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Structure-Activity Relationships in the Adrenergic-Blocking Agents

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CONTENTS

Drugs that owe their biological acitivity to their chemical configuration are the ones that have contributed enormously to the development of the drug-receptor interaction concept that sometimes provides the only simple explanation of many drug effects. Subtle changes in the molecule may result in profound alteration in the activity of a compound. Studies based on structure-activity relationship find their justification in the compounds belonging to this group. Falling in this category are the adrenergic-receptor blocking agents, the chemical compounds whose usefulness as pharmacological tools and as effective therapeutic agents constitute a great advance. This review aims toward discussing the literature on adrenergic drugs mainly from the chemical and the pharmacological point of view.

Langley (1) postulated a "receptor" substance to account for the antagonistic behavior of pilocarpine and atropine. Dale (2) found that epinephrine exerted two types of actions in the spinal cat, a stimulatory action that could be changed into an inhibitory action by treatment with ergotoxine. Cannon and Bacq (3), Cannon (4), and Cannon and Rosenblueth (5) suggested that excitatory and inhibitory transmitters released from sympathetic nerves combined with a receptive substance to form sympathin E (excitatory) and sympathin I (inhibitory), respectively. Since norepinephrine has been found to be the transmitter for all adrenergic nerves irrespective of the nature of response, it became apparent that the effector cell determined the excitatory or inhibitory nature of response. Ahlquist (6) tested a number of closely related catecholamines on different tissues and came to the conclusion that only two sets of structure-activity relationships could exist in these amines. The relative potencies of catecholamines on smooth muscles that produced contraction were epinephrine > norepinephrine > α-methylnorepinephrine > isoproterenol and, on the smooth muscles that produced relaxa-

tion, the order of potency was isoproterenol > epinephrine > norepinephrine > α-methylnorepinephrine. This led him to designate two types of receptors, alpha-receptors that subserve the excitatory responses, the intestinal receptors being inhibitory; and beta-receptors that subserve the inhibitory responses except in the heart where the response is excitatory. All the excitatory effects of the alpha-receptors can be viewed as membrane effects brought about by depolarization, and all the inhibitory effects of beta-receptors can be interpreted as linked to repolarization phenomenon (6, 7). The distribution as well as the responses obtained by the stimulation of alpha- and beta-receptors in various tissues are summarized in Table I (9, 10).

The true chemical nature of the adrenergic receptor is still a matter of speculation although attention has been directed toward constructing working hypothetical models (11, 12). Since virtually nothing is known about the precise nature of these receptors, some known physicochemical characteristics of compounds found to be active on these receptor sites have served as the guiding principles in postulating such receptor models (13). Receptors are characterized not by their composition, shape, size, or location, but by the chemical molecules that bring about a physiological response which has been identified with the activity of the receptor.

The specificity with which it selects and differentiates between chemical entities is the most fundamental property of a receptive substance. The optical isomers of epinephrine and norepinephrine provide a good example, the *levo* isomer being 10–100 times more active than the *dextro* isomer. The absolute configuration of these isomers has been worked out, the *levo* form having L or R configuration (14). In order to explain the difference in potency between the optical isomers, a three-point attachment to the receptor was envisaged. Belleau (12) presented a series of sketches to show what an adrenergic receptor should look like in different stages of its activity with agonists and antagonists. The characteristic feature of this illustration is the incorporation of Ca^{++} as an integral part of the primary receptor site. Calcium plays a key role in a multitude of biochemical processes in the body and might be expected to participate in adrenergic mechanisms. Though stimulating, these considerations grossly overlook a great possibility that the relative disposition of structures in the vicinity of the receptor site may influence physicochemical characteristics of the receptor. In each instance they undergo a similar change themselves by virtue of their being in a dynamic state coincident with the activity of the cell as a whole. This would imply that the structural groups forming a receptor site would be constantly undergoing conformational changes, some conformations occurring more frequently than others, depending upon the extrareceptor activity and the relative stability of such configurations. To conceive of a rigid receptor structure with its functionally active groups oriented in a rigid conformational pattern seems no longer justifiable in view of the fact that molecules differing in structure can elicit response at one and the same receptor and a single chemical molecule can be active on different types of receptors. This means that for a given molecule of a drug, the capability to interact with the receptor will depend upon: (*a*) the intrinsic nature of the receptor, *i.e.*, the nature and arrangement of the active chemical groups forming it; (*b*) its ability to acquire different conformations and their relative frequency of occurrence depending upon their relative stability; (*c*) the nature of the receptor environment and the degree of its influence on the receptor substance, which is controlled by the activ-

Table I—Comparison of Actions of Norepinephrine and Isoproterenol and the Types of Adrenergic Receptors in Various Tissues[a]

Tissues	Action of Norepinephrine (N)	Action of Isoproterenol (I)	Receptors
Heart	Increased rate	Increased rate (I > N)	β
	Increased force	Increased force (I > N)	β
Blood vessels	Constriction	Dilatation	α, β
Bronchial smooth muscle	Relaxation	Relaxation (I > N)	β
Intestinal smooth muscle	Relaxation	Relaxation (I > N)	α, β
Vas deferens	Contraction	Inhibition of contractions	α, β
Pilomotor muscles	Contraction	No contraction	α
Uterus, rabbit and human	Contraction	Relaxation (I > N)	α, β
Uterus, rat and non-pregnant cat	Relaxation	Relaxation (I > N)	α, β
Dilator pupillae	Contraction	No contraction	α
Nictitating membrane	Contraction	Inhibition of contractions	α, β
Muscle	Glycolysis	Glycolysis (I > N)	β
Liver	Potassium release; glycolysis	No potassium release; glycolysis	α, β
Adipose tissue	Fatty acids released	Fatty acids released	α, β

[a] Bowman *et al.* (86).

ity of the whole cell; and (*d*) the nature of the drug molecule. The failure to isolate a receptor substance has been a central problem of pharmacology because the controlling forces that help induce certain conformational patterns in a number of chemical groups forming a receptor are lost the moment the receptor environments are disturbed. Any such effects will be intermolecular in origin and may be called the "environmental factor." This factor involves two main problems: the stereochemistry of molecules in different stages of aggregation, and the effect of temperature on the molecules in a given state of aggregation. It will be clear that the environmental factor depends on the operation and magnitude of intermolecular forces. A change in its surroundings may cause altered behavior of the receptor in different organ systems that sometimes makes it desirable to postulate many subtypes of the receptor responding differently to a single chemical entity (15–17). Table I compares the relative actions of norepinephrine and isoproterenol on different organs of various species. It has been emphasized that this classification of the adrenergic receptors into two types agrees well with the antagonists of catecholamines much more than with the amines themselves (18). The element of uncertainty that lies in fitting metabolic, intestinal, cardiac, and CNS effects of catecholamines into this scheme is a challenge in itself, and there is no clear evidence as to whether differences between alpha- and beta-receptors are related to basic structural features, to flexible conformational variants, or to relative accessibility of receptors (19).

The evolution of alpha- and beta-receptor-blocking agents, a term coined by Moran and Perkins (20), in the last two decades is the immediate consequence of Ahlquist's classification. Many symposia and excellent reviews are reminiscent of the remarkable progress that has been made in the field (21–30). Various methods are in use for the screening of adrenergic antagonists. A brief review of some of those commonly employed will be given here.

PREPARATIONS WITH ALPHA-RECEPTORS

The isolated vas deferens of the guinea pig, without the nerve supply, has been extensively used (31–33). This preparation with an intact nerve supply which can be electrically stimulated using intracellular microelectrodes has also been described (34, 35). The sensitivity of the preparation decreases in the order norepinephrine > epinephrine > acetylcholine > histamine. Stone and Loew (36) used the isolated seminal vesicles of the guinea pig in a similar manner. The isolated rat seminal vesicle preparation has also been used (36a). Epinephrine-induced contraction of the nictitating membrane of the anesthetized cat *in vivo* or *in vitro* is very sensitive (36, 37). Another preparation described by Lewis and Koessler (39) consists of strips of rabbit aorta. This is extremely sensitive to very low concentrations of epinephrine and norepinephrine (40). The sensitivity of this preparation decreases in the order norepinephrine > histamine > acetylcholine. Pissemski (41) and Schlossmann (42) observed the vasoconstrictor action of catecholamine on perfused vessels. Fastier and Smirk (43) and Burn (44) described the use of perfused rabbit ear and perfused rat hindquarter. The sphinctor pupillae muscles have been used to a limited extent (45).

The activity of compounds on alpha-receptors can be assessed in experiments on the blood pressure of spinal or anesthetized animals and in man and the factors involved have been discussed in detail (46, 47). Contraction of the sympathetically innervated sphinctor pupillae produces dilation of the pupil, and can be used to measure the activity at the alpha-receptor. To increase the sensitivity, the superior cervical ganglion can be removed sometime before the experiment (48, 49). However, this preparation is not very well suited to quantitative determination *in vivo* since the dose range is too narrow to study drug effects. A general method described by Levy and Ahlquist (50) consists in recording arterial pressure, heart rate, intestinal contraction, and contraction of the retractor penis in the anesthetized dog. Four test amines were used: epinephrine and ethylnorepinephrine (alpha- and beta-activators), phenylephrine (alpha-activator), and isoproterenol (beta-activator). In human subjects, changes in blood pressure and in blood volume passing through the limb are the criteria employed to assess activity at the alpha-receptor. Both these changes can be brought about by action at either type of receptor and it is not feasible to block only the beta-receptor in man (26).

PREPARATIONS WITH BETA-RECEPTORS

Among the isolated preparations, the rabbit uterus has been the test object of choice (30) although the cat uterus (51) and the pregnant uterus of the rat (52) have been used. The relative sensitivity of alpha- and beta-receptors in the hormone-dominated rabbit uterus has been studied (53, 54). Miller (55) has thoroughly reviewed the work pertaining to the types of adrenergic receptors in the myometrium. It appears that all mammalian uteri contain both alpha- and beta-receptors. Stimulation of alpha-receptors results in contraction and stimulation of beta-receptors in inhibition. The rat uterus has been considered a different type of receptor (56). It differs from the beta-receptors in the heart since it is blocked by dihydroergotamine. Not all alpha-blocking agents block the rat uterus response, and it is not certain whether inhibition is due to both alpha- and beta-responses. Castillo and De Beer (57) described the isolated guinea pig tracheal chain. The whole bronchial tree, including the lungs, has also been used by many workers (58–60). With the rabbit intestine which has high spontaneous activity, it is not necessary to use any spasmogen (61). Sympathetic stimulation and addition of catecholamines produce relaxation of the muscles. This preparation is also useful for distinguishing antagonists and those substances which prevent the release of a sympathetic transmitter from the nerve ending. The isolated preparation of the muscles of the fundus of the rat's stomach also relaxes in response to catecholamine (62, 63); it is uncertain whether this preparation has only beta-type receptors. Evidence has been presented to show the presence of both types of receptors in the canine ileum (64).

A modification of the epinephrine "reversal" test (65) that consists of blocking the responses at alpha-receptors

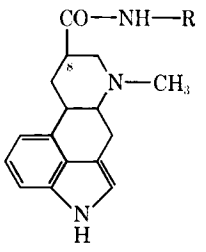
thereby exaggerating those at beta-receptors, has been devised (66, 67). Dornhorst and Herxheimer (68) made use of the effects on the passage of air through the lungs in anesthetized animals and found that these effects can be determined in conscious man. Another method consists in reducing or blocking the positive chronotropic and inotropic effects of isoproterenol on the heart (69). The spontaneously beating auricles of the guinea pig or rabbit have been used as have perfused whole hearts (70–72). Bohr (73) has discussed the type of adrenergic receptor in coronary arteries. Small coronary arteries possess almost entirely beta-type receptors whereas large coronary arteries contain both.

SAR OF ALPHA-ADRENERGIC BLOCKING AGENTS

Drugs that antagonize the effects of sympathomimetic amines are classified into alpha- and beta-receptor-blocking agents depending upon whether the type of the action blocked is associated with the alpha- or the beta-receptor stimulation. Drugs which exert effects within the cerebrospinal axis, at the autonomic ganglion or along the postganglionic fibers, and interfere with the transmitter release at the sympathetic nerve endings are described as adrenergic neuron-blocking drugs. They will not be discussed here. Each of these classes of adrenergic-blocking drugs is further divided on the basis of its chemical structure. Compounds that block the alpha-receptor do not show a great deal of structure selectivity and various groups of compounds derived from structures unrelated to one another have been found to possess potent antagonistic property.

Table II gives the types of chemical structures and the names of the representative drugs that have been in medical use.

Ergot Alkaloids—Historically, these are the most important compounds. During investigations of methods for the bioassay of tissue extracts, Dale (2) discovered that ergot alkaloids (ergotoxine) possessed antiadrenergic activity. Stoll and Hoffmann (74) showed that "ergotoxine" was a mixture of three alkaloids: ergocristine, ergokryptine, and ergocornine. The ergot alkaloids are derivatives of lysergic acid amide. There are 12 naturally occurring alkaloids consisting of six isometric pairs; the optical activity depends on the lysergamide group, the *levo* isomer in each pair being more active pharmacologically than the *dextro* isomer, which is less soluble also. The *levo* isomers are said to be derived from lysergic acid, whereas the *dextro* isomers are from isolysergic acid. These acids differ only in the arrangement of the carboxyl group and hydrogen atom at the 8-position (I). The chemistry and pharmacology of the ergot alkaloids have been discussed (75–83).



I

There are three main actions of ergot alkaloids—they cause the plain muscles of uterus to contract, they cause an intense vasoconstriction, and they block the alpha-type of adrenergic receptors. The vasoconstriction is very long-lasting and it has been suggested that this might be a stimulant action on adrenergic receptors (84). Ergotamine, first isolated by Stoll (85), has both adrenolytic and sympatholytic properties. It has only a weak oxytocic action. The saturation of the double bond in ergotamine produces dihydroergotamine (DHE) with much less vasoconstrictor and oxytocic activity, but a greater antiadrenergic activity. DHE is the most potent epinephrine antagonist in the ergot group, and combines reversibly with alpha-receptors. Its action is competitive (86). Ergonovine (2-aminopropan-1-ol amide of lysergic acid) is the simplest and the most powerful oxytocic amongst the ergot alkaloids. Methylsubstitution in the aminopropanol chain of ergonovine does not increase adrenergic-blocking activity. The relative activities of ergot alkaloids and their dihydroderivatives in antagonizing the effects of epinephrine on the rabbit uterus and on the guinea pig seminal vesicles indicate that the activity is greatest with large substituents on the tricyclic polypeptide residue and that the activity is considerably increased by hydrogenation of the double bond (83). DHE prevented the inhibitory response of epinephrine in the isolated rabbit intestine (87). Evidence to support the alpha-blocking action of DHE is sufficient, but there is no convincing proof of its ability to block beta-receptor although it has been suggested that DHE has a slight beta-blocking activity (88, 89). Ariëns (90), however, has recently pointed out the erroneous use of the terms alpha- and beta-adrenergic-blocking drug with such drugs as DHE, since they do not produce specific or competitive blockade. Barlow (26), on the other hand, has some doubt as to the real significance of the term competitive blockade. Recently Van Rossum (91) has discussed the merits and limitations of the mathematical approach to drug-receptor interaction at molecular levels. De Bonnevaux *et al.* (92) observed that DHE depressed central sympathetic action following compression of both carotids in chloralosed dogs, and that this action preceded the peripheral adrenergic blockade.

