STUDIES ON CYCLOPROPANE SENSITIZATION TO ADRENALINE-INDUCED CARDIAC ARRHYTHMIAS

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ABSTRACT

Small doses of adrenaline (0.1-2.0 µg./kg.) injected over 60 seconds into thiopental-cyclopropane anaesthetized dogs produce bigeminal rhythms characterized by an exceptionally constant interval between the coupled beats. Phenylephrine also causes this arrhythmia but methoxamine does so rarely. An elevation in the systolic blood pressure is required for the appearance of the bigeminy but the arrhythmia can be elicited consistently only in the presence of an increase in blood pressure and a sympathomimetic amine with cardiac stimulant action. Thus, isoproterenol does not produce the arrhythmia unless the depressor response is reversed mechanically. The arrhythmia may be elicited in some dogs anaesthetized with either cyclopropane or thiopental, but both anaesthetic agents are required for the consistent production of this arrhythmia by adrenaline. Thiopental also modifies other arrhythmic responses to adrenaline so that multifocal ventricular rhythms and ventricular fibrillation occur at doses which animals anaesthetized with cyclopropane alone tolerate well. Tachyphylaxis to adrenaline-induced arrhythmias occurs more readily in the cyclopropane-anaesthetized animal than the animal receiving thiopental in addition to cyclopropane. The duration of the cardiac effects of thiopental greatly exceeds its expected anaesthetic action.

A parasystolic focus of automaticity has been excluded in the

genesis of the bigeminal rhythm by the demonstration of constancy of the coupling interval with sudden changes in the dominant rate. Bigeminal and multifocal rhythms are interconvertible through appropriate changes in the systemic blood pressure and both are abolished by injections of acetylcholine into the left circumflex coronary artery. Thiopental also acts in the distribution of this artery, presumably at the atrioventricular node or upper bundle of His.

Stimulation of the vagus in the presence of a sympathomimetic amine allows the emergence of ventricular foci of automaticity through inhibition of supraventricular centres. No difference was noted between the sensitized (cyclopropane) and the nonsensitized (pentobarbital) preparation when this technique was employed. The evidence indicates that the bigeminal and multifocal arrhythmias occurring with low doses of adrenaline in the sensitized preparation are not due to the emergence of ventricular foci of automaticity.

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SECTION I

INTRODUCTION

A. GENERAL INTRODUCTION

The administration of adrenaline during hydrocarbon anaesthesia remains one of the most useful pharmacological procedures for the experimental production of cardiac arrhythmias and one of the significant hazards of clinical anaesthesiology. Sudden death during hydrocarbon anaesthesia was noted as early as 1895 when Oliver and Schafer made the observation that administration of adrenal extracts to cats anaesthetized with chloroform resulted in death of the animals (1). This observation was not developed further and the lethality of the adrenal extract was not related to the anaesthetic agent by these authors. Five years later MacWilliam described sudden halving of the pulse rate and the appearance of pulse irregularities on applying pressure to the abdomen of the chloroformed cat but did not comment on this observation (2). In 1910 Blumenfeld presented a paper to the Anaesthesiology Section of the Royal Society of Medicine describing a case of sudden cardiovascular collapse following administration of adrenaline during light chloroform anaesthesia for nasal surgery (3). Blumenfeld attributed this phenomenon to "nasal reflexes" but the several discussants of the paper commented on similar responses in a variety of surgical procedures associated with the concomitant use of chloroform and adrenaline. This empirical association of adrenaline with chloroform in producing cardiovascular collapse was investigated by Goodman Levy who published his observations on animals in the following year (4,5). He noted that ventricular fibrillation occurred spontaneously in cats lightly anaesthetized with chloroform and that this arrhythmia could be produced consistently by the administration of adrenaline. The requisite conditions for spontaneous

and adrenaline-induced arrhythmias were investigated and an attempt was made to relate experimental observations to the hitherto unexplained deaths occurring during clinical chloroform anaesthesia (6,7).

The acceptance of Levy's experimental observations led to revision of anaesthetic techniques with chloroform and greater safety in administration of this agent. The importance of his contribution goes much beyond this. "Sensitization" of the heart to adrenaline had been demonstrated clearly and a technique was made available for the experimental study of cardiac arrhythmias and for the assessment of anti-arrhythmic agents.

In 1929 Lucas and Henderson described the anaesthetic properties of cyclopropane and noted the occurrence of pulse irregularities following administration of this agent to animals (8). The production of spontaneous arrhythmias by cyclopropane was confirmed (9,10) and in 1937 Meet et al. reported on sensitization of the heart to adrenaline by cyclopropane (11). This was the first of a series of communications and review articles by Meek and his group (12-18) which established the cyclopropane-adrenaline preparation as a basic tool in the study of cardiac arrhythmias. Acceptance of this preparation probably was predicated on several important considerations. Several authors found cyclopropane to sensitize the canine heart (9-11). The dog appeared to be closer phylogenetically to man than were the cat or rabbit which had previously been employed. Moreover, since cyclopropane was a gaseous anaesthetic it could be administered in known concentrations. The recognition by Meek that the arrhythmic response to adrenaline varied with the rapidity of injection probably was of major importance. His group demon-

strated that the intravenous administration of 10 µg./kg. of adrenaline over 50 seconds consistently produced ventricular rhythms but seldom ventricular fibrillation (11). In effect, they shifted interest from chloroform-adrenaline "syncope" (ventricular fibrillation) to less severe ventricular rhythms which lent themselves better to experimental investigation. In so doing they introduced a standardized test preparation (11).

B. SPONTANEOUS AND ADRENALINE-INDUCED ARRHYTHMIAS DURING HYDROCARBON ANAESTHESIA

1. The Role of Anaesthetic Concentrations

Observations made on chloroform-anaesthetized cats indicated that deep anaesthesia tended to abolish spontaneous arrhythmias (4,5) and that the ease with which adrenaline produced arrhythmias was inversely related to the depth of anaesthesia (7). It was later demonstrated that the production of arrhythmias during light anaesthesia was facilitated by an antecedent period of deep anaesthesia (19). In contrast, it is acknowledged generally that the production of spontaneous and adrenaline-induced arrhythmias under cyclopropane is directly related to the depth of anaesthesia (9,11,18). The only report to the contrary is that of Guedel who advanced the concept of an "arrhythmic range" for cyclopropane (20). He believed that spontaneous arrhythmias occurred only within a specific range of cyclopropane concentrations. Although Thienes et al. confirmed this experimentally in dogs (21), there is no mention in either communication of the adequacy of pulmonary ventilation. The extreme concentrations of cyclopropane required to exceed the "arrhythmic range" would be expected to produce severe hypoxia and hypercarbia (see follow-

ing section). Lee et al. were not able to demonstrate this phenomenon in adequately ventilated animals (18).

Close inspection of the literature suggests that the reported differences under light and deep anaesthesia with the two agents may be a function of the species employed. Chloroform was studied mainly in cats whereas cyclopropane has been studied almost exclusively in dogs. Embley has noted the dog to be relatively insensitive to spontaneous arrhythmias under chloroform (22) and Meek et al. have demonstrated the sensitivity of the dog to chloroform-adrenaline arrhythmias to increase with the depth of anaesthesia (11). Under cyclopropane anaesthesia, the cat is said to be more sensitive to spontaneous arrhythmias than is the dog, and the dog to be more sensitive to adrenaline-induced arrhythmias (17,18).

2. The Roles of Hypoxia and Hypercarbia

Spontaneous or adrenaline-induced arrhythmias are produced less readily in the chloroform-anaesthetized cat (7) or dog (23) under artificial respiration than when the animal is breathing spontaneously. Several authors (9,10,18,21,24) have demonstrated that spontaneous arrhythmias in cats or dogs anaesthetized with cyclopropane occur at the point of respiratory arrest and that institution of artificial respiration abolishes these arrhythmias (9,10,24). The appearance of such arrhythmias appeared to be related to the retention of carbon dioxide (24) rather than to hypoxia (18). However, hypercarbia is not essential for the development of spontaneous arrhythmias since they will occur in animals receiving artificial respiration if the cyclopropane concentration is sufficiently high (9,10,24). Lurie et al. demonstrated that spontan-

eous arrhythmias occur at normal end-expiratory carbon dioxide tensions in patients under cyclopropane anaesthesia, but that administration of carbon dioxide increases the incidence of such arrhythmias (25).

The mechanism of the carbon dioxide effect has not been defined adequately. It is well known that carbon dioxide may stimulate the vasomotor centre and increase the activity of the sympathetic nervous system. Price et al. demonstrated increased plasma levels of catecholamines following administration of carbon dioxide to patients anaesthetized with cyclopropane and related increased sympathetic activity to the occurrence of arrhythmias (26). Because the level of catecholamines at which arrhythmias occurred was much lower than the levels required when exogenous adrenaline was administered, this group inferred that the circulating catecholamines reflected release at sympathetic nerve endings. They also observed that bilateral infiltration of the stellate ganglia with local anaesthetics increased the threshold of carbon dioxide required for arrhythmias. Although local anaesthetics are antiarrhythmic agents, it is unlikely that sufficient systemic absorption would occur to influence this observation.

Levy reported that asphyxia protected against chloroform arrhythmias (27). Several other reports indicate that hypercarbia induced by the administration of carbon dioxide or by decreasing alveolar ventilation protects against cyclopropane-adrenaline arrhythmias (16,28,29). It is apparent from the values given for arterial pH, pCO_2, pO_2, or percent carbon dioxide administered that these animals were in severe respiratory acidosis. Price and Helrich have demonstrated cardiac depression to be produced by metabolic or respiratory acid-

osis (30).

It would appear that the superficially conflicting reports on the effects of carbon dioxide can be reconciled. The data indicate that moderate retention of carbon dioxide sensitizes to arrhythmias by stimulation of the sympathetic nervous system, and that more gross disturbances inhibit the production of arrhythmias through a cardiac depressant effect. In this context it is interesting to note that spontaneous arrhythmias have been reported to occur when elevated arterial carbon dioxide tensions are reduced suddenly (21,25,26,29).

3. The Role of the Nervous System

a. The Sympathetic Nervous System

The spontaneous arrhythmias which occur in the sensitized preparation probably require an intact autonomic nervous system. Levy noted that sudden deaths occurred more frequently during induction of chloroform anaesthesia or during recovery from this agent and was able to demonstrate that sensory stimulation of the lightly anaesthetized cat produced ventricular rhythms and even ventricular fibrillation (7, 27). This observation was confirmed by Brow et al. (31).

Although endogenous catecholamine release probably is involved in the response, it is difficult to quantitiate the relative importance of the sympathetic innervation of the heart and of circulating neurohumours in the genesis of such arrhythmias. It has been demonstrated that stimulation of either the right stellate ganglion (7,27,31) or of the splanchnic nerves (27) produces arrhythmias. Because spontaneous chloroform arrhythmias occurred in animals subjected to bilateral stellate ganglionectomy, Levy considered release of catecholamines from the adre-

nal medulla to be of primary importance (7). Although he was unable to abolish such arrhythmias by bilateral adrenalectomy, he attributed this failure to the presence of residual chromaffin tissue. Nahum and Hoff demonstrated that neither bilateral adrenalectomy nor bilateral stellate ganglionectomy protected against spontaneous arrhythmias in the benzol-sensitized cat, but that protection was complete when these surgical procedures were combined (32). It has been reported, however, that spontaneous arrhythmias occurring in the cyclopropane-sensitized cat are prevented if removal of the thoracic sympathetic chain as far as T6 is combined with bilateral stellate ganglionectomy (24,33).

Many authors have sought to implicate the sympathetic nervous system in the genesis of adrenaline-induced arrhythmias in the sensitized preparation. Although Levy demonstrated that chloroform-adrenaline ventricular rhythms and ventricular fibrillation occurred following cardiac denervation and pithing of the spinal cord (7), Bouckaert and Heymans claimed that carotid sinus denervation protected dogs against chloroform-adrenaline "syncope" (ventricular fibrillation) (34). This was confirmed in vagotomized dogs sensitized with benzol (35). These authors suggested that carotid sinus denervation allowed continued release of neurohumours at the heart during the pressor response to adrenaline, and that this prevented the cardiac dilatation which appears to precede ventricular fibrillation. Although these results suggest that sympathetic innervation of the heart may be important in the genesis of fibrillation, it is of interest that less severe arrhythmias were not prevented by carotid sinus denervation (35).

Extensive removal of lumbar sympathetic chains and plexuses has

been stated to protect against chloroform-adrenaline ventricular fibrillation (36). Allen et al. (37) and Stutzman et al. (38,39) have shown that many surgical procedures including abdominal evisceration, extensive lumbar sympathectomy, section of the spinal cord, decerebration or stellate ganglionectomy, protect against cyclopropane-adrenaline arrhythmias. They suggested that cyclopropane acted on receptors in the region of the mesentery and postulated a reflex reaching a midbrain level. The efferent impulses of the arc were stated to reach the heart by the cardiac sympathethic nerves, and to there "sensitize" the myocardium to exogenous adrenaline. Although these results are quoted widely in the anaesthetic literature, their validity is in serious doubt. Rennick et al. have demonstrated conclusively that extensive cardiac sympathectomy does not protect against cyclopropane-adrenaline arrhythmias (40). In these experiments functional removal of all postganglionic fibres was ensured by the concomitant use of tetraethylammonium, a ganglionic blocking agent.

b. The Parasympathetic Nervous System

Section of the vagi (41,42,43) or the administration of atropine (43,44) protects in large measure against adrenaline-induced arrythmias in the nonsensitized preparation although arrhythmias may still be obtained if sufficiently large doses are employed (43,45). Riker et al. suggest that adrenaline stimulates all centres of automaticity including the sinoatrial node, the atrioventricular node and potential ventricular pacemakers, the lower centres manifesting their activity only when the SA node is depressed by vagal activity (43). Dresel has demonstrated, however, that the vagal effect on conduction through the

atrioventricular node is of sufficient magnitude that artificial maintenance of the atrial rate does not change the threshold dose of adrenaline necessary to induce cardiac arrhythmias. He has shown AV-nodal block to precede initiation of arrhythmia both in the presence and in the absence of atrial drive (46). These authors agree that a brief period of ventricular slowing is required for the emergence of the ventricular pacemaker in the nonsensitized preparation.

Vagotomy or the injection of atropine does not protect against ventricular arrhythmias produced by adrenaline in the sensitized preparation (11,34,43,47-50). On the contrary, severance of the vagi, or administration of atropine in the lightly-chloroformed cat may produce cardiac irregularities (17,27). It has been claimed that intravenous atropine produces bigeminal rhythm in cyclopropane-anaesthetized man (51).

Stimulation of the vagus (42,52,53) or injection of acetylcholine (42) will produce ventricular rhythms in the nonsensitized animal in the presence of subeffective doses of adrenaline. In contrast, vagal stimulation during chloroform or cyclopropane anaesthesia will abolish or prevent arrhythmias (7,31,54) other than ventricular fibrillation (54,55).

4. The Role of the Systemic Blood Pressure

Levy initially speculated that the adrenaline-induced increase in the systemic blood pressure might be a factor in the production of arrhythmias in the sensitized preparation (5) but later rejected this possibility (27). He found that ventricular fibrillation produced by strychnine in the sensitized cat was prevented by bilateral

stellate ganglionectomy although this procedure did not modify the pressor response to the drug. He also demonstrated that tetrahydroxypapaveroline, which is cardioactive and produces a depressor response, nevertheless induced ventricular fibrillation in this situation. He concluded that neither multifocal nor fibrillatory rhythm was related to blood pressure (27). This conclusion was predicated on his view that multifocal and fibrillatory rhythms of the ventricle were the same basic phenomenon, differing only in degree.

Other authors have sought to implicate the pressor response to adrenaline in the production of ventricular fibrillation. Shen demonstrated that adrenergic blocking agents such as yohimbine and the benzodioxanes F993 and F883 protected in large measure against chloroform-adrenaline ventricular fibrillation (35,56). He contended that an increase in systemic blood pressure was important in the genesis of this arrhythmia, the rate of rise of the pressure being considered of greater importance than the absolute pressure achieved. VanDongen showed, however, that F993 raised the threshold for electrically-induced fibrillation of the heart and that it still protected if administered simultaneously with adrenaline to the sensitized preparation (57). He concluded that these agents protected against ventricular fibrillation by a direct action on the heart and not by preventing the pressor response to adrenaline. Neither of these authors concerned themselves with arrhythmias other than ventricular fibrillation. Brockman and Huggins have reported that preliminary haemorrhage to 50 mm. Hg reduced the pressor response to 10 µg./kg. of adrenaline and protected against ventricular fibrillation in cyclopropane-sensitized dogs (58). How-

ever, since the animals employed in their investigation were only ventilated "when necessary" the possibility exists of severe myocardial depression due to the combined effects of anaemic and anoxic hypoxia.

Although the possibility cannot be excluded that the pressor response to sympathomimetic amines is important in the production of ventricular fibrillation in the sensitized preparation, it is certainly not requisite for the development of this arrhythmia. Several authors have demonstrated ventricular fibrillation to occur in response to isoproterenol in the sensitized preparation (48,59,60).

The role of the systemic blood pressure in the production of ventricular arrhythmias other than fibrillation has been studied more adequately. Although Levy did not consider the pressor response to adrenaline to be of importance, he demonstrated that ventricular beats could be produced by elevation of the systemic blood pressure, and that spontaneous chloroform arrhythmias could be abolished by procedures lowering the blood pressure (27). He interpreted the latter phenomenon to be due to decreased blood supply to the heart, and suggested that the protection afforded by this manoeuver was analagous to that provided by asphyxia.

Much of the interest in the role of blood pressure in the genesis of such adrenaline-induced ventricular rhythms in the sensitized preparation has stemmed from the observation that such arrhythmias are prevented by pretreatment with α-adrenergic blocking agents, which do not block any other measurable cardiac action of the sympathomimetic amines (61). It is interesting that the protection afforded by appropriate doses of these agents is virtually complete and is of a

different order of magnitude than that provided by cardiac depressants such as procaine (16,49,62). A major controversy has centered on whether the protection afforded by such agents rests in their ability to prevent the pressor response to adrenaline or whether they act directly on the heart to prevent some cardiac action of adrenaline. Considerable information on the role of pressure in arrhythmias has developed from the several investigations performed to clarify this point.

Moe et al. investigated the protection afforded against cyclopropane-adrenaline ventricular tachycardia by Dibenamine, a β-haloalkylamine (47). They found that elevation of the systemic blood pressure simultaneous with the administration of adrenaline would produce ventricular arrhythmias in spite of prior administration of the blocking agent. Nickerson and Nomaguchi showed that the results of Moe's group could be confirmed only when small doses of the blocking agent were administered (48). Larger doses of Dibenamine produced protection against adrenaline-induced ventricular rhythms which could not be reversed by raising the blood pressure. They also pointed out that the dose of blocking agent required to protect against arrhythmias is greater than that required to prevent the adrenaline-induced hypertension, a finding which is consonant with the observations of other investigators (59,63). Although Acheson et al. have shown Dibenamine to possess a quinidine-like action (64), this did not appear to be implicated in the protection (48). Nickerson and Nomaguchi concluded that other factors were involved in the protective action of adrenergic blocking agents and postulated a direct non-quinidine-like action on the myocardium (48).

Although Nickerson and Nomaguchi disagreed with Moe's inter-

pretation of the mechanism of Dibenamine blockade, they did agree that the rise in blood pressure produced by sympathomimetic amines was important in the induction of ventricular rhythms. Moe's group demonstrated that the amount of adrenaline required for the production of ventricular tachycardia was inversely related to the initial blood pressure when varying degrees of hypertension were produced mechanically prior to the injection of adrenaline. Nickerson and Nomaguchi contended that the absolute blood pressure achieved rather than the rate of rise or the increment in pressure was the important factor in the production of such arrhythmias.

Nevertheless, the increase in blood pressure produced by sympathomimetic amines cannot be the only factor involved in the production of ventricular arrhythmias. Nickerson and Nomaguchi have demonstrated that such arrhythmias will occur in response to isoproterenol in the sensitized preparation (48) and Murphy et al. have shown that prevention of the pressor response to adrenaline by a pressure regulator does not protect completely against such arrhythmias (65). Moe et al. demonstrated, however, that such a manoeuver increased the adrenaline threshold 4 to 8 fold (47).

A summation of the evidence presented for adrenaline-induced ventricular tachycardia thus indicates that a rise in the systemic blood pressure is involved, but is not the only factor of importance in the genesis of this arrhythmia. The mode of action of the adrenergic blocking agents in preventing these arrhythmias is still unresolved. The fact that such diverse agents as the β-haloalkylamines (47,48,49,59, 62,63,66,67,68), phenothiazines (69), yohimbine (16,56), and the benzo-

dioxanes (16,17,35,56) all possess this action suggests that this property is associated with the common ability to block the α-receptor actions of adrenaline. Nevertheless, it cannot be concluded from the evidence presented that these agents act solely through preventing the pressor response to adrenaline.

It should be noted that stabilization of the blood pressure in the nonsensitized preparation protects almost completely against adrenaline-induced arrhythmias (42). The mechanism believed to be operative in this circumstance is prevention of the reflex stimulation of the vagus.

C. OTHER CARDIAC EFFECTS OF CYCLOPROPANE

The recent reviews of Price (70,71) emphasize the effects of cyclopropane on the peripheral vascular and other organ systems. The following comments will be restricted to the effects of this agent on the myocardium and the conduction system of the heart.

There is general agreement that the canine heart lung preparation is depressed by cyclopropane (18,30,60,72). Exposure of this preparation to cyclopropane produces an increase in right atrial pressure and a decrease in cardiac output (30,60). Moe et al. (72) demonstrated a decrease in the cardiac output when the right atrial pressure was increased mechanically under cyclopropane. They also noted that moderate increases in the arterial resistance produced marked elevations of the right atrial pressure. Increasing the venous pressure in decerebrate dogs by the administration of saline during treatment with cyclopropane has been reported to produce no roentgenographic evidence of cardiac dilatation (73). Moe et al. have shown however, that mechanically induced increases in the systemic arterial pressure of intact dogs anaes-

thetized with cyclopropane produced marked elevations of the right atrial pressure (72). The latter authors concluded that cyclopropane produced a decreased "cardiac reserve". Brace et al. have reported cardiac dilatation and increased stroke volume in intact dogs following a 5-minute exposure to 50 percent cyclopropane (74). The interpretation of these results is complicated by the concomitant use of pentobarbital and the high concentration of cyclopropane employed. However, a cyclopropane concentration of 20 percent has also been reported to cause cardiac dilatation in intact animals (75).

Several authors have reported that the administration of cyclopropane to the human premedicated with morphine produces a decrease in cardiac output and an increase in central venous pressure and in pulmonary artery pressure (162,76,77). The right atrial pressure of non-premedicated man is increased by cyclopropane, but stroke volume and cardiac output are increased in this situation (162,78). Robbins and Baxter also have reported increases in stroke volume and cardiac output in trained, unpremedicated dogs (79). Price considers pretreatment with morphine to materially influence the cardiovascular response to cyclopropane (78).

Price et al. (26,80) have demonstrated increases in circulating catecholamines following administration of cyclopropane. Release of adrenaline from the adrenal medulla appears not to be involved since similar changes are observed in adrenalectomized patients (71). Price has suggested that cardiovascular depression produced by cyclopropane results in a homeostatic mechanism wherein sympathetic nervous system activity is increased. The increase in cardiac output noted in the un-

premedicated subject is considered a reflection of such activity. There is no direct evidence in support of this proposal. Certainly the demonstration of sensitization of the carotid sinus by cyclopropane (81) does not support this theory, since an abnormally sensitive carotid sinus would be expected to decrease sympathetic tone rather than produce an increase.

The effects of cyclopropane on the conduction system of the heart have not been studied adequately. Acierno and DiPalma have reported cyclopropane to decrease the refractory period as well as the contractility and electrical excitability of the isolated cat atrium (82). Smith et al. (83) and Galindo and Sprouse (84) demonstrated that the absolute refractory period and the threshold for electrical stimulation of the canine ventricular myocardium is increased by cyclopropane. The PR-interval of the driven heart also was increased, implying slowed conduction between the atria and ventricles. Interpretation of these data is complicated by the use of thiobarbiturates by these authors.

