# CARDIAC PHARMACOLOGY

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Cardiac Pharmacology today is too vast and complex a field to permit a comprehensive review of the contributions of the last few years to be made in a paper of restricted length. On the other hand, the extraordinary development of the biological sciences has meant that investigators have had to limit their interest to progressively more specific subjects, while their concern with those not intimately related to their own work has correspondingly diminished.

Having spent several months collecting and analysing the bibliographic material for a review of Cardiac Pharmacology, and after going through the nine volumes already published by the *Annual Review of Pharmacology*, we decided to eliminate the cardiac glycosides from present consideration since there is little to add to the excellent works compiled on the subject in recent years (1, 2). For comparable, though contrasting, reasons we decided to deal fairly extensively with the aspects of antiarrhythmic medication and coronary circulation, including the action of sympathomimetic amines and adrenergic blockade of the heart. These constitute the main subjects of the present review, both because they have undergone many changes in recent years, and because they are the most closely related to the work we are now doing.

## ANTIARRHYTHMIC DRUGS

### TERMINOLOGY AND SOME RECENT GENERAL CONCEPTS CONCERNING ARRHYTHMIAS AND ANTIARRHYTHMIC DRUGS

At the outset one is confronted with the use and meaning of the terms antifibrillatory and antiarrhythmic, terms which some authors continue to employ synonymously. However, no drug can be considered specifically "antifibrillatory," and fibrillation is only one of various types of arrhythmias, not even the most common. We propose, therefore, that only the term "antiarrhythmic drugs" be used. Moreover, considering the differences in the action of antiarrhythmic drugs on the various cardiac tissues, we propose that the term "cardiac depressants" be discontinued for the designation of these substances (3). Indeed, some of the more recently introduced antiarrhythmic drugs have little if any influence on cardiac contractility.

Experimental and clinical studies of antiarrhythmic medications have shown that there are antiarrhythmic drugs that act predominantly on active arrhythmias, which may be classified as those resulting from "discharge of an ectopic focus", while others act primarily upon the arrhythmias of the type which "perpetuate themselves by means of re-entry mechanisms." The first group includes premature beats, coupled beats (bigeminy, trigeminy, and parasystole) and supraventricular and ventricular tachycardias. In arrhythmias resulting from the re-entry phenomenon, one mechanism initiates the disturbance (premature beats closely coupled to the previous beat), while a second perpetuates the arrhythmia, though in order to bring them to an end the perpetuation mechanism must be interrupted (4). We include flutter and fibrillation, both atrial and ventricular, among these arrhythmias.

It has also been postulated (5–9) that there are re-entry mechanisms involved in certain tachycardias which occur at the A-V node and the His-Purkinje system as well as in parasystole. The group of arrhythmias perpetuated by a discharge of an ectopic focus responds especially to drugs which depress ectopic automaticity, whether by causing hyperpolarization, by decreasing the rate of diastolic (phase 4) depolarization, or by depressing excitability (10). The second group responds to drugs which prolong the duration of the refractory period of the tissue[1] or, rather, the wave-length of the impulse defined as the product of conduction velocity and refractory period duration (15). This mechanism applies to atrial flutter and fibrillation. Other arrhythmias due to re-entry mechanisms originating in conduction disorders (decremental conduction) may yield to the correction of the disturbance, as outlined below.

It is also possible that a strong depression of excitability and conduction velocity may prevent the transmission of high frequency impulses and thus lead to cessation of the circus movement (16).

Figure 1 shows a clear example of the different action of antiarrhythmic drugs in two well-defined types of arrhythmia: one, an ectopic focus of atrial tachysystole caused by the application of aconitine, the other, atrial flutter due to circus movement (17). Since both are produced in the same atrium and recorded simultaneously, this preparation is a good model from which to study the comparative action of a drug on both types of arrhythmia. Parts A and B of Figure 1 illustrate the action of potassium (17), which terminates the arrhythmia caused by aconitine without appreciably affecting the arrhythmia due to circus movement. Parts C and D show an experiment in which the antihistaminic drug clemizole (18) causes cessation

[1] Agreement on the most suitable method of determination of the refractory period, and the term by which it should be designated is desirable. This would facilitate the comparison of data which at present are not strictly comparable. In our opinion the measurement of the briefest attainable interval between two propagated responses (11) (not between two stimuli) offers the most accurate and simple method. In the designation of this refractory period the terms functional and effective have been employed (11–14).

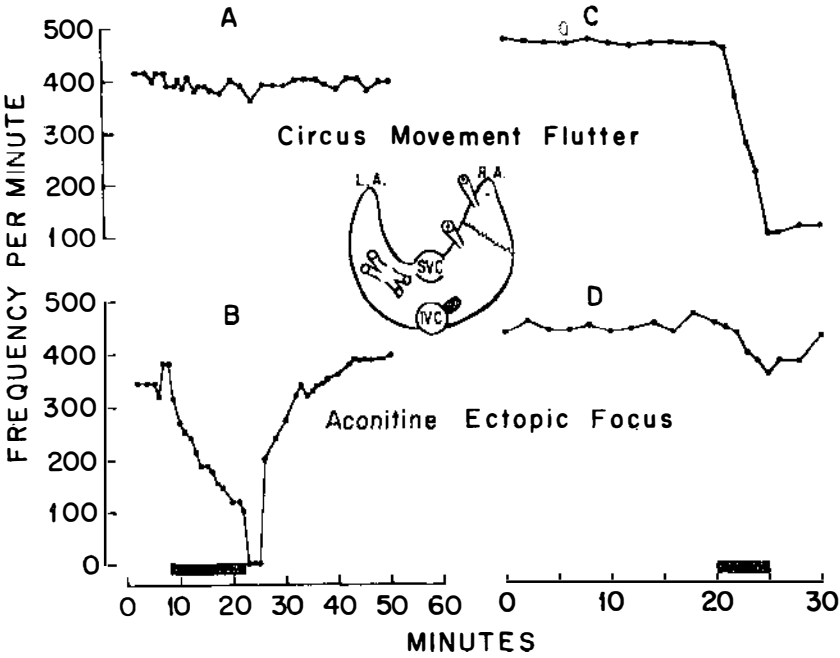


FIG. 1. Action of potassium and of clemizole on circus movement flutter and on the aconitine focus. Panels A and B indicate the action of potassium and panels C and D the action of clemizole. Horizontal bars indicate continuous infusion. L.A. left auricle; R.A. right auricle; SVC and IVC, superior and inferior vena cava.

