THE PHARMACOLOGY OF ADRENERGIC BLOCKADE

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Among agents selectively blocking the effects of various portions of the nervous system, drugs inhibiting responses to the sympatho-adrenal division have always been the least satisfactory. Over forty years ago, Dale (86) clearly defined the action of ergot in blocking and "reversing" many responses to circulating epinephrine and sympathetic nerve stimulation, but subsequent progress in the field has been slow. The use of adrenergic blocking agents in research and therapy has been seriously handicapped by the lack of specificity, the incompleteness of action and the high toxicity of available agents.

Agents which induce or block responses of sympathetically innervated effector cells may be conveniently grouped under the term "adrenergic" proposed by Dale (88). The term "adrenergic blocking agent" is employed in this review to designate compounds which specifically inhibit certain responses of effector cells to epinephrine, related amines and sympathetic nerve impulses. The action of adrenergic blocking agents is quite distinct from the action of substances which can prevent a sympatho-adrenal discharge by blocking nervous impulses at ganglia (tetraethylammonium ions), along peripheral neurons (local anesthetics) or within the central nervous system (barbiturates and other central nervous system depressants). The absurdity and complication involved in referring to barbiturates as adrenergic blocking agents or "sympatholytics" are obvious. It is equally confusing to refer, as some authors do, to the central nervous system effects of the ergot alkaloids as "sympatholytic."

The term "adrenergic blocking agent" is preferred to "sympatholytic" and "adrenolytic." Neither nerve ending, nor mediator nor effector cell is "lysed" by these agents (see also 90). The term "adrenolytic" has been employed more correctly by some authors (91) to refer to those factors responsible for the destruction or inactivation of epinephrine in tissue. In addition, any sharp distinction between "adrenolysis" and "sympatholysis" appears to be artificial. Although certain compounds (*e.g.*, 933F) block the effects of circulating epinephrine considerably more effectively than they block responses to sympathetic nerve activity, this does not constitute a qualitative distinction. All adrenergic blocking agents appear to be more effective against responses to circulating sympathomimetic agents than against responses to sympathetic nerve activity; all degrees of effectiveness against these two stimuli may be found within the group, and even within a single series of compounds (47).

The present review is concerned largely with the major lines of progress in the field of adrenergic blockade during the past decade. No attempt has been made to include all publications relating to the subject during this period. Older work has been sighted only when necessary to help clarify recent contributions. Many details of the older work in this field are enumerated in the recent book of Bovet and Bovet-Nitti (40).

Extended consideration is given to the actions of the various agents other than the production of adrenergic blockade, in order to provide a basis upon which to evaluate experimental results. The literature on adrenergic blockade is replete with reports which merely record a single over-all effect of a blocking agent without any experimental analysis of the mechanism involved. Emphasis on the fact that most adrenergic blocking agents have multiple and complex pharmacological properties may serve to call attention to the inadequacy of much previous experimentation in this field.

I. β-HALOALKYLAMINES

The β-haloalkylamines, of which Dibenamine (N,N-dibenzyl-β-chloroethylamine) may be considered as the prototype, represent the most recently discovered series of adrenergic blocking agents. At the present time, the blockade produced by members of this group of compounds appears to be more complete and more specific than that produced by members of other series. Although N,N-dibenzyl-β-chloroethylamine was characterized in the American literature by Eisleb in 1934 incidental to a patent description of certain synthetic intermediates (102), its pharmacology was first reported by Nickerson and Goodman (285) in 1945. Additional reports soon appeared describing more completely the pharmacology of Dibenamine and of certain congeners whose activity was suggested by an early report of the structure–activity relationship within the group (296). In general, only quantitative differences between the various active members of this series have been reported; consequently the properties of Dibenamine, the most thoroughly studied compound, may be considered representative except where different properties of other agents are specifically mentioned. Many pharmacological characteristics of members of this group are included in summaries which appeared during the past year (279, 287).

Adrenergically active β-haloalkylamines have a very low aqueous solubility, except in the presence of high acidity, and undergo quite rapid decomposition in neutral or alkaline aqueous solutions to form readily soluble alcohol derivatives (288). They may be prepared as stable stock solutions in acidified propylene glycol or alcohol (286). Decomposition in aqueous solution may account for one report (31) which failed to confirm many of the generally substantiated pharmacological observations on Dibenamine.