SECTION II

METHODS

A. METHODS OF ANAESTHESIA

1. Induction of Anaesthesia with Barbiturates

a. Sodium thiopental

Eighty-four mongrel dogs unselected as to sex and weighing from 4 to 11 kg. were anaesthetized initially with 20 mg./kg. of sodium thiopental administered into a cephalic vein. The trachea was cannulated and 100 percent oxygen was administered by a Palmer Ideal respiration pump at a rate of 18/minute and a tidal volume of 20-25 ml./kg. body weight. Most of the required operative procedures were performed under the barbiturate anaesthesia and the gas mixture routinely was changed to 20 percent cyclopropane in oxygen following preparation of the animal. Anaesthesia was maintained in animals showing premature wakening by the early addition of cyclopropane to the system or occasionally by a single further administration of 5 mg./kg. of thiopental. Addition of cyclopropane was delayed in an additional seven animals maintained in surgical anaesthesia for several hours by the repeated administration of thiopental.

b. Other barbiturates

Eight dogs were anaesthetized with 30 mg./kg. of sodium pentobarbital intravenously. Four of these animals received no other anaesthetic, and four subsequently received cyclopropane. Ten dogs were given other barbiturates intravenously before the administration of cyclopropane. Four received 40-80 mg./kg. of sodium secobarbital, 2 were given 30 mg./kg. of sodium methitural, and 4 received 40-80 mg./kg. of sodium amobarbital.

2. Induction and Maintenance of Anaesthesia with Cyclopropane

Sixty-seven unpremedicated dogs weighing from 3 to 11 kg. were anaesthetized with 30 to 50 percent cyclopropane in oxygen by means of an animal face mask. After tracheal cannulation the animals were connected to the Palmer Ideal pump which delivered 20 percent cyclopropane in oxygen.

Cyclopropane, U.S.P., and oxygen, U.S.P. were supplied by a Heidbrink anaesthesia machine, the flow meters of which were calibrated at three-monthly intervals by measuring the volume of water displaced by the gases delivered. The gases were led to a mixing bag, and thence to a face mask or the Palmer pump. Expired gas was returned to the bag through a carbon dioxide absorber containing fresh barium hydroxide, U.S.P. (Baralyme). A semi-closed system was used in all experiments, 10 to 25 percent of the expired gases being vented to the atmosphere. The rebreathing bag was emptied frequently to prevent accumulation of nitrogen. A period of at least 30 minutes of cyclopropane administration preceded experimental procedures. This time has been found adequate for tissue equilibration with this gas (85).

B. SURGICAL PROCEDURES

1. Thoracotomy and Pericardiotomy

The sternum was exposed by electrocautery in 33 animals and cleaved in the midline over its entire length. In an additional 40 dogs electrocautery was employed to expose the intercostal muscles of the left thorax and the pleural space was entered between the 4th and 5th ribs by blunt dissection. A small incision was made in the pericardium over the right atrial appendage when the heart was paced electri-

cally. When intralumenal pressures were recorded or drugs injected into the coronary arteries, the pericardium was incised widely lateral to the left phrenic nerve.

2. Procedures for Mechanical Control of the Systemic Blood Pressure

Mechanical elevation of the systemic blood pressure usually was achieved by reversible occlusion of the thoracic aorta. A loose ligature approximately 3 mm. in diameter was placed around the descending thoracic aorta and the ends were brought out through a stiff rubber tube. Reversible occlusion of the vessel was achieved by compression against the rubber tubing. The systemic blood pressure was held constant or altered in other experiments by means of a pressure regulator. This consisted of a 50-litre pressure tank connected to a 2-litre reservoir primed with donor blood diluted no more than 50 percent with 6 percent dextran in 0.9 percent sodium chloride. The reservoir was connected to the animal by means of a cannula of 5 mm. internal diameter which was inserted into the abdominal aorta below the renal vessels. In some experiments, the midline abdominal incision was closed after positioning of catheters; in others, the exposed peritoneal contents were covered with warm pads moistened with saline.

3. Preparation of Spinal Animals

Eight dogs were anaesthetized with open drop ether and the trachea was cannulated. The animals were maintained in surgical anaesthesia by connecting an ether vaporizer to a Palmer respiration pump supplying 100 percent oxygen. After section of the vagi, cannulation of the right carotid artery for blood pressure recording, and applica-

tion of a loose tie around the left common carotid artery, the animal was placed in a prone position with the head acutely flexed over a support. An incision extending approximately 10 cm. caudad from the external occipital protruberance was made in the midline by electrocautery. The spine and arch of the second cervical vertebra were cleared of muscular attachments by electrocautery and periosteal elevators and the cephalad portion of the spine of this vertebra was removed with bone rongeurs. The ligamentum flavum was incised and the dura was cut in the midline. Two ties were placed around the spinal cord with an aneurysm needle. The ligatures were tightened and the cord severed between ties. The left common carotid artery was ligated and a metal rod 5 mm. in diameter was inserted cephalad through the foramen magnum to pith the brain. The foramen magnum was packed immediately with surgical sponges and bone wax. Apparent blood loss during this procedure was less than 10 ml. The systolic blood pressure rarely fell below 100 mm. Hg. The skin incision was closed with loose ligatures following completion of the spinal section and the animal was returned to the supine position. Ether administration was stopped and artificial respiration with 100 percent oxygen was continued for the rest of the experiment. No experimental procedures were carried out for at least 30 minutes to ensure that most of the ether had been excreted.

C. OTHER EXPERIMENTAL PROCEDURES

1. Vagus Nerves

All experiments reported were performed on animals in which bilateral vagotomy was performed at a mid-cervical level. This usually was done immediately after induction of anaesthesia but was delayed approximately 30 minutes in 9 experiments where integrity of the vagi was

necessary for the study.

2. Pressure Recordings

The systemic blood pressure was taken as the end pressure recorded in the right common carotid artery. This vessel was cannulated with number 260 polyethylene tubing (2 mm. I.D.) which was connected to the pressure transducer. Other intralumenal pressures were recorded as lateral pressures. The right and left ventricles were pierced by 15 gauge hubless needles at points approximately 2 cm. lateral to the left anterior descending coronary artery and 2 cm. proximal to the apex. Pressures within the main pulmonary artery were recorded by a 15 gauge hubless needle inserted through a small purse-string suture at a point approximately 1.5 cm. distal to the pulmonary valve. All needles were connected to pressure transducers by number 260 polyethylene tubing.

3. Injection of Pharmacological Agents

Intravenous injections were made into an exposed femoral vein through 27 gauge needles; infusions were given through polyethylene tubing inserted into a femoral vein and advanced into the inferior vena cava.

The main branches of the left coronary artery were visualized by reflecting the left atrial appendage (Figure 1). The left anterior descending and the left circumflex coronary arteries were exposed for lengths of approximately 5 mm. at points approximately 1.5 cm. distal to their common origin. Loose nylon ligatures were placed around the arteries by means of a fine aneurysm needle to stabilize the vessels. The arteries were entered in the direction of blood flow with 27 gauge

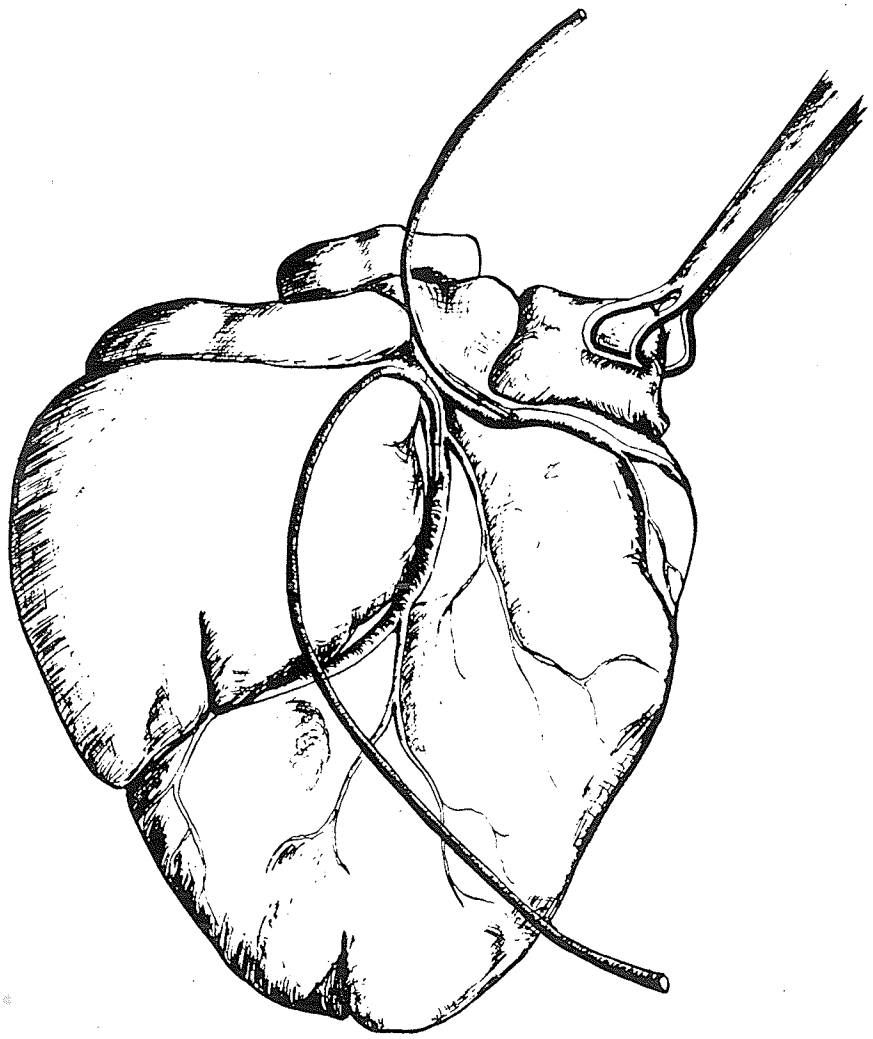

Figure 1. Schematic diagram of the heart showing position of hubless needles in main branches of the left coronary artery. The left atrium has been reflected to show the left circumflex coronary artery. The markings of the coronary arteries have been exaggerated. Dissection was confined to the immediate areas of the arterial punctures.

hubless needles connected to 3-way stopcocks by means of 20 cm. lengths of number 10 polyethylene tubing (0.28 mm. I.D.). The tubing was filled with heparinized saline, and the position of the needle within the lumen could be confirmed periodically by opening the stopcock to the atmosphere and observing the return of arterial blood. Extreme care was taken to prevent even transient occlusion of the coronary arteries during positioning of the needles. Animals were discarded in which such occlusion was believed to have occurred or in which excessive dissection was required to expose the coronary vessels. The absence of local thrombosis at the site of needle puncture was confirmed by necropsy of all animals subjected to this experimental procedure.

D. STIMULATION AND RECORDING TECHNIQUES

Bipolar clip electrodes attached to the right atrial appendage were used to pace the heart. A Tektronix stimulator supplied rectangular pulses of 1.0 msec. duration and approximately twice threshold intensity at rates of 25-45 beats/minute greater than the sinus rate.

The peripheral end of the severed right vagus nerve was stimulated by means of bipolar ring or hook electrodes. A Grass model SD5 stimulator supplied 1.0-2.0 msec. rectangular pulses at a frequency and voltage sufficient to slow the heart maximally without loss of sinus dominance (10-30/sec., 5-20 volts). Drying of the nerve was prevented by reflecting loose skin flaps to construct a bath filled with mineral oil.

Lead II electrocardiograms were taken in all dogs using subcutaneous needle electrodes and atrial electrograms were recorded in many open-chest animals. A Statham P23AA transducer was used to measure arterial pressure. Right ventricular and pulmonary artery pressures were

sensed with a Statham P23BB transducer. All parameters were recorded on a Grass ink-writing polygraph at a paper speed of 25 mm./sec.

E. DRUGS EMPLOYED

1. Barbiturates

Barbiturates employed for induction of anaesthesia were injected rapidly into a cephalic vein by percutaneous puncture.

Solutions of sodium thiopental in 0.9 percent sodium chloride were prepared in concentrations of 2 µg./ml.-20 mg./ml. 0.1 ml. of solution was injected into a coronary artery over 5 seconds and 0.1 ml. of heparinized saline was used to flush the drug through the catheter. As control for the high pH of the solution, injections were preceded and followed by injections of 0.9 percent sodium chloride adjusted to the same pH (approximately 11.2) with sodium hydroxide.

2. Sympathomimetic Amines

0.05 to 128 µg./kg. of l-adrenaline diluted to 3.0 ml. with 0.9 percent sodium chloride were injected into a femoral vein over the course of 60 seconds. The interval between injections was 15 minutes for doses less than 4.0 µg./kg., and 20-25 minutes for larger doses. Isoproterenol and phenylephrine in doses of 0.5 to 60 µg./kg. and 25 to 50 µg./kg. respectively, were given as the racemic mixtures by the same method. Sufficient time was allowed between injections of these agents for the blood pressure to return to control values. Animals received only one injection of dl-methoxamine (0.8 mg./kg.). Intravenous infusions of adrenaline at rates of 0.06 to 4.0 µg./kg./min. were administered by a Palmer slow injection apparatus or a Harvard infusion pump.

The infusions were of 7 to 22 minutes duration; 20 to 30 minutes were allowed between infusions.

The tartaric acid salt of adrenaline was employed in all experiments and doses are expressed as the base. All other sympathomimetics were administered as the hydrochloride salts and doses are expressed as such.

3. Adrenergic blocking agents

Dichloroisoproterenol (DCI) and nethalide (ICI 38174, Alderlin^{R}) were administered intravenously in doses of 2-10 mg./kg., and 5-10 mg./kg. respectively. Both agents were injected over 5-10 minutes, and an interval of 30 minutes was allowed for the development of blockade.

4. Acetylcholine

0.5 to 50 µg. of acetylcholine was injected into the coronary arteries. No other routes of administration were employed with this agent.

F. ANALYSIS OF RECORDS

Intervals on the electrocardiograms were determined by means of a measuring magnifier graduated to 0.1 mm. This allowed a precision greater than $\pm$6 msec. at the paper speed of 25 mm./sec. used in recording. Because of the difficulty in finding a standard reference point for measurement in some abnormal complexes, it is probable that the measurements were not more accurate than $\pm$12 msec. The heart rate was read directly from the electrocardiogram. Systolic and diastolic blood pressures were taken from the pulse tracing. In closed-chest animals in which there was considerable respiratory artefact, the peak pressure observed in the 6

seconds preceding experimental procedures was taken as the control blood pressure.

SECTION III

ON THE MECHANISM OF CYCLOPROPANE-ADRENALINE ARRHYTHMIAS

A. INTRODUCTION

It is generally believed that the phenomenon of hydrocarbon sensitization of the myocardium to the production of aberrant rhythms by sympathomimetic amines involves increased susceptibility of ventricular tissue to pacemaker formation (12,13,47,86). It is difficult to reconcile such an effect with the known depressant action of sensitizing agents on the heart. Several suggestions have been made which attempt to explain ventricular automaticity in the face of depression of the myocardium. Riker et al. suggest that adrenaline-induced automaticity of the atrioventricular node normally prevents the development of automaticity of lower centres (43). Multiple ventricular foci of automaticity are thought to emerge in the presence of a hydrocarbon through depression of this primary pacemaker (43). DiPalma and Schultz have advanced the hypothesis that the effect of adrenaline is greater on locally depressed areas than on more normal areas of myocardium (87).

Preliminary investigations to determine whether atrioventricular block preceded cyclopropane-adrenaline arrhythmias revealed that the nature of these arrhythmias changed from ventricular tachycardia to a coupled rhythm as the dose of adrenaline was reduced. The investigations reported here concern themselves with the factors involved in the genesis of this latter arrhythmia.

B. RESULTS

1. Electrocardiographic Changes Induced by Minimal Doses of Adrenaline

The administration of small doses of adrenaline to dogs anaesthetized with cyclopropane consistently produces a bigeminal rhythm. The coupling usually results in a bigeminal rhythm characterized by alternation of normal and abnormal QRS complexes in which the interval between the normal and the abnormal beats is constant or varies within very narrow limits. The abnormal complex occludes the next expected normal beat and produces a "compensatory pause" before the following sinus beat.

Constantly-coupled bigeminal rhythms lasting from 15 seconds to several minutes were produced in 75 of 80 dogs by 0.1-2.0 μg./kg. of adrenaline injected over 60 seconds. The minimum effective dose in most animals was 0.25-1.0 μg./kg. Two of the five dogs in which the arrhythmia was not produced by doses of 2.0 μg./kg. or less displayed isolated "coupling" while three animals were resistant to large doses of adrenaline (4-20 μg./kg.). Bigeminy was induced with equal ease in open- and close-chest animals. The bigeminal rhythm was also produced in 9 non-vagotomized dogs and in 2 dogs which had been subjected to acute bilateral carotid sinus denervation.

Typical records are shown in Figure 2. The signal artefact in Figure 2A indicates the beginning of the one minute injection of 2.0 μg./kg. of adrenaline. The control arterial pressure was approximately 100/75 mm. Hg and the rate of the undriven heart 150/minute. The injection was completed 7 seconds before the first abnormal complex. The arterial pressure had reached 200/165 mm. Hg and the heart rate 180/minute immed-

iately before the onset of the bigeminal rhythm. Figure 2B illustrates the response to 1.0 μg./kg. of adrenaline in an open-chest animal whose atrial rate was regulated at 120/minute. The bigeminy began 5 seconds after completion of the injection. The arterial pressure had risen from 135/110 to 270/185 mm. Hg.

The bigeminal rhythm began and terminated abruptly in most experiments. Isolated ventricular beats ("coupling") were observed before the development of sustained bigeminy in some cases. Multifocal rhythms preceded or followed the bigeminal rhythm if the dose of adrenaline employed was increased. A "pure" bigeminal rhythm could be produced in these cases by decreasing the dose of adrenaline.

The coupling interval has been defined as the time between the R wave of the normal and that of the abnormal complex. At an atrial rate of 170/minute (353 msec. interval) the coupling interval varied between 196 and 332 msec. in different bigeminal rhythms; similar variability was noted at other atrial rates. The coupling intervals observed after any one injection were remarkably constant, varying by no more than $\pm$10 msec. after the first 2 or 3 coupled beats, which usually had a somewhat longer interval and a different configuration (Figure 2).

When the coupling interval is relatively long, the upstroke of the P-wave of the replaced normal beat is sometimes observed before the beginning of the abnormal complex. Figure 3 illustrates a deflection which preceded the T wave of the abnormal beat. This deflection probably represents a P-wave arising through retrograde conduction of the bigeminal beat to the atria. Atrial deflections corresponding to this wave and identical in contour to those associated with the P-wave of the sinus

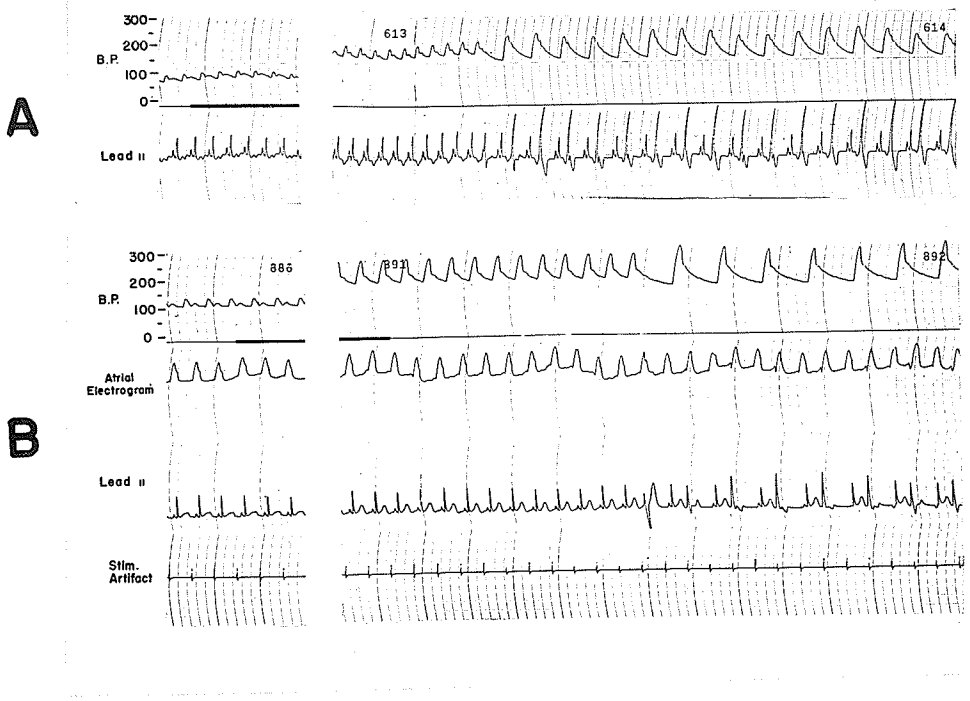

Figure 2. Two typical records showing induction of bigeminal rhythm by adrenaline. A. After 2.0 μg./kg. in a dog in which thoracotomy had not been performed. B. After 1.0 μg./kg. in an open-chest dog with atrial rate controlled at 120 beats/min. Note in both records the constant interval of the bigeminal rhythm after the first two or three coupled beats.

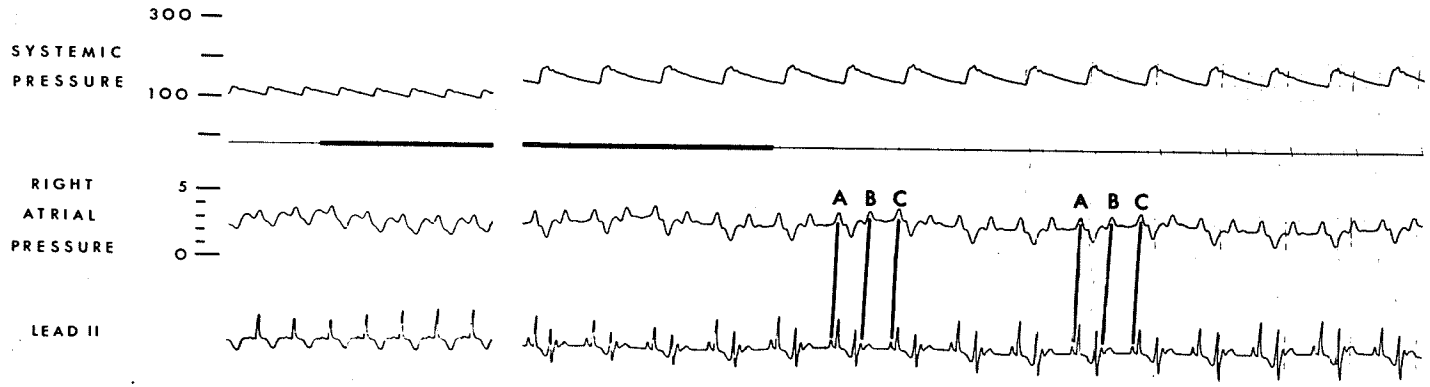

Figure 3. Right atrial pressure recorded in open-chest dog during adrenaline-induced bigeminal rhythm. Systemic and atrial pressures expressed in mm. Hg. Upright deflection preceding T-wave of abnormal beat corresponds to B. The intervals between B and deflections in right atrial pressure tracing corresponding to P-waves of sinus beats (designated A and C) are not equal (448 and 484 msec. respectively).

beat may be observed in the right atrial pressure tracing.