of the arrhythmia due to circus movement, while hardly affecting that due to an ectopic focus.

Arrhythmias produced by the application of aconitine have contributed to the present confusion surrounding the terms atrial flutter and atrial fibrillation. The majority of pharmacologists and clinicians use the terms flutter and fibrillation as an expression of the rate of atrial impulses. Thus, the term flutter is applied to an experimental or clinical atrial arrhythmia with a given rate, while fibrillation is used to designate any atrial arrhythmia of a higher rate exhibiting a disorganized electrical tracing. Others reserve the term flutter or "pure" flutter for the circus movement type, and apply the term fibrillation to the disorder produced by the fractionation of the flutter wave or by the establishment of multiple waves with an independent and haphazard course.

The actions of potassium and clemizole as illustrated in Figure 1, and the actions of these and other substances to be discussed later suggest, as has been mentioned above, that some cases of flutter are the result of circus movement (4) and others may be caused by an ectopic focus which dis-

charges at the rate commonly encountered in flutter and in which the electrocardiographic tracing simulates flutter due to circus movement. For example, the observation that potassium may restore sinus rhythm in some cases of clinical flutter (19) has been interpreted to mean that in these cases the dysrhythmia was caused by a tachysystolic focus firing at a rate characteristic of a circus movement flutter.

Some reconsideration of the terminology of tachysystolic atrial rhythms seems desirable; if "flutter" and "fibrillation" are used merely to define the underlying frequency, it is clear that the terms have no meaning with respect to mechanism. "Flutter" resulting from an ectopic focus will respond to potassium and will be little affected by agents which prolong the refractory period; "flutter" due to a circus movement will respond in the opposite manner.

The following account of the antiarrhythmic drugs in use or under experimental study, or both, emphasizes their predominant actions upon the different active arrhythimias and the experimental evidence justifying such predominance.

## Brief Analysis of the Antiarrhythmic Drugs

*Quinidine.*—This drug has been used about fifty years for the treatment of a wide variety of ectopic active beats and rhythms, ranging from premature beats to atrial fibrillation. It has been well known since the time of Lewis (20) that the action of quinidine on atrial flutter and atrial fibrillation is the result of the prolongation of the refractory period of the atrium. This has been confirmed experimentally in the cells of rabbits' atria (21). It has also been observed in the Purkinje cells of dogs (13) and in other cells of dogs' atria and ventricles. The coincidence of these results is in sharp contrast with the differences in their interpretation (13, 21–23). The action of quinidine on arrhythmias resulting from an ectopic focus may be attributed to a depression of excitability (13, 24) or to a decrease of the rate of diastolic depolarization (10, 21), or both, which are probably conditioned by changes in ionic permeability (decrease of permeability to sodium) (25). However, this has not been proved with concentrations of quinidine comparable to those achieved with therapeutic doses. Tested on the preparation illustrated in Figure 1, quinidine shows a comparatively greater activity on the latter condition (17).

*Procainamide.*—Employed clinically especially in ventricular tachycardia, experimentally procainamide prolongs the refractory period of the atrium and of the ventricle with a less intense and less sustained action than that of quinidine (24) and at the same time, it depresses to a considerable degree the basal excitability and conduction velocity of both atrium and ventricle (24, 26). Its action on experimental flutter resulting from circus movement (27) and in some cases of clinical fibrillation may derive from a marked depression of these two properties.[2] In isolated Purkinje fibers, it

decreases the rate of diastolic depolarization without prolonging the repolarization phase (10). Its therapeutic effect on arrhythmias resulting from an ectopic focus probably results from its action on mechanisms which depress automaticity; mechanisms which have not yet been studied with regard to possible alterations of ion interchange. Its action on automaticity may account for the fact that, occasionally, small doses terminate bouts of ventricular tachycardia. Its marginal usefulness in clinical flutter and fibrillation and the danger inherent in using it in large doses (28) probably derive from its depressant action on conduction velocity.

*Antihistaminic drugs.*—In the last few years, laboratory and clinical studies of some antihistamines have been undertaken. These studies have shown that some drugs of this type show material differences in action upon both experimental and clinical arrhythmias.