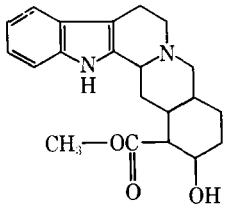
Ergot alkaloids inhibit the increase in metabolic rate and blood sugar by epinephrine (93, 94). Other effects include a fall in systolic pressure rather than a rise produced by epinephrine in hypertensive subjects after large parenteral doses of ergot alkaloids; reduction in

Table II—Adrenergic-Blocking Drugs

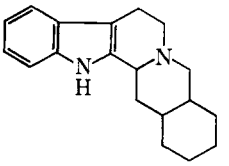
Type of Chemical Structure	Main Compounds in Medical Use	Type of Receptor Blocked
Lysergic acid amides	Ergot alkaloids	α (some β)
Yohimbine-like alkaloids	None	α
Benzodioxanes	Piperoxane	α
Phenoxyalkylamines	Gravitol	α
Haloalkylamines	Phenoxybenzamine	α
Imidazolines	Phentolamine	α
Dibenzazepines	None	α
Pyrrolidines	None	α
Aminotetrazoles	None	α
Analogs of isoproterenol	Propranolol	β

the incidence of ventricular fibrillation and ectopic beats caused by cyclopropane; and relief from renal ischemia caused by epinephrine, asphyxia, and electrical stimulation of splanchnic nerves (95). Ergot alkaloids do not antagonize epinephrine-induced vasodilatation in skeletal muscles of the isolated limb and the positive inotropic effect of epinephrine on the isolated heart *in situ* (96). DHE produces sympatholytic effects in lower doses than are required to produce adrenolytic effects. The adrenergic blockade develops slowly with these compounds which led to the criticism (26) on the ability of ergot alkaloids to produce competitive blockade (97).

Yohimbine and Related Alkaloids—Yohimbine (II) and a number of other naturally occurring alkaloids and their semisynthetic derivatives have been shown to possess sympatholytic and adrenolytic properties. Chemically they resemble the ergot alkaloids in containing an indole grouping as part of a complex molecule, yet their alpha-receptor-blocking activity is not very high. The yohimbine molecule is remarkably flat (77), the ester group being equatorial. Changing the con-



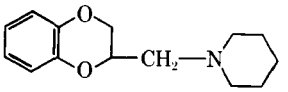
II



III

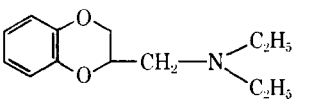
figuration of the ester group from equatorial to axial (as in corynanthine) decreases the ability to antagonize the effects of epinephrine on the blood pressure (88). Unsaturation of the ring bearing the alcoholic hydroxyl and the ester groups (99) as well as the removal of any of these groups reduces activity; but the ester and the hydroxyl groups are not the essential requirements for activity, since desoxyyohimbol (III) is not inactive (100). Yohimbine has many other pharmacological actions that include vasodilating, ADH-releasing, and local anesthetic properties.

Benzodioxans—Many of these compounds were synthesized by Fourneau and the first synthetic compounds with potent adrenergic-blocking activity, piperoxan (F933) (IV) and prosympal (V), were described by Fourneau and Bovet (101).



IV

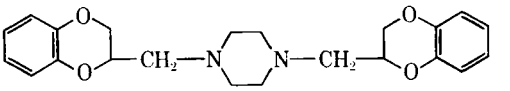
The most potent and the most toxic among the basically substituted benzodioxans was the diethylaminomethylbenzodioxan, also known as prosympal or F883 (102, 103). It is both adrenolytic and sympatholytic. However, F883 and F933 did not reduce the toxicity of epinephrine in mice (104). The *levo* isomer of prosympal was found to be about six times more active than the *dextro* form in blocking the pressor response of epinephrine in cats (105, 106). The toxicity of the secondary amines increases with molecular weight, but the epi-



V

nephrine antagonism reaches a maximum between the 2 and 3 carbon atoms. Piperidine substitution diminishes sympatholytic property whereas antiepinephrine activity is maintained. Piperoxan is the most active of the piperidine-substituted benzodioxans.

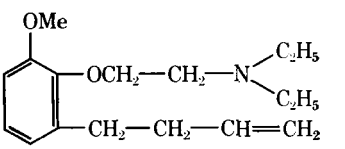
The most recent addition to this group is dibozane (VI). O'Leary (107) showed that it lowered the mean blood pressure in the anesthetized dog and was 5–20 times more active than piperoxan in antagonizing hypertensive response to carotid occlusion, and about equally potent in antagonizing the hypertensive effect of epinephrine.



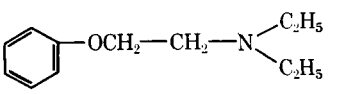
VI

Ahlquist and Levy (108) used dibozane as a typical alpha-blocking agent for production of epinephrine "reversal" and the prevention of the inhibition of intestinal motility in anesthetized dogs. Raplea and Green (110) tested dibozane, azapetine, and phenoxybenzamine for their ability to block the adrenergic receptor in the skeletal muscles of the dog. They found that dibozane and phenoxybenzamine were equipotent in antagonizing the effects of norepinephrine and epinephrine, whereas azapetine was much less active. The effectiveness of these agents increased progressively with increasing doses of agonist, showing that a noncompetitive blockade was produced. A persistent blockade produced by the largest dose of dibozane was not observed with the largest dose of any of the other two compounds. In man, dibozane does not produce consistent effects (111).

Phenoxyethylamines—These compounds have not been found useful therapeutically because of many of their untoward effects (112). They bear a close chemical resemblance to different groups of drugs including adrenergic neuron-blocking agents (*e.g.*, xylocholine), antihistaminic compounds (*e.g.*, thymoxyethyldiethylamines, F929), and local anesthetics (*e.g.*, procaine). Eichholtz (113) and Schmidt and Scholl (114) described the oxytoxic action of gravitol (VII). Many reports have shown that these compounds also possess the ability to antagonize some of the effects of epinephrine (112, 115–119).

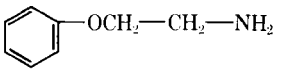


VII



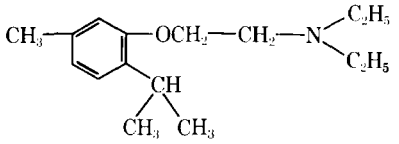
VIII

The simplest member of this group, phenoxyethyldiethylamine (F-928) (VIII) is active in blocking the pressor action of epinephrine. It is also the starting point in the development of antihistaminic compounds belonging to this series. The parent compound phenoxyethylamine (IX) is sympathomimetic. In all other phenolic ethers of

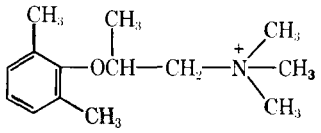


IX

tertiary alkylamines, the position of the phenolic OH groups has a profound effect on the adrenergic-blocking activity of these compounds. Substitution in the *o*-position is consistent with antiadrenergic activity, whereas compounds substituted in the *m*- and *p*-positions have, respectively, pressor and nicotine-like activities. Replacement of the phenolic OH group by a tertiary alkyl group in the *o*-position produced the antihistaminic compound (F929) (X). Bulky substituents on the nitrogen atoms yielded compounds with depressor activity resembling isoproterenol.



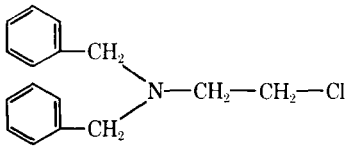
X



XI

In general, secondary and tertiary phenoxyethylamines exert an adrenergic-blocking action which is relatively weak and of short duration. A quaternary derivative (XI) has been shown to interfere with the norepinephrine synthesis from dopamine and to deplete amine stores (120).

Beta-Haloalkylamines—Nickerson and Goodman (121) were the first to observe that *N,N*-dibenzyl-2-chloroethylamine (XII) antagonized the pressure actions of injected epinephrine in the cat.



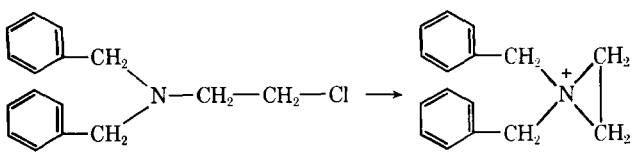
XII

This was soon followed by a considerable interest in this series of compounds and hundreds of compounds related to it were tested for their hypotensive property (112, 122–124). Like phenoxyethylamines, these compounds have not proved useful as therapeutic agents, but have served as valuable tools in the investigation of the pharmacology of drug-receptor interaction.

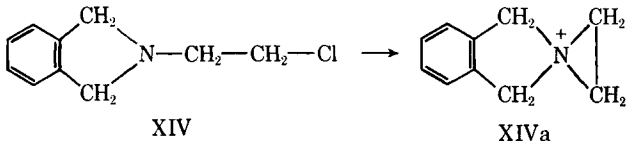
In contrast to other classes of adrenergic-blocking agents that produce competitive, reversible blockade, beta-haloalkylamine blockade has been designated by Furchgott (125) as "irreversible competitive antagonism," by Nickerson (126) "nonequilibrium antagonism," and by Gaddum (127) as "unsurmountable antagonism." The persistent effect of beta-haloalkylamines (128), even after supposedly complete removal of the drug from the tissue, was designated as complete blockade occurring only in the second stage due to covalent bond formation between the receptor and the drug; the first stage of this reaction is reversible, competitive, and surmountable (129).

The original explanation by Nickerson *et al.* (130) that ethyleneiminium ion (El ion) might be involved in this persistent blockade now seems to be true. Many experimental factors endorsing the view that these substances owe their activity to the ring closer followed by El-ion formation are: (*a*) among the halogens, chlorine, bromine, and iodine produced active beta-haloalkylamines, whereas fluorine did not (131); (*b*) the rates of formation of halide ions, of hydrogen ions, and of El ions determined by means of thiosulfate titration for a number of compounds indicate that there is a close correlation between the degree of adrenergic-blocking activity and El-ion concentration (132, 134); and (*c*) compounds in the series $RR'NCH_2CH_2X$, where R and R′ are kept constant and only the halogen atom X is altered, have the same duration and intensity of adrenergic blockade showing that the same El ion is produced (132, 134, 135), although they differ in the rate of onset of blockade depending upon the ease of El-ion formation. Harvey and Nickerson (133), however, observed that *N,N*-dicyclohexyl-beta-chloroethylamine was devoid of activity. This indicates that the ease of formation of El ions, its stability, its activity at the receptors, and the stability of the complex formed with the receptors, all contribute to the observed activity.

Not only the rate and concentration of El ions but also the structure of this ion is important in order that a stable drug-receptor complex could be formed. Belleau (136) examined a number of dibenamine analogs in which the nitrogen is part of a ring, and concluded that the stability of various 2-chloroethylamines to produce El ions was dependent on the size of the ring and therefore on conformational factors. He showed that whereas Compound XIII could give rise to El ion (XIII*a*), Compound XIV was too rigid to produce its corresponding El ion (XIV*a*). On the basis of the doses of dibenamine and its analogs required to block the pressure effect of epinephrine in anesthetized cats, it appears that only 3,4-dihydroxyphenylisopropyl grouping gives rise to a better compound than dibenamine with a 4–10-fold increase in potency (137). Similarly, the introduction of methyl or methoxy substituents into the aromatic rings produces little change in potency; *ortho*- and *para*-methylphenyl isomers have decreased rate of onset of action. Addition of Cl or an alkyl group bigger than methyl proved detrimental to activity except *m*-chlorophenyl which still retained some activity (138). Graham

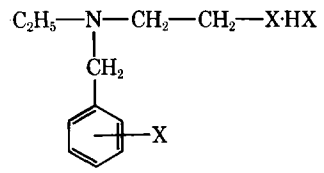


XIII XIIIa



XIV XIVa

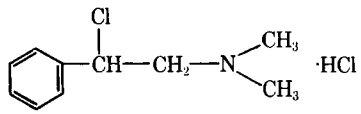
(139) studied the effect of halogen substitution in the phenyl ring in a series of compounds having the structure (XV) and showed that the position of halogen in the phenyl ring was important for antagonism, with *o*- and



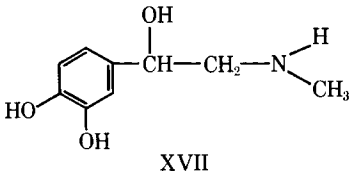
XV

m-substitution being more active than *p*-substitution. Bromo- and iodo-compounds were more active than chloro-compounds in their ability to release El ions. A similar situation occurs with dibenzyl-2-haloethylamines; the bromo-compound being five times more effective than the chloro-compound and having a rapid action with greater toxicity (140).

The degree of activity of the substituted beta-haloalkylamines belonging to the series of *N,N*-dimethyl-2-chlorophenethylamine (DMEA) (XVI) is dependent upon the closeness of the structure to that of epinephrine (XVII). Chapman (141) and Graham and James (142) studied this series of compounds and showed that

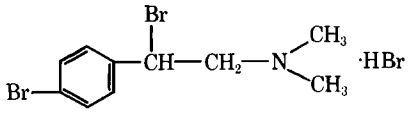


XVI

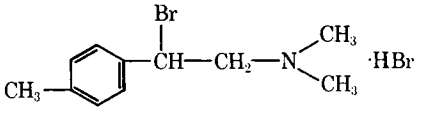


XVII

(XVIII) and (XIX) were 10–20,000 times more active than dibenamine. The structural requirements for activity include (*a*) an aromatic ring; (*b*) a beta-halogenoethyl

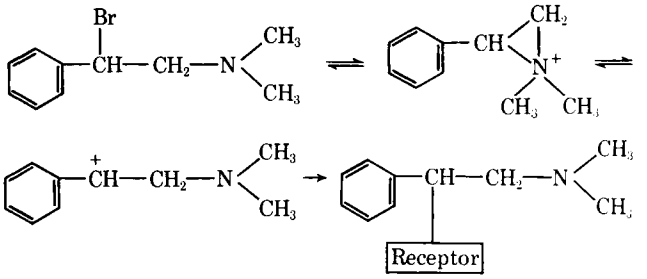


XVIII



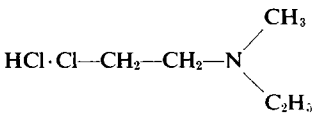
XIX

group; and (*c*) a secondary or tertiary amino group. *Para*-substitution in the phenyl ring favors activity. Here again, bromo- and iodo-compounds have greater activity than chloro-compounds. They act more rapidly and have shorter duration of activity than dibenamine and much more toxicity. It was proposed that these compounds alkylate alpha-receptors by way of a carbonium-ion formation, yet their site of action is not different from that of dibenamine (143, 144). This mechanism can be represented diagrammatically as shown in (Scheme I).

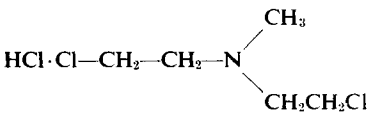


Scheme I—Alkylation mechanism by beta-haloalkylamines

DMEA (XV) has been shown to possess muscarinic and nicotinic properties (145). Replacement of the phenyl group by a hydrogen atom and a methyl group on nitrogen by ethyl (XX) or chloroethyl group (XXI) changes the compound into a cholinesterase inhibitor (146).