The QRS complexes of the abnormal beats were identical or extremely similar throughout a given response in approximately 80 percent of injections. Some variation in the appearance of the abnormal QRS complexes was noted in the remaining injections. Such variations usually were associated with changes in the coupling interval. However, the coupling interval corresponding to each configuration remained constant. Some of the variations in the fixed-interval bigeminy are illustrated in Figure 4. Figure 4A shows an unusual alternation of two types of coupled beats, each with a characteristic coupling interval (285 and 350 msec. respectively). Figure 4B illustrates a very rare arrhythmia during which the configuration of the abnormal QRS changed without a significant change in the coupling interval of 240 msec. It must be emphasized that Figure 4 illustrates relatively uncommon types of bigeminal rhythm. The typical fixed-interval bigeminy is that shown in Figures 2 and 5.

2. Effects of Other Sympathomimetic Amines

Phenylephrine, a pressor amine which has been shown to induce multifocal ventricular tachycardia when large doses are administered to sensitized preparations (14,59), produced a fixed-interval bigeminy in each of 4 dogs tested when injected intravenously in doses of 25-50 μg./kg. The bigeminal rhythm was associated with a multifocal ventricular rhythm when doses greater than 40 μg./kg. were employed. Methoxamine, a pressor amine with minimal or no direct cardiac action (88,89), caused bigeminy in only 1 of 6 dogs when injected in a dose of 0.8 mg./kg., in spite of the prolonged pressor effect which was always at least equal to that produced by doses of adrenaline causing bigeminy.

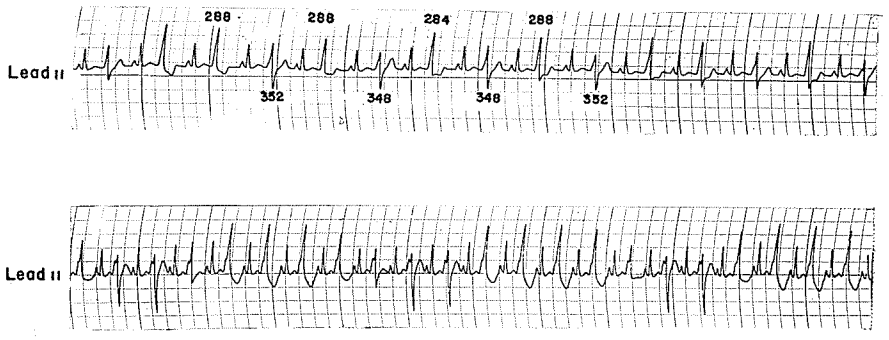

Figure 4. Unusual types of complex coupled rhythms. A. Record begins 21 seconds after completion of injection of 0.5 μg./kg of adrenaline. Note alternation in configuration of the abnormal complexes, correlated with 2 different coupling intervals. B. Record from different dog. The coupling intervals, varying from 232 to 244 msec., are not correlated with the altered appearance of the abnormal QRS complex.

Isoproterenol, a depressor amine with strong cardiac actions which has been shown to cause multifocal ventricular arrhythmias when given in large doses to sensitized preparations (43,48,59,67) did not induce bigeminy in doses of 0.5 to 60 μg./kg. in 7 dogs (17 injections). 0.5-4.0 μg./kg. of isoproterenol generally produced a sinus tachycardia, although a few ventricular beats were observed in this dose range. Although 2 animals developed ventricular fibrillation in response to 5 μg./kg., the usual response to higher doses of isoproterenol was a ventricular or nodal tachycardia.

3. The Role of Foci of Automaticity in the Production of Bigeminal Rhythms

The long compensatory pause after the abnormal beat makes it improbable that an independent ventricular focus of automaticity is involved in the genesis of bigeminal rhythm. A focus discharging at a rate equal to or greater than the sinus rate would be expected to discharge during this pause. One of the more plausible mechanisms of bigeminal rhythm due to ectopic focus formation would involve a parasystolic ventricular focus. According to this concept there exist two independent pacemakers, the sinoauricular node and an autonomous area in the ventricle, each of which discharges at its own rate. To explain a constantly-coupled bigeminal rhythm on this basis, the focus would have to discharge at a frequency precisely one half that of the sinus rate, and would have to be protected from the preceding sinus beat by an "entry block". The interval between the two abnormal complexes would represent the rate of firing of the parasystolic focus.

Figure 5 illustrates results which make ectopic focus formation an untenable explanation for the production of bigeminy. In these experiments bigeminal rhythm was induced by adrenaline both in the normally beating and in the driven heart. The atrial drive was stopped abruptly in Figure 5A, and in Figure 5B the drive was started suddenly. The change in heart rate had no effect on the coupling interval, although the duration of the compensatory pause after the abnormal systole was changed considerably. This constancy of the coupling interval with sudden alterations in the heart rate was a constant finding in all of the open-chest animals in which these manoeuvers were attempted.

4. Effect of Arterial Blood Pressure and of Heart Rate on the Induction of Bigeminy

The bigeminal rhythm produced by adrenaline usually occurred near the end of the sixty-second injection and not at the time the drug would be expected to reach the heart. There was an increase in the blood pressure and usually a tachycardia at the time of onset of the arrhythmia. The means and standard deviations of the control systolic and diastolic pressures were 135 ± 25 and 110 ± 25 respectively. The corresponding values at the point bigeminy was induced were 185 ± 40 and 150 ± 25. The minimal pressor response in animals showing a bigeminal rhythm in response to adrenaline was 20 mm. Hg. The rate of the undriven heart increased by a mean of 20 beats/minute, although in 40 percent of injections there was no increase in the heart rate at the time the bigeminal rhythm began.

Because adrenaline-induced bigeminy was associated with a considerable rise in the blood pressure, and because only pressor

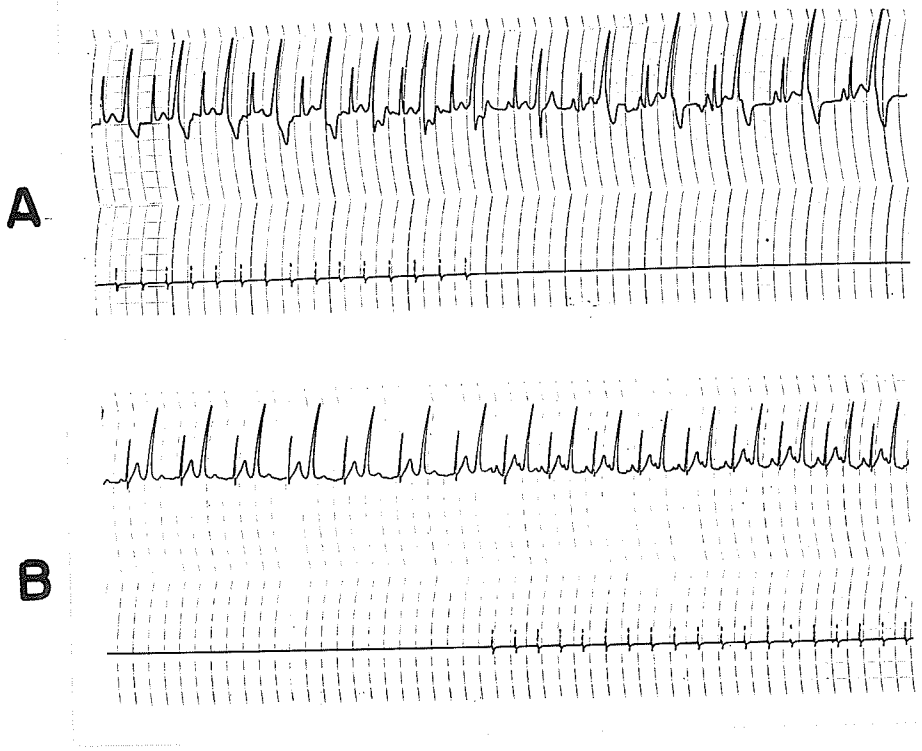

Figure 5. Lack of effect of changes in atrial rate on the coupling interval in two different dogs. A. Bigeminal rhythm with coupling interval of 260 msec. during atrial drive of 187 beats/min., as indicated by the stimulus artefact. The coupling interval is unchanged when the atrial drive is stopped, changing the rate to 145/min. B. Rate prior to atrial stimulation is 171 beats/min. with a coupling interval of 240 to 244 msec. The coupling interval is unchanged by atrial stimulation at a rate of 208 beats/min.

amines with direct cardiac actions caused this irregularity, it appeared probable that the bigeminy was causally related to the hypertension and possibly to the tachycardia.

A fixed-interval bigeminy of long duration was induced in 9 of 10 dogs by constant infusion of adrenaline in doses of 0.06 to 3.0 μg./kg./minute. This arrhythmia could be converted to a sinus rhythm by lowering the systemic arterial blood pressure with a pressure regulator, and could be reinduced at will be again raising the pressure. Although the blood pressure level at which bigeminy was induced or reinduced varied in different experiments, it appeared to be quite constant during any one infusion of adrenaline. This blood pressure "threshold" is strikingly illustrated in Figure 6. The thorax had not been opened in this animal and there was considerable rhythmic variation of the blood pressure with the artificial respiration. Infusion of 3.0 μg./kg./min. of adrenaline resulted in an increase in pressure just sufficient to associate the bigeminy with the phasic changes in arterial pressure. Bigeminy occurred whenever the systolic pressure reached 235 mm. Hg. and conversion to sinus rhythm occurred when the systolic pressure decreased below this point. Controlled alteration of the arterial pressure by means of a pressure regulator had the same effect in this dog: bigeminy appeared at a systolic pressure of 235 mm. Hg with conversion to sinus rhythm below this pressure.

The response to further elevation of the systemic blood pressure during a bigeminal rhythm was of considerable interest. Multifocal ventricular rhythms were produced consistently. Restoration of the initial pressure resulted in conversion of the multifocal rhythm to bi-

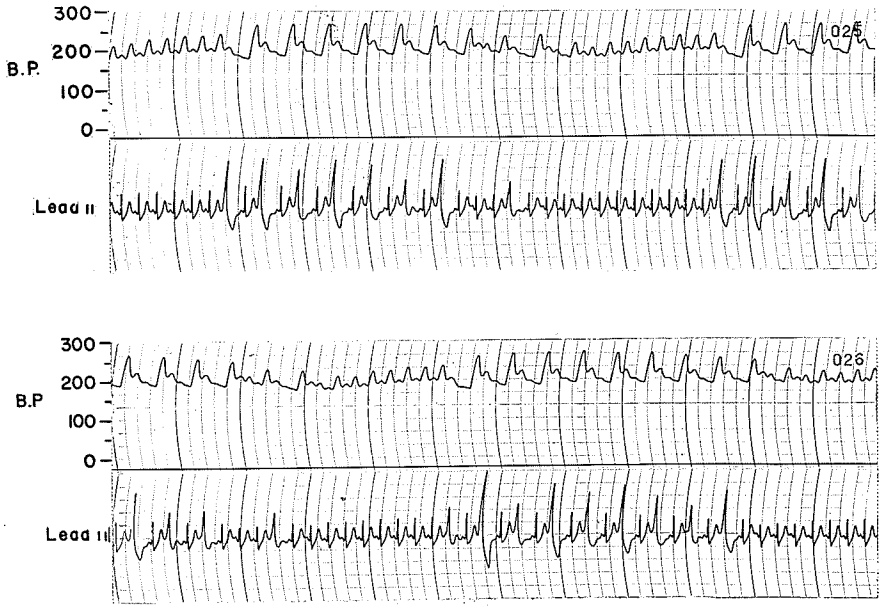

Figure 6. Dependence of the bigeminal rhythm on the systemic blood pressure. Continuous record obtained during continuous infusion of 3.0 μg./kg./min. of adrenaline in close-chest dog. Control blood pressure 165/120 mm. Hg. Note dependence of bigeminy on respiratory fluctuations in blood pressure. See text for details.

geminal rhythm, and to sinus rhythm as the pressure was lowered still further. Ventricular fibrillation was never observed. Figure 7 provides a representative example of one such experiment.

The threshold dose of adrenaline for the induction of bigeminy was determined in three dogs. No changes in threshold were observed when the atrial rate was controlled by stimulation at a frequency of 25 to 35 beats/minute greater than the preinjection sinus rate.

Blood pressure and/or heart rate also were altered without injection of a sympathomimetic amine. Tachycardia induced by stimulation of the atrial appendage caused bigeminal rhythm of short duration in only 3 of 31 open-chest dogs. An increase in blood pressure comparable to that induced by an effective dose of adrenaline, but achieved by rapid infusion of a blood-dextran mixture from the pressure stabilizer, induced bigeminy in only 1 of 9 trials in three dogs. When this increase in blood pressure was combined with tachycardia, bigeminal rhythm was induced in 6 of 14 trials in the same animals.

When the depressor response to isoproterenol was reversed by means of the pressure regulator, by constriction of the thoracic aorta, or by prior infusion of 6 percent dextran in saline, 1-4 μg./kg. of this drug induced bigeminy in three of six animals.

5. The Site of Production of Bigeminal and Multifocal Ventricular Rhythms

Dresel and Sutter have reported that vagal stimulation abolished bigeminal rhythms and that multifocal ventricular rhythms were changed to bigeminal or sinus rhythms by this procedure (54). These changes, which were blocked by atropine, were not related to the fall

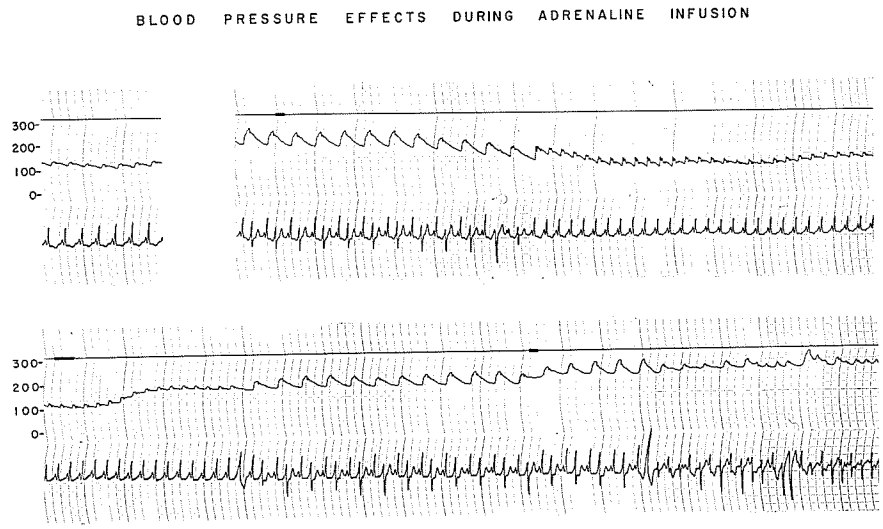

Figure 7. The effect of changes in systemic blood pressure during continuous infusion of 2.0 μg./kg./min. of adrenaline. Signal marker, systemic blood pressure, and lead II electrocardiogram are indicated in each record. Strip at top left is preinfusion control; remainder of record is continuous. First signal: start of bleed-out into arterial pressure reservoir, leading to conversion to sinus rhythm. Second signal: beginning of reinfusion of shed blood, re-establishing bigeminy. Third signal: infusion of extra blood resulting in multifocal arrhythmia.

in systemic blood pressure induced by vagal stimulation. These results have been confirmed in the present investigation.

Dresel and Sutter suggested that the atrioventricular node and the bundle of His are involved in the production of bigeminal and multifocal arrhythmias. The known antiarrhythmic properties of acetylcholine (41,50) and the anatomical evidence that the left circumflex coronary artery supplies the atrioventricular node (see appendix) suggested that their hypothesis could be tested by injections of acetylcholine into this artery.

Acetylcholine in doses of 0.5-50 μg. was injected into the main branches of the left coronary arteries of two dogs during sinus rhythm. Complete heart block uniformly followed injections into the left circumflex coronary artery, but never injections into the left anterior descending artery. Figure 8 illustrates the responses to injection of 5 μg. of acetylcholine into the two arteries. Doses of acetylcholine in excess of 10 μg. injected into the circumflex artery usually were associated with the production of atrial arrhythmias. This is not surprising since this artery supplies the left atrium (90,91) and choline esters are known to produce atrial arrhythmias (41,92).

Doses of 0.5-50 μg. of acetylcholine were injected into either the left circumflex or the left anterior descending coronary arteries of 3 dogs during sustained bigeminal or multifocal rhythms produced by infusions of adrenaline. The bigeminal rhythms were converted to sinus rhythms by injection of small doses of acetylcholine into the left circumflex artery, but this effect was not observed after injection into the left anterior descending artery. Figure 9A illustrates the response to

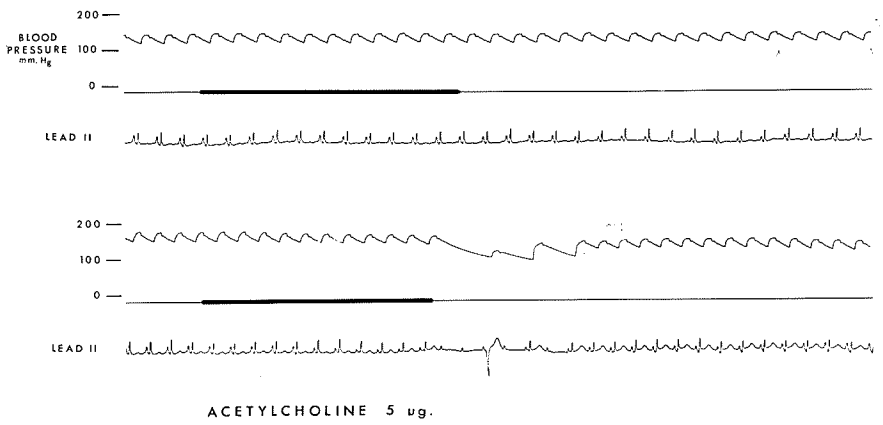

Figure 8. Effect of injection of acetylcholine into the main branches of the left coronary artery during sinus rhythm. Upper panel: Injection of 5.0 μg. of acetylcholine into the left anterior descending coronary artery. No change in the rate or rhythm of the heart is produced. Lower panel: Injection of 5.0 μg. into the left circumflex coronary artery produces a 3-second period of atrioventricular block with one "escape" beat.

0.5 μg. of acetylcholine injected into the two branches of the left coronary artery during bigeminal rhythm, and Figure 9B shows the blockade of the response by atropine.

Interpretation of the response to acetylcholine is complicated by the occurrence of transient atrioventricular block and of hypotension when injections were made into the circumflex artery. Figure 9A shows a transient fall in the systemic blood pressure associated with conversion to sinus rhythm. However, the bigeminal rhythm recurred after 18 seconds at the lower pressure. Thus the possibility that acetylcholine abolishes bigeminal rhythm by lowering the blood pressure can be excluded. This agrees with the observation of Dresel and Sutter who showed that vagal stimulation can abolish such arrhythmias without producing hypotension (54).

When large doses of acetylcholine (20-50 μg.) were employed, injection into the left circumflex coronary artery resulted in brief periods of atrial flutter-fibrillation before conversion of bigeminy to sinus rhythm. Injection of large doses of acetylcholine into the left anterior descending coronary artery during bigeminal rhythm sometimes resulted in conversion to sinus rhythm. This response was never immediate and was associated with a considerable fall in systemic blood pressure due to recirculation. At this time, recirculation also would be expected to result in perfusion of the left circumflex coronary artery with the drug.

Injection of acetylcholine into the left circumflex coronary artery during a multifocal ventricular rhythm usually resulted in a brief change to atrial tachycardia before appearance of the sinus rhythm. Lar-

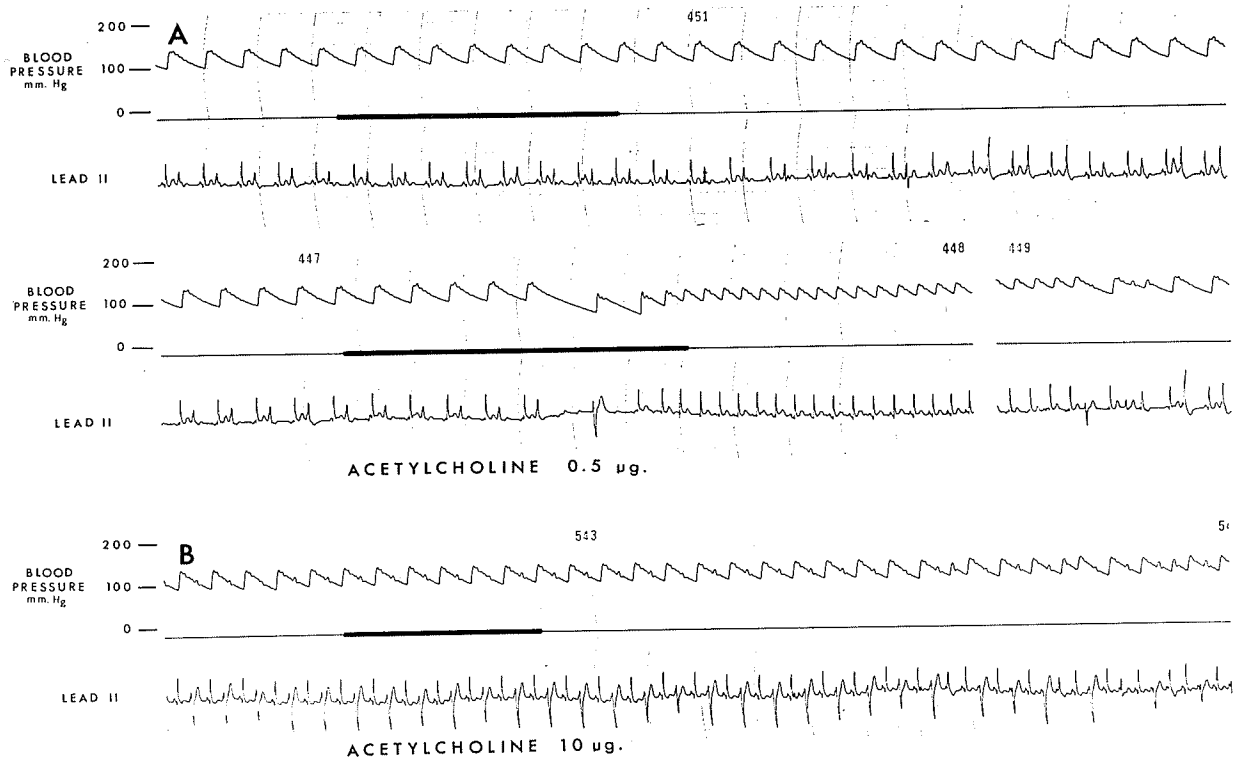

Figure 9. Effect of injection of acetylcholine into left coronary artery during bigeminal rhythm. A. Upper panel: 0.5 ug. of acetylcholine into left anterior descending coronary artery. Lower panel: same dose into left circumflex coronary artery. 10 seconds of sinus rhythm have been deleted from the record. B. Response to 10 ug. of acetylcholine into the left circumflex coronary artery following treatment with 2.0 mg./kg. of atropine.

ger doses of acetylcholine were required to produce conversion of a multifocal rhythm than of a bigeminal rhythm. The response to 10 μg. of acetylcholine injected into the circumflex artery is illustrated in Figure 10. Injections into the anterior descending coronary artery were not effective in abolishing multifocal arrhythmias.

6. Effect of Agents Blocking the Cardiac Actions of Adrenaline

a. Dichloroisoproterenol

Dresel has shown that dichloroisoproterenol (DCI) is a very potent antagonist of ectopic pacemaker induction by adrenaline in barbiturate anaesthetized dogs (93). Moran et al. have reported that adrenaline-induced arrhythmias in unanaesthetized dogs with surgically-produced myocardial infarctions are minimized by administration of large doses of DCI (94). This agent also will prevent or minimize the multifocal ventricular arrhythmias produced by noradrenaline in the presence of cyclopropane (95) or of electrical stimulation of the ventricle (96). Consequently, it was of interest to compare the effect of this blocking agent on the major arrhythmias (ventricular tachycardia and ventricular fibrillation) and on bigeminy induced by adrenaline in the sensitized preparation.