(*a*) Meclizine and Clemizole. These two agents have the peculiar ability to convert to sinus rhythm experimental atrial flutter resulting from circus movement, while having only a slight effect on atrial tachysystole resulting from the application of aconitine (see Figure 1) (16, 18). Pyrilamine (30) also conforms to this pattern of action. Clemizole is much more potent than meclizine and has no effect on arterial blood pressure (18). These features made it a good candidate for a clinical trial, in which ten out of fifteen cases of atrial flutter were converted to sinus rhythm (31). Atrial fibrillation, however, is converted into atrial flutter, but not into sinus rhythm (32). Clemizole (and meclizine) prolongs the refractory period of the atrium with very little effect on conduction velocity, a characteristic which accounts for a notable increase in the wavelength of the impulse (18). Further, it prolongs the repolarization phase of the action potential (18). In patients, doses of more than 3mg/kg may cause atrial premature beats, while at the same time decreasing the rate of flutter or converting it to sinus rhythm (31). The fact that a single drug leads to the cessation of one active arrhythmia while simultaneously favoring the initiation of a second certainly does not substantiate the unitary theory of arrhythmias. The action of clemizole has provided pharmacologic evidence for a circus mechanism in atrial flutter (18). This mechanism has been confirmed in experiments during which the activation course of the excitation wave is followed in the atrium, while the cancellation of the circus movement is also observed when bands of nonconductive tissue are placed in its path (33). The differences between atrial flutter sustained by a circus movement and the tachysystolic rhythm resulting from aconitine have also been indicated (33).

(*b*) Antazoline. Antazoline has been employed in premature atrial and ventricular beats, in paroxysmal supraventricular and ventricular tachycar-

[2] On a purely speculative basis, but as a mere working hypothesis, the possibility exists that digitalis, which produces an early depression of atrial excitability and conduction velocity (29), may act through this mechanism in some cases in which it suppresses atrial flutter and fibrillation of recent appearance.

dias and in ectopic beats and rhythms due to digitalis intoxication (34–38). Its effectiveness in these arrhythmias resulting from an ectopic focus is in contrast to its marginal value in atrial fibrillation and atrial flutter. Experimentally, it is much more effective against tachysystole resulting from aconitine than against flutter caused by circus movement (16). Part of its effect on the aconitine focus derives from its anticholinergic action, which is also observed clinically. It shortens rather than prolongs the wavelength of the impulse, and depresses basal excitability and conduction velocity (16). Its negative effect on wavelength accounts for its minimal value in countering atrial flutter and atrial fibrillation. To the best of our knowledge, the action of antazoline on intracellular potentials has not been studied, though there are observations which indicate (38) that with concentrations of 5 μg/ml the velocity of depolarization of the action potential of the cells of rats' atria decreases, which may suggest a reduction in permeability to sodium. This action, together with the depression it produces on excitability, may account for its effect on arrhythmias resulting from an ectopic focus.

*Potassium.*—In the double arrhythmia preparation (Fig. 1), potassium, in sharp contrast to clemizole, causes the cessation of activity of the aconitine focus while hardly affecting the cycle rate in flutter due to circus movement (17). In this case, too, experimental results concur with clinical experience, since the intravenous infusion of potassium in doses of 0.5 to 1.0 meq/min. suppresses ectopic beats and rhythms in nearly 80 per cent of patients, while having no effect either on atrial flutter or atrial fibrillation (39). Its effect on ectopic beats and rhythms resulting from digitalis intoxication has been well known for almost forty years.

The cellular antiarrhythmic action of potassium has been excellently reviewed in a recent paper (40). Its effect on arrhythmias resulting from an ectopic focus probably derives from a diminution in the rate of diastolic depolarization, as has been observed in Purkinje fibers (10, 41, 42), and which has been attributed to an increased permeability to potassium (42, 44). A moderate increase in the concentration of extracellular potassium also results in a shortening of the action potential (40, 42) and of the QT interval, thus accounting for its lack of effect on experimental and clinical arrhythmias caused by circus movement (17, 39). On the other hand, low concentrations of extracellular potassium increase the rate of diastolic depolarization in Purkinje fibers (41–43), and may even provoke automatic activity in cells, such as those of the papillary muscle, which normally exhibit no automaticity (41). Automaticity in muscle cells with no Purkinje tissue has also been produced by aconitine, ouabain,[3] and barium (41, 45).

[3] It is worth noting that the production of automaticity in cells which under normal conditions do not exhibit it may derive from a different alteration in ionic interchange. For example, it has been suggested that the automaticity resulting from a reduction in extracellular potassium, from barium, and from digitalis intoxication is the result of a decrease in the permeability to potassium (43, 45). On the other hand, the action of aconitine has been attributed to an increased sodium current (46).

Extracellular concentrations of potassium of from 5.5 to 6.5 meq/l generally produce no effects other than those indicated, but a rapid increase in concentration may lead to bradycardia and myocardial depression (47). The action of the above mentioned concentrations on A-V conduction is variable. In some patients it has alleviated second and third degree blocks, in others it has had no effect whatsoever, while in still others a depression of the A-V conduction has been seen, one of the crucial factors being the state of the conduction system of the diseased heart (40). The improvement of conduction occasionally produced by potassium has been attributed to its effect of decreasing the rate of diastolic depolarization, which would, itself, increase membrane responsiveness and the margin of safety for propagation of the action potential, thus modified (48). It is by means of this mechanism that the action of potassium and of other antiarrhythmic drugs has been explained in arrhythmias attributed to decremental conduction (48).

*Diphenylhydantoin.*—A recent review of the results of treating almost 1,000 patients with diphenylhydantoin (DPH), including 774 episodes of arrhythmia treated by the authors themselves (49), points out the drug's variable success when used on arrhythmias of the most diverse origins caused by an ectopic focus and which ranged from premature beats to ventricular tachycardia. Fifty five per cent of ventricular arrhythmias and 82 per cent of arrhythmias induced by anaesthesia responded. However, only 17 per cent of supraventricular paroxysmal tachycardias responded and it failed in cases of atrial flutter and atrial fibrillation. Of the 54 cases of flutter and fibrillation treated, conversion to sinus rhythm occurred in only a single case of flutter. Other authors (50–52) find DPH valuable in digitalis-induced ectopic arrhythmias but of little use in other ectopic arrhythmias. Moreover, several deaths from ventricular fibrillation or ventricular standstill have been reported in association with its use (49). Recently, three cases of cardiac arrest (53, 54) and one of ventricular fibrillation (55) have been reported.