XX



XXI

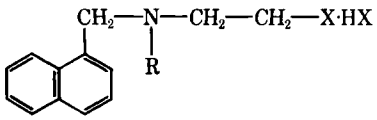
In general, the only conclusion that can be drawn from the structure-action relationship of beta-haloalkylamines is to quote the results of Nickerson and Gump (147) that a compound could act like dibenamine if it (*a*) has a tertiary or quaternary nitrogen atom, which is attached to at least one beta-haloalkyl group capable of forming an El ion; (*b*) has an unsaturated ring structure attached to nitrogen atom to stabilize the intermediate by resonance; and (*c*) has all the substituents on the ring lying in its plane.

Mechanisms of Action of Beta-Haloalkylamines—Several detailed reviews on the proposed mechanism of action of beta-haloalkylamine are available (123, 124, 148, 149). The only certainty is the ability of beta-haloalkylamine to effect covalent bond formation *via* El ion at or around the receptor site (150, 151), a property shared by nitrogen mustards (152). Recently, Belleau (12) proposed an interesting explanation as to how alkylation is brought about. This beautiful, step-by-step diagrammatic treatment is just enough to make one feel comfortable momentarily, yet how far this oversimplification leads in the direction of reality still remains an uncertainty. Belleau visualized the El ion of dibenamine alkylates as a carboxylate ion at the accessory site of the alpha-receptor; the carboxylate ion being normally an acceptor of a phosphoryl group in a phosphoryl-transfer process linked with the Ca^{++} release into the cell. In their dynamic receptor concept, Bloom and Goldman (153) preferred a phosphate radical to represent the

nucleophilic site at the alpha-receptor. However, current evidence lends support to Belleau's choice of the carboxylate ion.

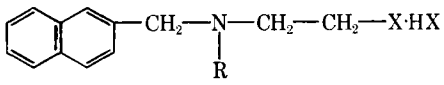
Graham and Al Katib (154) carried out an interesting experiment on the isolated vas deferens of the guinea pig using various hydrolases—*viz.*, trypsin, alpha-chymotrypsin, alkaline and acid phosphatase, phosphodiesterase, Naja venom, and papain, and determined their effects on the stimulants: epinephrine, norepinephrine, dopamine, histamine, acetylcholine, bradykinin, K^+, and three beta-haloalkylamines (dibenamine, SY28, and L_2). Only trypsin reversed the blockade. The ease of reversal is in the order L_2 > SY28 > dibenamine. There was a linear relationship between the concentration of trypsin and the degree of blockade produced. From this, they suggested that trypsin may catalyze the recovery of alkylated alpha-receptors. This it would do by action at an ester linkage on L-arginine or L-lysine, implying that the anionic acceptor site in the alpha-receptor is a free carboxyl rather than a phosphate, and that the receptor is in part an amino acid chain containing arginine or lysine or both. Chymotrypsin or higher concentrations of trypsin desensitizes the receptors to all agonists possibly by rupturing peptide bonds. However, another report from Moran *et al.* (155) does not confirm the role played by trypsin in the regeneration of adrenergic receptors. Using tritium-labeled *N*-(2-bromoethyl)-*N*-ethyl-1-naphthylamine (SY28), they blocked norepinephrine responses on the isolated vas deferens of rabbit and incubated this preparation with trypsin. They noticed a 20% increase in the response to norepinephrine of both the treated and the control preparations. From this, they implied that the recovery of response following trypsin is probably unrelated to alpha-receptor regeneration. Moreover, ^{3}H-SY28 alcohol stays longer on the receptor. Trypsin action is dependent upon the pH of the solution, alkaline pH destroys the enzyme. Since none of these reports has indicated the pH of the solution, it is not at all certain that both the experiments were carried out under identical optimum conditions for enzyme activity. A more convincing proof of the influence of trypsin on this regeneration process of the alpha-receptor can be provided by blocking the ε-amino group of arginine and lysine with amine reagents and showing that in that case, trypsin does not affect alpha-receptor activity.

What has been said before for other series of beta-halogenoalkylamines also applies to dibenamine analogs in which the *N*-benzyl group is replaced by a naphthylmethyl moiety (XXII) where R may be an alkyl or an aryl



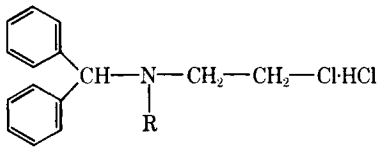
XXII

group and X a halogen atom. These compounds have the dual property of blocking certain effects of both histamine and epinephrine (156–158). The most effective compounds were *N*-ethyl-*N*-2-chloroethyl-1-naphthylmethylamine (SY14) and *N*-ethyl-2-bromomethyl-1-naphthylmethylamine (SY28). The point of attachment of the naphthalene group to the rest of the molecule is also important. Graham and Lewis (159) discovered that 1-naphthylmethyl derivatives (XXII) were more effective than 2-naphthylmethyl derivatives (XXIII).



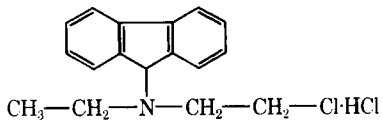
XXIII

As usual, the nature of halogen in the haloethyl group was important, Br-derivatives being more active than Cl-derivatives, and F-derivatives being inactive. The compounds in which R = Ph, Me, Et and X = F had no antiepinephrine and only slight antihistaminic activity. On oral administration to mice, *N*-alkyl-*N*-(2-chloroethyl)-benzhydrylamines (XXIV), which are devoid of antihistaminic properties, exerted a moderate



XXIV

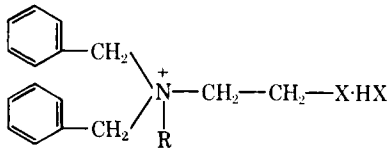
degree of blockade of the excitatory responses to epinephrine and sympathetic nerve stimulation (160). Benzhydryl derivatives like naphthylmethyl derivatives of beta-haloalkylamine are devoid of anticholinergic properties. On the other hand, *N*-ethyl-*N*-(2-chloroethyl)-9-fluorenamine (SY21) (XXV) potentiated acetylcholine spasm on isolated seminal vesicles of the guinea pig (36).



XXV

Increasing the size of the alkyl group on the nitrogen in fluorenyl compounds progressively decreased antiadrenergic activity. The ethyl group produces the optimum effect (161). In all these different series of compounds related to beta-haloalkylamine no parallelism could be established between the relative order of potency with respect to antagonism to epinephrine, histamine, and acetylcholine although the underlying mechanism in all these instances is based on their ability to behave as alkylating agents.

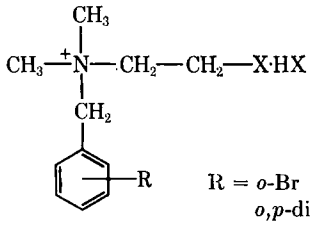
Kerwin *et al.* (162, 163) examined a number of beta-haloalkylammonium compounds (XXVI) for antiadrenergic activity. These compounds were devoid of any such activity indicating that El-ion formation was not possible in these compounds. In contrast to this observation, salts of benzyl-*N*,*N*-dimethyl-*N*-ethylam-



XXVI

monium (XXVII) and its *ortho*-bromo and 2,4-dibromo derivatives exhibit considerable activity in decreasing

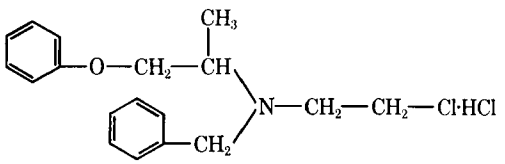
arterial pressure in animals and blocked contraction of the nictitating membrane in response to electrical stimulation of the pre- and postganglionic sympathetic nerves (164). Hence these compounds block transmission of impulses on the level of presynaptic adrenergic structures. Besides, the position of Br-substitution in the



XXVII

phenyl ring is critical; in the *o*-position Br exhibits a weak sympatholytic property; in the *m*-position Br gives a sympathomimetic activity, and in the *p*-position it produces a nicotine-stimulating and adrenolytic activity. The sympatholytic activity is probably based on the inhibition of spontaneous norepinephrine release.

Phenoxybenzamines—The attempt to combine the phenoxyethyl grouping with the beta-haloalkylamine has been fruitful, and resulted in the evolution of compounds with enhanced activity. Many of these compounds are considerably more active, more specific, and more rapid in action. Phenoxybenzamine (XXVIII) is highly effective, both orally and intravenously, in doses of about one-tenth of those of dibenamine. The structure action relationship of these compounds has been discussed in detail by Nickerson and Nomaguchi (165) and by Gump



XXVIII

and Nikawitz (138, 165a), and only salient features need be mentioned here.

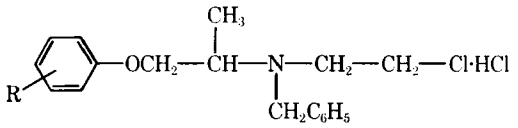
(*a*) Phenoxyethyl-alkyl-beta-haloalkylamines are somewhat active, but diphenoxyethyl and phenoxyethyl-benzyl-beta-haloalkylamines are very potent adrenergic-blocking agents.

(*b*) *Ortho*-methyl substitution of the aromatic ring of phenoxyethylamines produces a considerable increase in activity while *meta*- and *para*-substitutions significantly reduce activity. Increasing the size of the alkyl substituent from methyl to isopropyl produces a progressive increase in activity, but *n*-amyl decreases activity. Compounds with an alpha-methyl substituent on the oxyethyl chain are an exception to this rule in that unsubstituted or methyl-substituted derivatives exhibit maximal activity.

(*c*) A definite potency relationship exists with each series of similarly substituted phenoxyethylamines, the phenoxyethyl-alkyl-diphenoxy-ethyl and phenoxyethyl-benzyl derivatives increasing in activity in that order.

(*d*) Replacement of a phenoxyethyl grouping by a phenylthioethyl causes a reduction in activity.

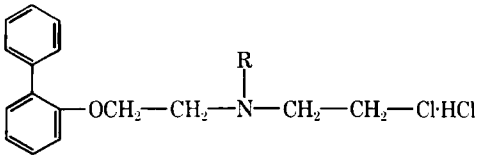
Kerwin *et al.* (163) investigated the effects of the introduction of an alkyl and halogen group into *N*-(aryloxy-isopropyl)-beta-haloethylamines (XXIX) and came to the conclusion that a methyl group at Position 1 was



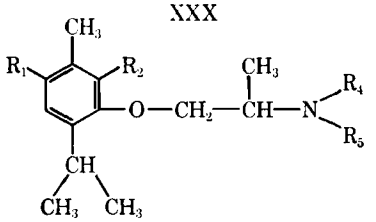
XXIX

necessary for oral activity and a methyl or an isopropyl group at Position 2 would increase intravenous activity in the cat. The bromo analog was not active orally, as its greater chemical activity makes it more susceptible to destruction in the gastrointestinal tract. Decreased activity also results from substitution in the phenoxy ring. However, Lindenstruth and Vander Werf (166) reported that a fluoro- or a trifluoromethyl group in the *para*-position of the phenoxy ring produced an active compound, whereas similarly substituted *meta*- and *para*-compounds were one-fifth or one-half as effective.

Loew and Micetich (167) observed the antagonism produced by 2-biphenyl derivatives of the type XXX to epinephrine, histamine, and acetylcholine in dogs and mice and showed that this series of compounds was only moderately active against epinephrine and diminished the depressor action of histamine in dogs. Their anti-acetylcholine action was the weakest among the beta-haloalkylamines. The effects of some compounds derived from $C_6H_5CH_2OCH_2CH_2NRCH_2CH_2X$ and R'-$CH_2OCH_2CH_2NRCH_2CH_2X \cdot HX$ were tested for their ability to antagonize the blood pressure responses to epinephrine in cats and dogs (168). All these compounds in which R = Me, Et, benzyl, or naphthylmethyl, and R′ = 1,4-benzodioxan-2-yl, and X = Cl or Br were weak adrenergic antagonists except the one [*N*-benzyl-*N*-(2-bromomethyl)-2-aminoethyl-1,4-benzodioxan-2-ylmethyl ether·HBr] which was two to three times more active than dibenamine. Recently, the thymol ether derivatives of beta-haloalkylamines (XXXI) have been described (169). 1-(4-Chlorothymoxy)-*N*-(2-chloroethyl)-*N*-ethyl-2-propylamine (WVOO62) is superior to phenoxybenzamine, has good enteric absorption, and has a good



XXX



XXXI

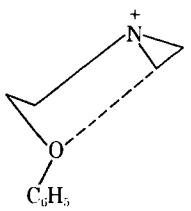
therapeutic index. Its analog without a chlorine atom at the 4-position of the thymoxy ring (WVOO80, R_1 = H) has the same activity but three times more toxicity. On the other hand, changing chloroethyl group to bromoethyl and changing isopropyl to ethyl group (R_3 = H; R_4 = CH_2CH_2Br) in WVOO62 yielded WV823 [*N*-(2-

bromoethyl)-1-(4-chlorothymoxy)-diethylamine] which has the same therapeutic index but only one-fourth the enteral activity of the parent compound. The adrenolytic effects are not improved if the Cl in the 4-position is replaced by Br, I, F, NH_2, NO_2, or CH_3CO; nor are they improved if the Cl or the ethyl group in the side chain is replaced by another halogen or hydroxyl group, or if the nonhalogenated ethyl moiety is replaced by a methyl or a phenyl group.

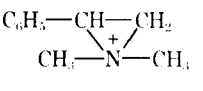
Another recent inclusion in the phenoxybenzamine series is the introduction of phenoxathiinium compounds. Shriver and Rudzik (170) tested two of such compounds, MPT (10-methylphenoxathiiniumtetrafluoroborate) and its 2-chloro derivatives (ClMPT). ClMPT is 10 times more active than MPT or phenoxybenzamine in antagonizing the cardiovascular effects of epinephrine in dogs. Besides, it produces a diphasic blockade not observed with phenoxybenzamine. On the cat nictitating membrane, ClMPT and phenoxybenzamine have approximately the same activity, whereas MPT was about half as active.

Mechanism of Action of Phenoxybenzamines—It is now clear that phenoxyethylamines and phenoxybenzamines do not affect adrenergic blockade by a common mechanism. Some of the earliest observations (147) that electron-withdrawing groups in the molecule that decrease the availability of electrons in the benzene ring would also decrease the stability of the El ion, and that electron-releasing groups, by increasing the electron density in the ring, would contribute to the stability of the El ion, and the substituents that produce ^+I or ^+E effects would enhance activity unless they interfere with binding at the *para*- and *meta*-positions of the ring (148), made it very desirable to consider the electrical properties of these compounds in conjunction with their adrenergic-blocking activity. Not only the formation and stability of the El ions are important, but their ability to quickly absorb and rapidly alkylate the receptor site involves stereochemical considerations as one of the prerequisites of the desired activity. Belleau (171) has also discussed these factors in detail.

The fact that replacement of the ethereal oxygen in $PhOCH_2CH_2NRCH_2CH_2X$ by a methylene group to get $PhCH_2CH_2CH_2NRCH_2CH_2X_2$ results in complete loss of activity (122) led Belleau (172, 173) to speculate on the conformational characteristics of the alkylating El ions. He supposed that in order to alkylate the anionic site, the distance relationship between the carbonium ion and benzene ring must be such as to reproduce the distance relationship characteristics of the phenethylamine pattern (XXXII). Lately, Belleau (12) has abandoned the



XXXII



XXXIII

role of carbonium ion derived from the *N,N*-dimethyl-2-phenyl aziridinium ion (XXXIII) in the alkylation process. To differentiate from dibenamine and to account for the lack of specificity of the receptor toward the optical isomers of aziridinium ion, he assumed a two-point attachment, simultaneously pushing the electrophilic benzylic carbon atom out of the plane of the receptor surface.