The threshold for bigeminal rhythm was determined before and 30 minutes after the intravenous administration of DCI. A dose of 4.0 mg./kg. of DCI was used most commonly because this appeared to be close to the largest dose with which blocking specificity is retained without nonspecific cardiac depression (97). The effect of a dose of adrenaline (20 μg./kg.), which caused fibrillation in most unprotected animals, was observed subsequently. Representative records from 1 of 5 such experi-

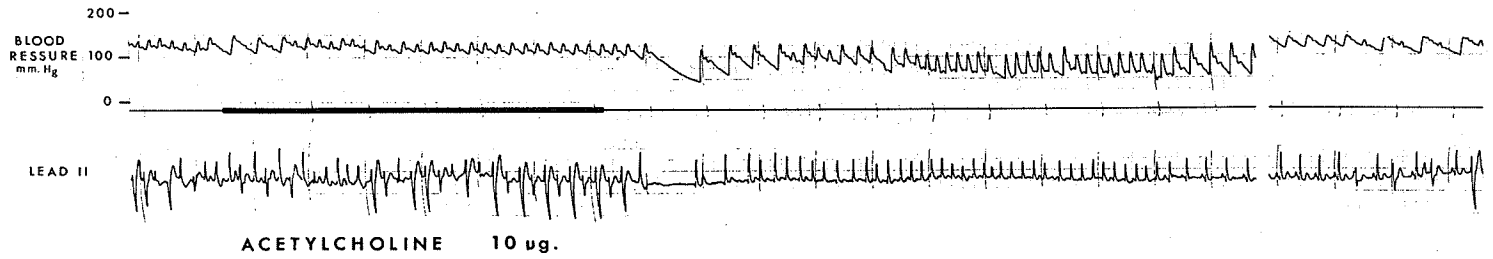

Figure 10. Effect of injection of 10 ug. of acetylcholine into the left circumflex coronary artery during multifocal rhythm produced by infusion of 2.0 ug./kg./min. of adrenaline. There is a brief period of atrioventricular block and a 9 second period of supraventricular arrhythmia before establishment of sinus rhythm. 18 seconds of sinus rhythm have been deleted from the record.

ments are shown in Figure 11, which also illustrates the expected sinus tachycardia due to the intrinsic sympathomimetic activity of the blocking agent. It is evident that the threshold for bigeminy was unchanged by 4.0 mg./kg. of DCI, whereas the major arrhythmia expected in response to the larger dose of adrenaline was prevented, bigeminy of long duration being the only abnormal rhythm produced. The threshold for bigeminy was unaltered in 3 of 5 dogs and was doubled in the remaining two animals. Ventricular fibrillation was prevented in all animals.

b. Nethalide (ICI 38174, Alderlin^{R})

Sutter and Dresel investigated the mechanism of the failure of DCI to block consistently the bigeminal rhythm induced by minimal doses of adrenaline (98). They confirmed the above results and also showed that previously ineffective mechanical elevation of the blood pressure induced bigeminy in animals which had received DCI, but in which there had been no change in the adrenaline threshold for bigeminy. Sequential administration of methoxamine and DCI (neither of which alone produced bigeminy) induced bigeminal rhythms in 7 of 8 animals. They interpreted these results to indicate that the intrinsic activity of DCI was involved in the failure to block bigeminal rhythm. The evidence presented in subsections 2 and 4 above suggested that a sympathomimetic with cardiac actions and an increase in the systemic blood pressure were required for the induction of bigeminy. Sutter and Dresel suggested that adrenaline provided the increase in blood pressure through peripheral vasoconstriction, and DCI the cardiac sympathomimetic action through its intrinsic activity.

Since an agent is now available which blocks the inhibitory and

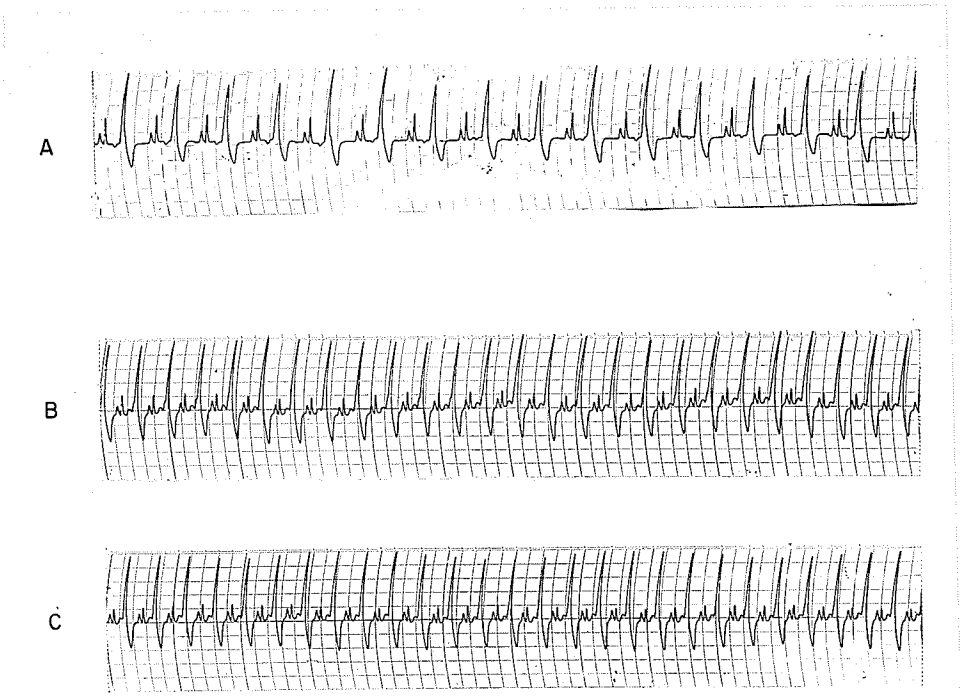

Figure 11. Effect of dichloroisoproterenol on major and minor arrhythmias. A. Effect of control threshold dose of 2.0 μg./kg. of adrenaline. B. Effect of the same dose 30 minutes after 4.0 mg./kg. of DCI. C. Effect of 20 μg./kg. of adrenaline 40 minutes after DCI.

cardiac actions of adrenaline but which is reputed to have little or no intrinsic activity (99) the experiments of Sutter and Dresel were repeated using this agent, nethalide. The results were essentially the same as those presented for DCI. The adrenaline threshold was doubled in 2 of 3 dogs, and unchanged in the remaining dog after 5 mg./kg. of nethalide. Bigeminal rhythms were produced in the two dogs in which larger doses of adrenaline were given (16 and 20 μg./kg. respectively). In the one dog in which it was attempted, mechanical elevation of the blood pressure did not cause an arrhythmia after nethalide, nor did injection of 0.5 mg./kg. of methoxamine.

The failure of nethalide to prevent the bigeminal rhythm was unexpected, although the results with methoxamine and pressure changes are in full agreement with the interpretation of the DCI effect advanced by Sutter and Dresel. However, in the case of nethalide, the blockade with 5 mg./kg. is not complete since adrenaline in doses of 2-4 μg./kg. still produces a 15-20 beat/minute increase in the heart rate of the vagotomized animal. It is therefore possible that adrenaline still exerted enough effect on the heart to produce bigeminy but not enough to produce major arrhythmias. Larger doses of nethalide were not used in these experiments because of the risk of non-specific cardiac depression.

7. Changes in the Pulse Wave Associated with Bigeminal Rhythm

The pulse deficits seen in Figures 2 and 3 were associated with the bigeminal rhythm in all but two experiments. The pulse wave corresponding to the abnormal beat was absent in most experiments, but pulsus alternans was observed occasionally. The magnitude of the pulse deficit did not appear to be related to the length of the coupling interval.

While no attempt has been made to investigate the mechanism of the associated pulse deficit, certain pertinent observations were made. The apparent rate of ventricular contraction as judged visually in the open-chest animal during bigeminal rhythm is one-half the electrical rate. The ventricles do not contract, or at least do not contract fully, during the bigeminal beats. Figure 12 shows a bigeminal rhythm which followed the injection of 2.0 μg./kg. of adrenaline. The heart rate is only 120/minute and the coupling interval of 452 msec. is unusually long. Although this coupling interval should allow ample time for diastolic ventricular filling, the pulse deficit is complete.

Pressures were recorded within the ventricular chambers and from the pulmonary artery by means of large bore needles inserted through the walls of these structures. This allowed recording of intralumenal pressures without producing valvular incompetence. Figure 13A shows the systemic blood pressure, the electrocardiogram, and the right and left ventricular pressures before and 60 seconds after beginning infusion of 2.0 μg./kg./min. of adrenaline. Bigeminal rhythm is associated with a complete deficit in the systemic pulse wave, a virtually complete deficit in the left ventricular pressure tracing, and a pulsus alternans in the right ventricular tracing. The arrhythmia illustrated in Figure 13B began 24 seconds after the beginning of infusion of 0.8 μg./kg./min. of adrenaline and shows a pulsus alternans in the right ventricle and pulmonary artery, and a complete pulse deficit in the systemic system. While these results support the thesis that there is a derangement of the mechanical contraction of the ventricles during the bigeminal beat, it is possible that diastolic filling also may be compromised when the coupling interval is short.

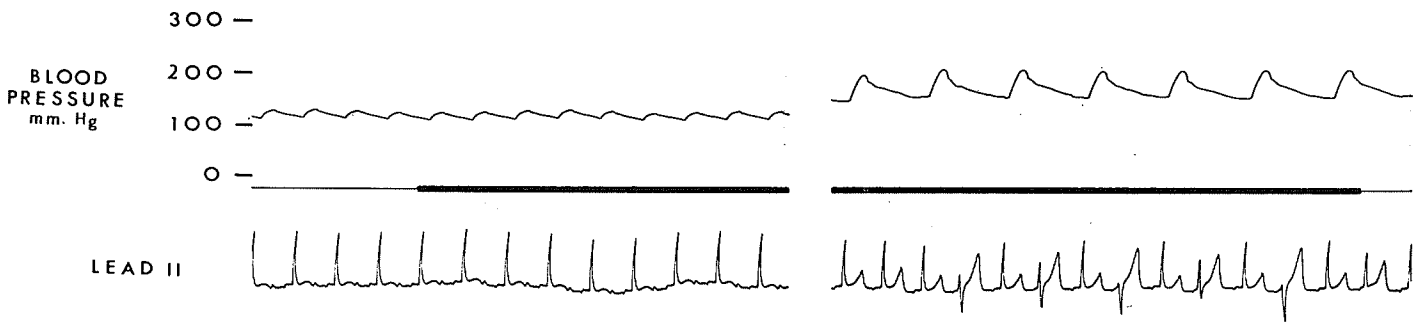

Figure 12. Bigeminal rhythm associated with complete pulse deficit in spite of unusually long coupling interval. The beginning and end of injection of 2.0 ug./kg. of adrenaline is shown. Note the complete pulse deficit despite heart rate of 120/min., and the coupling interval of 452 msec.

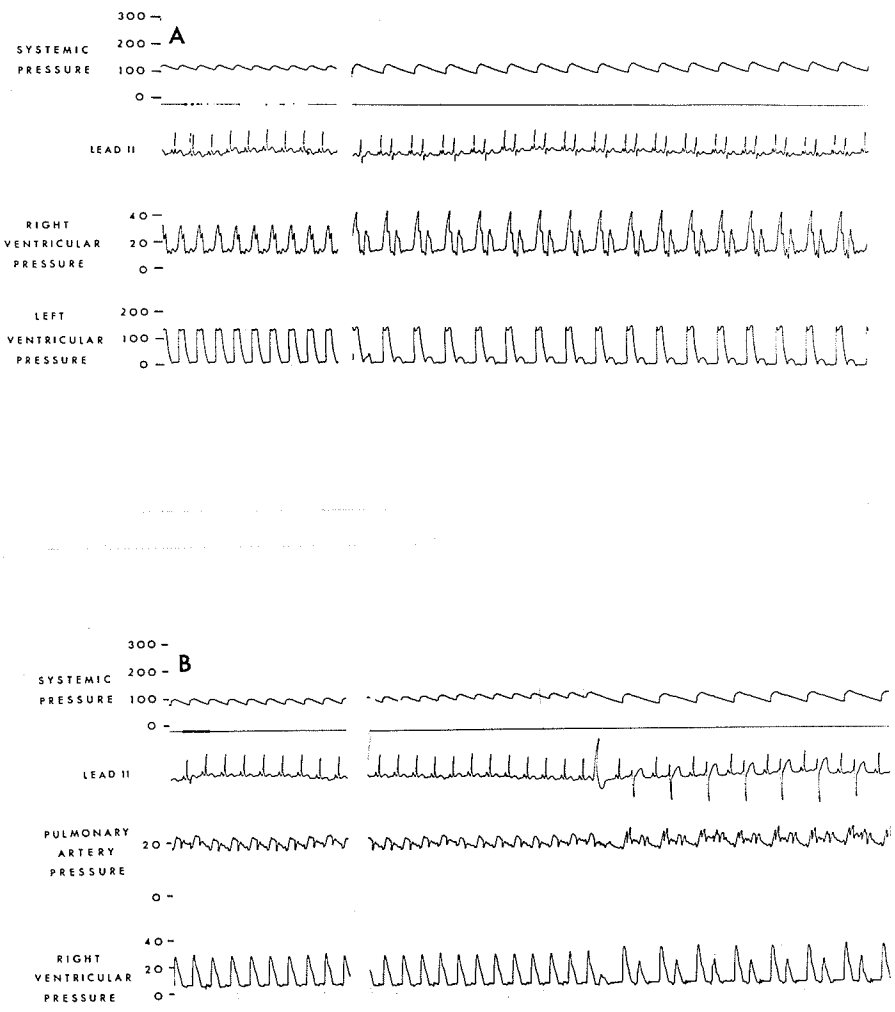

Figure 13. Left and right ventricular and pulmonary arterial pressures during bigeminal rhythm. Note pulsus alternans in right ventricular and pulmonary arterial tracings. The pulmonary arterial tracing shows considerable movement artefact. All pressures are expressed as mm. Hg.

C. DISCUSSION

Although many experimental techniques are available for the production of arrhythmias in vivo, most have the disadvantage that the types of arrhythmia produced are not predictable and do not lend themselves well to experimental study. Experimental cardiologists and physiologists have sought for many years to produce a model arrhythmia which would mimic the "constantly-coupled" arrhythmias which are commonly seen in clinical practice (100).

Bigeminal rhythms have been noted in a variety of experimental circumstances. In most cases no electrocardiograms were recorded and the presence of bigeminal rhythm was inferred from the pulse contours. Few authors comment on the coupling intervals. Allen has described a "bigeminal pulse" occurring in unanaesthetized rabbits on exposure to irritant vapours, only some of which were sensitizing hydrocarbons (101,102, 103). It is not clear from the short electrocardiographic tracing presented whether this represents a constantly-coupled bigeminal rhythm. Walker has described an apparently constantly-coupled bigeminal rhythm occurring in response to intracisternal injection of potassium phosphates in the non-sensitized dog. In the first description of this phenomenon, the bigeminal rhythm is mentioned but other arrhythmias are emphasized and illustrated (104). In a later publication it is inferred that the bigeminal rhythm is the main arrhythmia produced (105). The techniques of Allen and Walker probably both evoke maximal autonomic discharge.

Allen also has described a bigeminal pulse occurring after intravenous administration of adrenaline to the non-sensitized rabbit (106).

However, it is clear from the electrocardiogram presented in this report that the bigeminal pulse is due to the coupling of two ventricular beats. Several authors comment upon "bigeminal rhythms" occurring in response to sympathomimetics in dogs anaesthetized with morphine and barbiturates (107,108). Dresel has noted the occasional production of bigeminal rhythm in dogs anaesthetized with pentobarbital (46).

The occurrence of a bigeminal rhythm has been related to an increase in the systemic blood pressure by several of these authors (106,107,108). This rhythm occasionally may be induced by elevations of the systemic blood pressure regardless of the type of anaesthetic agent present. Thus Levy produced bigeminal rhythms by elevating the systemic blood pressure in the presence of either chloroform or ether (27) and Moe induced bigeminy in the heart lung preparation by increasing the arterial resistance (47). Bigeminal rhythms also have been noted in response to mephentermine in the cyclopropane-sensitized dog (109), to pitressin both in the unanaesthetized and anaesthetized dogs (110,111) and to methoxamine in the barbiturate anaesthetized dog (112, 113). These authors did not provide electrocardiographic records nor did they comment on the type of bigeminal rhythm or the coupling interval. Only Ellis (112,113) documents the frequency of occurrence of bigeminal rhythm. Methoxamine induced bigeminy in only 10 percent of his experiments.

Injection of hypertonic saline, barium chloride and other agents into the ventricular myocardium is stated occasionally to produce constant coupling of beats (114). Dresel was unable to confirm these results using the first mentioned irritant (personal communica-

tion). Several authors have noted a constantly-coupled bigeminal rhythm following infusion of the antimalarial amodiaquin (115,116,117), and Alousi documents the sensitivity of this arrhythmia to the level of systemic blood pressure (115). Pressure-sensitive bigeminal rhythms have been noted by Gruber to occur for a short time after induction of anaesthesia with thiobarbiturates (see SECTION IV).

It should be emphasized that the term "bigeminal rhythm" may be applied to many of these arrhythmias only in the generic sense of indicating coupling of beats. Only the amodiaquin and thiopental bigeminal rhythms are known to be constantly-coupled. With the single exception of the amodiaquin arrhythmia, none of the procedures appears to provide an arrhythmia of sufficient stability and reproducibility for experimental study.

There are few notations of a bigeminal rhythm occurring during cyclopropane anaesthesia. Johnstone has noted a 90 percent incidence of bigeminal rhythm in patients anaesthetized with cyclopropane after thiopental premedication (118). This occurred only when hypoxia was allowed to develop. The release of endogenous catecholamines and the increased sympathetic tone in this situation makes this observation a clinical counterpart of the experiments described in this report.

The cyclopropane-adrenaline preparation has been employed since 1937 in the study of major cardiac arrhythmias. During this time, little or no attention has been given to the minimal effects produced by small doses of adrenaline. Moe et al., in the course of an investigation on the effects of arterial pressure on the major ventricular arrhythmias, reported a bigeminal rhythm following the rapid injection of 0.5 µg./kg.

of adrenaline in a dog anaesthetized with cyclopropane (47). It appears from their illustration that this bigeminy had a constant coupling interval. Greisheimer et al. employed a similar technique of injection and commented that "the commonest irregularity noted after epinephrine was a bigeminal rhythm" (119). However, their illustrations show "coupling" of beats rather than a sustained bigeminal rhythm. Deterling et al. illustrate an apparently constantly-coupled bigeminal rhythm following infusion of noradrenaline at 0.5 µg./kg./min. (120). All three groups of authors employed cyclopropane concentrations similar to those employed in this study and routinely used thiopental for premedication. The above appear to be the only notations of bigeminal rhythm following small doses of adrenaline or noradrenaline, although there are references to bigeminal rhythm following larger doses of adrenaline, usually during recovery from multifocal ventricular tachycardia (49,69).

The failure to appreciate the frequency with which bigeminal rhythms occur in cyclopropane-anaesthetized dogs may be attributed to differences in technique. The response to a given dose of adrenaline depends in large measure upon the rate at which the dose is delivered to the heart. Most authors reporting on administration of small doses of adrenaline have given the drug over a few seconds. Those employing longer periods of injection usually have followed Meek's protocol (standard dose of 10 µg./kg.) (11). The technique employed in the current study of administering small doses of adrenaline over a sixty-second period appears to be unique.

Spontaneous arrhythmias under cyclopropane were not observed in the present study. This probably is referable in part to the use of

a relatively low concentration of cyclopropane. Since the incidence of spontaneous arrhythmias under cyclopropane is related to the concentration employed (11), the use of a low concentration would minimize the occurrence of such arrhythmias. Possibly of more importance is the fact that cyclopropane was delivered to the animal by means of a respiration pump. The explosive risk inherent in this procedure was accepted to ensure that the animal would be ventilated adequately. It appears unlikely that hypoxia or hypercarbia could exist under the conditions of these experiments. Neither condition was present on a few occasions when partial pressures of arterial oxygen and carbon dioxide were measured. The fact that the threshold dose of adrenaline for the production of bigeminal rhythm was remarkably reproducible in the present investigation is probably a reflection of the stability of the preparations and indicates that extraneous factors were not operative.

The presence of a sympathomimetic amine with cardiac actions appears to be necessary for the development of bigeminal rhythm. Methoxamine, which has little or no cardiac activity, produced approximately the same incidence of bigeminy in the sensitized preparation as Ellis reported in the nonsensitized preparation (approximately 10 percent) (112, 113). These results are consonant with those of several authors (59,88, 121) who have reported methoxamine not to produce major arrhythmias in the sensitized preparation.

The development of bigeminal rhythm is also dependent upon an increase in the systemic blood pressure. Isoproterenol, which has strong cardiac actions, but which lacks vasoconstrictor activity, caused bigeminal rhythm only when the depressor response was reversed mechanically.

The finding of a systolic pressure threshold for induction of bigeminy supports the conclusion previously reached in connection with the major arrhythmias that it is the blood pressure level reached rather than the extent of the pressure rise which is decisive in the induction of arrhythmias (48). It was of considerable interest to note that if the blood pressure was elevated mechanically during a bigeminal rhythm, multifocal ventricular rhythms were produced which could be changed to bigeminal rhythm by restoring the initial pressure, or converted to sinus rhythm by lowering the pressure still further. However, Dresel and Sutter have pointed out that ventricular fibrillation is never produced by mechanical increases in pressure although systolic pressures as great as 460 mm. Hg were obtained (54). In this context it is interesting that Moe et al. have reported that increasing the arterial resistance of the cyclopropane-sensitized heart lung preparation during injection of adrenaline produces ventricular tachycardia but not ventricular fibrillation (47).

It also has been demonstrated that vagal stimulation does not alter the threshold dose of adrenaline required for ventricular fibrillation, but will abolish adrenaline-induced bigeminal rhythms and produce conversion of multifocal ventricular rhythms to bigeminal or sinus rhythms (54). The latter changes, which were blocked by atropine, were not related to the fall in systemic blood pressure induced by vagal stimulation. These investigations suggest a basic similarity between adrenaline-induced bigeminal and multifocal rhythms and tend to disocciate these rhythms from ventricular fibrillation. On the basis of these results Dresel and Sutter suggested that bigeminal and multifocal ventricular

rhythms arise in a supraventricular locus and sought to implicate the atrioventricular node or the bundle of His in the genesis of these arrhythmias (54).

There is excellent anatomical and pharmacological evidence that the atrioventricular node derives its blood supply from the left circumflex coronary artery (see Appendix I). Conversion of adrenaline-induced ventricular arrhythmias in the sensitized preparation by parenteral injection of choline esters has been reported previously (41,92). Acetylcholine has been demonstrated in the present investigation to abolish adrenaline-induced bigeminal and multifocal arrhythmias when injected into the left circumflex coronary artery but not when injected into the left anterior descending coronary artery. This finding strongly supports the thesis that the region of the atrioventricular node is involved in the genesis of these arrhythmias.

There is strong evidence that the bigeminal rhythms produced by adrenaline are not due to the induction of a focus of automaticity in the ventricle. A ventricular focus discharging at a rate equal to or greater than the sinus rate would be expected to activate the heart during the long compensatory pause which follows the bigeminal beat. A parasystolic focus of automaticity discharging at a slower rate could produce a bigeminal rhythm, but the rate of discharge of such a focus would have to be exactly one half the sinus rate for constant coupling to occur. Any change in the sinus rate would alter this temporal relationship and produce a change in the coupling interval. The changes in heart rate produced by stopping and starting atrial drive, and illustrated in Figure 5, were of sufficient magnitude to cause major changes in

the coupling interval were this mechanism involved.

Scherf and Schott (122) have attempted to reconcile automaticity with dependency on supraventricular beats by suggesting that oscillatory afterpotentials are produced in an area or cell in the ventricle by the normal impulse, and that activation of the myocardium occurs when the potentials reach a critical level. Coupling which remains fixed in spite of changes in atrial rate could be explained on this basis. Oscillating potentials have never been observed in the region of the atrioventricular node but have been confirmed by microelectrode studies of isolated ventricular myocardium exposed to aconitine (123). It should be noted that the arrhythmia induced by subepicardial injection of aconitine is a monofocal ventricular tachycardia which is not dependent on supraventricular beats and which usually leads to ventricular fibrillation (100). Vagal stimulation makes this arrhythmia more severe by depressing supraventricular centres (100).