Experimental work with DPH indicates that in digitalis intoxication it decreases or eliminates ventricular ectopic automaticity and corrects A-V depression, whether due to digitalis or to a combination of digitalis and procainamide (56, 57).

In normal Purkinje fibers (58), in concentrations of from $10^{-8}$ to $10^{-5}$M, it shortens the duration of the action potential at the expense of phase 2, reduces the refractory period, and increases excitability. Moreover, it decreases the rate of diastolic depolarization. Resting potential, depolarization velocity, membrane responsiveness, and conduction velocity are increased when previously depressed by hypoxia, strttching of the fiber, or by ouabain. In Purkinje fibers subjected to these abnormal conditions (58), DPH also shortens the duration of the action potential and of the effective refractory period. These actions of DPH have led to the idea that its action on some arrhythmias derives from a suppression of the decremental conduction which originates them.

In atrial cells (59) exposed to high concentrations of ouabain the toxic effects of digitalis are reversed. In other experiments on atrial cells and on cells of Bachmann's bundle (59), also with concentrations of from $10^{-8}$ to $10^{-5}$M, an increase in depolarization velocity and membrane responsiveness has been observed, without the other effects which have been observed in ventricular cells. It has been suggested that the differences in the action of DPH on atrial and ventricular cells (59) may derive from an increased ionic current due to calcium which may be absent in atrial cells. It has also been suggested (58, 59) that the actions of DPH on resting potential, depolarization velocity, membrane responsiveness, and excitability may be caused by an increased "sodium carrier" activity or increased sodium-potassium exchange pumping. This has also been suggested to occur in brain (60).

From a practical standpoint, some experimental actions of DPH may explain its action at the clinical level. The decrease in the rate of diastolic depolarization could account for its action on ventricular arrhythmias of ectopic origin. With regard to the atria, there is only the information deriving from its action on aconitine and delphinine foci (61). Its marginal action on the refractory period of atrial cells (59) is consistent with its failure to act upon atrial flutter and atrial fibrillation, while its action in digitalis intoxication may be related to the correction of sodium-potassium exchange pumping alterations.

Thus, DPH is a drug of limited value in cardiac therapy, but one that has peculiar and interesting effects upon the electrical phenomena of cardiac cells.

*Lidocaine.*—After experimental and clinical tests performed during the years from 1950 to 1965, the use of lidocaine has come into fashion in the last three years for the treatment of ventricular arrhythmias, especially for those observed following myocardial infarction. We may go so far as to say that today it is the first-choice drug in coronary-care units for ventricular arrhythmias. One report (62) states it to be "Admirably suited for suppressing ectopic mechanisms in the patient with acute myocardial infarction". In more than 80 per cent it completely abolished ectopic activity (62–64). It was also effective in nearly 80 per cent of ventricular arrhythmias of various etiologies and in 88 per cent of digitalis-induced arrhythmias (65). Because of its depressant action on ventricular automaticity it is not recommended in A-V block with slow ventricular rhythm, or in slow nodal or idioventricular rhythms (65, 66). An injection of 1 to 2 mg/kg generally acts within 60 seconds. Because it is swiftly degraded in the liver, its effect is usually transient and so it is often given by intravenous infusion. Significant toxic effects have not been observed with doses not exceeding 0.055 mg/kg per min (65, 66). Its effectiveness in ventricular arrhythmias contrasts with its slight value in atrial arrhythmias, including atrial flutter and atrial fibrillation (63, 65, 67). It is of questionable usefulness in treatment of supraventricular ectopic beats (65, 67) and virtually ineffective in cases with supraventricular tachycardia with or without A-V block (63, 65, 67).

Hemodynamic studies have shown that the above mentioned doses of lidocaine have no adverse effects of clinical significance on cardiac output, left ventricular pressure, heart rate, or systemic or pulmonary pressures (63–66, 68–70). In several cases, intravenous infusion of lidocaine has been continued for 5 days or more (62, 65). The side-effects encountered during continuous infusion include drowsiness (in 47 per cent of the cases with a single injection), apprehension, disorientation, stupor, tinnitus, and minor nervous effects (65). As with other local anaesthetics, excessive doses of lidocaine may cause convulsions and respiratory arrest.

The validity of the presumption that the prophylactic use of the drug in cases of myocardial infarction with ventricular premature beats lowers mortality by reducing the incidence of ventricular fibrillation (62) has been questioned in a recent paper (71), in which 7 deaths are reported among 33 cases of infarction in which lidocaine was administered; two of these occurred during the infusion. This suggests the necessity of further evaluation of lidocaine therapy in myocardial infarction.

There are few laboratory studies which may be related to the therapeutic actions of lidocaine. In dogs, doses comparable to those used on human beings do not produce significant effects on ventricular contractility nor on conduction velocity of the atrium or ventricle. However, they have a slight depressant effect on ventricular automaticity in hearts with complete A-V block (72). There are no modern studies concerning the physiological properties of the atrium or isolated atrial cells which might account for the ineffectiveness of the drug in atrial arrhythmias, including flutter and fibrillation. Recent studies (73, 74) utilizing isolated Purkinje fibers and ventricular muscle fibers reveal
mal and adrenergically-induced automaticity in Purkinje fibers. Lidocaine also shortens the action potentials of Purkinje fibers and of ventricular muscle fibers, with a parallel reduction of the effective refractory period of the Purkinje fibers. No significant changes in conduction velocity or membrane responsiveness were observed. These effects on automaticity constitute the first step towards a possible explanation of the action of lidocaine in ectopic ventricular arrhythmias.