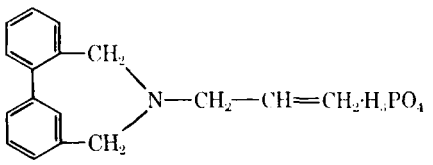
In view of their ability to alkylate tissue, it should not be surprising that these compounds have antihistaminic, antiserotonin, and antimuscarinic properties. They inhibit cholinesterase and have the ability to release some of the norepinephrine from the storage site and prevent its uptake, potentiating the amine action on the heart and on the β-receptor. They do not, however, affect the release of the sympathetic transmitter by nerve impulses or by acetylcholine acting at the nerve endings (86). Recently, Boullin *et al.* (174) have shown that blockade of adrenergic receptors by phenoxybenzamine causes overflow of norepinephrine in the cat colon after nerve stimulation, and suggested that phenoxybenzamine prevents the reincorporation of nerve-liberated norepinephrine by preventing the transmitter from combining with the adrenergic receptors rather than by a direct action on the nerve ending. This action makes phenoxybenzamine an invaluable tool for studies of sympathetic nerve ending since the amount of norepinephrine escaping into the blood may represent the amount of transmitter actually released and bound to receptors. During repetitive stimulation, the efflux of norepinephrine progressively declines and in 15 min. practically ceases although less than 10% of the amine stores have been released. This indicates that in the presence of phenoxybenzamine, the vesicles are selectively depleted of the transmitter by repetitive stimulation.

Many authors have maintained the view that higher concentrations of an adrenergic-blocking agent are needed for sympatholytic effect than are required for adrenergic blockade (175–178). However, DHE and prosympal have been known to cause sympatholysis at lower doses, a property that has also been claimed for phenoxybenzamine. Levin and Beck (179) examined the ability of alpha- and beta-blocking agents to modify neurogenically and humorally induced constriction in the perfused extremity of the dog. Phenoxybenzamine reduced the vasoconstriction produced by pre- and postganglionic sympathetic nerve stimulation significantly more than the constriction response produced by intra-arterially injected norepinephrine. Phentolamine blocked the responses to norepinephrine and nerve stimulation to the same extent. Consistent with this is another evidence on the ability of phentolamine to suppress blood pressure rises in smaller doses than those blocking the direct hypertensive effect of epinephrine (180). It seems reasonable to ascribe the greater sympatholytic activity of alpha-adrenergic blockers to their central effects. Supporting evidence has been afforded by Boissier *et al.* (181) who noted that phenoxybenzamine, dibenamine, phentolamine, yohimbine, DHE, methyldopa, and propranolol reduce spontaneous locomotor activity of the mouse and potentiated an infra hypnotic dose of pentobarbital. A definite answer can not be provided at the moment as to the nature of the factor that determines the efficacy of these drugs on nerves and on the receptor. Nevertheless, a compromise

can be obtained between the classical view and the present state of affairs by assuming that a qualitative change in the receptor decides whether or not the receptor responds more vigorously or becomes abnormally more sensitive to nervous stimulation. Any agent that depresses nervous activity should, therefore, produce a greater blockade of this abnormal receptor response. Consistent with this view are the results of Varma (182) that sympathetic denervation of the cat nictitating membrane specifically affects the antagonistic effect of adrenergic-blocking agents, and that hypertensive patients showed more exaggerated blood pressure responses to pressor stimuli and drugs than normotensive controls (183, 184).

Dibenzazepines—With failure to obtain a clinically useful compound from a vast group of beta-haloalkylamines, search was directed to develop molecules without a chlorine atom since it became apparent that the untoward effects of dibenamine series were the manifestations of the presence of the chlorine atom in the molecules. A new series of adrenergic blockers were synthesized on the framework of 6,7-dihydro-5*H*-dibenz(*c*, *e*)-azepines.

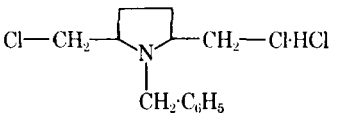
First described by Wenner (185), these compounds were studied by Randall and Smith (186). The most active member of this series is azapetine, [6-allyl-6,7-dihydro-5*H*-dibenz(*c*, *e*)azepine phosphate] (Ro-2-3248) (XXXIV) which has many properties in common with benzylimidazolines and resembles closely tolazoline in



XXXIV

its short duration of action. It has a sympatholytic as well as a direct action on the blood vessels (187). Slightly higher doses are needed to cause sympatholytic effects than those which produce adrenergic blockade. Azepetine also exerts a papaverine-like action on coronary arteries in animals (186). It prevents hyperglycemia resulting from stimulation of the sympathetic nerves (188) and mesenteric vasoconstriction caused by norepinephrine and epinephrine (189). These compounds have no appreciable activity on acetylcholine and histamine receptors. The fact that a substitution larger than propyl on the nitrogen atom destroyed all adrenergic-blocking activity and that the most active compound Ro-2-3248 has an allyl group indicates that the stereoelectronic properties of the molecule are of initial significance; a group that increases the polarizability of the nitrogen will result in enhanced activity.

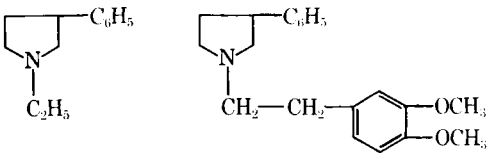
Pyrrolidines—Pyrrolidine derivatives are just one example in which the N—CH_2 part of the beta-haloalkylamine group is transformed into a component of the heterocyclic ring. Schipper *et al.* (190) first described a series of such compounds. The most effective compound, 1-benzyl-2,5-bischloromethyl pyrrolidine (ERL-491) (XXXV) inhibits the pressor response to epinephrine in the anesthetized dog and, compared to dibenamine, is several hundred times more effective with a considerably more favorable therapeutic index.



XXXV

In contrast to beta-haloalkylamines, substitution of the benzyl group of ERL-491 by 1-naphthyl, and 4-methylbenzyl led to a moderate loss in activity, and by 4-methoxybenzyl to a marked loss in activity. The 4-chlorobenzyl analog exhibited a low order of adrenolytic activity, whereas the 2-bromobenzyl analog was approximately as active as ERL-491. The addition of phenoxyalkyl group, however, did not improve the activity; 1-(2-phenoxyethyl)-2,5-bischloromethylpyrrolidine and its 2-phenoxyisopropyl analogs were about as active as ERL-491. The mechanism proposed by the authors takes into consideration the ability of the El ions derived from the 2,5-bischloromethylpyrrolidine to conform to Belleau's celebrated phenethylamine pattern; and the steric factors that contribute to the stability of the El ion and its fixation at the receptor surface.

A shift from adrenolytic to sedative property occurs when the ethyl group in 3-phenyl-*N*-ethylpyrrolidine (XXXVI) is replaced by a homoveratryl group (XXXVII) (191).



XXXVI XXXVII

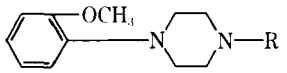
Unlike XXXVI in which the adrenergic-blocking property is due to the presence of phenylethylamine group in the heterocyclic structure, the presence of a phenmethylamine grouping in 2-phenylpyrrolidine (XXXVIII) and in 2-phenylpiperidine derivatives (XXXIX) (192) is compatible with adrenergic blocking activity.

XXXVIII XXXIX

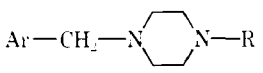
Piperazines—This class of compounds is unique insofar as its very varied pharmacological characteristics are concerned. Adrenolytic, sympatholytic, and antihistaminic properties of 1-phenylpiperazines (XL) were first mentioned by Bovet and Bovet-Nitti (98). Numerous papers have since appeared (193–199). In 1-arylpiperazine series, hypotensive, vasodilating, and neuroleptic effects have also been emphasized.

XL XLI

Among the 1,4-disubstituted piperazines (XLI), a great variety of substituents have been tried and it is only occasionally worthwhile to discuss structure-activity relationship in this series of compounds. For example, only one compound, 1-methyl-4-phenylpiperazine, has a potent adrenergic-blocking activity, whereas other piperazines with one alkyl and one aryl substituent groups showed only a trace activity (196). This compound possesses weak anticholinergic, weak antihistaminic, and a potent local anesthetic activity comparable to procaine. It appears that the adrenolytic but not the hypotensive property is greatly susceptible to structural changes. A change in the following compound (XLII) from R = $(CH_2)_3OCH_3$ to R = H results in a marked loss of adrenergic-blocking activity without affecting hypotensive activity (200).



XLII

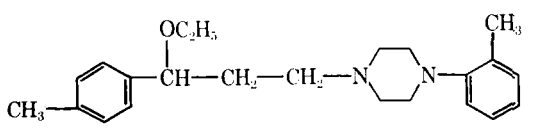


XLIII

There is no correlation between the degree of effectiveness of a compound as antiadrenergic, antihypertensive, and antihistaminic, as each property varies independently with an alteration in the molecule.

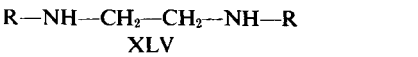
Substituted 1,4-diaryl piperazines (XLIII) exhibit maximum activity when Ar = 3,4-$(CH_3O)_2C_6H_3$; R = H, C_6H_5, $(CH_3O)_2C_6H_3$, or 2-C_5H_4N (201, 202). In anesthetized cats and dogs, these compounds produce both hypo- and hypertensive responses depending upon the dose; 3,4-dimethoxybenzylpiperazine has a direct musculotropic action as strong as that of papaverine. 1-[3-Ethoxy-3-(*p*-tolyl)-propyl]-4-(*o*-tolyl)-piperazine dihydrochloride (SU-12080) (XLIV) has been shown to possess strong antiadrenergic, weak antihistaminic, weak anticholinergic, and potent direct spasmolytic activity (203–205). Similarly, the compound 1,4-bis-(1,4-benzodioxan-2-ylmethyl)piperazine (McN-181) was more active than dibozane both in its sympatholytic and adrenolytic activity and was without any hypotensive effect (206).

The ring structure of piperazine is not essential for activity although it increases the activity over that found in open-chain compounds. An example is the *N,N'*-disubstitution of ethylenediamines (XLV) and piperazines with benzodioxanylmethyl and phenoxyethyl groups. Symmetrical secondary amines with two benzodioxanylmethyl or phenoxyethyl groups are active but comparable derivatives of piperazines are even more active. In both series, replacement of either of these substituents with phenyl or carbethoxy decreases activity, and a greater loss in activity occurs if both the substituents are replaced by phenyl, benzyl, phenoxypropyl, or ethoxyethyl groups. Substitution on the benzodioxane ring and on carbon atoms of the piperazine ring also produces compounds with decreased activity (207). R = benzodioxanylmethyl or phenoxyethyl.

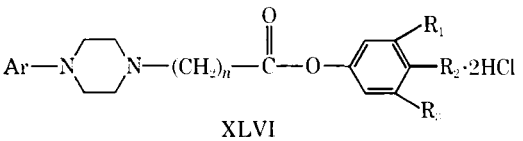


XLIV

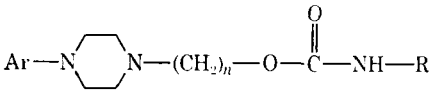
Phenylpiperazine esters (XLVI) and carbamates (XLVII) possess moderate antiadrenergic activity, and on intravenous injection in the dog bring about a sustained hypotensive effect. As expected, these are also sedatives (208). Surprisingly, amides (XLVIII) have no



XLV

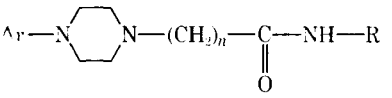


XLVI



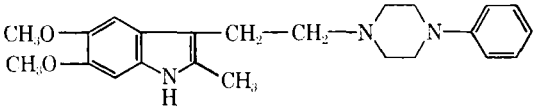
XLVII

antiadrenergic activity, but they are potent sedatives as well as hypotensive (209).



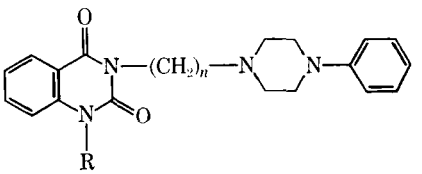
XLVIII

Substituted indolylalkylphenylpiperazines form a group of tranquilizers (210a) and a member of this group 1-[5,6-dimethoxy-2-methyl(3-indolyl)-ethyl]-4-phenylpiperazine (XLIX) has been shown to possess norepinephrine-depleting action on sympathetic nerves, adrenolytic, and antiarrhythmic properties (211).



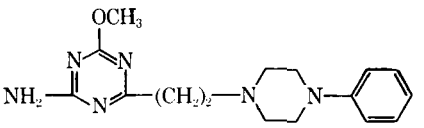
XLIX

Replacing the substituted indolyl group by 3-substituted 2,4-quinazolinediones (L) results in complete disappearance of antiadrenergic activity whereas sedative and hypotensive properties become more pronounced (212). Recently, triazine substitution has yielded a compound: 2-amino-4-methoxy-6-[2-(4-phenylpiperazine-1-yl)-ethyl]-S-triazine (LI), capable of producing long-lasting alpha-receptor blockade with central, peripheral and direct dilator effects (213). Lastly,



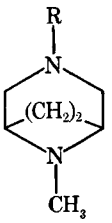
L

an attempt to convert the piperazine moiety into one of

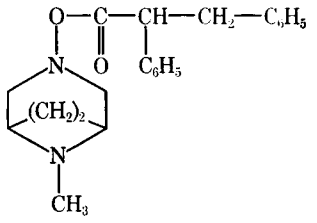


LI

diazabicyclooctane has not been successful. Boissier *et al.* (214) investigated a number of 3-alkyl-, 3-aralkyl-, and 3-acyl-substituted 8-methyl-3,8-diazabicyclo(3.2.1)-octanes (LII) and noticed the antagonistic activity of the 3-methyltropyl derivative to acetylcholine showing that these compounds correspond well to tropane derivatives and cannot be considered as *N*-methylpiperazine analogs. Obviously, a modification of the size and shape of the ring would affect the molecule as a whole, resulting in loss of affinity for the receptor. On the other hand, the tropyl ester of 2,3-diphenylpropionic acid (LIII) is sympatholytic (215).

