplete or complete right or left bundle branch block. In the remaining two patients, electrocardiographic records are inconclusive but at least suggestive of the pattern of right or left conduction disturbance.

BIBLIOGRAPHY

1. Bellet, S.A. Clinical Disorders of the heart beat. (1st Ed.) Philadelphia: Lea & Febiger, 1953.

2. Bellet, S., Wasserman, F., & Brody, J.I. Effect of molar sodium lactate in increasing cardiac rhythmicity. JAMA, 1956. 160, 1293-1298.

3. Bjork, V.O., Discussion on pumps. In J. Garrott Allen (Ed.) Extracorporeal circulation. Springfield, Ill.: Charles C. Thomas, 1958. pp. 21-40.

4. Burch, G.E., & Winsor, T. A primer of electrocardiography. (3rd Ed.) Philadelphia: Lea & Febiger, 1955.

5. Cecil, R.L., & Loeb, R.F. A textbook of medicine. (10th Ed.) Philadelphia: W. B. Saunders, 1959.

6. Dick, H.L.H., & McCawley, E.L. A comparison study of drugs in experimental and clinical auricular fibrillation. Amer. Heart J., 1955. 50, 442-448.

7. Dick, H.L.H., McCawley, E.L., Voiss, D.V., & Krueger, J.D. Electrocardiographic evaluation studies on quinidine-induced changes of myocardial conduction. Amer. Heart J., 1958. 56, 396-404.

8. Dimond, E.G., & Everton, M. dos S. Complications following commissurotomy with special reference to auricular fibrillation. J. Kansas Med. Soc., 1954. 55, 120-123.

9. DiPalma, J.R., & Schultz, J.E. Antifibrillatory drugs. Medicine, 1950. 29, 123-168.

10. Dodge, H.T., & Grant, R.P. Mechanisms of QRS complex prolongation in man. Amer. J. Med., 1956. 21, 534-550.

11. Effler, D.B., & Groves, L.K. Elective cardiac arrest with potassium citrate. In J. Garrott Allen (Ed.) Extracorporeal circulation. Springfield, Ill.: Charles C. Thomas, 1958. pp. 459-465.

12. Fraser, H.R.L., & Turner, R.W.D. Auricular fibrillation with special reference to rheumatic heart disease. Brit. Med. J., 1955. 4953, 1414-1419.

13. Giannelli, S., Molthan, M.F., Best, R.J., Dull, J.A., & Kirby, C.K. The effects produced by various types of pump oxygenators during two-hour partial infusion in dogs. J. Thor. Surg., 1957. 34, 563-569.

14. Gold, H. Quinidine in disorders of the heart. New York: Harper & Brothers, 1950.

15. Goldman, M.J. Principles of clinical electrocardiography. (2nd Ed.) Los Altos, Calif.: Lange Medical Publications, 1958.

16. Goodman, L.S., & Gilman, A. The pharmacological basis of therapeutics. (2nd Ed.) New York: The Macmillan Co., 1956.

17. Grant, R.P. Clinical electrocardiography. New York: McGraw-Hill, 1957.

18. Grant, R.P., & Dodge, H.T. Mechanisms of QRS complex prolongation in man. Amer. J. Med., 1956. 20, 834-852.

19. Harrison, T.R., Adams, R.D., Bennett, I.L., Resnik, W.H., Thorn, G.W., & Wintrobe, M.M. Principles of internal medicine. New York: McGraw-Hill, 1958.

20. Holzman, D., & Brown, M.G. The use of quinidine in established auricular fibrillation and flutter. Amer. J. Med. Sci., 1951. 222, 644-652.

21. Lam, C.R., Gahagan, T., Sergeant, C., & Green, E. Acetylcholine asystole - an adjunct in open heart operations with extracorporeal circulation. In J. Garrott Allen (Ed.) Extracorporeal circulation. Springfield, Ill.: Charles C. Thomas, 1958. pp. 451-458.

22. Lewis, T. Croonian Lecture - Upon the motion of the mammalian heart. Proc. Roy. Soc. London, Series B, 1915-1917. 89, 560-573.

23. Lipman, B.S., & Massie, E. Clinical unipolar electrocardiography. (3rd Ed.) Chicago: YearBook Publishers, 1956.

24. McGinn, S., & White, P.D. The duration of the QRS complex in the normal and in the abnormal electrocardiogram. Amer. Heart J., 1934. 9, 642-653.

25. McMillan, R.L., & Welfare, C.R. Chronic auricular fibrillation. JAMA, 1947. 135, 1132-1136.

26. Nudelman, P. Thrombocytopenic purpura following quinidine. JAMA, 1948. 137, 1219-1230.

27. Paneth, M., Sellers, R., Gott, V.L., Weirich, W.L., Allen, P., Read, R.C., & Lillehei, C.W. Physiologic studies upon prolonged cardiopulmonary by-pass with the pump oxygenator with particular reference to (1) acid base balance (2) siphon caval drainage. J. Thor. Surg., 1957. 34, 570-579.

28. Prinzmetal, M., Corday, E., Brill, I.C., Oblath, R.W., & Kruger, H.E. The auricular arrhythmias. (1st Ed.) Springfield, Ill.: Charles C. Thomas, 1952.

29. Read, J.M. Fatal ventricular fibrillation following procaine amide hydrochloride therapy. JAMA, 1952. 149, 1390-1391.

30. Roberts, C.H., Crawford, J.H., Abramson, D.I., & Cardwell, J.C. Experimental bundle branch block in the cat. Amer. Heart J., 1931-1932. 7, 505-513.

31. Smith, J.F., Keyes, J.W., & Durham, R.M. Myocardial infarction: A study of the acute phase in nine hundred and twenty patients. Amer. J. Med. Sci., 1951. 221, 508-521.

32. Sodi-Pallares, D., & Calder, R.M. New bases of electrocardiography. St. Louis, Mo.: C. V. Mosby, 1956.

33. Sokolow, M. The present status of therapy of the cardiac arrhythmias with quinidine. Amer. Heart J., 1951. 42, 771-795.

34. Sollmann, T. A manual of pharmacology. (8th Ed.) Philadelphia: W. B. Saunders, 1957.

35. Starzl, T.E., & Gaertner, R.A. Chronic heart block in dogs. A method for producing experimental heart failure. Circulation, 1955. 12, 259-269.

36. Voiss, D.V. A new method for experimental evaluation of drugs for use in chronic atrial fibrillation. Unpublished master's thesis, Univ. of Oregon Medical School, 1957.