*β-Adrenergic blocking agents.*—Recently much has been written on the use of β-blocking agents as antiarrhythmic drugs. Three of the several published reviews are cited here (75–77). For the pharmacologist, deciding which of the drugs' actions may be attributed to blockade of the β-cardiac receptors and which not may be a problem.

The most outstanding and specific therapeutic contribution of these agents is their action on sinus tachycardia. Here the explanation is simple: the partial restriction of sympathetic action on the sinoauricular node permits a vagal predominance which, in turn, is responsible for the reduction in cardiac rate.

The action in supraventricular paroxysmal tachycardia may, to a large extent at least, be explained in similar terms. This arrhythmia may respond

to those procedures or drugs that increase the acetylcholine concentration in atrial cells: vagal stimulation, the injection of acetylcholine or neostigmine, cardiac glycosides, pressor amines, or β-blocking agents. When those atrial cells responsible for ectopic automaticity are exposed to above-normal concentrations of acetylcholine, or are deprived of adrenergic influence, the rate of diastolic depolarization is diminished (41, 78). Naturally, this is not the sole mechanism by which an attack of supraventricular tachycardia can be stopped. It can also be done by drugs which depress atrial or nodal automaticity by means of other mechanisms mentioned above. Results reported thus far indicate that β-blocking agents are not the first choice in treatment of attacks of supraventricular tachycardia. That is to say, they have not proved capable of replacing digitalis. Their usefulness in the prevention of recurrences of supraventricular tachycardia is more clearly defined.

Only rarely do β-blocking agents convert atrial flutter or fibrillation to sinus rhythm. A combination of propranolol and quinidine in small doses has been reported useful in atrial fibrillation (79, 80), both in converting it to sinus rhythm and in preventing its recurrence. Nevertheless, according to a recent report, this combination converts fibrillation to sinus rhythm in only one third of the cases, and may produce serious depression of the A-V transmission system (81). In patients suffering from chronic atrial fibrillation or flutter, β-blocking agents reduce ventricular rate. In this case the mechanism of action is sympathetic inhibition with the resulting vagal predominance which lengthens the duration of the A-V nodal refractory period (82–85). β-Blocking agents are also useful in slowing ventricular rate in those relatively rare cases where digitalis drugs have failed to reduce it to the required levels. In such cases, the digitalis action prolonging the duration of the A-V node refractory period through vagal action and peripheral sympathetic inhibition (86, 87) is complemented by the sympathetic inhibition induced by the β-blocking agent. In these cases careful regulation of dosage is necessary to prevent excessive depression of the A-V node (82, 83). The employment of β-blocking agents in digitalis intoxication is hardly comparable to that of other, more easily manipulated antiarrhythmic drugs, such as potassium. The same may be said of their action in supraventricular and ventricular premature beats and ventricular tachycardias, unless a sympathetic component in the origin of the arrhythmia is suspected. In digitalis induced or other experimental arrhythmias (88, 89) and in isolated fibers (14, 90) direct action has been encountered in addition to the antiadrenergic effect. With several β-blocking agents in which the effects of the D and L-isomers have been compared, it has been observed that the L-isomers possess the antiadrenergic action and are far more active in adrenergically induced arrhythmias provoked by certain anaesthetics and catecholamines. In this type of arrhythmia, the D-isomers are much less effective, but their action is apparent in experimental arrhythmias where no obvious adrenergic element is involved (89, 91-93). Dextro-propranolol has been used experimentally on patients. It evinces no action in sinus arrhythmias, nor does it reduce ventricular rate in patients suffering from atrial flutter or fibrillation, but it is

as effective as DL-propranolol in supraventricular and ventricular arrhythmias caused by an ectopic focus, including those resulting from digitalis intoxication (94).

Antiadrenergic action might also explain the effectiveness of β-blocking agents in repeated crises of "ventricular fibrillation." In this disorder there may be an increase in heterogeneity of the refractory period of the ventricular fibers, which would be decreased by sympathetic inhibition. Some other term might better describe this disturbance, since it is difficult to comprehend how a ventricle of the size of that in man can overcome a crisis of fibrillation spontaneously.

Not all β-blocking agents possess the same antiarrhythmic properties. In arrhythmias resulting from an ectopic focus, their action does not derive from their adrenergic blocking activity, but is probably related to their local anaesthetic effect (92). Among β-blocking agents effective in nonadrenergic arrhythmias resulting from an ectopic focus may be included DL-propranolol and its two isomers (92) and H 56/28 (91) [1-(O-allylphenoxy-3-isopropylamino-2-propanol-HCl)]. In man, this latter compound is less potent than propranolol, though its antiarrhythmic action is similar in all respects (95). Other blocking agents which have no local anaesthetic action such as MJ 1999 [4-(2-isopropylamino-1-hydroethyl) methanesulfonanilide HCl] and Inpea (N-isopropyl-*p*-nitrophenylethanolamine HCl) do not affect nonadrenergic arrhythmias resulting from an ectopic focus (93, 96).

With regard to the action of β-blocking agents on the physiological properties of the heart and the action potential of isolated cardiac fibers, it has been reported that propranolol diminishes excitability in atrial cells (90). It also reduces the rate of depolarization (14, 97, 98) and lengthens the duration of the absolute refractory period (90). Reduction in the rate of depolarization seems to be brought about only by those blocking agents which possess a local anaesthetic activity and which act upon nonadrenergically induced arrhythmias. In Purkinje cells, propranolol is said to diminish the rate of depolarization, shorten the action potential at the expense of phase 2, and reduce the duration of the effective refractory period (14). In ventricular cells it diminishes the rate of depolarization without affecting other action potential parameters (14). It decreases the ability of Purkinje fibers to follow high frequency stimulation, "an effect interpreted to indicate a lengthening of the refractory period" (14). However, it is not easy to reconcile the increase in the functional refractory period connoted by the reduction in ability to follow high frequency stimulation with the shortening of the effective refractory period reported. The increase observed in the refractory period in the atrium might, perhaps, account for the effects produced by small doses of propranolol and quinidine in combination upon atrial fibrillation. Low doses of propranolol blocked the increase in Purkinje diastolic depolarization induced by epinephrine (14), a fact which probably explains why β-blocking agents prevent epinephrine-induced ventricular arrhythmias.