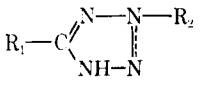


LII

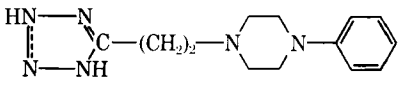


LIII

Tetrazoles—Since the earlier reports by Gross *et al.* (216–220) on the convulsive, analeptic, and sedative properties of aminoalkyl- and aminophenyltetrazoles, only a few papers have discussed the antiadrenergic action of this series of compounds. Search for potential antihypertensive agents in all sorts of compounds has led to the discovery of potent tetrazole derivatives that antagonize the adrenergic response. None of these compounds, however, has brought a significant advance over those that are already existing; but they do provide a new basic structure on which new compounds can be designed with better and selective effects. Recently, Hayao *et al.* (221) have reported that most of the aminoalkyltetrazoles possess potent alpha-adrenergic-blocking activity, the 5-[2-(4-aryl-1-piperazinyl)ethyl]-tetrazoles being the most active series. This is to be anticipated since it was shown in the preceding section that phenyl-, phenylmethyl-, and dimethoxyindolyl-piperazines constitute a large series of compounds with a wide range of pharmacological activity, including potent sympatholytic and adrenolytic effects. Rodriquez *et al.* (222) examined a whole series of phenylpiperazine-tetrazole derivatives and recognized in compounds the formula (LIV) a high degree of adrenergic-blocking activity, where R_1, R_2 are alkyl, aryl, aralkyl, and substituted phenylalkylpiperazyl groups. Their results in-

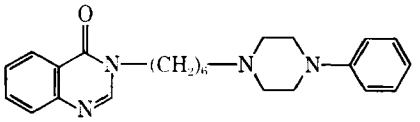


LIV



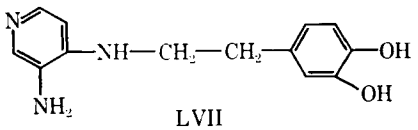
LV

dicate that 5,2-(4-phenyl-1-piperazyl)ethyltetrazole dihydrochloride (NA 1277) (LV) is outstanding in its antiadrenergic action. It blocked aortic strip and nictitating membrane responses to epinephrine, antagonized the vasoconstrictor responses to norepinephrine, and reversed the blood pressure response to epinephrine. It did not, however, block tachycardia resulting from reflex mechanisms and/or sympathetic nerve stimulation. It resembles DHE in its ability to exhibit greater *in vivo* than *in vitro* activity, but, unlike DHE, it does not cause stimulation of the smooth muscle. The compound has a rapid rate of onset of action and produces an effect that lasts longer than that of phentolamine and azapetine. Comparable adrenergic-blocking activity is also exhibited by a nontetrazoline derivative of phenylpiperazine (MA 1211) (LVI), which resembles phentolamine in its mode of action.



LVI

A recent paper (223) has described some pharmacological effects of ω-substituted alkylamino-3-aminopyridines. Aminopyridines have long been known for their CNS and sympathomimetic effects (224–226). All attempts at evolving a selective and potent adrenergic blocker have resulted in the formation of anticonvulsants and pressor agents. Exchange of substituted 3-aminopyridine group with aminoquinolines, and corresponding imidazo and triazolo groups, has not yielded any substantial gain. A new compound, 4-(3,4-dihydroxyphenethyl)amino-3-aminopyridine (LVII) has been claimed to be capable of blocking both alpha- and beta-receptors and to produce persistent hypotension

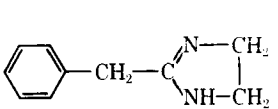


LVII

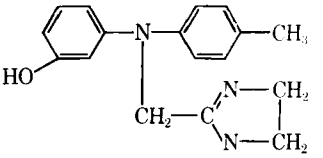
at a high dose and hypertension at a low dose.

Imidazolines—Hartmann and Isler (227) studied the effects of 2-substituted imidazoline on blood vessels. Among the alkyl-substituted imidazoline derivatives, vasodilator and vasodepressor activity could be found if the alkyl group was from six to eight atoms in length. Tolazoline, 2-benzylimidazoline (LVIII), exhibits a wide range of pharmacological activity including a powerful hypotensive, relatively feeble adrenolytic, sympatholytic, cholinergic, and histaminic properties (228). Alpha-adrenergic blockade produced by tolazoline appears to be competitive (21, 97). Introduction of phenolic or methoxy groups into the benzene ring (*e.g.*, trimethoxybenzyl, phedracin), or the exchange of benzyl for alpha-naphthyl (naphazoline) or an indolyl group reverses the activity from depressor to pressor.

Phentolamine (LIX) presents an almost entirely different structure with greatly enhanced adrenolytic activity (229). Phentolamine is five to seven times more



LVIII



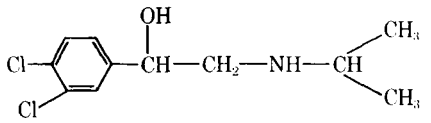
LIX

active than tolazoline on the alpha-receptors in the dog hind limb, and even much more so on the rabbit aortic strips and perfused ear (230). In addition to its anti-

adrenergic action, phentolamine acts directly on tissues and affects cholinergic receptor sites.

BETA-RECEPTOR BLOCKING AGENTS

Until 1957, Alhquist's concept of an adrenergic receptor had only the status of a hypothesis. The synthesis of dichloroisoproterenol (DCI) (LX) by Mills (231) and the evaluation of its pharmacological properties by Powell and Slater (232) not only brought a fitting recognition to Ahlquist's classification, but also marked the beginning of a renewed interest in adrenergic drugs. Adrenergic beta-receptor-blocking drugs, in fact, have attained a position which was once considered to be the sole criteria of ergot alkaloids. The search for greater specificity for beta-receptor blockade has made it possible to discover new kinds of pharmacological activity unrelated to adrenergic blockade as a by-product.



LX

Following the fortunate discovery of DCI, several other potent compounds were introduced in quick succession: in 1962, pronethalol by Black *et al.* (233); in 1964, propranolol by Black *et al.* (234); MJ 1999 by Larsen and Lish (235); methoxamine analogs by Burns *et al.* (236); in 1965, KÖ-592 by Engelhardt (237); INPEA by Somani and Lum (238); and in 1966, H 56/28 by Brändstrom *et al.* (239). Pronethalol, the first beta-blocking agent thought to be useful clinically, had to be withdrawn from clinical trials when it was shown to possess carcinogenic property in the mouse (240). The only other compound to offer some promise of safe and potent action is propanolol which is being used in Europe while the search for an ideal beta-blocking drug is on.

The subject of beta-adrenergic blocking drugs has been thoroughly covered in a conference of New York Academy of Sciences (29). An excellent review on the beta-blocking drugs has been presented by Moran (241) that covers all essential points. For structure-action relationship, papers by Ariëns (242) and by Biel and Lum (24) may be consulted. A very recent review by Ahlquist (30) is concerned with the pharmacodynamics of these compounds. The following discussion is intended mostly to bring up important aspects of recent progress in this area.

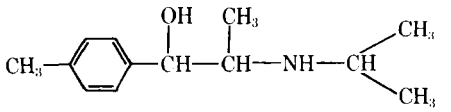
Adrenergic beta-receptor-blocking agents that have been introduced so far bear a remarkable structural resemblance to isoproterenol. This makes it possible to work out a definite SAR among these blocking agents. In synthesizing the new beta-blocking agents, the chemical structure of isoproterenol has been attacked at critical points deemed necessary for beta-adrenergic activity. For a molecule to behave as a potent beta-receptor agonist it must have a phenylethylamine structure with dihydroxy substitution at the 3,4-positions of the benzene ring (243–245), with a hydroxyl group at the beta-carbon atom of the ethylamine side chain (246–251), and an isopropyl group at the terminal nitrogen end (252, 253). The importance of these structural characteristics in affecting a drug-receptor interaction has been postulated on the basis of stereochemical considerations (11) and has been subjected to frequent revision (12). Whereas many alternatives can be thought of to describe the union of drug molecule with the receptor, the lack of the knowledge of the true chemical nature of adrenergic receptors thus far indicates that a solution cannot be achieved without recourse to more practical approaches.

SAR OF BETA-RECEPTOR BLOCKING AGENTS

The search for a compound with a selective bronchodilator effect free from stimulatory effects of isoproterenol on cardiac muscles led to the discovery that the manipulation of phenethanolamine structure of isoproterenol could give rise to structures with varying degrees of stimulating and inhibitory action on the bronchial smooth muscles and the muscles of the heart. Among the variously substituted phenoalkanolamines (Table III) it can be concluded:

(*A*) Halogen substitution in the ring of isoproterenol produces analogs which are more potent than those of epinephrine (DCE) which, in turn, are stronger than those of norepinephrine (DCNE). DCI first stimulates, and then depresses, the rabbit heart, whereas both DCE and DCNE have only a depressant action (20, 254). Replacement of the beta-hydroxyl group by a chlorine atom produces alpha-receptor blockade (50). The 2-chlorophenyl analog is a potent bronchodilator with prolonged action in the perfused rabbit lung (255) and is effective orally in man (256). All other halophenyl analogs of isoproterenol produce blockade of bronchial relaxation (257, 258). Unlike DCI, the 2,4-dichloro analog is devoid of positive chronotropic effect on the heart. Bringing 4-methyl and 3,4-dimethyl groups to positions other than 3 and 4 results in weak anti-adrenergic, weak antiarrhythmic, and strong negative inotropic activity.

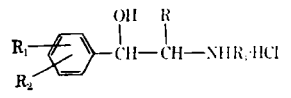
(*B*) The 3,4-dimethyl- and 4-methylphenyl analogs of DCI are potent blocking agents with considerable stimulating effect on the heart rate (259). H-35-25 (LXI) appears to be capable of producing a selective blockade of beta-receptors in femoral vascular structures in a dose range that has little blocking action on cardiac beta-receptors (259a). 2-Chloro-4-methyl substitution



LXI

has no sympathomimetic effect (260). The introduction of an alpha-methyl group into the beta-phenethanolamine side chain of DCI results in the diminution of positive inotropic effect blocking property, whereas the vasodilator-blocking effect is maintained (261, 262). Substitution of the alpha-alkyl group abolishes the positive inotropic effect of DCI with a concomitant decrease in beta-receptor-blocking ability (259). This relationship is maintained in alpha-alkyl-substituted 3,4-dimethyl analogs of DCI. *p*-Tolyl compounds are analogous to

Table III—Structure-Activity Relationships in Phenylalkanolamines

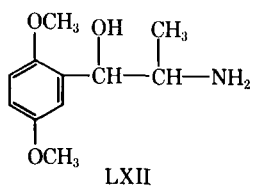


	R_1	R_2	R_3	R_4	Antiarrhythmic Potency	Bronchodilator Effect	β-Receptor-Blocking Effect	Chronotropic and Inotropic Effect
DCI	4-Cl	3-Cl	H	$CH(CH_3)_2$	Enhanced	Block	1	+
Nethalide	Naphthyl		H	$CH(CH_3)_2$	0.1		1.2	?
	$4\text{-}CH_3$	$3\text{-}CH_3$	H	$CH(CH_3)_2$	1		1.2	+
	$4\text{-}CH_3$	$3\text{-}CH_3$	CH_3	$CH(CH_3)_2$	0.2		0.2	
	4-Cl	3-Cl	CH_3	$CH(CH_3)_2$	0.05		0.08	Weak
	$4\text{-}CH_3$	$3\text{-}CH_3$	CH_3	$n\text{-}C_4H_9$	0.2		0.1	
	$4\text{-}CH_3$	$3\text{-}CH_3$	CH_3	$CH(C_2H_5)_2$	0.1		0.06	
	$4\text{-}C_2H_5$	$3\text{-}C_2H_5$	H	$CH(CH_3)_2$	0.1		0.08	?
	$4\text{-}CH_3$	3-H	H	$CH(CH_3)_2$	0.2		1.2	+
	4-Cl	3-Cl	C_2H_5	$CH(CH_3)_2$	0.05		0.15	
	$5\text{-}CH_3$	$2\text{-}CH_3$	CH_3	$CH(CH_3)_2$	0.2		0.06	
	$4\text{-}C_2H_5$	H	CH_3	$CH(CH_3)_2$	0.04		0.2	
	$4\text{-}CH_3$	H	CH_3	$CH(CH_3)_2$	0.1		0.2	
	H	$3\text{-}CH_3$	CH_3	$CH(CH_3)_2$	0.2		0.2	
	4-Cl	$3\text{-}CH_3$	H	$CH(CH_3)_2$			1.0	
	$4\text{-}C_2H_5$	H	H	$CH(CH_3)_2$			0.15	+
	$4\text{-}CH_3$	$3\text{-}CH_3$	H	$CHCH_2CH_2$			0.08	
	$4\text{-}(CH_2)_2CH_3$	H	H	$CH(CH_3)_2$			0.1	
	$4\text{-}CH_3$	3-Cl	H	$CH(CH_3)_2$			1.0	
	$4\text{-}CH_3$	$2\text{-}CH_3$	CH_3	$CH(CH_3)_2$			0.03	
	H	$3\text{-}CH_3$	CH_3	$CH(CH_3)_2$	0.04		0.05	
	4-Cl	3-Cl	H	H			0.1	
	4-Cl	3-Cl	H	CH_3			0.5	
	H	3-Cl	H	$CH(CH_3)_2$		Moderate block		
	4-Cl	H	H	$CH(CH_3)_2$				
	4-Cl	2-Cl	H	$CH(CH_3)_2$		Block		
	$4\text{-}CH_3$	2-Cl	H	$CH(CH_3)_2$		Block	1	
	5-Cl	2-Cl	H	$CH(CH_3)_2$		Block		
	H	2-Cl	H	$CH(CH_3)_2$		Dilator		
	$4\text{-}CH_3O$	$3\text{-}CH_3O$	H	$CH(CH_3)_2$			—	
	$4\text{-}C_2H_5O$	$3\text{-}C_2H_5O$	H	$CH(CH_3)_2$				
	$4\text{-}CH_3O$	$3\text{-}CH_3O$	CH_3	$CH(CH_3)_2$				
	$5\text{-}CH_3O$	$2\text{-}CH_3O$	CH_3	$CH(CH_3)_2$	Enhanced			Weak
	$5\text{-}CH_3O$	$2\text{-}CH_3O$	CH_3	t-but-C>H15				
	$5\text{-}CH_3O$	$2\text{-}CH_3O$	CH_3	$CH{>}CH_3$	Enhanced			
	$4\text{-}NHSO_2CH_3$	H	H	$CH(CH_3)_2$			1	Decrease
	4-Tolyl	H	H	$CH(CH_3)_2$			0.5	
	Tetralin		H	$CH(CH_3)_2$			1	
	$4\text{-}NO_2$	3H	H	$a{+}(CH_3)_2$			1	

3,4-dimethyl compounds, but tetralin analogs lack the sympathomimetic activity of 3,4-dimethyl derivatives without changing the blocking activity (260).

(*C*) The presence of the *N*-isopropyl group is crucial irrespective of whether the drug is a blocker or an agonist. Cyclization of this group into cyclopropyl occurs at the expense of all of the activity (259).