Although no direct evidence can be advanced to explain the mechanism of bigeminal rhythm, the development of a reentry type of conduction defect occurring in the region of the atrioventricular node seems an attractive hypothesis. The main argument against a reentry mechanism has been the long period which such a beat would have to be delayed for such a hypothesis to be feasible. Such an argument becomes less compelling with the recent measurements of conduction velocities on the order of 0.02-0.05 metres/sec. in the superior portion of the atrioventricular node (124,125) and of the renewed interest in the concept of decremental conduction in cardiac tissue in general (124). An additional valid argument against reentry occurring in the node or

main bundle is the assumption that a beat "originating" above the bundle branches should have the same QRS configuration as a sinus beat. However, direct irritation of the atrioventricular node, in the absence of trauma to areas below the bundle of His, has been reported to produce abnormal QRS complexes (126).

D. SUMMARY

Small doses of adrenaline (0.1-2.0 μg./kg.) injected over 60 seconds into thiopental-cyclopropane anaesthetized dogs produce bigeminal rhythms characterized by an exceptionally constant interval between the coupled beats. Phenylephrine also causes this arrhythmia but methoxamine does so only rarely. Isoproterenol does not produce the response unless the depressor response is reversed mechanically. An elevation in systolic pressure is required for the appearance of bigeminy, but the arrhythmia can be elicited consistently only in the presence of both an increase in pressure and a sympathomimetic amine with cardiac stimulant action. A parasystolic focus of automaticity has been excluded in the genesis of the abnormal ventricular beat by demonstrating the constancy of the coupling interval despite sudden changes in the atrial rate. Circumstantial evidence indicates that bigeminal and multifocal ventricular rhythms may be produced by similar mechanisms, and that the locus of production of these arrhythmias probably is in the region of the atrioventricular node.

SECTION IV

THE ROLE OF THIOPENTAL IN CYCLOPROPANE-ADRENALINE ARRHYTHMIAS

A. INTRODUCTION

Cyclopropane was employed for both induction and maintenance of anaesthesia in the basic investigations of Meek et al. on sensitization to adrenaline by cyclopropane (11, 14-18). Since this time, however, it has become common laboratory practice to employ thiopental for induction of anaesthesia in the study of cyclopropane-adrenaline arrhythmias. Although textbooks of pharmacology speak of the smooth and rapid induction of anaesthesia with cyclopropane, a well-marked excitement stage occurs in the untrained animal. Thiopental has the very definite advantage of preventing this stage with its accompanying endogenous release of catecholamines. Most authors assume that the duration of its cardiac effects would be equal to that of the anaesthetic effect. Implicit in the use of thiopental is the assumption that it does not alter the response to adrenaline under cyclopropane anaesthesia.

Thiopental itself has been reported to produce cardiac arrythmias. Gruber (127) and Gruber et al. (128) have reported that 20 mg./kg. of thiopental sodium produces a bigeminal rhythm in lightly etherized or decerebrate cats, dogs and rabbits. Their illustrations indicate this is a constantly-coupled rhythm, and the blood pressure records, obtained with a mercury manometer, indicate a slowing of the pulse. Gruber recognized that the pulse tracing probably reflected a pulse deficit due to bigeminal rhythm (127). Gruber et al. produced the arrhythmia with 34 of 41 injections of thiopental in dogs. Bigeminal rhythm was induced in the remaining 7 by occlusion of the common carotid arteries (128). This manoeuver became progressively less effective as the anaesthesia lightened, and arrhythmias could not be pro-

voked when the animals showed signs of wakening (129). Production of the arrhythmia appeared to be associated with a slow rise in blood pressure produced by thiopental, and the bigeminal rhythm could be abolished by depressor agents such as acetylcholine, histamine, quinidine and nitrates, or by haemorrhage (128). Although the arrhythmia could be produced in vagotomized or atropinized animals, vagal stimulation was stated both to induce bigeminal rhythm and to abolish an existing bigeminy (127,128). The latter phenomenon, which was blocked by atropine, was attributed to the concomitant fall in blood pressure. The arrhythmia also was abolished by adrenaline. It is not clear whether the adrenaline experiments were performed on vagotomized dogs, nor is it certain whether conversion to sinus rhythm occurred during the pressor response or during a subsequent depressor response.

Several authors have confirmed the observation that administration of thiopental may produce arrhythmias which are usually of a bigeminal nature (130-134) although others have reported their absence (135-141) or an incidence of arrhythmias of less than 10 percent (142).

Gruber's group described a latent period of several minutes after administration of the thiobarbiturate before arrhythmia developed. They almost consistently noted some elevation of the blood pressure during this interval. It is difficult to understand how thiopental produces this pressor response. Several investigations on the effect of thiopental on the dog heart-lung preparation agree that thiopental causes an increase in right atrial pressure, a decrease in cardiac output, and a diminished cardiac reserve (30,140,142). Interpretation of results in intact animals is complicated by the use of other agents to

maintain basal anaesthesia. Such studies indicate, however, that acute administration of thiopental results in decreased ventricular contractile force, stroke volume, and cardiac output (137,143-145). Cotton et al. have reported a slight decrease in the contractile force of the myocardium on administration of 20 mg./kg. of thiopental to unanaesthetized dogs (139). Gruber himself has observed cardiac dilatation and a decrease in the force of contraction (127). These data suggest that the hypertensive response of thiopental may be a peripheral effect. Since thiopental is a respiratory depressant, the pressor response may have been a consequence of increased vasomotor tone produced by hypoxia or hypercarbia.

Gruber did not give artificial respiration to the dogs employed in his experiments. He comments in his first publication that bigeminy was produced regularly in cats and rabbits breathing spontaneously, but occurred rarely under artificial respiration (127). Bigeminal rhythm was not produced by thiopental in monkeys unless they were premedicated with relatively large doses of morphine (2.5-5.0 mg./kg.) (127). Without exception, those authors corroborating Gruber's results also did not provide artificial respiration (130-134), while those reporting minimal or no arrhythmias under thiopental ensured adequate pulmonary ventilation (135-142).

Woods et al. reported that arrhythmias similar to those described by Gruber were produced in animals breathing spontaneously, but were produced only terminally when the animals were in "almost complete peripheral vascular failure" if artificial respiration was given (140). Johnstone found that no arrhythmias were produced by thiopental in well-

ventilated patients, but that bigeminal rhythms could be produced by exclusion of the carbon dioxide absorber from the system, and abolished again by reintroducing the soda lime (141). It seems probable, therefore, that the "spontaneous" bigeminal rhythm occurring after administration of thiopental is related to inadequacy of pulmonary ventilation and probably to carbon dioxide retention.

It is probable that animals subjected to respiratory depressants are in a more physiological state when artificial respiration is used than when they are breathing spontaneously. All experiments reported in SECTION III were performed on animals ventilated with a pump supplying an excess of oxygen and connected to a carbon dioxide absorber. Arterial blood gases were within normal limits on the few occasions that they were measured. Nevertheless, it was thought necessary to determine whether thiopental influenced cyclopropane-adrenaline arrhythmias under the conditions of these experiments.

B. RESULTS

1. Arrhythmias Occurring in Dogs Anaesthetized with Thiopental

a. Experiments in Intact Dogs

i. Spontaneous arrhythmias

Eight dogs receiving 20 mg./kg. of thiopental were subjected to immediate tracheostomy; artificial respiration was initiated within 2 minutes of induction of anaesthesia. Observation of the electrocardiogram was begun before induction of anaesthesia and was continued until the animals showed signs of wakening. No spontaneous arrhythmias were observed.

ii. Adrenaline-induced arrhythmias

Seven dogs were anaesthetized with 20 mg./kg. of thiopental. Artificial respiration was instituted, bilateral vagotomy performed, and the animals challenged with 4.0 µg./kg. of adrenaline within 5 minutes of the administration of the thiobarbiturate. Doses of 8 and 16 µg./kg. were given at 10-minute intervals if the initial dose produced no arrhythmias; if arrhythmias were induced, the dose was decreased to 1 or 2 µg./kg.

Adrenaline produced bigeminal rhythm in only 2 of 7 animals at doses of 2.0 µg./kg. or less; 4.0 µg./kg. was effective in one additional animal. Bigeminal rhythm could be produced with adrenaline in these three animals for a period of 30 minutes after induction of anaesthesia. However, only two of the animals continued to show arrhythmias in response to adrenaline after a second injection of 20 mg./kg. of thiopental. Although the duration of anaesthesia after the second dose exceeded 75 minutes, bigeminy was unobtainable in the two animals after 25 and 50 minutes respectively although the dose of adrenaline was increased. The remaining animals showed no arrhythmias even at the largest dose of adrenaline employed, although repeated injections of thiopental to cumulative doses as high as 80 mg./kg. were administered over 90-180 minutes.

The systolic pressure at which bigeminal rhythm was induced in the 3 animals showing this arrhythmia following adrenaline was quite characteristic for each animal (180,200 and 290 mm. Hg. respectively). The remaining 4 dogs showed systolic pressures ranging from 180 to 305 mm. Hg. in response to similar doses of adrenaline. The systemic blood

pressure was raised mechanically at the point of maximal pressor response to adrenaline in one animal in which adrenaline consistently had been ineffective in producing an arrhythmia. This manoeuver reproducibly caused bigeminal rhythm at a systolic blood pressure of 350 mm. Hg. This experiment suggested that the bigeminy might be dependent upon pressure alone. This was investigated further in spinal dogs and is reported in the following section.

Twenty percent cyclopropane subsequently was administered to 6 of the 7 animals. In spite of the long period of thiopental anaesthesia (2-4 hours) and the large doses of thiopental administered (cumulative doses of 40-80 mg./kg.) all animals now showed a bigeminal rhythm in response to 2.0 µg./kg. of adrenaline or less. The systolic blood pressure at which bigeminal rhythm was induced ranged from 110 to 170 mm. Hg in different animals. The seventh animal received only 10 percent cyclopropane through a technical error and did not display bigeminal rhythm.

b. Experiments with Spinal Dogs

Six vagotomized spinal dogs were used to examine further the relationship between thiopental, adrenaline and blood pressure. The chest was opened in four of these dogs and a sling placed around the descending thoracic aorta. The systolic blood pressures of these animals ranged from 85 to 115 mm. Hg and remained remarkably stable.

The responses to 2.0 µg./kg. of adrenaline and to mechanical elevation of the blood pressure (individually and in combination) were determined. Twenty mg./kg. of thiopental was administered and adrenaline was repeated within 5 minutes of injection of the thiobarbiturate and at 15-20 minute intervals thereafter.

Adrenaline produced no arrhythmias when administered to untreated animals. Mechanically-induced elevations of the blood pressure also were ineffective, even when applied at the peak of the adrenaline-induced pressor response. Following administration of the thiobarbiturate, one of the six dogs showed bigeminal rhythm in response to adrenaline but arrhythmia could not be produced with subsequent injections. The systolic blood pressure was elevated mechanically in four of these dogs at the point of maximal pressor response to adrenaline. Bigeminal rhythm was produced consistently by this manoeuver in two animals. Bigeminy also resulted in three of the four dogs when the pressure was increased in the absence of adrenaline (see Table V, subsection 4). No arrhythmias other than bigeminy were observed.

The mean and standard deviations of the systolic pressures required for the induction of bigeminal rhythm in the presence and absence of adrenaline were 240 $\pm$ 35 and 200 $\pm$ 30 mm. Hg respectively. These pressures consistently were greater than those resulting from the injection of 2.0 μg./kg. of adrenaline under the conditions of these experiments (mean: 165 $\pm$ 30 mm. Hg). It would appear that adrenaline produces this arrhythmia only if the pressor response is sufficiently great.

The experiments reported in this section comprised part of a comparative study of the arrhythmic response to adrenaline in the same animals under different conditions of anaesthesia. These experiments are reported more fully in subsection 4.

2. Arrhythmias Occurring under Cyclopropane Anesthesia

a. General Observations

Sixty-five dogs were anaesthetized with cyclopropane without preliminary treatment with thiopental. The convention will be adopted of referring to these dogs as "cyclopropane-anaesthetized" animals to distinguish them from dogs in which anaesthesia was induced with thiopental. The latter will be termed "thiopental-cyclopropane-anaesthetized" animals.

The level of anaesthesia maintained by 20 percent cyclopropane in cyclopropane-anaesthetized dogs was somewhat lighter than the level produced by the same concentration in thiopental-cyclopropane-anesthetized animals. It was necessary to increase the cyclopropane concentration to 25 to 30 percent in 5 dogs in order to produce sufficiently deep anaesthesia for the respiration pump to overcome spontaneous respiratory movements. Four animals were discarded because cyclopropane concentrations in excess of 30 percent were necessary to achieve this effect.

The systolic and diastolic blood pressures and heart rates were measured in cyclopropane-anaesthetized animals approximately 60 minutes after beginning anaesthesia and were compared to a group of thiopental-cyclopropane-anesthetized animals maintained in anaesthesia with the same concentration of cyclopropane. To ensure that the two groups were comparable, only those animals were considered on which no surgical procedures other than tracheostomy, bilateral vagotomy and cannulation of the carotid artery had been performed. 26 animals met this criterion in the cyclopropane group, and 33 in the thiopental-

cyclopropane group. The mean values and standard deviations of these parameters are indicated in Table I. (All values have been rounded to the nearest five).

Since all animals had been subjected to bilateral vagotomy, the tachycardia must represent an increase in sympathetic tone to the heart. This may reflect either the lighter anaesthesia or stimulation of the sympathetic nervous system by cyclopropane as reported by Deutsch et al. in unpremedicated animals (146).

b. Electrocardiographic Changes Induced by Adrenaline During Cyclopropane Anaesthesia

23 of 32 animals anaesthetized with cyclopropane and challenged with 2.0 μg./kg. of adrenaline remained in sinus rhythm. Four displayed bigeminal rhythms; nodal or ventricular rhythms were observed in the remaining 5 dogs. Eight of 16 dogs receiving 4.0 μg./kg. of adrenaline showed no arrhythmias; bigeminal rhythms were observed in 2 animals, and 6 displayed ventricular or nodal extrasystoles. None of these animals was tested at the lower dose. Even 8.0 μg./kg. did not produce arrhythmias consistently in the animals tested. Table II presents the responses to doses of 2.0,4.0,8.0 and 16.0 μg./kg. of adrenaline in a series of 10 animals. To avoid the possibility of tachyphylaxis (see SECTION V) the first three doses were not administered in a fixed sequence. Because of the possibility of ventricular fibrillation, 16.0 μg./kg. was usually the last dose administered. Not all dogs were tested at the two largest doses.

The experiments described in the preceding section demon-

TABLE I

SYSTEMIC BLOOD PRESSURES AND HEART RATES IN CYCLOPROPANE- AND THIOPENTAL-CYCLOPROPANE-ANAESTHETIZED DOGS

	CYCLOPROPANE	THIOPENTAL-CYCLOPROPANE
SYSTOLIC BLOOD PRESSURE	150 ± 30	140 ± 20
DIASTOLIC BLOOD PRESSURE	125 ± 25	115 ± 20
HEART RATE	180 ± 40	145 ± 25 *

* $P < .001$

TABLE II

ARRHYTHMIAS PRODUCED BY ADRENALINE IN CYCLOPROPANE-ANAESTHETIZED DOGS

Dose µg./kg.	Sinus tachycardia	Isolated nodal or ventricular	Bigeminy ± multifocal	Multifocal Ventricular	Ventricular fibrillation
2.0	7/10	1/10	2/10	-	-
4.0	5/10	2/10	2/10	1/10	-
8.0	3/8	2/8	3/8	-	-
16.0	1/6	1/6	1/6	2/6	1/6

strated that bigeminal rhythm rarely is produced by adrenaline in thiopental-anaesthetized dogs. The data presented in Table II indicates that this is also the case in cyclopropane-anaesthetized dogs. Fully 50 percent of animals remained in sinus rhythm after 4.0 μg./kg. of adrenaline when thiopental was omitted. In those animals in which bigeminal rhythm was induced by adrenaline, the arrhythmia appeared at pressures of 165 $\pm$ 25/145 $\pm$ 20 (mean $\pm$ standard deviations).

In contrast to results obtained in cyclopropane-anaesthetized animals, 2.0 μg./kg. of adrenaline will produce bigeminal rhythm and 4.0 μg./kg. more severe ventricular rhythms in thiopental-cyclopropane-anaesthetized dogs. Although exact quantitation is difficult because of the phenomenon of tachyphylaxis (SECTION V), these results indicate that thiopental greatly influences the response to adrenaline in animals anaesthetized with cyclopropane.

3. The Effect of Cyclopropane and Thiopental Administered Sequentially

Since pretreatment with thiopental appeared to modify the response to adrenaline in the cyclopropane-sensitized animal, it was expected that administration of thiopental to animals previously anaesthetized with cyclopropane would have the same effect. Nine dogs were anaesthetized with cyclopropane and alternate large and small doses of adrenaline were administered at 15 minute intervals to a total of 4 or 5 injections. Thiopental (20 mg./kg.) was then administered intravenously over 5 minutes without discontinuing cyclopropane. Most animals showed a fall in blood pressure in spite of the slow injection and two

died within 10 minutes of cardiac failure characterized by a fall in the systemic blood pressure, pulmonary oedema, and bradycardia which progressed to cardiac arrest. The blood pressures and heart rates of the remaining animals returned to control values within 15 minutes after the administration of the thiobarbiturate. In contrast to animals in which anaesthesia was induced with thiopental, there was no relative bradycardia when cyclopropane and thiopental were given in reverse order. One-half hour after receiving the thiobarbiturate, the 7 dogs were challenged with the same doses of adrenaline received during the control period. The results are shown in Table III.

It is apparent from the data presented in Table III that the arrhythmias produced by a given dose of adrenaline tended to be more severe after the addition of thiopental. A greater incidence of ventricular fibrillation in response to moderate doses of adrenaline was observed. An unexpected finding was the rarity of adrenaline-induced bigeminal rhythm. In thiopental pretreated animals this arrhythmia can be produced in 95 percent of animals, whereas in the present series only 2 of 7 animals displayed this arrhythmia.

One possibility for this differential response was the development of tachyphylaxis to the arrhythmic effects of adrenaline during the period of approximately 150 minutes which preceded the addition of thiopental. Three cyclopropane-anaesthetized dogs were maintained with 20 percent cyclopropane for 150 minutes and then challenged with a single injection of 4.0 μg./kg. of adrenaline. 20 mg./kg. of thiopental was then administered and 2.0 and 4.0 μg./kg. of adrenaline administered 30-40 minutes later. The results are shown in Table IV. Thiopental

TABLE III

EFFECT OF THIOPENTAL ON THE ARRHYTHMIC RESPONSE TO ADRENALINE IN CYCLOPROPANE-ANAESTHETIZED DOGS

Adrenaline (μg./kg.)	SINUS TACHYCARDIA		ISOLATED NODAL OR VENTRICULAR		BIGEMINAL ± MULTIFOCAL VENTRICULAR		MULTIFOCAL VENTRICULAR		VENTRICULAR FIBRILLATION	
	Before Thio.	After Thio.	Before Thio.	After Thio.	Before Thio.	After Thio.	Before Thio.	After Thio.	Before Thio.	After Thio.
1-2	4/7	3/7	1/7	2/7	2/7	1/7	0/7	1/7		
3-4	2/7	0/7	2/7	2/7	2/7	2/7	1/7	2/7	0/7	1/7
6-8	1/6	0/6	2/6	0/6	3/6	0/6	0/6	3/6	0/6	3/6
12-16	2/5	0/2	0/5	0/2	2/5	0/2	3/5	1/2	0/5	1/2

appeared to lower the threshold for multifocal arrhythmias, but the expected bigeminal rhythm due to low doses of adrenaline was not observed.

The observation that 2 of 12 animals receiving thiopental died an acute cardiac death suggested that full anaesthetic doses of this agent might produce excessive depression of the myocardium in cyclopropane-anaesthetized dogs. To test this hypothesis, thiopental was administered by slow intravenous infusion so that rapid redistribution of the anaesthetic throughout the body prevented the exposure of the heart to high initial blood levels.

Three cyclopropane-anaesthetized dogs were tested with a single injection of 2.0 μg./kg. of adrenaline. Twenty mg./kg. of thiopental was then infused intravenously over a 60-minute period and adrenaline was repeated 15 minutes after the end of the infusion. None of the animals responded with arrhythmia before thiopental. Typical bigeminal rhythm was observed in each of the animals in response to 1-2 μg./kg. of adrenaline after the infusion of the thiobarbiturate.

The importance of initial high blood levels of thiopental is emphasized by experiments in which 5 mg./kg. of thiopental was administered over 2 minutes to cyclopropane-anaesthetized dogs. None of these animals had responded to 2.0 μg./kg. of adrenaline prior to thiopental. Three of the five animals showed bigeminal rhythm in response to the same dose of adrenaline after thiopental. The remaining animals, however, did not show arrhythmias although the injection of thiopental was repeated at 60-minute intervals to a cumulative dose of 20 mg./kg.

Figure 14A illustrates the response to 2.0 μg./kg. of adrenaline in an animal anaesthetized with cyclopropane only. Figure 14B shows

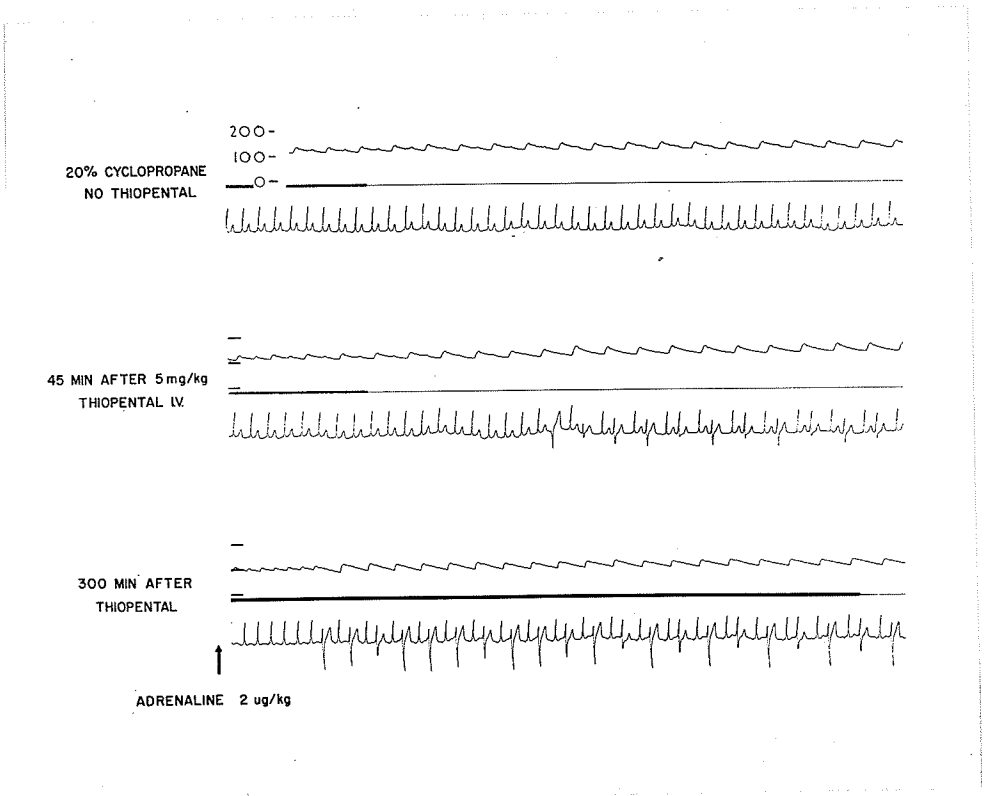

Figure 14. Effect of small dose of thiopental on the response to adrenaline under cyclopropane anaesthesia. A. Response to 2.0 µg./kg. of adrenaline under cyclopropane anaesthesia. No arrhythmias are produced. B. Response to same dose of adrenaline 45 minutes after administration of 5 mg./kg. of thiopental intravenously. C. Response to same dose 300 minutes after administration of thiopental.