*Ajmaline.*—Ajmaline has been employed by several European clini-

cians over the past few years (99, 100) and is another of the antiarrhythmic drugs which act on ectopic focus arrhythmias but not on atrial flutter or fibrillation due to a re-entry mechanism. One paper (99) gives an account of its employment in 757 cases of arrhythmia and reports four deaths, while according to another a fatality occurred when a large dose was used in a case of supraventricular tachycardia (101). The action of ajmaline upon the physiological properties of cardiac tissues or isolated cardiac fibers has not been studied using modern techniques. We are aware of one recent communication, which reveals a notable reduction in excitability of atrial and ventricular tissues (102).

*Bretylium tosylate.*—This antiadrenergic agent, which has, moreover, local anaesthetic effects, raises the threshold of ventricular fibrillation in dogs (103) and is reported in a recent pilot study (104) to have suppressed episodes of "ventricular fibrillation" in patients. It also acts on ectopic focus arrhythmias following myocardial infarction or cardiac surgery (104). In isolated ventricular fibers of rabbits, bretylium tosylate produces cellular hyper-polarization with increased rate of depolarization, increased action potential amplitude, and improved conduction velocity. Its antifibrillatory action is attributed to these effects, which would tend to regularize the propagation of the excitation wave (105). It does not depress contractility, having, rather, a positive inotropic effect (103). It produces orthostatic hypotension consequent upon its antiadrenergic action but, since it has not been administered chronically nothing is known about possible development of tolerance to its actions.

*Final comment.*—The last few years have witnessed the stimulation of pharmacological study and clinical testing of new antiarrhythmic drugs. The preeminence of digitalis and quinidine since 1914 was first abridged by procainamide in 1950 and then, since 1963, by other antiarrhythmic drugs, for which we have summarized the pharmacology and clinical value in this review. As was the case with digitalis and quinidine, clinical use of these new antiarrhythmic drugs has all too frequently preceded their investigation in the laboratory.

A more systematic approach to the experimental and clinical study of antiarrhythmic drugs would be highly desirable. Research upon the antiarrhythmic activity of a drug is still done using randomly chosen experimental arrhythmias without regard to their nature and mechanisms. Useful ectopic focus arrhythmias include the aconitine-induced ectopic focus, the majority of arrhythmias produced by digitalis, arrhythmias induced by epinephrine during certain types of anaesthesia, and those induced by ligation of a coronary artery. The production of flutter by means of circus movement offers a simple experimental method to use to screen drugs for action against atrial flutter and fibrillation. These methods provide data which constitute valuable, though not complete, information. Nevertheless, a systematic study of the action of antiarrhythmic drugs using these methods, integrating the results with those obtained by studying their action on the physiological prop-

erties of cardiac tissues and on the transmembrane action potential, may well advance our theoretical and practical knowledge in this important field.

## CORONARY CIRCULATION

Rowe (106), in his review of pharmacology of the coronary circulation two years ago, made an excellent analysis of the so-called coronary vasodilators and in the same volume of *Annual Review of Pharmacology* Ahlquist (107) reviewed agents which block adrenergic $\beta$-receptors. However, neither author emphasized the action of sympathomimetic amines and of adrenergic blockade on the coronary circulation. It is our aim to supplement these reviews by reporting some of the investigations undertaken during the last two years concerning coronary vasodilators. We will also attempt to analyse the effects of the catecholamines and the present state of research on adrenergic receptors and adrenergic blockade in the coronary circulation.

### The Coronary Vasodilators

The demonstration that nitroglycerin increases coronary flow in a normal heart but not in the hearts of patients with coronary sclerosis (108–112) has changed our concept of the action of drugs in coronary insufficiency. The effect of nitroglycerin and other nitrites which can be given by the sublingual route has been attributed to a relaxation of the smooth muscle of the artery wall, and to a reduction in cardiac work with a consequent diminishing of oxygen requirements (108).

It has been found that tolerance to exercise is increased by nitroglycerin (113–115). This has been attributed to an attenuated circulatory response to exercise; cardiac output is maintained, but arterial and end-diastolic pressure and cardiac oxygen consumption are reduced (116). The prevention of angina is related to a reduction in cardiac work, taking as indices of this latter the rate-pressure product (115, 117) or the tension-time index (118). The precipitation of angina on the other hand correlates well with the level reached by the product of heart rate and systolic blood pressure (119). In a series of nine patients (115) treated with nitroglycerin, the only one who failed to improve was also the only one in whom no modification of the rate-pressure product was observed.