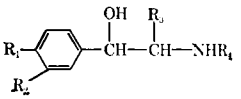
(*D*) The "methoxamine" series has created another example of receptor selectivity. Methoxamine (LXII) causes a long-lasting vasoconstriction and rise in blood pressure in doses about 100 times those of epinephrine and norepinephrine (263), and restores the epinephrine pressor response after the response had been reversed by phenoxybenzamine and dibenamine (264). Karim



LXII

(265), on the other hand, observed the antagonizing effect of methoxamine on the cardiac-stimulating action of epinephrine, norepinephrine, and isoproterenol in the cat and rat perfused heart, and the isolated rabbit atrial preparation. These demonstrations lead one to believe that methoxamine has alpha-stimulating and beta-blocking properties, a conclusion not acceptable to Alhquist (30). Isoproterenol itself exhibits this dualistic behavior; the *l*-isomer acts as an alpha-adrenergic agonist while the *d*-isomer acts as alpha-adrenergic-blocking agent (251, 266, 267). Not only this, isoproterenol has been shown to block its own action in large doses on beta-receptors on vascular smooth muscles of the cat (268) and on the isolated rat uterus (269). Obviously, a conventional mode of reasoning cannot be considered to provide adequate explanation for these seemingly anomalous phenomena, and must, of necessity, give way to newer interpretations based on a broadened outlook. *N*-Isopropylmethoxamine (IMA) and methoxamine have been denied the status of a typical beta-blocking agent since they failed to block significantly the increase in femoral flow, intestinal inhibitory, and positive chronotropic effects produced by isoproterenol in the anesthetized dog (270). They do,

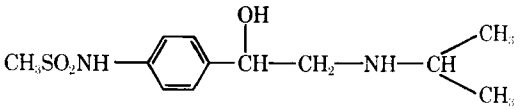
Table IV—Structure-Activity Relationships in Sulfonamido Substituted Phenylalkanolamines



Compd.	R_1	R_2	R_3	R_4	Activity
MJ 1999	CH_3SO_2NH	H	H	$CH(CH_3)_2$	Depressor
MJ 1998	CH_3SO_2NH	H	CH_3	CH_3	Pressor
MJ 1996	H	CH_3SO_2NH	H	CH_3	Pressor and β-receptor stimulation
MJ 1995	H	CH_3SO_2NH	H	$CH(CH_3)CH_2OC_6H_5$	β-Receptor stimulation, depressor
MJ 1994	H	$ArSO_2NH$	H	$CH(CH_3)CH_2OC_6H_5$	β-Receptor depressor
MJ 1993	OH	CH_3SO_2NH	H	CH_3	β-Stimulation, pressor
MJ 1992	OH	CH_3SO_2NH	H	$CH(CH_3)_2$	β-Stimulation, depressor
MJ 1991	OH	CH_3SO_2NH	H	$CH(CH_3)CH_2OC_6H_5$	Depressor, α-block

however, produce ethylnorepinephrine and isoproterenol "reversal" which can be prevented by dibenamine (254). The reversal is thought to be brought about by a vasoconstrictor action of these agents not involving beta-receptors. Their ability to block inhibitory responses on the rat uterus (56) and to block metabolic effects of catecholamine, as does DCI (271–273) leads to the proposal that either the drugs have a great degree of tissue specificity or the beta-receptors are not alike in all the tissues (274). A more probable explanation would be based on the essential role played by the "environmental factor." *N-tert*-Butylmethoxamine (TMA) exerts its blocking effect on the vasodilator responses to isoproterenol and ethylnorepinephrine in the anesthetized dog and shares this activity with DCI, pronethalol, IMA, and methoxamine on the isolated rat uterus. But like IMA and methoxamine, it does not have a broad-spectrum beta-blocking activity. TMA differs from IMA in many respects: it does not produce bradycardia and a gradual increase in mean arterial pressure, it does not have an appreciable effect on blood pressure or on heart rate, and it reduces the femoral flow response to intraarterial isoproterenol (274). A new addition to this class of selective beta-receptor-blocking agents is dimethylisopropylmethoxamine which closely resembles TMA (275). The selective beta-blockade produced by the alpha-substituted DCI analogs, methoxamine, IMA, and TMA indicates that not only alpha-alkyl substitution is important in segregating beta-blocking effects, but a change at some point in the molecule affects the molecule as a whole that accounts for the altered physiological behavior. The emerging situation is critical. The appearance of selective beta-receptor-blocking agents and the lack of confidence in defining the beta-receptor functions make it imperative to choose a universally acceptable criterion and each new compound must conform fully to this criterion in order to qualify as a beta-receptor-blocking agent. Individual reactions can be blocked or elicited by different mechanisms, but a fundamental mechanism must be common to all the reactions controlled by a receptor. An agonist by triggering this mechanism must produce all receptor effects, and an antagonist as defined by Ahlquist causes disappearance of all. Characteristically, a beta-receptor-blocking agent will produce the following responses: (*a*) decrease in heart rate unless there is no significant ongoing adrenergic influence on the heart; (*b*) some decrease in force of myocardial contraction unless there is no significant ongoing adrenergic influence; (*c*) a possible increase in intestinal and myometrial activity; and (*d*) a possible depressor response in intact animals due to the effects on the heart (30).

(*E*) *p*-Methylsulfonamido substitution into the phenyl ring produced compounds whose activity ranged from depressor to pressor and from beta-stimulation to alpha-blockade (276). The most outstanding compound in this series was MJ 1999 (LXIII) (277–279).

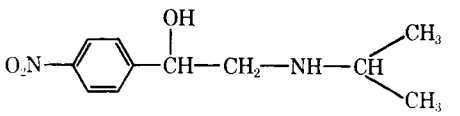


LXIII

The results of Larsen and Lish (276) are reproduced in Table IV.

From the foregoing table, it is evident that the *para*-position of the methylsulfonamido group is crucial to beta-blocking activity; moving it to the *meta*-position of the phenyl ring completely abolishes all the beta-receptor-blocking property in this series.

(*F*) Nitro-derivatives of isoproterenol behave in much the same way as the methylsulfonamido derivatives. The most active compound of this series is 1-(4-nitrophenyl)-1-hydroxy-2-isopropylaminoethane (INPEA) (LXIV). Somani *et al.* (280) examined a series of these compounds on the isolated rabbit heart preparation.

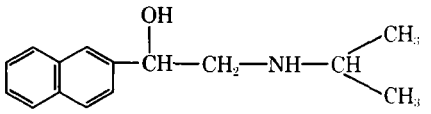


LXIV

Their results indicate that substitution with a single NO_2 group in the *para*-position of the phenyl ring yields the most active compound, activity decreases on moving the NO_2 group to the *meta*- or *ortho*-positions. The adrenergic-blocking activity is also decreased by substituting with two NO_2 groups in the 2,4- and 3,5-positions and also by substitution with *p*-NH_2 or *p*-CH_3SO_2 groups in the ring.

Bicyclic aromatic alkanolamines have yielded therapeutically active compounds. First introduced by Black

and Stephensen (281), pronethalol [2-isopropylamino-1-[2-naphthyl]-ethanol] (LXV) decreases the heart rate



LXV

in intact cats without greatly affecting positive inotropic effects. This compound, however, is not entirely devoid of sympathomimetic effects although it is much weaker than DCI. It may stimulate or depress the heart rate and the force of contraction depending upon the dose and route of administration (238, 282–284). Pronethalol also elicits a fall in blood pressure on intravenous injection due to peripheral vasodilation and myocardial depression (238, 281–283). It has no effect on the vasodilator responses of histamine and acetylcholine (238).

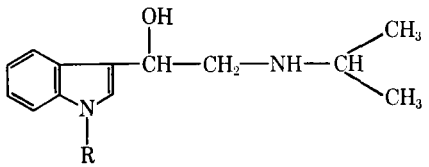
Crowther *et al.* (285, 286) established structure-activity relationships and arrived at the following conclusions:

(*a*) Isopropyl-, *sec*-butyl-, and *t*-butyl-substitution on the nitrogen atom gave potent compounds (287) and cycloalkylamino moieties yielded inactive compounds (24). Di-substitution on the nitrogen also resulted in inactivation.

(*b*) Branching at the alpha-carbon atom was detrimental for beta-receptor-blocking activity (286).

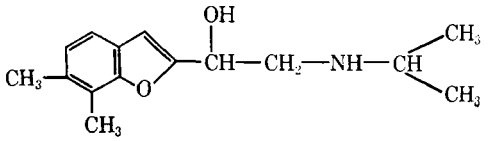
(*c*) Alteration of the hydroxyl group at the beta-carbon atom resulted only in decreased activity (286).

(*d*) Moving the alkanolamine side chain to the alpha-position of the naphthalene ring increased sympathomimetic activity without an appreciable effect on blocking activity. Halogenation or alkoxylation of the remote phenyl ring decreased both blocking and stimulant action at the beta-receptor. Replacement of the naphthalene group by polycyclic ring structures produced less-active compounds. Indole derivatives (LXVI), however, retained blocking as well as sympathomimetic activity (286).



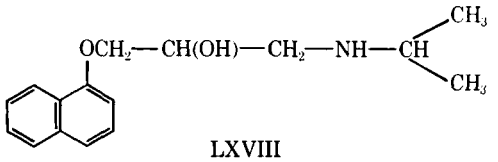
LXVI

Another heterocyclic compound, Ro3-3528[6,7-dimethyl - α - (isopropylamino) - methyl] - 2 - benzfuranmethanol (LXVII), has recently been shown to have considerable activity on the isolated rabbit atria and the heart *in situ* (287a).



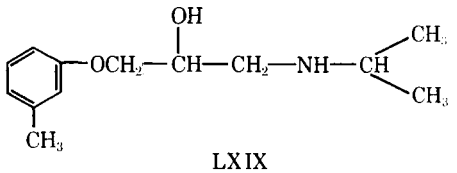
LXVII

Moderate activity is found in compounds in which naphthalene ring is separated by a methylene group from the ethanolamine side chain. Changing this side chain beta- to alpha-position on the naphthalene ring increases the activity manyfold, but a corresponding compound with an ether linkage between the naphthalene and the side chain exhibits a sharp rise in activity as in propranolol (LXVIII) (288–290).



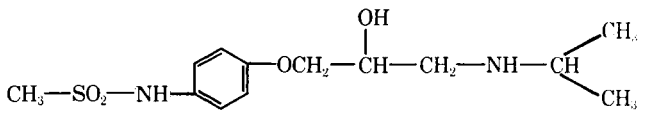
LXVIII

Propranolol is not only 10 times stronger than pronethalol but is also less toxic (234). Exchange of the naphthalene moiety with substituted phenyl retained full activity; an example is KÖ-592 [1-(3-methylphenoxy)-3-isopropylaminopropanol] (LXIX) which is as active as propranolol (237, 291) although three times less active orally and, unlike the latter is sympathomimetic (292).



LXIX

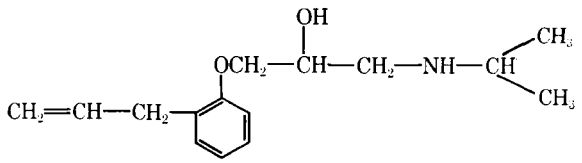
Lish *et al.* (277) described methanesulfanilides (LXX) related to KÖ-592 which contain the methylsulfonamido radical at the *para*-position of the phenyl ring. These compounds produce potent and selective blockade to the effects of isoproterenol on respiratory,



LXX

uterine, and cardiac muscles, but have no anesthetic activity.

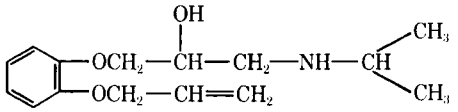
Ablad *et al.* (293, 294) have extensively studied a new compound, 1-(*o*-allylphenoxy)-3-isopropylamino-2-propanol H-56/28 (LXXI), and showed it to be equally potent to propranolol in antagonizing positive chronotropic and inotropic effects of isoproterenol or electrical stimulation of the cardiac sympathetic nerves. H-56/28 also exhibits a moderate degree of beta-receptor stimulation on the heart muscle of the reserpinized cat. This stimulatory effect is blocked by propranolol. Quite



LXXI

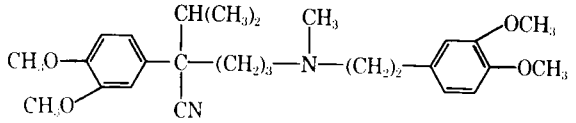
interestingly, an allyloxy derivation of H-56/28 (trasicor) has been shown recently to possess hypotensive, antiarrhythmic, and chronotropic activity in man. Unlike propranolol, which produces depression, this compound caused stimulation of the central nervous system. Trasicor (39089-Ba) (LXXII), however, is slightly less

potent than propranolol (295).



LXXII

A compound that has no structural resemblance to isoproterenol is verapamil (LXXIII). Iproveratril was studied by Haas and Hartfelder (296, 297) and was shown to antagonize the effects of isoproterenol on the heart, blood pressure, and phosphorylase activity. Pretreatment with iproveratril reduced the toxic effect of K-strophanthin on the guinea pig heart and decreased heart frequency. Such effects were not affected by quinidine or reserpine pretreatment (298). It is a potent coronary dilator (299).



LXXIII

STEREOCHEMICAL ASPECTS

Ever since Cushny (300) drew attention to the biological relations of optically isomeric substances, it became increasingly a matter of great concern to relate physiological activity to chemical constitution of biologically active molecules (301). As a result, it was necessary to determine the absolute configuration of catecholamines in order to materialize their own, as well as their antagonists' association with the receptor, in stereochemical terms. Finally, it has been established that the active isomers of catecholamines and the active isomers of the antagonists have D-configuration (14, 302). Isomers with L-configuration are either less active or inactive (303). Optical isomers of beta-receptor-blocking agents can be used to dissociate effects that are due to beta-receptor stimulation from those that are unrelated to it. *Levo* isomers of both DCI and pronethalol were 40 times more effective than *dextro*-isomers in their ability to block isoproterenol-induced tachycardia in chloralosed cats and paralleled the bronchodilating action of the corresponding analog of isoproterenol in guinea pigs (304). Both *d*- and *l*-isomers of DCI are cardiac stimulants (304) whereas the *l*-isomer of pronethalol has beta-adrenergic-blocking as well as antiarrhythmic properties and the *d*-isomer is devoid of beta-blocking action but has antiarrhythmic activity (305). The *dextro* and *levo*- isomers of H-56/28 and propranolol can abolish ouabain-induced ventricular tachycardia on intravenous injection in the unanesthetized dog. But *dextro* H-56/28 differs from *levo* H-56/28 and propranolol in having a rapid onset and longer duration of antiarrhythmic action (306). Intra-arterially administered racemic propranolol and racemic H-56/28 were equipotent in their effects on basal blood flow and on isoproterenol-induced vasodilation whereas the *dextro* H-56/28 was a much weaker beta-adrenergic-blocking agent (307). The *levo* isomer of INPEA was five times more active than its racemate (308), which in its turn was much more potent than the *dextro* isomer on the rabbit heart preparation (309). The weak beta-receptor-blocking activity of the *dextro* isomers of the beta-receptor-blocking agents means that beta-OH in these compounds and beta-OH in catecholamine bind to the same site on the receptor (280).

Table V—Comparison of Potency of Beta-Receptor-Blocking Agents and Their Isomers

	Rabbit Left Atria	Guinea Pig Tracheal Chain PA_2	Guinea Pig Atria PA_2	Papillary Muscle of Kitten PA_2
dl-Pronethalol	1	7.3		
dl-KÖ-592	7.9		8.2	8.2
dl-Propranolol	6.7	8.5	8.5	8.8
DCI	6.34		7.8	7.8
l-Pronethalol	2.08		7.1	7.3
l-MJ 1999	1.8	6.8	6.2	6.6
d-Propranolol	0.76	6.5	6.5	6.8
dl-MJ 1999	0.62			
d-Pronethalol	0.14	5.2		
dl-MJ 1998	0.12			
d-MJ 1999	0.06	5.15		
l-IMA		6.53	5.5	5.5
l-MA		6.25	5.1	5.3
dl-Des MA		5.09		
dl-Des IMA		4.85		
d-MA		4.37		
d-IMA		>3.5		
l-TMA		7.2		
d-TMA		>4.0		
dl-Pseudo TMA		>4.0		
l-INPEA		6.5	6.5	6.5
d-INPEA		4.22		
dl-H-56/28	6.7	8.5		8.8

Table V summarizes the relative potencies of beta-receptor-blocking agents on electrically driven rabbit left atria (310), on the isolated guinea pig atria and atria and papillary muscles of kittens (311), and on the isolated guinea pig tracheal chain (303, 312).