TABLE IV

EFFECT OF THIOPENTAL ON THE ARRHYTHMIC RESPONSES TO ADRENALINE IN CYCLOPROPANE-ANAESTHETIZED DOGS

Dog	Before Thiopental	After Thiopental	
	Dose adrenaline µg./kg.	Dose adrenaline µg./kg.	
	4.0	2.0	4.0
83	sinus tachycardia	sinus tachycardia	sinus tachycardia
84	sinus tachycardia	sinus tachycardia	bigeminy + multifocal
85	isolated coupling	multifocal	multifocal

the response to the same dose of adrenaline 45 minutes after the administration of 5 mg./kg. of thiopental. The response illustrated in Figure 14C, obtained 5 hours after the injection of thiopental, demonstrates the very long duration of the cardiac effect of this small dose.

4. The Effects of Various Anaesthetics on Responses to Adrenaline in the Spinal Dog

Six spinal dogs were employed, 4 of which were prepared for reversible occlusion of the descending thoracic aorta. The effects of mechanical elevation of the systemic blood pressure and of injection of 2.0 μg./kg. of adrenaline, either alone or in combination, were tested under the following conditions: 1. no anaesthesia, 2. 20 percent cyclopropane, 3. 20 mg./kg. thiopental, 4. thiopental plus cyclopropane. It was not possible to randomize the sequence of experiments because of the persistent effect of thiopental. In half of the animals, however, condition 2 above was omitted. At least 30 minutes was allowed for equilibration with cyclopropane, and 30-45 minutes for excretion of this agent. These times have been found by Robbins to be adequate for these purposes (85). Adrenaline was not administered more frequently than every 15 minutes.

Table V summarizes the results of these experiments. 2.0 μg./kg. of adrenaline produced no arrhythmias in six animals when no anaesthetic agent was present. Only 1 of 6 animals treated with thiopental showed bigeminy in response to this dose of adrenaline. Bigeminal rhythm was produced in 2 of 3 animals when cyclopropane was the only anaesthetic agent present. It should be noted, however, that such small doses

TABLE V

THE INCIDENCE OF BIGEMINAL RHYTHM IN RESPONSE TO ADRENALINE AND/OR MECHANICAL ELEVATION OF THE SYSTEMIC BLOOD PRESSURE IN THE PRESENCE OF CYCLOPROPANE AND/OR THIOPENTAL (SPINAL DOGS)

	No Anaesthesia	Cyclopropane	Thiopental	Thiopental plus cyclopropane
Adrenaline 2 µg./kg.	0/6	2/3	1/6	4/5
Pressure alone	0/4	0/2	3/4	0/4
Adrenaline + pressure	0/4	0/2	2/4	-

of adrenaline usually do not produce arrhythmias in cyclopropane-anaesthetized dogs (see subsection 2). 2.0 µg./kg. of adrenaline produced bigeminy in 4 of 5 dogs when both thiopental and cyclopropane were present. These results support the conclusion that both thiopental and cyclopropane are required for the consistent production of bigeminal rhythm. It is of interest that pressure alone was instrumental in producing bigeminal rhythm only in dogs treated with thiopental. The failure of increases in pressure to induce the arrhythmia under thiopental-cyclopropane anaesthesia is in agreement with results obtained in intact animals (see SECTION III). The observation that mechanical elevation of the blood pressure leads to bigeminal rhythm more readily in thiopental-treated dogs than in those treated with both thiopental and cyclopropane is not easy to explain.

Figures 15 to 18 are representative of results obtained in these experiments. All are from the same animal under different conditions. Figure 15 illustrates the response to 2.0 µg./kg. of adrenaline and to mechanical elevation of the systemic blood pressure when no anaesthetic agent was present. No arrhythmias were produced although systemic pressures as high as 240/150 mm. Hg were obtained. Figure 16 illustrates a bigeminal rhythm at a pressure of 225/175 mm. Hg in response to 2.0 µg./kg. of adrenaline in the presence of cyclopropane. No arrhythmia was produced when the same pressure was reached by combining mechanical elevation of the systemic blood pressure with a smaller dose of adrenaline (1.0 µg./kg.).

Figure 17 illustrates the responses in the thiopental-treated animal. 2.0 µg./kg. of adrenaline produced a blood pressure of 170/140

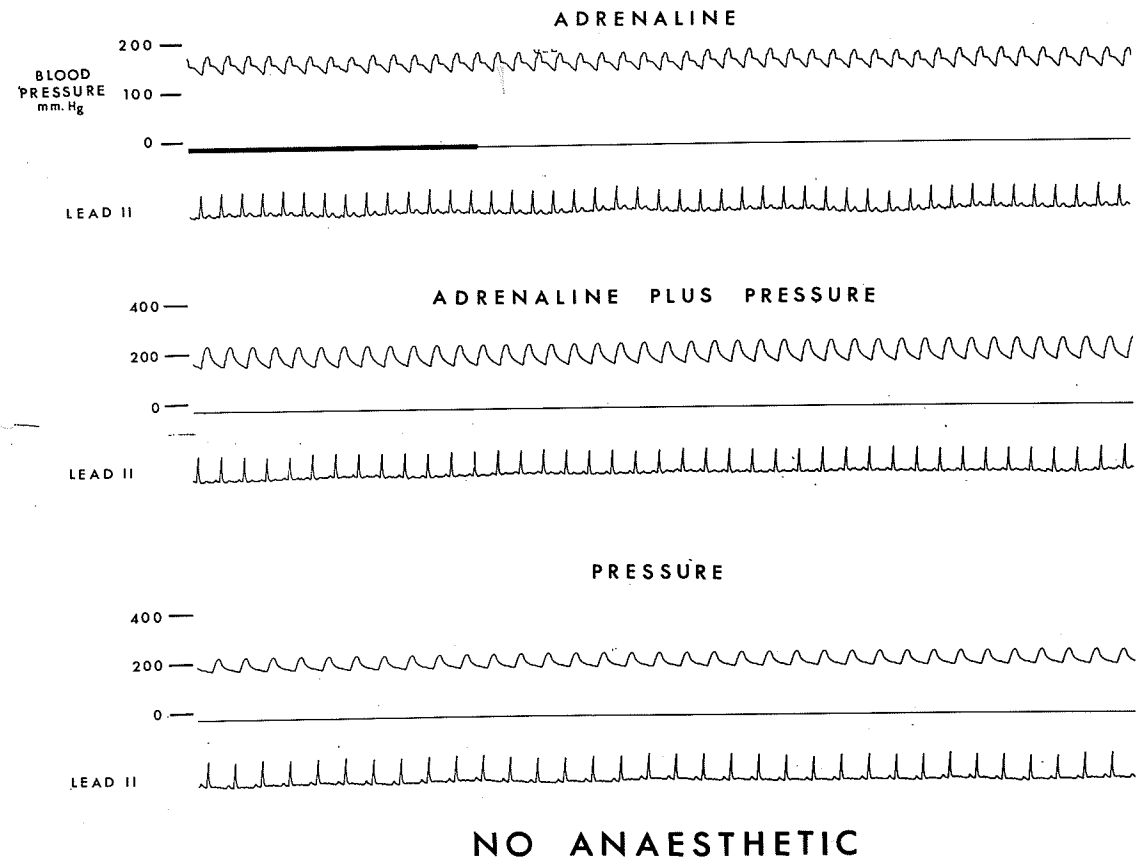

Figure 15. Effect of adrenaline and of mechanical elevation of the blood pressure in untreated spinal animal. 2.0 μg./kg. of adrenaline, either alone (first panel) or in combination with mechanical elevations of pressure (second panel) produces no arrhythmias although systolic pressures of 175 and 240 mm. Hg respectively were obtained. Lower panel: no arrhythmias were produced by mechanical elevation of the systolic pressure to 225 mm. Hg. in the absence of adrenaline.

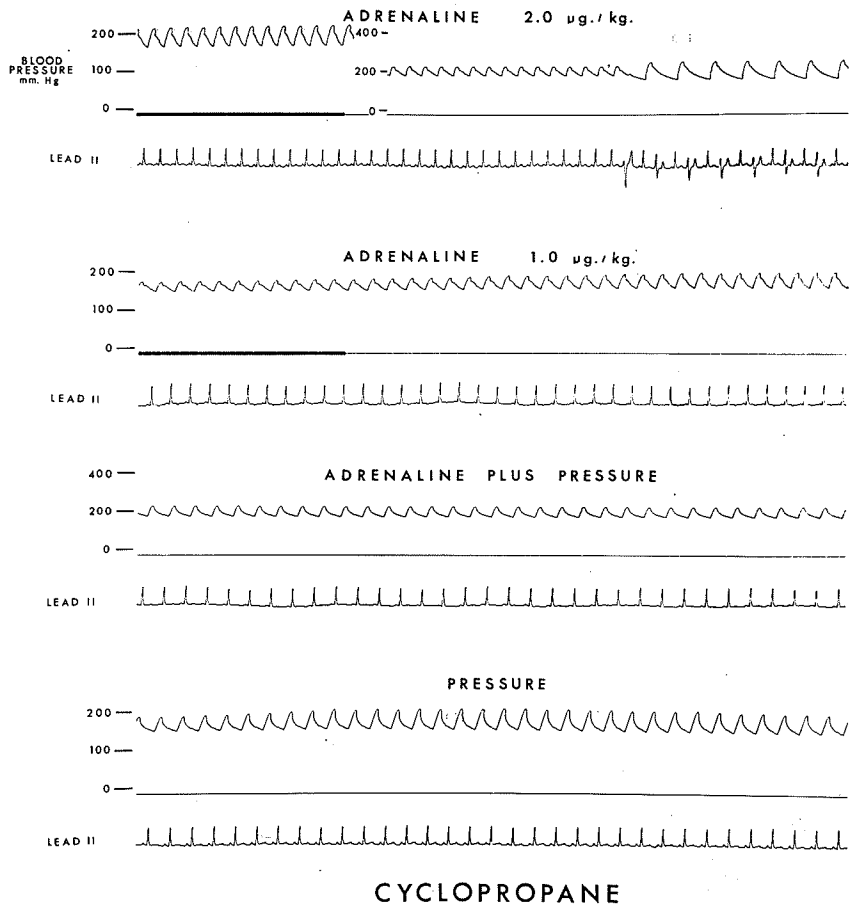

Figure 16. Effect of adrenaline and of mechanical elevation of the blood pressure in spinal animal after treatment with 20 percent cyclopropane. First panel: 2.0 µg./kg. of adrenaline induces bigeminal rhythm at a systolic blood pressure of 225 mm. Hg. Second and third panels: 1.0 µg./kg. of adrenaline produces no bigeminal rhythm although a systolic pressure of 225 mm. Hg. was reached when combined with mechanical elevation of the blood pressure. Lower panel: no arrhythmias were produced by mechanical elevation of the systolic pressure to 215 mm. Hg. in the absence of adrenaline.

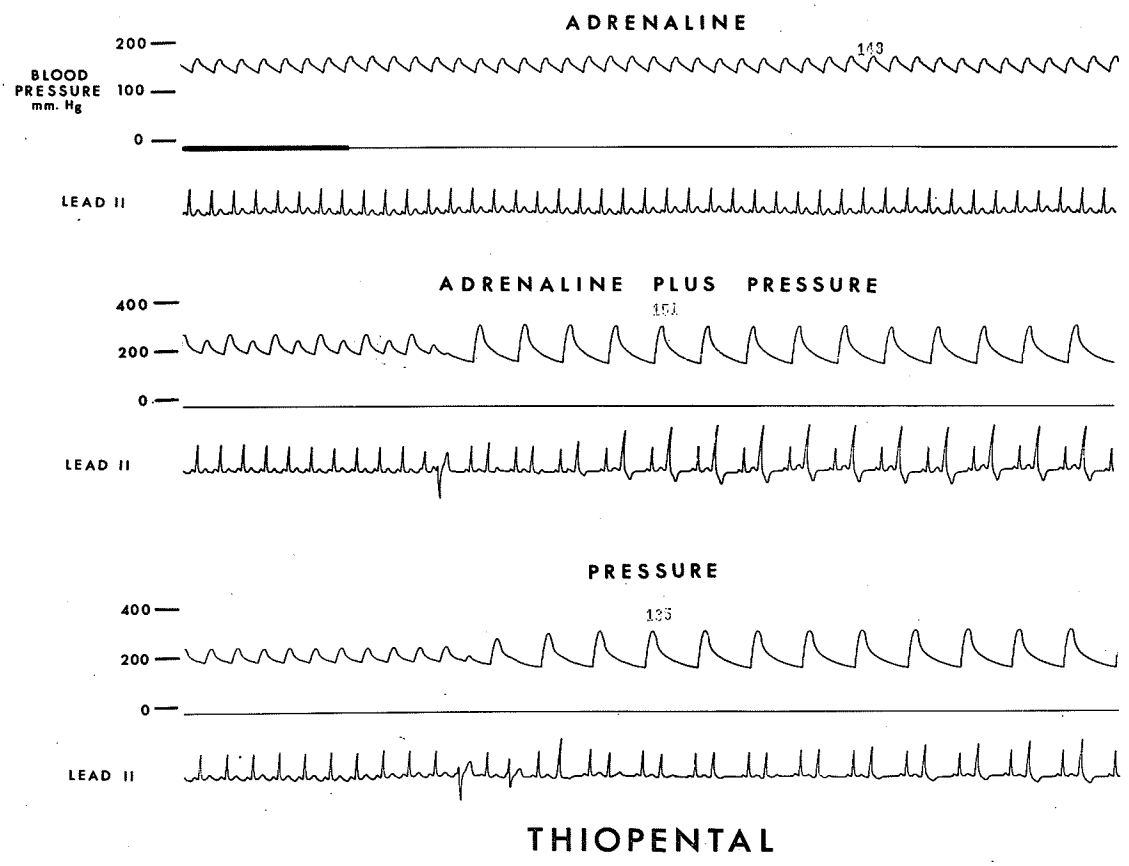

Figure 17. Effect of adrenaline and of mechanical elevation of the blood pressure in spinal animal after treatment with 20 mg./kg. of thiopental. First and second panels: 2.0 μg./kg. of adrenaline produced a blood pressure of 175/140 mm. Hg. but no arrhythmia, although bigeminal rhythm was obtained by increasing the pressure still further to 275/190 mm. Hg. Lower panel: mechanical elevation of the blood pressure in the absence of adrenaline produces a bigeminal rhythm at a systolic pressure of 240 mm. Hg.

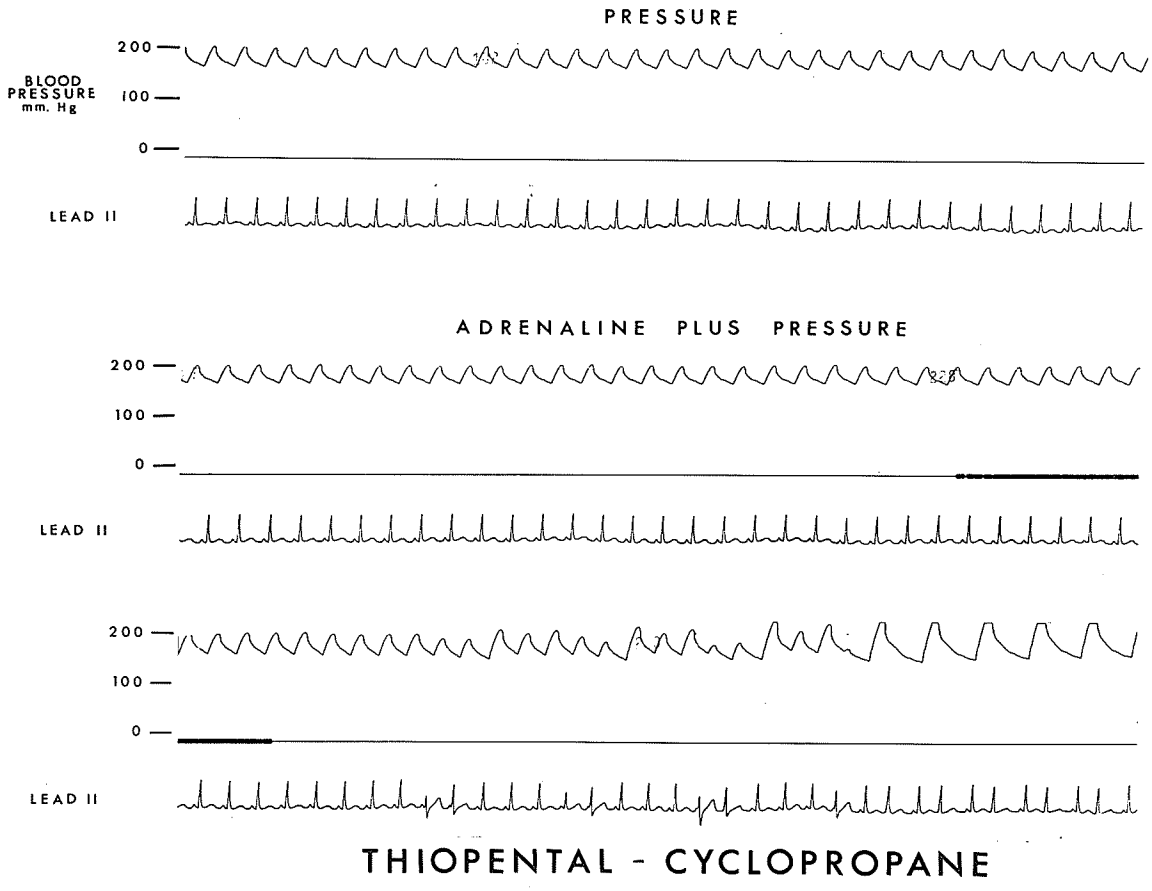

Figure 18. Effect of adrenaline and of mechanical elevation of the blood pressure in spinal animal following treatment with 20 mg./kg. of thiopental and administration of 20 percent cyclopropane. First panel: Mechanical elevation of the blood pressure in the absence of adrenaline produced no arrhythmia although a systolic pressure of 210 mm. Hg. was obtained. Second and third panels: the pressure was raised to 210 mm. Hg. without producing arrhythmia. The signal artefact indicates the beginning and end of a 60-second injection of 0.5 μg./kg. of adrenaline during maintained hypertension. Although no further change in pressure was produced, bigeminal rhythm was induced.

mm. Hg but no arrhythmias, although bigeminal rhythm could be obtained by increasing the pressure still further to 275/190 mm. Hg. A mechanically-induced increase in pressure in the absence of adrenaline produced the same response at approximately the same pressure. Adrenaline appears to produce a bigeminal rhythm in this condition by virtue of its pressor activity only.

Figure 18 illustrates that this is almost certainly not the case when thiopental and cyclopropane are both present. 2.0 μg./kg. of adrenaline produced bigeminy at a pressure of 190/170 mm. Hg. No arrhythmia was produced by mechanical elevation of the blood pressure to 205/165 mm. Hg. However, bigeminal rhythm was induced with 0.5 μg./kg. of adrenaline injected at the time of mechanical elevation of the blood pressure although no further increase in blood pressure occurred.

5. Localization of the Site of Action of Thiopental

The above results indicated clearly that there was an interaction between thiopental and cyclopropane in the causation of the typical cardiac arrhythmias induced by small doses of adrenaline. Previous data had indicated that the atrioventricular node or the upper bundle of His were the most probable sites of origin of the bigeminal and multifocal ventricular rhythms observed in thiopental-cyclopropane-anaesthetized animals. It seemed possible that thiopental was acting in the same region.

Fourteen dogs were anaesthetized with 20 percent cyclopropane in the absence of thiopental. Following preparation of the animals for intra-coronary arterial injections, 2.0 μg./kg. of adrenaline

was injected intravenously as control. If this dose caused any electrocardiographic abnormality, progressively smaller doses were tested and one-half of the minimal dose causing such abnormality was used as a challenge dose in that animal. The challenge doses of adrenaline ranged from 0.5-2.0 µg./kg. in different animals.

2.0 mg. of thiopental (approximately one percent of the usual intravenous dose) was injected into either the left anterior descending coronary artery or the left circumflex coronary artery. Approximately 5 seconds after the termination of the 5-second intra-coronary arterial injection, the challenge dose of adrenaline was repeated. Injections of thiopental were bracketed at 15-minute intervals by injections of 0.9 percent sodium chloride adjusted to the same pH (approximately 11.2) with sodium hydroxide. The effect of injections of thiopental into the coronary arteries without sequential intravenous adrenaline also was tested.

No arrhythmias were produced when thiopental was injected into either branch of the left coronary artery. Depression of the ST-segment of the electrocardiogram commonly was seen upon injection into the left circumflex and occasionally upon injection into the left anterior descending coronary artery. Saline injections occasionally produced the same result.

Injection of thiopental into the left circumflex coronary artery followed by intravenous injection of adrenaline produced a bigeminal rhythm in each of 13 animals; bigeminal rhythm followed by a multifocal rhythm was observed in one of the animals. Bigeminal rhythm persisted for 12 to 60 seconds but could be maintained for approximately 5 minutes

if the intravenous adrenaline was continued by infusion at the same rate. Saline injections into this artery did not modify the adrenaline response; arrhythmias were never produced.

The thiopental-adrenaline combination produced bigeminal rhythm in only 2 of 10 animals when thiopental was injected into the left anterior descending coronary artery. In one of these animals, the control injections of saline produced the same result. Only sinus tachycardia was produced by adrenaline in the remaining 8 animals. Table VI summarizes the results of these experiments. Figure 19 illustrates the responses in a typical experiment. The intra-coronary artery injection is indicated in the first segment of each panel, and the records are resumed at the termination of 60-second intravenous injections of 0.5 μg./kg. of adrenaline. Injection of thiopental into the left circumflex coronary artery combined with intravenous adrenaline produced the typical constantly-coupled bigeminal rhythm. The characteristic pulse deficit is also noted.

The combination of intra-coronary arterial thiopental and intravenous adrenaline was not effective in producing arrhythmias in two spinal dogs. After 30 minutes of cyclopropane administration, the combination produced bigeminal rhythm in both animals.

The minimal effective dose of thiopental was found to be 0.2, 20.0, and 200 μg. respectively in three cyclopropane-anaesthetized animals. The standard dose of 2.0 mg. employed probably was greatly in excess of that required in most animals, but was utilized routinely because of the variability noted.

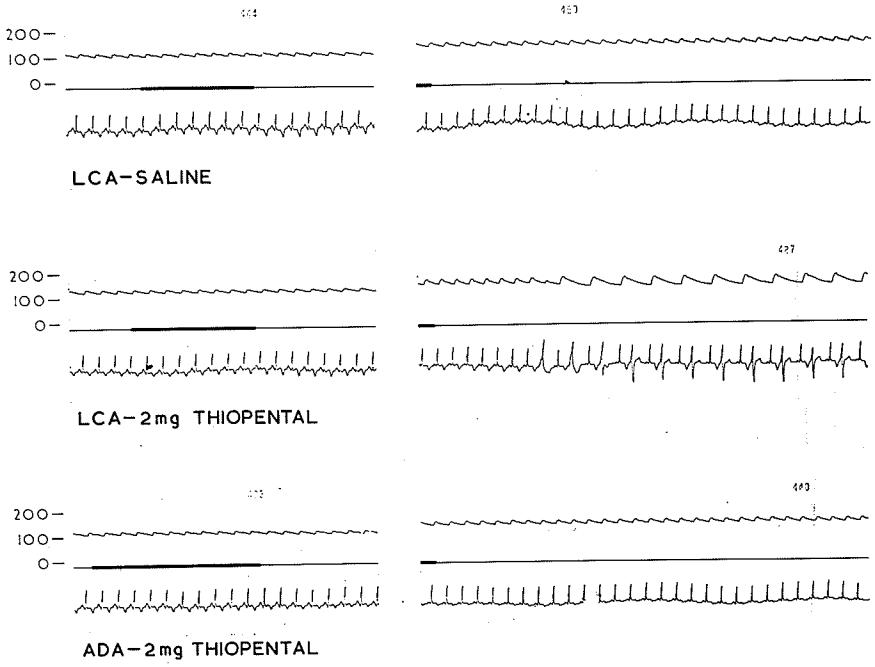

Figure 19. Effect of injections of thiopental or of saline into the main branches of the left coronary artery, combined with a subarrhythmic intravenous dose of adrenaline. The first segment of each panel shows the response to injection into the coronary artery. The second segment of each panel begins at the termination of a 60-second intravenous injection of 0.5 μg./kg. of adrenaline. First panel: injection of saline into the left circumflex coronary artery combined with intravenous adrenaline produces no arrhythmias. Second panel: the combination of thiopental into the left circumflex coronary artery and of intravenous adrenaline produces the characteristic bigeminal rhythm. Third panel: no arrhythmias are produced when the thiopental is injected into the left anterior descending coronary artery.