Consideration of the action of the nitrites brings up the question of whether their effects on patients with coronary insufficiency may be explained by the hemodynamic changes indicated above, for it seems strange that other vasodilator agents fail to produce an effective improvement in the coronary patient or to prevent the electrocardiographic pattern of coronary insufficiency. The extreme case is provided by dipyridamol (Persantin), whose coronary vasodilator action interested some investigators, but which has been shown by several clinical studies to be ineffective in patients with coronary heart disease (120, 121). On the other hand, only the nitrites, large doses of papaverine and a special xanthine preparation are capable of modifying the electrocardiogram on exercise in the standardized test (121,

122). Differences have been reported between the action of the nitrites and that of dipyridamol which perhaps explain the discrepancy in their therapeutic effects. In chronic ischemia in dogs, nitroglycerin promotes retrograde coronary flow, by dilating the collateral vessels, without producing sustained effects on total coronary flow (123). Nitroglycerin reduces the resistance in the large conductive vessels including collateral channels; dipyridamol, on the other hand, reduces total resistance by dilating the small resistance vessels (124). Another possible explanation of the effect of nitrites resides in a reduction of myocardial metabolic heat production with a resultant increase in the efficiency of utilization of metabolic free energy (125) already suggested by earlier work in which it was observed that the proportion of $O_2$ consumption dissipated as heat was reduced by nitroglycerin (126). But it should not be forgotten that nitroglycerin may also act by suppressing coronary spasm, which may provoke an attack of angina (124, 127).



### Sympathomimetic Amines and Adrenergic Receptors

The years pass and the argument goes on about the action of the catecholamines on coronary vessels. The disagreement turns upon whether or not the increase in coronary flow produced by epinephrine and norepinephrine is preceded by a vasoconstrictor effect. Over the last few years, while some have continued to encounter an initial vasoconstrictor action (128–133), others have insisted on a primary vasodilator effect (134–141).

No satisfactory explanation for this discrepancy has been found, but it may be of interest to point out that almost all those who have utilized the heart *in situ* observe primary vasodilation, but those working with isolated hearts obtain initial vasoconstriction. It has been suggested (129) that the procedures and instruments employed in measuring coronary flow in the heart *in situ* provoke a state of abnormal tension in the vessels which modifies the response to the catecholamines. Indeed, the vasodilator effect of epinephrine and norepinephrine upon the heart *in situ* has been converted into a vasoconstrictor effect when dipyridamol was used to reduce the tone of the coronary vessels (142). With the isolated heart, the cannulations are outside the coronary vessels in the brachiocephalic trunk and the pulmonary artery. Furthermore, it is logical that the intrinsic reactions of the coronary vessels should be better observed in an isolated heart, in which perfusion is at a constant pressure and whose vessels are hardly submitted to ventricular pressure, so that inotropic and metabolic activity are comparatively less. Nor are reflex vascular or intercoronary effects produced in the isolated heart.

In regard to the action of isoproterenol all the investigators who have used it (134, 137, 143–145), with the exception of a single group (128, 129), agree that it has a primary vasodilator effect. The dissenting group reported initial vasoconstriction in the isolated heart with isoproterenol as well as with epinephrine and norepinephrine; they maintain that the effect is due to

activation of the β-receptors in the coronary vessels, since it is inhibited by propranolol.

That the coronary vasoconstrictor effect of the catecholamines is caused by activation of the β-receptor is denied by those who maintain that coronary vasoconstriction by sympathomimetic amines is the result of activation of α-receptors (131, 133, 136, 137, 139, 143, 146–148), a position which implicitly concurs with earlier work (149–151). All these authors report vasoconstriction due to epinephrine or norepinephrine after β-blockade with dichloroisoproterenol, pronethalol, or propranolol, and some have been able to eliminate this effect with α-receptor blocking agents (131, 136, 137). However, others have been unable to obtain vasoconstriction after β-blockade (128, 129, 141, 145), and still others (138) have observed only a "slight tendency toward vasoconstriction."

An analysis of the work of those who affirm that vasoconstriction induced by epinephrine and norepinephrine after β-blockade is due to activation of α-receptors (136, 137) gives rise to possible reservations, since phenoxybenzamine was used to inhibit the effect and it is uncertain whether adequate dosage was employed or whether sufficient time was allowed for the blocking agent to take effect. Another interpretation of the results lends itself to this consideration: initial vasoconstriction in the heart *in situ* has been obtained invariably by some investigators (152) and occasionally by others (137); it is possible that some have failed to observe it because, for technical reasons noted above, the vasodilator effect may impinge upon and obscure the vasoconstrictor effect. Moreover, if the dose of β-blocking agent was inadequate, or if insufficient time was allowed for it to take effect, the metabolic effect may have been inhibited while still permitting the vasoconstrictor effect to be observed. The coronary vesssels have been reported to be more sensitive to vasoconstrictor effects than to vasodilator effects (128, 129, 132). Moreover, it has been observed that in experiments with an isolated heart in crossed circulation with an anaesthetized dog (129), phenoxybenzamine (5 mg/Kg given 60 min before the cathecholamines) and Zolertine[4] inhibit the action of epinephrine and norepinephrine on the arterial pressure of the donor dog, but have no action upon their initial vasoconstrictor or secondary vasodilator effects, in the isolated heart.

It seems odd that those who attribute the coronary vasoconstrictor action of epinephrine and norepinephrine to the activation of α-receptors have not tested more thoroughly the action of specific α-activators such as methoxamine or phenylephrine. Methoxamine produces, at most, a slight coronary vasoconstrictor effect (129) accompanied by a minor positive chronotropic effect, presumably due to β-receptor stimulation. The difficulty which the study of this agent occasions derives from the fact that in the isolated heart

[4] Zolertine is the generic name of 4-phenyl-1-2(5-tetrazolyl) ethyl piperazine trihydrochloride, which has previously been referred to as MA1277 or phenpiperazole (153).

the effect of a second injection is blocked by the action of the first (129). This may represent a $\beta$-blocking property that has been attributed to the agent (154). The phenylephrine-induced coronary vasoconstriction that has been observed has been attributed to activation of $\alpha$-receptors (137), although the authors did not study its action under the influence of adrenergic blocking agents to define the type of receptor.