EFFECTS OF ADRENERGIC-BLOCKING AGENTS ON THE NERVOUS SYSTEM

Both alpha- and beta-blocking agents are capable of potentially influencing the functional physiology of the entire nervous system from brain to nerve endings. These actions, for the most part, are not related to adrenergic-receptor blockade, and include a wide spectrum of pharmacological activity. However, they constitute an easily accessible means to explore the mechanism of action of many nonadrenergic drugs. For example, the finding that both alpha- and beta-receptor-blocking agents, except DCI, antagonize the anticonvulsant effect of acetazolamide lends support to the view that catecholamines are involved in the mechanism of action of acetazolamide which is also inhibited by amine-depleting agents like reserpine, alpha-methyltyrosine, and several benzoquinolizine derivatives (313). The failure of adrenergic blocking agents, except phenoxybenzamine, to antagonize the anticonvulsant effects of diphenylhydantoin and chlordiazepoxide supports the results of Rudzik and Mennear (314) that catecholamine depletion is not involved in this case. Propranolol and pronethalol are CNS depressants whereas INPEA is CNS stimulant (315, 308). Vaughan Williams (316) has emphasized the need to demonstrate whether any apparent effect is truly on the CNS or secondary to some

peripheral action. As observed by Haley and McCormick (317) and Feldberg (318), catecholamines produce soporific or anesthetic effect in cats, dogs, and mice following the injection into the cerebral ventricles, and as shown by Dell (319), marked cortical arousal and facilitation of postural reflexes follow the intravenous injection and the endogenous release of epinephrine. This dual behavior is best explained by considering that the total effect of a drug is the algebraic sum of possible negative and positive influences at different sites (316). A study of the effects of beta-receptor-blocking agents will signify the importance of these suggestions.

The activity of beta-blocking agents at sympathetic nerve terminals is one of the factors that determines the extent of intrinsic sympathomimetic activity, antiarrhythmic activity, and the suitability for experimental and clinical use. There is no correlation between the activity at the nerve endings and the activity of the beta-receptor. Both of these effects may occur in the same dose range as is the case with pronethalol, or they may be sufficiently separated by dose as in MJ 1999 and MJ 1998 (320). In any one tissue, the adrenergic antagonist may have one or more of three separate actions: it may (*a*) occupy a receptor; (*b*) prevent the uptake of norepinephrine; and (*c*) lower the norepinephrine content either by prevention of uptake or by interfering with the binding of norepinephrine (299). Thus, pronethalol inhibits accumulation or uptake of norepinephrine into the heart following norepinephrine infusion in the anesthetized rat. Doses larger than necessary for beta-receptor blockade are required to produce a decrease in endogenous levels of norepinephrine (299). In the rat heart propranolol has no such action (299). Verapamil produces a very weak inhibition of norepinephrine, but does produce a significant decrease in the amine content of rat heart after daily injections for several days (299). However, propranolol induced a transient vasodilation followed by a sustained vasoconstriction in the denervated autoperfused hind limbs of the dogs. The alpha-receptor-blocking agents phentolamine and phenoxybenzamine abolished the pressor response to propranolol. The pressor response is not obtained in spinal dogs, or in dogs whose adrenal glands were excluded from the circulation. These results suggest that the pressor response to propranolol is due to the reflex release of catecholamine from adrenal medulla or that a direct CNS effect of propranolol induces catecholamine release (321). Reflex mechanism, however, seems less significant in view of the fact that pronethalol is taken up strongly by central nervous tissue (233) and affects spinal reflexes (316, 322, 323).

DCI and phenoxybenzamine afford an example of tissue selectivity in their ability to prevent norepinephrine uptake. In the cat, phenoxybenzamine prevented uptake of norepinephrine by the kidney but not by the uterus; DCI prevented the uptake of norepinephrine by the uterus but not by the kidney. In the rat, phenoxybenzamine prevented the uptake of norepinephrine by the heart, spleen, and uterus, and reduced the uptake by the duodenum. DCI and phenoxybenzamine lowered the content of norepinephrine of some tissues of the rat. Farrant *et al.* (324), therefore, concluded that the way in which these adrenergic antagonists affect the storage sites for norepinephrine varies between organs, and that activity at the receptors bears no apparent relationship with the activity at the storage site. In another study, Dhalla (325) has provided evidence that DCI can produce sympathomimetic effects by directly stimulating the beta-receptor, or indirectly, by releasing norepinephrine. Pretreatment of rats with reserpine abolished the phosphorylase activation by DCI in the atria but not in the diaphragm indicating that both direct and indirect mechanisms were involved. On the electrically driven rat atria, the positive inotropic effect of DCI and nicotine, but not of tyramine or norepinephrine, was inhibited by morphine, imipramine, iproniazid, tranylcypromine, and hexamethonium. The effects of DCI, tyramine, and nicotine were blocked by both propranolol and cocaine, whereas the action of norepinephrine was potentiated by cocaine and antagonized by propranolol. On the spontaneously beating rat atria, pentolinium, hemicholinium, phenoxybenzamine, and methylxylocholine ether inhibited the positive inotropic and chronotropic actions of DCI and nicotine but did not alter the effects of tyramine and norepinephrine. MJ 1999 antagonized the cardio-stimulant effects of DCI, tyramine, nicotine, and norepinephrine, whereas atropine and piperoxan were ineffective. When the atria were made tachyphylactic to tyramine, DCI and nicotine, unlike norepinephrine, failed to produce a sympathomimetic action. These results indicate that unlike tyramine, DCI and nicotine release norepinephrine by depolarization of the sympathetic nerve terminals and the amine then produces its usual positive chronotropic and inotropic effects. It is interesting to note that the beta-receptor-blocking agents not only can affect release of norepinephrine from the nerve endings but also can displace alpha-receptor-blocking agents to restore the catecholamine responses. In dogs and on the isolated rabbit aortic strip, propranolol interacts with a previously blocked alpha-receptor, in some undefined way, to displace phenoxybenzamine, phentolamine, and tolazoline, restoring the normal pressor response to norepinephrine (326). This property is also shared by methoxamine and ephedrine (327).

ANTIARRHYTHMIC PROPERTIES

Experience has shown that beta-adrenergic blocking agents suppress certain types of arrhythmias (328–333), but this action cannot be attributed entirely to beta-receptor blockade (238, 305, 334–336). The extent of the antiarrhythmic action of beta-blocking agents depends on the nature of the agent that produced the arrhythmia, the nature of the beta-blocking agent, the electrical characteristics of the cardiac muscle, and the metabolic state of the cell. The last two factors have been very ably discussed by Trautwein (337). The ability of beta-receptor-blocking agents to prevent the experimental catecholamine-induced cardiac arrhythmias has been ascribed to specific and competitive beta-receptor blockade (338–342). However, the concept of nonspecific antiarrhythmic action arose when it was shown that DCI could reverse ouabain-induced arrhythmias in experimental animals (334) and that both *levo* and *dextro* isomers were capable of reversing digitalis-induced arrhythmias (343, 344) although the *levo* isomer was 40

times more potent in its beta-blocking action than the *dextro* isomer (304).

The way this nonspecific antiarrhythmic effect manifests itself depends on several factors that are affected to varying degrees by beta-receptor blocking agents. These include (*a*) a direct effect on the rate of the pacemaker potential which is more marked in the heterotropic pacemakers than in the sinus node; (*b*) a decrease in diastolic excitability; (*c*) prolongation of the absolute and relative refractory periods, and a decrease in vulnerability of the heart to stimuli during these periods; and (*d*) a reduction in conduction velocity in all cardiac fibers (337). Quinidine and procainamide exhibit their antiarrhythmic properties by reducing the increase of Na^+ conductance brought about by depolarization, altering the time constant of this effect and by raising the threshold for excitation (337). Hoffman and Singer (345) have demonstrated that pronethalol also affects the cardiac electrical activity probably by a direct action on the cardiac cell membrane. These observations are in agreement with the general view that the antiarrhythmic property of beta-blocking agents is due to their local anesthetic action (346–348). Standaert and Roberts (320) determined the neurotoxic effects of pronethalol on the soleus motor nerve terminal preparation and suggested that the capacity of pronethalol to prevent the digitalis-induced ventricular arrhythmia may be related to its nerve terminal-depressing action. Supporting evidence to this view has been provided by many workers. It consists of the ability of pronethalol to affect equally the adrenergic nerve endings and injected catecholamine (241), the weaker activity of MJ 1999 and MJ 1998 than pronethalol on motor nerve terminals as well as on adrenergic nerves (279), and the greater efficacy of beta-TM10, procaine, and diphenylhydantoin against digitalis-induced ventricular arrhythmias due to their strong depressing action at motor nerve terminals (349–350). MJ 1998 has no antiarrhythmic activity since it produces a very slight depression of the nerve terminal (279). Pronethalol, propranolol, and quinidine equally reduced the maximal rate at which the guinea pig isolated atrium followed an electrical stimulus. They were equal in their effect in increasing the toxic dose of ouabain in the guinea pig (351). H-56/58 (293), INPEA (238), and MJ 1999 (347) do not suppress ouabain-induced cardiac arrhythmias or arrhythmias due to coronary artery ligation. As expected, pronethalol is also without effect on arrhythmias due to coronary artery ligation (238). A recent report describes the effectiveness of propranolol in antagonizing Ba-induced cardiac arrhythmias in rats, dogs, and rabbits (352). Barium causes K^+ loss from the myocardium and propranolol appears to antagonize this effect through beta-receptor blockade and a quinidine-like action; also Ba-tolerance is increased by atropine whereas reserpine is ineffective. It is not yet certain whether propranolol together with $MgSO_4$ and K^+ could be used effectively in Ba-induced arrhythmias. Following reversion of ouabain-induced ventricular tachycardia by *dextro* H-56/28 or propranolol, there was a consistent slowing of the heart rate below the initial value. H-56/28 did not produce a pronounced bradycardia because of its slight intrinsic sympathomimetic activity in contrast to the sympathetic blocking action of propranolol (306).

Bowman and Raper (353) demonstrated the presence of beta-receptors in skeletal muscle fibers, and the presence of alpha-receptors in the motor nerve endings. Raper and Jowett (354) investigated the antiadrenergic and antifibrillary activities of beta-receptor-blocking drugs on isolated rabbit auricles and spontaneously fibrillating chronically denervated skeletal muscle. They observed that (*a*) despite the differences in the species, the tissues, and the method of assessment used, there was sufficient similarity in the orders of potency of the range of drugs used to suggest that antifibrillary action in denervated muscle might be the result of the same effect as that responsible for prolongation of the effective refractory period in muscles; (*b*) the local anesthetics procaine and lignocaine produce similar effects indicating that membrane stabilization may be the basic property underlying both effects. Consistent with this hypothesis is the fact that MJ 1999 which is devoid of local anesthetic activity (277) is also without antifibrillary activity in denervated muscle and, as compared to procainamide, is the least effective quinidine-like drug on cardiac muscle. Another important aspect of their study is the similarity between the action of methoxamine, IMA, and TMA and that of quinidine, procainamide, procaine, and lignocaine on cardiac muscle in that antiadrenergic actions occurred only in doses which also produced some quinidine-like effect. In denervated muscle, for a given degree of antiadrenergic effect, the decrease in background fibrillation was less than that produced by quinidine and the local anesthetics. Furthermore, antiadrenergic activity outlasted the depressant action on fibrillation. Denervated muscle therefore provides a useful test preparation for distinguishing antiadrenergic activity from quinidine-like activity (354).

In contrast to its action on the immobilized laboratory animals, propranolol in a dosage of 2.5 to 5 mg./kg. intravenous had no effect on the telemetrically recorded heart rate of unrestrained normal dogs. The difference is ascribed to emotional reactions in the restrained animals. The tachycardia occurring in the latter seems to be due chiefly to a decrease in parasympathetic tone (355). Propranolol, KÖ-592, and INPEA showed no correlation between the decrease in heart rate and cardiac output on intravenous injection. INPEA in doses of 50 mg. had no blocking activity whereas propranolol and KÖ-592 had steeper dose-response curves. INPEA antagonized the positive chronotropic effects of isoproterenol and its optical isomers were not different in activity (356). Alprenolol (H-56/28) blocked both positive chronotropic and inotropic effects of isoproterenol and electrical stimulation of cardiac sympathetic nerve in doses equal to that of propranolol (293). In the reserpinized cat, alprenolol caused a moderate increase in cardiac rate and contractile force that could be inhibited by propranolol. Higher doses of both the *levo* and the *dextro* isomers of alprenolol, like propranolol, are equally effective in producing direct cardiac depression (293). In human studies, alprenolol and propranolol were equipotent blockers of the cardio-

vascular effects of isoproterenol, but they influenced the basal hemodynamics differently (357). Cardiac output decreased after propranolol (22 ± 4.2%) but not after H-56/28. Mean arterial blood pressure was not significantly altered by either agent. On the basis of results from animal studies with the two compounds, Forsberg and Johnsson (357) concluded that propranolol reduced cardiac output by inhibiting endogenous sympathetic tone on the cardiac beta-receptors and H-56/28 inhibited endogenous sympathetic tone on the heart to the same degree as propranolol, but the hemodynamic consequences of this action of H-56/28 were overcome by a cardiac stimulation due to the slight "intrinsic" beta-receptor-stimulating action of this drug. The potency and time-effect relationships of intravenously administered racemic H-56/28, the *levo* form H-56/28, and racemic propranolol were studied in man (358) and in the cat (359) by recording heart rate and blood pressure responses to repeated intravenous infusions of isoproterenol. The ratios of equipotent intravenous doses were found to be about 2:1:2. All agents had the same time-effect relationship and the effect was maximal within 10–15 min. after the administration and still persisted at the end of 2 hrs.

The ratios between the smallest (negative) inotropic dose and the smallest beta-adrenolytic dose were determined on the dog heart-lung preparation for propranolol, KÖ-592, prenylamine, and verapamil (360). They were 6.1 for propranolol, 4.9 for KÖ-592, 6.5 for prenylamine, and 1.3 for verapamil. This ratio for verapamil is too small to show a specific beta-receptor-blocking effect. Unlike propranolol and KÖ-592, prenylamine had positive inotropic and positive chronotropic effects in a smaller dose range. Even in marked negative inotropic doses, these drugs do not affect the spontaneous frequency of the heart, but a distinct depressing effect readily occurs in reserpine treated isolated hearts. Negative inotropic effect of beta-blockers depends on extracellular Ca^{++} concentration. At low Ca^{++} concentration, this effect is decreased to a larger extent than at higher concentration of Ca^{++}. In isolated guinea pig atria, the action of quinidine and the beta-receptor-blocking effect was the same at all concentrations of Ca^{++} (361). Beta-blockade can prevent the usual positive inotropic and chronotropic effects of nicotine that result in hypertension, increased cardiac output, and stroke volume as well as the indirect beta-dilator effect on peripheral vessels. In the presence of beta-blocking drugs, nicotine fails to cause an increase in heart rate indicating that the unopposed alpha-receptor activation by the norepinephrine released from the peripheral stores can result in more uniform blood vessel constriction with sufficient increase in total peripheral resistance to impair stroke volume and cardiac output (362). An example of physiological antagonism on the blood vessels is the isoproterenol vasomotor reversal by sympathomimetic amines in anesthetized cats and dogs (363, 364). Here, phenylephrine reverses the depressor response to isoproterenol by producing vasoconstriction rather than producing beta-receptor blockade (30).