TABLE VI

THE EFFECT OF INTRA-CORONARY ARTERIAL INJECTIONS OF THIOPENTAL ON THE CARDIAC RHYTHM WHEN COMBINED WITH INTRAVENOUS ADRENALINE IN CYCLOPROPANE-ANAESTHETIZED DOGS

Dog	L. Anterior descending coronary			L. Circumflex coronary		
	Saline	Thiopental	Saline	Saline	Thiopental	Saline
56	ST*	ST*	--	ST*	bigeminy + multifocal	ST*
57	--	--	--	ST	bigeminy	ST
58	ST	ST	--	ST	bigeminy	ST
59	ST	ST	--	--	bigeminy	ST
60	--	--	--	ST	bigeminy	ST
62	ST	bigeminy	ST	--	--	--
66	ST	ST	--	ST	bigeminy	ST
67	--	--	--	--	bigeminy	ST
68	--	bigeminy	bigeminy	ST	bigeminy	ST
69	--	ST	--	ST	bigeminy	--
70	--	--	--	ST	bigeminy	ST
75	ST	ST	--	ST	bigeminy	--
77	--	ST	--	--	bigeminy	ST
81	ST	ST	--	ST	bigeminy	ST

The saline solution used for control injections was adjusted to pH 11.2 with sodium hydroxide.

* ST: sinus tachycardia

6. Effect of Induction of Anaesthesia with Other Barbiturates

The ability of thiopental to modify the response to adrenaline suggested that other barbiturates might act in a similar manner. Four other barbiturates were injected in sufficient doses to induce anaesthesia. These were secobarbital, amobarbital, methitural (a thiobarbiturate), and pentobarbital (the oxygen analogue of thiopental). All animals were tested with a single dose of 16.0 µg./kg. of adrenaline following tracheostomy, bilateral vagotomy and initiation of artificial respiration. If arrhythmias were induced, progressive smaller doses were employed until the threshold dose of adrenaline was found. One of each group of four dogs anaesthetized with secobarbital, amobarbital and pentobarbital displayed bigeminal rhythm in response to adrenaline (theshold doses 4.0, 4.0 and 8.0 µg./kg. respectively). The remaining 9 dogs showed only sinus tachycardia after 16.0 µg./kg. of adrenaline. One of two dogs anaesthetized with methitural showed bigeminal rhythm at 1.0 µg./kg. of adrenaline and the other displayed only sinus tachycardia in response to 16.0 µg./kg.

After testing the effects of adrenaline in the presence of the various barbiturates, 20 percent cyclopropane was administered to each animal and the effects of adrenaline were redetermined.

Secobarbital-cyclopropane anaesthetized animals showed no arrhythmias in response to 2.0 µg./kg. of adrenaline. Four µg./kg. caused bigeminy in 3 of 4 animals. Ventricular fibrillation was produced in 3 of 4 animals by 16 µg./kg.

Following administration of cyclopropane to amobarbital-anaesthetized animals, bigeminy was observed in 1 of 4 animals after 4.0 µg./

kg. of adrenaline; 16.0 μg./kg. caused multifocal rhythm in each of three animals.

Two methitural-cyclopropane-anaesthetized dogs showed bigeminy in response to 16.0 μg./kg. of adrenaline. One of these animals showed the same arrhythmia after 4.0 μg./kg.

Adrenaline in a dose of 2.0 μg./kg. caused bigeminy in 1 of 4 dogs in the presence of pentobarbital and cyclopropane. Isolated ventricular beats, bigeminal rhythm and multifocal rhythm were each seen in a single dog after 4.0 μg./kg. of adrenaline. None of the animals received larger doses.

It is apparent that only secobarbital approaches thiopental in the ability to modify the response to adrenaline of the cyclopropane-anaesthetized dog.

7. Characteristics of the Bigeminal Rhythms Produced Under Various Experimental Conditions

It was noted in SECTION III that the characteristic bigeminal rhythm observed in thiopental-cyclopropane-anaesthetized dogs has a constant coupling interval which is independent of sudden changes in the atrial rate. The arrhythmia is abolished by lowering the systemic blood pressure or by stimulation of the vagus. Insofar as was possible, the bigeminal rhythms produced under the different experimental conditions described in subsections 1-6 above were tested for these characteristics.

The bigeminal rhythm occasionally produced by adrenaline in thiopental-anaesthetized dogs showed constant coupling. Stimulation of the vagus abolished the arrhythmia in the one animal tested and rapid

haemorrhage abolished bigeminy in each of three animals. The effect of sudden changes in atrial rate was not determined.

The unpredictable occurrence of bigeminal rhythm in response to adrenaline in cyclopropane-anaesthetized animals precluded systematic observations on the characteristics of the arrhythmia. This constantly-coupled rhythm was abolished in 2 dogs by stimulation of the vagus.

The bigeminal rhythm observed in the cyclopropane-anaesthetized dog when intravenous adrenaline was combined with injections of thiopental into the left circumflex coronary artery also had a constant coupling interval which was not changed by sudden alterations in the heart rate (9 trials in 5 dogs). Stimulation of the vagus abolished the bigeminal rhythm in each of the three dogs tested, and sudden haemorrhage abolished the arrhythmia in the one dog in which this procedure was done.

8. Application of Roberts' "Vagus-Amine Test" to Cyclopropane-Anaesthetized Dogs

Roberts et al. have reported that stimulation of the vagus in the presence of subeffective concentrations of sympathomimetic amines produces escape beats in the nonsensitized preparation (52,53). Dresel and Sutter have shown that vagal stimulation will abolish bigeminal and multifocal arrhythmias produced by adrenaline in thiopental-cyclopropane-anaesthetized dogs (54). Preliminary observations in the present investigation indicated that ventricular arrhythmias occurring in response to large doses of adrenaline in animals anaesthetized with cyclopropane

alone could sometimes be abolished by stimulation of the vagus, but that combination of vagal stimulation and adrenaline sometimes produced ventricular rhythms in these dogs. The following experiments were performed to investigate this in more detail.

Four animals were anaesthetized with 30 mg./kg. of pentobarbital, and 7 animals were anaesthetized with cyclopropane only. The parameters of stimulation of the right vagus necessary for maximal cardiac slowing without loss of sinus dominance was determined and utilized throughout the course of the experiment. Adrenaline or isoproterenol was injected intravenously over 15 seconds and the vagus was stimulated for 15 seconds at intervals of one minute beginning 15-20 seconds after the injection. The initial dose of isoproterenol was usually 1.0 μg./kg. and that of adrenaline 2.0 μg./kg. Injections of isoproterenol were alternated with injections of adrenaline; large and small doses of the sympathomimetics were alternated to minimize tachyphylaxis. Periods of at least 15 minutes were allowed between injections. The smallest dose of each sympathomimetic amine which produced escape beats in the presence of vagal stimulation was considered the threshold for pacemaker induction.

Sympathomimetic amines in the doses employed did not produce arrhythmias in the absence of vagal stimulation in animals anaesthetized with pentobarbital. However, arrhythmias were produced without vagal stimulation in animals anaesthetized with cyclopropane. These were of bigeminal or multifocal ventricular type. The arrhythmias produced by a 15-second injection of a given dose of adrenaline in the cyclopropane-anaesthetized animal are more severe than those produced

by 1-minute injections of the same dose. They approximate in severity and duration those produced by 1-minute injections of the same dose under thiopental-cyclopropane anaesthesia. Thus, 15-second injections of 2.0 μg./kg. of adrenaline produced bigeminal rhythm in 50 percent of animals and 4.0 μg./kg. or larger doses produced multifocal ventricular rhythm. In contrast to adrenaline, isoproterenol did not produce bigeminal rhythm, and the ventricular arrhythmias induced by this amine lasted only 12-15 seconds before sinus dominance was reestablished.

Stimulation of the vagus in the presence of a sympathomimetic amine in the presence of either cyclopropane or pentobarbital produced two types of escape beat. The first of these usually was characterized by a deep S-wave and a high T-wave and by relatively long intervals between successive beats. This response, which is illustrated in Figures 20A and 20D, was identical to that illustrated by Roberts et al. (52). Larger doses produced the response which is illustrated in Figures 20B and 20C. These escape beats were characterized by a rate equal to or greater than the rate before the initiation of vagal stimulation. Their configuration was that usually associated with the monofocal ventricular arrhythmias produced by adrenaline in the non-sensitized preparation. Both types of escape beat were noted after adrenaline or isoproterenol under both anaesthetics. These escape beats are designated as Type 1 and Type 2 respectively in Tables VII and VIII.

In pentobarbital-anaesthetized dogs, escape beats in response to vagal stimulation occurred at the doses of sympathomimetic amines indicated in Tables VII and VIII. Multifocal arrhythmias were never

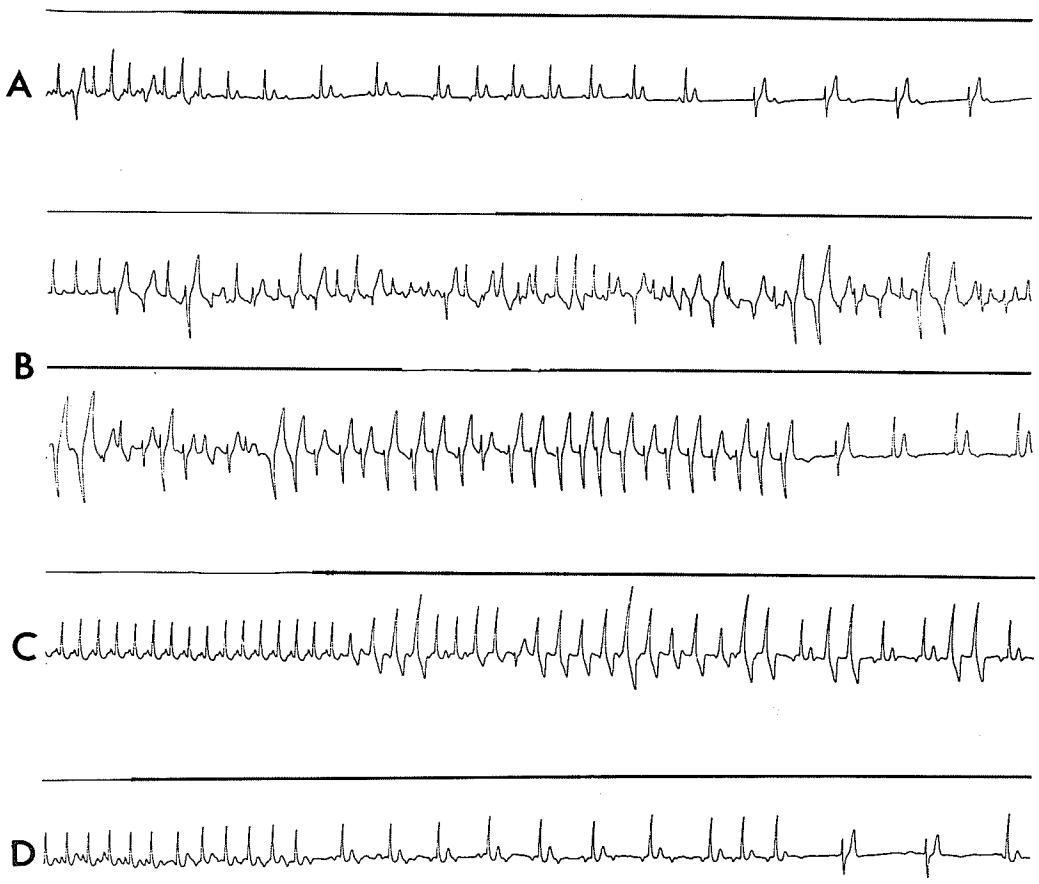

Figure 20. Effect of vagal stimulation in the presence of adrenaline under cyclopropane anaesthesia. Stimulation parameters: 10 volts, 20/sec. All records are from the same animal. A. Multifocal rhythm due to 2.0 µg./kg. of adrenaline is converted to a supraventricular rhythm by vagal stimulation. Characteristic Type 1 escape beats are noted. Arrhythmia returned when vagal stimulation was stopped. B. Multifocal rhythm due to 12.0 µg./kg. of adrenaline is changed to a monofocal rhythm (Type 2) after 8 seconds of vagal stimulation. One Type 1 escape beat is observed before establishment of a slow sinus rhythm. C. Same injection as B. Second period of vagal stimulation. The multifocal rhythm had spontaneously converted to sinus. Vagal stimulation induces Type 2 escape beats. D. Second period of vagal stimulation following 10 µg./kg. of adrenaline. The first period of vagal stimulation had converted a multifocal rhythm to sinus rhythm and had induced Type 1 escape beats. The second period again induced Type 1 beats.

produced during the "vagus-amine test". Although the number of animals tested is small, the thresholds for pacemaker induction are in general agreement with those reported by Roberts et al. (52).

In animals anaesthetized with cyclopropane, adrenaline induced bigeminal and multifocal beats at doses similar to those producing Type 1 escape beats, and considerably lower than those producing Type 2 escape beats in the presence of vagal stimulation. Thus the first one or two periods of vagal stimulation following injection of adrenaline characteristically abolished the existing bigeminal or multifocal arrhythmia but induced escape beats of either the first or second type dependent upon the dose of sympathomimetic amine. Figure 20A illustrates conversion of multifocal rhythm to sinus rhythm by stimulation. Continued stimulation caused Type 1 escape beats. Figure 20B shows an instance of change from multifocal rhythm to characteristic Type 2 escape beats when stimulation of the vagus was begun. Since the duration of adrenaline-induced arrhythmias was less than the duration of effectiveness of the amine in the "vagus-amine test", later periods of vagal stimulation often changed sinus rhythm to either Type 1 or Type 2 escape beats. This is illustrated in Figures 20C and 20D. The data are summarized in Table VII.

The use of isoproterenol for the "vagus-amine test" yielded results comparable to those for adrenaline. The arrhythmias produced in the absence of vagal stimulation differed from those produced by adrenaline in that bigeminal rhythms was never observed after isoproterenol. In addition, the multifocal arrhythmias produced by isoproterenol were usually of very brief duration (12-15 seconds). Accord-

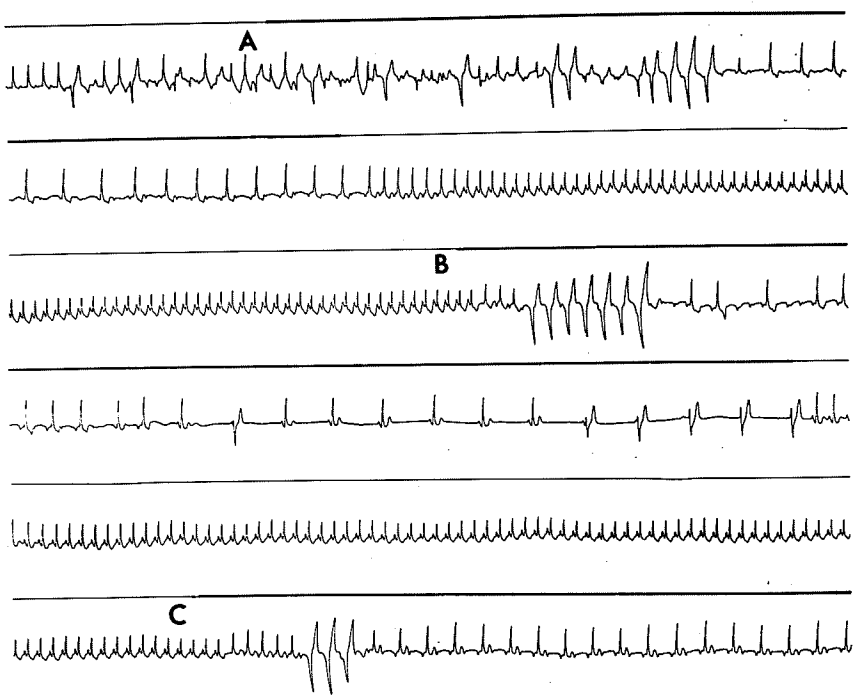

Figure 21. Effect of vagal stimulation in the presence of isoproterenol under cyclopropane anaesthesia. Continuous records of the response to 12.0 μg./kg. of isoproterenol and to three periods of vagal stimulation. A. First period of stimulation: the isoproterenol-induced arrhythmia converts to sinus rhythm after a burst of 5 monofocal beats. B. and C. Second and third periods of vagal stimulation respectively: Type 2 beats are again produced. The responses to large doses of adrenaline were similar except that multifocal arrhythmias usually reappeared when vagal stimulation was stopped.

TABLE VII

THE "VAGUS-AMINE TEST" USING ADRENALINE

Dog	Threshold for arrhythmias µg./kg.	Threshold for pacemaker induction	
		Type 1 escape beats µg./kg.	Type 2 escape beats µg./kg.
		Pentobarbital anaesthesia	
19	none	10.0	- *
20	none	4.0	6.0
24	none	5.0	-
		Cyclopropane anaesthesia	
17	2.0	2.0	-
18	4.0	-	8.0
22	2.0	2.0	-
25	4.0	1.0	12.0
26	2.0	2.0	12.0
88	2.0	1.0	-
89	3.0	2.0	-

-*: Thresholds were not determined

ingly, the change to supraventricular rhythm during vagal stimulation may have been coincidental. The data are summarized in Table VIII. Figure 21 illustrates the response to three consecutive periods of vagal stimulation following the injection of 12.0 µg./kg. of isoproterenol.

It is apparent from the data presented in Table VII and VIII that the doses of sympathomimetic amines required to produce Type 2 escape beats are approximately the same in pentobarbital- and cyclopropane-anesthetized dogs.

C. DISCUSSION

Thiopental alone did not cause arrhythmias in well-ventilated dogs, whereas Gruber reported a high incidence of bigeminal rhythm in spontaneously respiring dogs (127). It is probable that carbon dioxide retention was responsible for the arrhythmias noted by this author.

Adrenaline produced bigeminal rhythm in only 20 percent of animals anaesthetized with thiopental. Approximately the same percentage of animals anaesthetized with amobarbital, secobarbital or pentobarbital showed bigeminal rhythm in response to adrenaline. In the presence of both thiopental and cyclopropane, approximately 95 percent of animals responded with bigeminal rhythm to doses of 2.0 µg./kg. or less of adrenaline (SECTION III). This high incidence was not observed when other barbiturates were substituted for thiopental (subsection 6). Adrenaline rarely produced bigeminal rhythm in cyclopropane-anaesthetized dogs in the absence of thiopental (see below).

TABLE VIII

THE "VAGUS-AMINE TEST" USING ISOPROTERENOL

Dog	Threshold for arrhythmias µg./kg.	Threshold for pacemaker induction	
		Type 1 escape beats µg./kg.	Type 2 escape beats µg./kg.
		Pentobarbital Anaesthesia	
19	none	2.0	4.0
20	none	1.25	2.0
23	none	1.0	- *
		Cyclopropane anaesthesia	
17	> 8.0	6.0	-
18	2.0	-	2.0
22	2.0	2.0	-
25	3.0	0.5	3.0
26	2.0	2.0	8.0

- *: Thresholds were not determined

It is clear that thiopental is required for the consistent production of bigeminal rhythm in response to adrenaline. This is shown most clearly by experiments in which thiopental was administered subsequent to cyclopropane. Previously ineffective doses of adrenaline became effective in producing bigeminy if thiopental was given sufficiently slowly intravenously (subsection 3) or was administered into a coronary artery (subsection 5). Cyclopropane also is required for the bigeminal response since the combination of intravenous adrenaline and intra-coronary arterial thiopental produced no arrhythmias in spinal animals until cyclopropane was added.

The interaction between thiopental and cyclopropane to facilitate the production of bigeminal rhythm by adrenaline cannot be explained fully. It has been demonstrated that adrenaline-induced bigeminal rhythm occurs at a pressure which is characteristic for each animal. Intact or spinal dogs under thiopental anaesthesia showing bigeminal rhythm in response to adrenaline or to mechanically produced elevations in pressure did so at systolic pressures ranging from 175 to 220 mm. Hg. The corresponding ranges in the same group of animals were 165-220 mm. Hg for cyclopropane-adrenaline bigeminal rhythm and 110-170 mm. Hg for thiopental-cyclopropane-adrenaline bigeminy. These data suggest that thiopental and cyclopropane interact to lower the pressure threshold for the induction of bigeminal rhythm by adrenaline. This interpretation does not infer, however, that adrenaline is acting solely to provide an increase in pressure. Indeed this is almost certainly not the case since mechanical elevation of the blood pressure in thiopental-cyclopropane anaesthetized dogs in the absence of adrenaline is not ef-

fective in producing bigeminal rhythm. No explanation can be offered for the finding that mechanical elevation of the blood pressure induces bigeminal rhythm in dogs anaesthetized with thiopental, but rarely in thiopental-cyclopropane-anaesthetized animals.

The data indicate that for a given dose of adrenaline, arrhythmias are more severe in the cyclopropane-anaesthetized dog after thiopental treatment, and that the major arrhythmias of ventricular tachycardia and ventricular fibrillation are observed at doses of adrenaline which are well tolerated by the untreated cyclopropane-anaesthetized animal (Table III). Although it was not possible to quantitate these differences in the present investigation because of the phenomenon of tachyphylaxis (see SECTION V), general comparisons are possible. 2.0 µg./kg. of adrenaline produced bigeminal rhythm in thiopental-cyclopropane-anaesthetized dogs, but usually only sinus tachycardia in animals anaesthetized with cyclopropane. Animals induced with thiopental before cyclopropane administration usually showed multifocal rhythms after 4.0 µg./kg. while untreated animals displayed minimal or no arrhythmias. Animals anaesthetized with cyclopropane without premedication usually tolerated 16.0 µg./kg. without ventricular fibrillation. This was seldom the case in thiopental-cyclopropane anaesthetized dogs (Table III). It is apparent that thiopental alters quantitatively the entire spectrum of arrhythmic responses to adrenaline in the presence of cyclopropane.

Although the association of thiopental and increased sensitivity of the cyclopropane-anaesthetized animal to adrenaline has not been made previously, the results presented here are confirmed by a

critical survey of the literature. Meek et al. (11), and Morris et al. (147) reported that unpremedicated dogs anaesthetized with cyclopropane required 10 µg./kg. of adrenaline administered over a 50-second period for the consistent production of ventricular rhythms. In contrast, Cummings and Hays reported that the mean dose of adrenaline necessary for the production of ventricular rhythms in thiopental-cyclopropane anesthetized dogs was 2.0 µg./kg. (59). Graff et al. found the mean dose to be 1.5 µg./kg. (29), and McMillen et al., using the same preparation, reported ventricular extrasystoles at doses of 0.7-1.8 µg./kg. (66).

There has been only one previous comparison of responses to adrenaline in cyclopropane anaesthesia in the presence and absence of thiopental. Orth et al. reported on cross-over experiments employing a fixed dose of 10 µg./kg. of adrenaline (15). Five cyclopropane-anaesthetized dogs showed ventricular tachycardia in response to this dose of adrenaline. After thiopental, the duration of the arrhythmia was increased and one of the animals fibrillated. It is of interest that Orth et al. found a similar tendency to sensitization with secobarbital. This observation parallels the results obtained in the present investigation. Since these authors were concerned with attempting to demonstrate protection against cyclopropane-adrenaline arrhythmias by barbiturates, they commented only that these agents afforded no protection.