Because the coronary vasoconstrictor and positive inotropic effects of phenylephrine in the isolated heart are inhibited by intracoronary infusion of propranolol, these actions have been attributed to activation of $\beta$-receptors (129). In crossed circulation experiments (129) the $\alpha$-blocking agent zolertine counteracts the effect of phenylephrine on arterial pressure in the donor dog but does not affect its constrictor action on the coronary vessels of the isolated heart. These experiments also cast doubt upon the presence of $\alpha$-receptors in the coronary circulation of the isolated dog's heart.

Thus far the reviewers have made an appraisal of the discrepancies which have arisen over the last few years concerning adrenergic receptors in the coronary circulation, and the responses of coronary vessels to the catecholamines. However, it may well be that the next few years will see a change in our concept of the nature of adrenergic receptors in the myocardium. In fact, an interesting recent work (155) suggests that only a single adrenergic receptor exists in the myocardium. Simple experiments in the isolated hearts of frogs and rats show that mere changes of temperature provoke reactions to epinephrine which, through changes in metabolic conditions, would make it appear to be, on some occasions, a typical $\alpha$-receptor activator and on others a typical $\beta$-receptor activator. The extension of this concept to hearts of other species—and even to other tissues—changing the experimental conditions with this new objective in mind, might explain the different results obtained and clear up past discussions. We may mention, too, that the existence of a single receptor with different reactive capacities has been suggested previously (156), but the development of these ideas is still in its infancy.

## The $\beta$-Adrenergic Blocking Agents

The employment and study of $\beta$-blocking agents in coronary heart disease (defining this term as a clinical entity of long evolution and due to lesions of the coronary arteries) has been continued in the last two years (157–168). There is general agreement that these agents reduce myocardial oxygen requirement by reducing, at rest and exercise, the chronotropic and inotropic responses, such as heart rate, left ventricular isometric tension, and the product of heart rate and systolic pressure.

Further, the majority of authors encounter a reduction in output and stroke volume with an increase in left ventricular end diastolic pressure (157, 161, 169–173). A reduction in output without effect on stroke volume (168) and even reduction of left ventricular isometric tension development without changes in output (158) have also been reported. The effects of $\beta$-

blocking agents on these parameters of cardiac function have been explained as being the result of adrenergic blocking action in the absence of a direct depressant effect. With suitable doses of adrenergic blocking agent no depressant action was encountered in the papillary muscle after blockade (174). In dogs deprived of sympathetic nerve activity by epidural block (175), the blocking agent does not have a direct depressant effect on frequency, contractility, atrial pressure, or arterial pressure at doses of from 0.1 to 1 mg/Kg, which are sufficient to produce a decisive degree of $\beta$-adrenergic blockade. Naturally, this is not to say that hearts with diminished cardiac reserve do not deteriorate when the sympathetic tone is reduced by the blocking agent.

The majority of patients with coronary insufficiency (not those with acute myocardial infarction, in which $\beta$-blocking agents do not appear to be useful) (176) experience clinical improvement as indicated by lessening of pain and greater tolerance to exercise. However, some authors find that, while $\beta$-blocking agents have little influence on the electrocardiographic pattern typical of coronary insufficiency (159, 160, 164), the combination of propranolol and isosorbid dinitrate, apart from alleviating pain and improving exercise capacity, notably modifies the ischemic electrocardiographic pattern of selected patients with severe and refractory forms of angina (177). This combination of propranolol and isosorbid dinitrate produced persistent relief of symptoms in 109 of 115 patients including some with refractory angina (178). In twelve other cases of angina evaluated in a blind crossover study the combination of the two drugs produced a greater overall improvement than either drug alone (179).

The reduction in coronary flow due to an increase in coronary resistance, which has been reported earlier with the use of $\beta$-blocking agents, has been confirmed recently in patients (158) and attributed to a reduction in oxygen consumption deriving from reduction in heart rate and myocardial contractile force (134, 138, 180, 181). Two-thirds of this effect is attributed to $\beta$-blockade and one-third to direct action, since it is obtained following pre-treatment with reserpine and is also produced by D-propranolol, which is almost devoid of any adrenergic $\beta$-blocking action (182). It has also been suggested that the coronary vasoconstrictor effect may be the result of disguised $\alpha$-receptor activity occurring when the $\beta$-receptors are blocked (180).

In hearts arrested by potassium, or with the heart rate and work controlled (138), the catecholamines still exercise a significant metabolic effect. The blockade of this effect may influence by autoregulation the reduction in flow obtained with $\beta$-blocking agents. Coronary constriction has also been observed with the $\beta$-blocking agents Kö592, Ciba 3809-Ba, and MJ1999 (181).

The action of $\beta$-blocking agents in coronary insufficiency may be explained by their inhibiting effect on circulating catecholamines, for coronary patients show a greater adrenergic response than ordinary subjects to proce-

dures which stimulate the sympathetic system (183). In these patients, exercise increases oxygen extraction by the heart and reduces the oxygen saturation of coronary venous blood (184), effects similar to those obtained when epinephrine is injected in normal subjects (185). Furthermore, patients with angina pectoris post-infarction excrete more catabolites of norepinephrine (3-methoxy-4-hydroxy mandelic acid and normetanephrine) than those without angina post-infarction (186). However, the failure of $\beta$-blocking agents in a certain number of patients suffering from angina can not be satisfactorily explained. No relationship has been established between the action of $\beta$-blocking agents and the degree of possible influence of the sympathetic system in selected groups of patients. Nor has the possibility been pressed that the vasoconstrictor effect or norepinephrine observed in one patient (185) may act as a trigger mechanism in others for the production of angina.



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