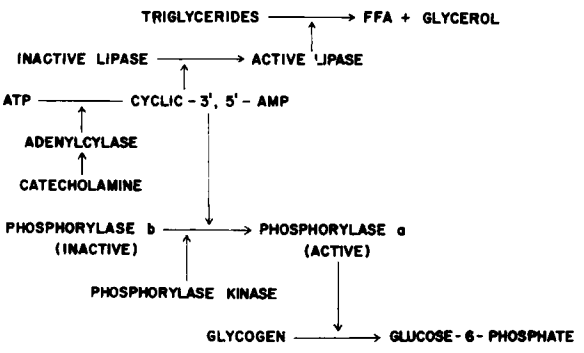


Figure 1—*Catecholamine-catalyzed metabolic pathways.*

METABOLIC EFFECTS OF ADRENERGIC-BLOCKING AGENTS

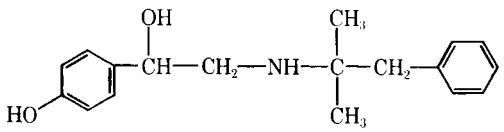
In recent years, many attempts have been made to classify metabolic actions of catecholamine into those exerted *via* alpha- or beta-receptors. It is becoming more and more imperative to treat metabolic effects of catecholamines and their inhibition by adrenergic receptor-blocking drugs on separate grounds which may be related to but not solely based on the known actions of the catecholamines and their antagonist on adrenergic receptors (365). A particular metabolic response, the hyperglycemic effect of epinephrine, can be the resultant of several different and independent actions of epinephrine, each of which may participate to a different extent in different species, or under different conditions in the same species (366). In the absence of the complete understanding of each of these independent metabolic routes, it is not predictable which of them is blocked by a blocking drug or whether all the different mechanisms are receptor-dependent. It is also highly improbable to assume that all the actions of catecholamines and those of their antagonists are exerted only *via* adrenergic receptors. Recently, Himms-Hagen (366) has admirably dealt with the whole spectrum of metabolic effects of adrenergic drugs in a very comprehensive review.

Conversion of ATP into 3,5-cyclic AMP (Fig. 1) under the influence of adenylcyclase and catecholamine is the most important event in the wide-range metabolic activity of the amine that manifests itself in hyperglycemia, lacticacidemia, and hyperlipidemia (367). To show that Furchgott's γ-receptor (15) is indeed adenylcyclase is the responsibility of posterity although such has been suggested (368). The inhibition of catecholamines by beta-receptor-blocking drugs causes considerable alterations of substrate concentrations in blood. Changes of blood levels in glucose, lactate, and pyruvate are considered to be parameters of metabolic effects of epinephrine. They are exceeded, if expressed in percentage as well as in significance, by fat mobilization and metabolization products. The lipolytic effects of epinephrine and the inhibitory effects of beta-blockers on adipose tissues are reflected in changes of concentrations of plasma fatty acids and glycerol (369). Propranolol in a dose of 20 mcg./kg./min. on intravenous administration in the anesthetized dog prevented completely the positive chronotropic, hyperglycemic, and plasma free fatty acid (FFA)-elevating action of isoproterenol administered intravenously at a

rate of 0.02 mcg./kg./min. A dose of 2 mcg./kg./min. of isoproterenol surmounted the blocking effect of propranolol showing that competitive blockade was produced. Propranolol affects the FFA level more readily than the glucose level (370). In anesthetized rats, the calorigenic and the positive chronotropic properties of different doses of epinephrine, norepinephrine, and isoproterenol were shown to be as follows (371):

isoproterenol–epinephrine–norepinephrine
1:5:8 = identical metabolic activity
1:4:10 = identical heart frequency

The order of potency of epinephrine and norepinephrine in this report is just the reverse of that on adipose tissue (372, 373). Not only catecholamines but also many aromatic amines related in structure to phenethylamine but lacking a catecholamine ring and a beta-OH group in the side chain have been shown to increase lipolysis in adipose tissue (374, 375) as is true of many polypeptide hormones, ACTH, TSH, glucagon, and others (376–378). Lipid-mobilizing action of ACTH is blocked by beta-receptor-blocking agents (379). Recently, Cepelik *et al.* (380–382) have undertaken studies on the problem of lack of specificity of the agents affecting lipid mobilization. Interactions of propranolol with norepinephrine and with ACTH were followed using the release of FFA from rat epididymal adipose tissue *in vitro*. Propranolol with ACTH produced a purely noncompetitive action (pD_2 = 3.83), whereas antagonism to norepinephrine was competitive (pA_2 = 5.48). It appears that ACTH does not affect the adrenergic receptor site in adipose tissue; its lipid-mobilizing action is due to a different trigger mechanism (373, 380). The dose-response curves of norepinephrine and phenyl-*t*-butylnoroxedrine (FtBuNOX) (LXXIV) for effecting the release of FFA from rat epididymal adipose tissue *in vitro* were studied *per se* and when interacting with propranolol, FtBuNOX started to exert an autoinhibitory action prior to reaching its maximum possible effect. Both sympathomimetics differed distinctly in



LXXIV

the slope of their dose-response curves. In the case of FtBuNOX the slope corresponded well to the usual presumption of a bimolecular reaction (drug and receptor) and the markedly steeper slope of the norepinephrine curve was in good agreement with the presumption of a trimolecular (2-receptors) reaction (382). The relative lipid-mobilizing potencies of isoproterenol, norepinephrine, and epinephrine (2:1:0.6) on rat epididymal adipose tissue were almost identical with those obtained on FFA release in blood plasma (0.5:33:0.2) *in vivo* and *in vitro* in the same animal (381, 383). Cepelik *et al.* (380) proposed that adrenergic lipomobilization characterizes a certain degree of beta-tropism, and this function could be considered for a specific adrenergic reaction. On the basis of hypothetical models of 1-receptor and 2-receptor reactions, Wenke *et al.* (381, 384) showed that whereas FtBuNOX could produce lipid mobilization in a single step, catecholamines exert a two-step reaction when affecting such mobilization. This and the dynamic receptor theory of Bloom and Goldman (153) center around a mechanism that involves the catecholamine nucleus and the beta-OH group as the basic structural requirement for lipid-mobilizing activity. Unfortunately, the real picture is not so simple as is being assumed. If differences in potency exist among structurally similar catecholamines, why are structurally dissimilar antagonists, pronethalol, DHE, IMA, and phenoxybenzamine, almost equally effective in blocking the release of FFA *in vitro* (385), despite the simultaneous interplay of many other variables, *e.g.*, penetration to receptor sites, difference in FFA passage across cell membrane, and change in ionic environment of enzymes? Added to this list of vaguely understood phenomena is the fact that differences in activity of epinephrine may be detectable in different seasons; also the ACTH response is minimum in February, March, and April (386). A recent report by Eisenfeld *et al.* (387) indicates that adrenergic-blocking agents can inhibit the extraneuronal metabolism of norepinephrine by preventing its access to the metabolizing enzymes. Specific transport mechanisms exist for the entry of extracellular catecholamine into sympathetic nerves. This finding lends support to the suggestion by Brooker *et al.* (385) that potency differences among catecholamines are due to their varying susceptibilities to COMT and MAO, and to the proposal by Ellis *et al.* (388) that the alpha-receptor may also be involved in catecholamine-induced increase in metabolic activity.

The situation becomes more complex when it is shown that the relative potencies of catecholamine in producing a particular response may vary from one tissue to another in one species, or from one species to another for one tissue (389), and when an analogous picture is presented by alpha- and beta-receptor-blocking agents. For example, the ability to activate phosphorylase or to induce glycogen breakdown in the rat liver decreases in the order epinephrine > norepinephrine > isoproterenol (390, 391), whereas a different order of potency has been shown for the same metabolic effect in the rat heart (390, 392), rat skeletal muscle (390), and dog liver (393). Similarly, the hyperglycemic response to epinephrine is inhibited by beta-adrenergic receptor blocking agents in the dog (394, 395); and this blocking action varies in the rat (390, 392, 397, 398). Moreover, alpha-blocking drugs do not affect epinephrine-induced hyperglycemia in the dog (394, 399) and man (396), yet they produce variable effects on phosphorylase activation (390, 392, 398, 400, 401) and on glycolysis (402, 403). In direct opposition to their irregular mode of action on epinephrine-induced lipolysis and hepatic glycolysis, and species differences, beta-receptor-blocking agents consistently block phosphorylase activation by epinephrine in heart and skeletal muscle whereas alpha-receptor-blocking drugs are without this effect (390–392, 401, 404). One aspect of the regulation of phosphorylase activity in the cell which has received little attention is the effect of ions on the enzymes of the cyclic AMP phosphorylase system (405). At least, a study of this kind would be needed to ensure that the difference in activity of alpha- and beta-recep-

tor-blocking agents in heart and skeletal muscle are dependent upon the nature of the receptors present, and are not due to some bioelectrical phenomenon. In the isolated, perfused guinea pig heart, the positive inotropic action and phosphorylase activity of isoproterenol are blocked by *levo*-IMA but are not affected by *dl*-IMA. However, the latter does transiently block stimulation of contractility and phosphorylase activity of norepinephrine. Neither *dl*-IMA nor *l*-IMA, however, reduces the phosphorylase activity to a greater extent than the mechanical actions. On the other hand, KÖ-592 completely abolishes all the actions of both norepinephrine and isoproterenol (406). Not only is phosphorylase activation by norepinephrine in the heart blocked to varying degrees by optical isomers of blocking drugs, but the inhibition of norepinephrine-induced lipolysis in isolated fat cells of the rat exhibits varying degrees of susceptibility to the blockade produced by 4-INPEA, 3-INPEA, and 2-INPEA—these isomers differing only in the position occupied by the nitro group in the phenyl ring. 4-INPEA was approximately 10 times as potent as 2- and 3-INPEA in antagonizing norepinephrine-induced lipolysis (407). During the course of discussion, it was emphasized that the *levo* isomers of adrenergic as well as adrenergic-blocking drugs possess the maximum activity on adrenergic receptors. A recent report by Bjorntorp *et al.* (408) showed that the *levo* form of H-56/28 in lower concentration ($5 \times 10^{-7} M$) inhibited norepinephrine-induced increase in lipolysis in the rat epididymal fat pad *in vitro* but in higher concentration ($5 \times 10^{-5} M$) had an intrinsic norepinephrine-like effect on lipolysis. The *dextro* form had no intrinsic activity and blocked the norepinephrine effect only in higher concentrations. In the anesthetized dog, the *levo* form of H-56/28 partially blocked the increase of FFA in plasma by norepinephrine and itself increased FFA concentration. The *dextro* form, as usual, had only slight blocking activity.

Isopropylmethoxamine has often been claimed to possess only the selective metabolic-blocking property (236, 273, 409, 410) that has raised doubts on its being a typical beta-adrenergic-blocking agent (30). Isopropylmethoxamine, however, has been shown to possess ability to block isoproterenol-induced relaxation of guinea pig tracheal chain to a moderate degree (pA_2IMA = 5.97, pA_2DCI = ~7.7) (380), and to exert a weak blocking action on the positive inotropic effect of epinephrine on isolated rabbit and turtle hearts (411).

Any explanation, like the one proposed by Northrop and Parks (398) that beta-blockers prevent formation of, and the alpha-blockers prevent the action of, preformed cyclic AMP, might point out the right approach to delineate the difference between the mode of actions of alpha- and beta-blocking agents on the metabolic actions of catecholamines.

The differences among catecholamines, and differences among organs and species in their response to a single catecholamine may lead to the supposition that many types of receptor for catecholamine might exist; these several receptors might simply be different adenylcyclases (isoenzymes), and the mixture of adenylcyclases present in a tissue would determine the response to a given catecholamine (366).

CONCLUSION

The literature on adrenergic-blocking drugs has been reviewed from the chemical and the pharmacological point of view. It has been pointed out that the traditional approach to structure-activity relationship based only on the chemical formula of the drug is not sufficient to derive conclusions on drug-receptor interaction since the introduction of a group into the molecule affects the whole molecule and the molecule as a whole determines the biological activity. It has been emphasized that drug-receptor interaction involves dynamic chemical entities that are susceptible to electrochemical and conformational alteration as a result of the influence of the presence of the various chemical entities forming the receptor environment. Such an environmental factor aids in the determination of the nature of the drug-receptor interaction and the type of response obtained.

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RESEARCH ARTICLES

Dissolution Rates of High Energy Polyvinylpyrrolidone (PVP)-Sulfathiazole Coprecipitates

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Abstract □ The apparent solubility and rate of solution of sulfathiazole from compressed tablets containing polyvinylpyrrolidone (PVP) were found to be greatly increased if sulfathiazole was previously coprecipitated with PVP. The increase noted was found to be a function of the chain length of the PVP used as a coprecipitate and the sulfathiazole to PVP weight ratio of the coprecipitate powder mixture used to compress the tablet. The 10,000-mol. wt. PVP yielded the most rapid sulfathiazole dissolution rate. The sulfathiazole rate of solution was (*a*) independent of the PVP weight fraction in the coprecipitated mixture at low PVP weight fractions; (*b*) increased with increasing PVP weight fraction at intermediate PVP weight fractions; and (*c*) decreased with increasing PVP weight fractions at high PVP weight fractions. A model was presented which utilized a controlling sulfathiazole external layer at lower PVP weight fractions and a controlling PVP external layer at higher PVP weight fractions. Several techniques were developed and used to elucidate the mechanisms involved and include (*a*) dissolution rate studies of mechanical mixes as well as coprecipitated mixtures of a number of sulfathiazole to PVP ratios; (*b*) X-ray diffraction studies of powders and tablets both before and after dissolution; (*c*) solubility determination of the various forms of sulfathiazole as a function of the PVP weight fraction in the coprecipitate and as a function of the PVP concentration in solution; (*d*) simultaneous release rates of PVP and sulfathiazole to determine regions of congruency and noncongruency; and (*e*) rates of solution using PVP solutions as a solvent. The data not only agreed very well with the model, but permitted a detailed characterization of all systems at all times during the dissolution process.

Keyphrases □ Sulfathiazole-PVP—coprecipitates □ Dissolution rates—sulfathiazole-PVP coprecipitates □ Solubility—sulfathiazole-PVP coprecipitates □ Tablets, sulfathiazole release rates—PVP effect □ X-Ray diffraction—sulfathiazole-PVP coprecipitates □ UV spectrophotometry—analysis □ Optical rotation—analysis

The interaction of polymers with chemical compounds to increase solubility has been reported for some time (1–3). More recently it has also been shown that the rates of solution of drugs were appreciably increased by coprecipitating the drug with polymers (4–6). This increase in dissolution rate of some systems, however, appears to be significantly greater than the expected increase calculated from the solubility increase due to the presence of polymer. Moreover, the increase was found to be sensitive to the method of preparation and the