It has been shown that thiopental, which modifies greatly the arrhythmic response to adrenaline in animals anaesthetized with cyclopropane, acts in the distribution of the left circumflex coronary art-

ery. This observation supports the conclusion reached previously that bigeminal and multifocal arrhythmias induced by adrenaline arise in the area of the atrioventricular node or the upper bundle of His (SECTION III).

Evidence has been presented that adrenaline-induced bigeminal rhythm is not due to emergence of a focus of automaticity (SECTION III). However, these data did not exclude completely the possibility of multifocal arrhythmias arising through such a mechanism. This was tested more directly by application of the "vagus-amine test" of Roberts (52, 53). This test appears ideally suited to the induction of true foci of automaticity. Unfortunately, the thiopental-cyclopropane preparation does not lend itself well to this type of study since relatively small doses of sympathomimetic amines will produce severe multifocal rhythms and even ventricular fibrillation. Vagotomized dogs anaesthetized with pentobarbital were compared in the present investigation to animals sensitized with cyclopropane.

The sympathomimetic amines caused arrhythmias only in the sensitized preparation. The arrhythmias due to adrenaline were abolished by vagal stimulation. Isoproterenol-induced arrhythmias also changed to supraventricular rhythms during vagal stimulation; this could not be attributed to stimulation of the vagus because of the short duration of the arrhythmia. Vagal stimulation would be expected to make arrhythmias induced by adrenaline more severe if such arrhythmias were due to the emergence of ventricular foci of automaticity. The fact that the converse occurred opposes any theory attributing the genesis of such arrhythmias to induced foci of automaticity.

Vagal stimulation may produce automatic escape beats in the sensitized preparation. However, the threshold dose of sympathomimetic amine required is approximately the same in sensitized and nonsensitized animals. It should be noted that the dose required for the induction of rapid "monofocal" beats is moderately large, and that multifocal ventricular rhythms are never produced by vagal stimulation even in the sensitized preparation. This latter finding is at variance with that of Dresel and Sutter, who reported that vagal stimulation in the presence of isoproterenol produced multifocal arrhythmias in the thiopental-cyclopropane preparation (54). These authors used much larger doses of isoproterenol than those reported here.

The data presented indicate that "sensitized" and "nonsensitized" preparations behave very similarly to a procedure which appears to induce true ventricular automaticity by supplying optimal conditions for the emergence of ventricular foci. The observation that "monofocal" beats may be produced in sensitized preparations by moderately large doses of sympathomimetic amines suggests that ectopic beats may arise through automatic foci, just as they do in the nonsensitized preparation. The data indicate however, that sensitization to adrenaline by cyclopropane does not normally occur by this mechanism.

D. SUMMARY

Induction of anaesthesia with thiopental alters the arrhythmic response to adrenaline in cyclopropane anaesthetized dogs. Adrenaline only occasionally produces bigeminal rhythm when thiopental is the only anaesthetic agent present. In the absence of thiopental, dogs anaesthetized with cyclopropane tolerate large doses of adrenaline with

minimal arrhythmias. Bigeminal rhythm is observed only occasionally. When both anaesthetic agents are present, bigeminy is produced by small doses of adrenaline and multifocal ventricular rhythms and ventricular rhythms are induced by doses of adrenaline which the animal tolerates well in the presence of cyclopropane alone. The duration of the potentiating action of thiopental is much longer than the duration of the anaesthesia produced by this agent. The site of action of thiopental has been localized to the distribution of the left circumflex coronary artery.

Arrhythmias produced by adrenaline in cyclopropane-anaesthetized dogs may be abolished by vagal stimulation. No difference was noted between the cyclopropane-anaesthetized and the nonsensitized preparation in a procedure which provides optimal conditions for the emergence of ventricular foci of automaticity.

SECTION V

OBSERVATIONS ON THE DEVELOPMENT OF TACHYPHYLAXIS TO ADRENALINE-INDUCED ARRHYTHMIAS

A. INTRODUCTION

In the experiments reported in SECTIONS III and IV, tolerance to induction of arrhythmias by adrenaline was observed when large doses of adrenaline were given repeatedly. Although most investigations on cyclopropane-adrenaline arrhythmias reported in the literature have employed repeated large doses of the amine, the only comment referable to the development of tachyphylaxis is a short description by Meek (12). His group later attributed this refractoriness to an "adrenolytic" effect of cyclopropane (148). The tolerance to adrenaline was attributed not to the repeated doses of the agent, but rather to the duration of the cyclopropane anaesthesia.

The intent of the present investigation was to determine the rapidity with which tolerance developed, whether it was attributable to an "adrenolytic" action of cyclopropane, and whether this phenomenon might influence the results presented in previous sections.

B. RESULTS

1. Tolerance to Adrenaline-Induced Arrhythmias in Cyclopropane Anaesthesia and Thiopental-Cyclopropane Anaesthesia

The threshold dose of adrenaline necessary for the induction of bigeminal rhythm was determined in 2 thiopental-cyclopropane anaesthetized dogs. This dose was repeated at 10-minute intervals for periods in excess of 6 hours. The threshold dose of adrenaline in the first animal was 0.75 µg./kg. at the beginning of the experiment and at 4 hours, increasing to 1.0 µg./kg. at the end of 5 hours. In the other dog, the threshold of 1.0 µg./kg. was unchanged at the end of 3

hours but increased to 1.25 µg./kg. at the end of 6 hours. It is apparent that very little tolerance develops to adrenaline-induced bigeminal rhythm.

A dose of 4.0 µg./kg. of adrenaline produced multifocal arrhythmias in 2 thiopental-cyclopropane-anaesthetized dogs. Although this dose was repeated at 15-minute intervals for 2 and 6 hours respectively, there was only a slight progressive decrease in the severity and duration of the arrhythmias. In contrast, although 4.0 µg./kg. of adrenaline produced multifocal arrhythmia when first injected into one cyclopropane-anaesthetized dog, the amount of adrenaline necessary to cause this arrhythmia on repeated injection increased to 8 µg./kg. within 45 minutes and to 10 µg./kg. within 90 minutes. After 165 minutes, a dose of 16 µg./kg. caused only sinus tachycardia. It would appear that tachyphylaxis to ventricular rhythms is more difficult to demonstrate in animals premedicated with thiopental.

Successively increasing doses of adrenaline ranging from 4.0 to 128 µg./kg. were injected at 15-minute intervals into 4 cyclopropane-anaesthetized dogs. None of these animals fibrillated in response to the largest dose employed (Table IX). Two thiopental-premedicated animals in which the same dosage schedule was employed fibrillated at 8 and 16 µg./kg. respectively (Table IX). Three unpremedicated animals given single injections of 24, 32, and 48 µg./kg. of adrenaline died of ventricular fibrillation.

Tachyphylaxis to adrenaline-induced arrhythmias can be demonstrated in thiopental-premedicated animals when the dosage schedule is adjusted so that very small initial doses are employed. Table X shows

TABLE IX

DEVELOPMENT OF TOLERANCE TO ADRENALINE-INDUCED VENTRICULAR FIBRILLATION

		CYCLOPROPANE ONLY			THIOPENTAL-CYCLOPROPANE	
Dose Adrenaline (μg./kg.)	Dog: 40	42	43	47	48	49
4.0	ST	V	-	-	VT	MFV
8.0	ST	-	-	V	VT	VF
16.0	-	B/MFV	N/MFV	VT	VF	
24.0	-	-	MFV	MFV		
32.0	B/VT	MFV	MFV	MFV		
48.0	N	-	-	-		
64.0	N/VT	-	MFV	MFV		
128.0	N/VT	VT	N/MFV	MFV		

ST: sinus tachycardia, V: isolated beats having a QRS configuration markedly different from the QRS of sinus beats, N: isolated or consecutive beats with a QRS configuration essentially the same as the normal beat, but not preceded by P waves, B: characteristic bigeminal rhythm, VT: ventricular tachycardia characterized by monofocal rhythm, MFV: rhythm characterized by variety of QRS configurations, FV: ventricular fibrillation

TABLE X

DEVELOPMENT OF TOLERANCE TO ADRENALINE-INDUCED VENTRICULAR FIBRILLATION

Dose Adrenaline (μg./kg.)	Dog:	THIOPENTAL-CYCLOPROPANE 52	53	51	54
1.0		B	ST	ST	B
2.0		B/MFV	B	N/B	MFV
4.0		B/MFV	B	MFV	MFV
8.0		B/MFV	MFV	MFV	VF
16.0		MFV	MFV	VF	
24.0		MFV	VT		
32.0		MFV	VT		
64.0		N/VT	VT		
128.0		VT	VT		

Abbreviations are the same as for Table IX

the responses of 4 animals. Definite tachyphylaxis was demonstrable in only two.

A change in the type of arrhythmia from multifocal ventricular rhythm to a predominantly monofocal ventricular rhythm was observed as tachyphylaxis developed. This may represent a change in the mechanism underlying the arrhythmias, but no evidence on this point has been obtained.

2. The "Adrenolytic Action" of Cyclopropane

Stutzman et al. have reported that cyclopropane possesses an adrenolytic action (148). In their experiments, adrenaline became less effective in producing arrhythmias as the duration of anaesthesia was extended. Although they administered repeated doses of adrenaline, they ignored the possibility of tachyphylaxis and interpreted the results to indicate that cyclopropane blocked the action of adrenaline. This action of cyclopropane was presumed to increase with increased duration of anaesthesia.

In the present investigation the animals showing tachyphylaxis had been subjected to cyclopropane for approximately 150 minutes at the time the largest doses of adrenaline were administered. To exclude the possibility that tolerance to adrenaline was due to an adrenolytic action of cyclopropane, two cyclopropane-anaesthetized animals were maintained under cyclopropane anaesthesia for a period of 150 minutes, during which time no experimental procedures were carried out. Two thiopental-cyclopropane-anaesthetized animals were treated in an identical manner. Each animal received a single injection of adrenaline at the end of this time. The two animals anaesthetized with cyclopropane

received 20.0 and 24.0 μg./kg. respectively, while the thiopental-cyclopropane-anaesthetized dogs received 8.0 and 16.0 μg./kg. respectively. Ventricular fibrillation ensued in each case. There was no suggestion that protection was due to the long period of cyclopropane anaesthesia. These experiments indicate that cyclopropane has no demonstrable "adrenolytic effect" under the conditions of the experiments.

C. DISCUSSION

Most studies on tachyphylaxis to the effects of sympathomimetic amines concern themselves with the unsensitized preparation and have centered around tolerance to the pressor effects (149,150) or the lethal effects (151,152). Several authors have made observations that might be interpreted as indicating tachyphylaxis to adrenaline-induced arrhythmias. Lynch commented that cyclopropane-anaesthetized animals which do not fibrillate in response to large doses of adrenaline usually tolerate larger subsequent doses (109). De Jongh demonstrated that pretreatment of dogs with adrenaline before administering chloroform protects against chloroform-adrenaline arrhythmias.(23). Similar observations were made by Brockman and Huggins in the case of cyclopropane anaesthesia (58).

Only two authors specifically comment on tolerance to the arrhythmic action of adrenaline. Ueda *et al.* noted rapid tolerance to adrenaline in nonsensitized dogs (153). Dresel noted minimal tolerance in this preparation (154). Meek noted in a review article that cyclopropane-anaesthetized animals become progressively tolerant to the arrhythmic action of adrenaline (12). However, his group attributed

this tolerance to an adrenolytic action of cyclopropane (148). No evidence for such an action was found in the present investigation. In reporting a study of agents protecting against cyclopropane-adrenaline arrhythmias, Cummings mentioned without presenting data his observations that no adrenolytic effect was demonstrable at a cyclopropane concentration of 16 percent (59). Cummings' results are in agreement with those reported here and differ from those of Stutzman and Allen (148). In the light of the present investigation, the use of Stutzman and Allen of repeated injections of adrenaline makes it difficult to accept their conclusion that cyclopropane has an adrenolytic action. However, because they routinely employed cyclopropane concentrations of 33 percent, neither the observations presented here nor those of Cummings completely negate this possibility at higher concentrations of cyclopropane.

The threshold dose of adrenaline required for the production of bigeminal rhythm in thiopental-cyclopropane anaesthetized animals is unchanged after many hours of repeated testing with adrenaline. There is little possibility of the phenomenon of tachyphylaxis influencing the results presented in SECTION III.

Tolerance to the production of multifocal ventricular rhythms appears to occur less readily in the thiopental-cyclopropane-anaesthetized dog than in the cyclopropane-anaesthetized animal. Tolerance to adrenaline-induced ventricular fibrillation occurs very rapidly in animals anaesthetized with cyclopropane only, but can be demonstrated in thiopental-cyclopropane-anaesthetized animals only if small initial doses of adrenaline are employed. It was noted in SECTION IV that the arrhythmic response to a given dose of adrenaline is more severe in the

thiopental-cyclopropane-anaesthetized animal than in the dog receiving cyclopropane without thiopental. One explanation for this differential response is the rapid development of tachyphylaxis to adrenaline in the latter situation. Two observations mitigate against acceptance of this explanation. Administration of moderate doses of adrenaline (4.0-8.0 μg./kg.) to cyclopropane-anaesthetized animals which have received no prior adrenaline still produces less severe arrhythmias than does administration of the same doses to thiopental-cyclopropane anaesthetized dogs. Moreover, administration of thiopental to animals anaesthetized with cyclopropane and previously tested with large doses of adrenaline nevertheless increases the severity of adrenaline-induced ventricular arrhythmias (SECTION IV). The possibility that tachyphylaxis exaggerates some of the quantitative differences reported in SECTION IV cannot, however, be excluded completely.

D. SUMMARY

Animals anaesthetized with cyclopropane after induction of anaesthesia with thiopental developed very little tolerance to the arrhythmic action of small doses of adrenaline. Tolerance to adrenaline-induced multifocal and fibrillatory ventricular rhythms occurred more readily in the cyclopropane-anaesthetized dog than the thiopental-cyclopropane-anaesthetized animal. The differential response to adrenaline under these two conditions of anaesthesia may not be explained on the basis of tachyphylaxis. No attempt was made to investigate the mechanism of tolerance to the arrhythmic action of adrenaline. The results do indicate, however, that this phenomenon cannot be explained on the basis of an "adrenolytic" action of prolonged cyclopropane anaesthesia.

SECTION VI

GENERAL DISCUSSION

GENERAL DISCUSSION

Evidence has been presented that administration of small doses of adrenaline to dogs anaesthetized with thiopental-cyclopropane will cause a constantly-coupled bigeminal rhythm. It was also shown that this arrhythmia could not be produced consistently in the absence of thiopental. Indeed thiopental modified the entire spectrum of arrhythmic responses to adrenaline under cyclopropane anaesthesia and influenced greatly the development of tachyphylaxis to adrenaline.

The finding of an interaction between thiopental and cyclopropane in the production of adrenaline-induced arrhythmias indicates that sensitization by cyclopropane to adrenaline does not occur to the degree commonly believed. What have been termed "cyclopropane-adrenaline" arrhythmias might more properly be called "thiopental-cyclopropane-adrenaline" arrhythmias. This information is relevant to clinical anaesthesiology since it is common practice to employ thiopental for rapid induction of anaesthesia before intubation and maintenance on cyclopropane. Since spontaneous arrhythmias appear to be dependent upon endogenous catecholamine release (see SECTION I), it is possible that premedication with thiopental is contraindicated in clinical cyclopropane anaesthesia.

In spite of the frequency with which constantly-coupled arrhythmias are observed clinically, it has previously been difficult to produce a sufficiently stable and reproducible bigeminal rhythm for experimental study. Although it was not the intent of the present investigation to develop a "field theory" to explain the genesis of adrenergic

arrhythmias in the sensitized preparation, enough information has evolved from the study of this arrhythmia to outline certain concepts. The remainder of this discussion will be confined to consideration of the mechanism of adrenergic arrhythmias.

It is convenient to consider adrenaline-induced ventricular arrhythmias other than ventricular fibrillation under the two classifications of monofocal ventricular rhythms and of bigeminal and multifocal rhythms. The characteristic arrhythmia observed in the nonsensitized preparation is a monofocal ventricular arrhythmia which occurs only when moderately large doses of the amine are employed. In the sensitized preparation, on the other hand, small doses of adrenaline produce bigeminal and multifocal arrhythmias.

These generalizations require qualification. In the present investigation, bigeminal rhythm was observed in response to adrenaline in the presence of a number of anaesthetic agents which are not considered to sensitize, including secobarbital, amobarbital, and pentobarbital. Multifocal arrhythmias may be observed occasionally in the pentobarbital-anaesthetized dog in response to adrenaline. On the other hand, monofocal arrhythmias, which are characteristic of the nonsensitized preparation, may be observed in the sensitized animal also. Thus it becomes difficult to document a qualitiative difference between the nonsensitized and the sensitized preparation although there is certainly a quantitative difference.

Bigeminal and multifocal arrhythmias occurring in response to adrenaline under thiopental-cyclopropane anaesthesia are not due to the

emergence of ventricular foci of automaticity. The constancy of the coupling interval of the bigeminal rhythm with sudden alterations in the dominant rate excludes focus formation in the genesis of this arrhythmia. Moreover, if either arrhythmia were due to such foci, stimulation of the vagus would be expected to worsen rather than abolish the arrhythmias. Both arrhythmias are interconvertible through appropriate changes in the systemic blood pressure and both appear to arise through a mechanism having a locus of action in the region of the atrioventricular node. Both are influenced by thiopental which appears to act in the same area. Vagal stimulation also abolishes the adrenaline-induced bigeminal and multifocal arrhythmias occurring in cyclopropane-anaesthetized dogs. It may be concluded that bigeminal and multifocal arrhythmias, whether occurring in the cyclopropane preparation or the thiopental-cyclopropane preparation occur by the same mechanism and that that mechanism is not the induction of ventricular automaticity.

The monofocal arrhythmia produced by large doses of adrenaline in the nonsensitized preparation may be observed in some animals after vagotomy, but production is facilitated by vagal discharge. Vagal stimulation in the presence of a sympathomimetic amine will produce this arrhythmia in the sensitized preparation also. However, the doses of amine required are essentially the same as in the nonsensitized preparation and are considerably greater than those producing bigeminal and multifocal arrhythmias. This observation that the "sensitizing" agents do not sensitize to ventricular automaticity is consonant with the finding of Dresel and Duncan that chloroform decreased the threshold to sympathomimetic-induced automaticity <u>in vitro</u> only by a factor of two (155).

It is proposed that the monofocal arrhythmia observed in the nonsensitized and occasionally in the sensitized preparation is due to the establishment of a focus of ventricular automaticity. The bigeminal and multifocal arrhythmias observed in the sensitized and occasionally in the nonsensitized preparation in response to low doses of adrenaline are not due to the emergence of such foci. This interpretation does not exclude the possibility of an occasional multifocal rhythm being due to the emergence of two or more ventricular foci of automaticity. However, this arrhythmia was never produced by strong vagal stimulation in the presence of moderately large doses of sympathomimetic amines.

The question of the mechanism of the production of ventricular fibrillation has been avoided deliberately. None of the experiments reported here was directed toward a study of this arrhythmia. The fact that this arrhythmia is not produced by elevations of the blood pressure in the presence of low doses of adrenaline (although multifocal arrhythmias are consistently induced by this manoeuver) argues against a common mechanism for these two arrhythmias. Moreover, Dresel and Sutter have demonstrated that the threshold dose of adrenaline required for this phenomenon is not increased by vagal stimulation. They have suggested that ventricular fibrillation occurs by a mechanism other than that producing bigeminal and multifocal arrhythmias (54).

One disturbing aspect of cyclopropane-arrhythmias is the observation that isoproterenol, which produces a fall in the systemic blood pressure, nevertheless may produce "multifocal" arrhythmias in the sensitized preparation. It is difficult to reconcile this observation with the pressure sensitivity of adrenaline-induced multifocal

arrhythmias. The observations by Moe et al. (47) and Murphy et al. (65) suggest, however, that increments in pressure are not necessary for the production of adrenaline-induced multifocal arrhythmias although larger doses are required if the pressor response is prevented. It would be interesting to know if the character of the arrhythmias produced by the larger doses of adrenaline also changed. Several authors, using different techniques, have now reported that isoproterenol is approximately 5-10 times as potent as adrenaline in producing what appear to be true automatic foci (52, 155, 156). The possibility exists that the isoproterenol-induced arrhythmia may occur be a different mechanism than that producing adrenaline-induced multifocal arrhythmias. It may well be that at least some of the arrhythmias produced by isoproterenol are due to the emergence of automatic foci, particularly when large doses of the amine are employed. It is of interest that Dresel and Sutter demonstrated that vagal stimulation during sinus or nodal tachycardia following large doses of isoproterenol (up to 300 μg./kg.) administered to thiopental-cyclopropane-anaesthetized dogs produced multifocal arrythmias (54). Such an observation is readily explained on the emergence of two or more ventricular foci of automaticity. It is unfortunate that the arrhythmia produced by isoproterenol lasts only 12-15 seconds before sinus dominance is reestablished. Such arrhythmias do not lend themselves well to experimental study, and one can only speculate on the mechanism of these irregularities.

The most appealing theory for the production of bigeminal and multifocal beats is that of reentry. The normal wave of excitation may encounter a region of unidirectional block, possibly in the atrioventri-

cular node. Activation of such an area would occur in a retrograde manner because of the block between the atria and the ventricles. If the delay in activation of such an area was sufficiently great that the rest of the myocardium had passed through its refractory phase, this would be expected to initiate a "new" beat. A modification of this theory holds that a portion of the normal excitation wave reaches a locally depressed area, and either "dies out" through decremental conduction or is sufficiently slowed that it emerges from the area at a time when the myocardium is again capable of responding. Since conduction in the superior portion of the normal atrioventricular node has been determined to be of the order of 0.02-0.05 M/sec., (124,125) it is conceivable that agents which depress the mode might grossly prolong conduction times through this structure.

Definitive evidence in favour of this explanation can not be offered, and will only be available when direct multiple electrode recordings are made from the conduction system and from the myocardium under various conditions of anaesthesia and during various arrhythmias. Such studies currently are being performed in this laboratory.

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APPENDIX

APPENDIX I

The Anatomical Distribution of the Left Circumflex Coronary Artery of the Dog

There is general agreement that the main blood supply of the sinoatrial node is derived from a branch of the right coronary artery in the dog. However, most authors comment that the major nutrient flow may be supplied by the left circumflex coronary artery in a small percentage of cases (157,158,159) and that anastomotic channels exist between branches of the left circumflex and right coronary arteries at this site (157,158).

There is also general agreement that there is no single large branch which supplies the atrioventricular node. Meek (157) states that the "region of the coronary sinus" is supplied by both the left circumflex and the right coronary arteries, and Pianetto (158) and Moore (91) also have localized the blood supply of the atrioventricular node to these two arteries. Lumb et al. conclude that the major supply to the atrioventricular node in the dog is derived from the left circumflex coronary artery (160). There appears to be no anatomical evidence that the atrioventricular node derives any of its blood supply from the anterior descending coronary artery.

Cannulation of the two branches of the left coronary artery was performed in two animals in the present investigation. These vessels were cleared with Tyrode solution immediately on death of the animal. Injection of different dyes into the arteries resulted in staining of the area of the coronary sinus only when injection was made into the left circumflex artery.

The anatomical evidence that the left circumflex coronary artery supplies the atrioventricular node in the dog is supported by the observations of West et al. (161) and of Dresel et al. (156) that injection of isoproterenol or adrenaline into this artery in sensitized and nonsensitized dogs consistently produced a nodal rhythm. Further evidence was obtained in the present experiments which demonstrated that small doses of acetylcholine produced transient complete atrioventricular block only when injected into the left circumflex coronary artery. Subsequent to these experiments it was found that West et al. had reported similar experiments with identical results (161).