A. Adrenergic blocking action

1. Responses to injected epinephrine. The most prominent action of Dibenamine is a specific blockade of certain excitatory responses to epinephrine and sympathetic nerve activity (286), an observation which has been confirmed and extended by numerous investigators.

Careful injection of moderate doses of Dibenamine into anesthetized animals (286, 408) or normal recumbent humans (158, 183) causes little change in blood pressure. Larger doses induce a moderate, slow decrease in pressure. This has been noted particularly in unanesthetized dogs (411). The drug has been re-

ported to cause some rise in blood pressure in certain schizophrenic patients (258). Rapid injection may lead to a precipitous fall in blood pressure which is probably unrelated to adrenergic blockade.

Pressor responses to exogenous and endogenous epinephrine and the direct pressor effect of splanchnic nerve stimulation are blocked and reversed in most species of animals. The depressor response to splanchnic nerve stimulation in adrenalectomized animals administered Dibenamine is small (286) and similar to the effect seen after large doses of ergotoxine (87). It is of interest that little or no reversal of the pressor response to epinephrine is observed in the rabbit, an animal in which adrenergic vasodilatation is apparently insignificant (65). Also, reversal is observed less regularly in the pithed cat (4) a preparation in which a high degree of vasodilatation exists prior to the administration of epinephrine. Reversal is presumably due to an inhibition of adrenergic vasoconstriction with a consequent unmasking of adrenergic vasodilatation. In chickens Dibenamine causes no reversal and even fails to inhibit the pressor action of epinephrine and most other sympathomimetic amines (397). A similar resistance of fowl to adrenergic blockade by ergot was noted many years ago (22, 86), and raises some interesting questions in comparative pharmacology. The action of Dibenamine in other species of birds has not been studied.

Minimal effective doses of the β-haloalkylamines may block the pressor effects of small but not large doses of injected epinephrine. However, adequate blocking doses ordinarily produce a complete blockade, *i.e.*, responses to all doses of epinephrine (as great as 10 mgm./kgm. intravenously) are completely reversed (286). This high "effectiveness," as distinct from "potency," (see I, C-2), is evident by other tests of Dibenamine action such as inhibition of retraction of the cat's nictitating membrane in response to nerve stimulation, epinephrine and norepinephrine (292), prevention of cyclopropane-epinephrine cardiac arrhythmias (298), and inhibition of epinephrine vasoconstriction in frog extremities (155). Dibenamine blockade develops quite slowly even after intravenous administration (286, 373); this is probably due to the necessity for *in vivo* formation of active intermediates (see I, D-1).

The adrenergic blockade produced by members of the Dibenamine series is not significantly altered by anesthetic agents (286) and is not overcome by cocaine (295). Comparable results have been obtained with unanesthetized and pithed animals and those under barbiturate, urethane, ether and cyclopropane anesthesia. This is in contrast to the well known inhibition of ergot blockade by barbiturates (see 66). However, heparin may significantly reduce the effectiveness of small doses of Dibenamine (295), presumably on the basis of a direct interaction similar to that occurring between the β-haloalkylamines and thiosulfate (see I, D-1).

Dibenamine (286, 312) and several congeners (197, 240, 295) provide marked protection against the lethal effects of epinephrine. Protection of this type in mice has been employed as an assay for adrenergic blocking activity (197, 240). Although the results are roughly parallel to those obtained by assay based on reversal of the pressor response to epinephrine in anesthetized cats (295), wide

quantitative discrepancies exist (see also I, D-3). Methacholine (240) and papaverine (313) have also been shown to provide significant protection against epinephrine toxicity in rodents, although they are not adrenergic blocking agents.

The lack of specificity observed in protection against epinephrine toxicity is probably related to the mechanism of epinephrine-induced death in mice and rats. It has been shown that death from intraperitoneally administered epinephrine in rats is primarily due to respiratory failure and that the rise in systemic arterial pressure *per se* is an important etiological factor in the observed respiratory embarrassment (282). Systemic hypertension obviously does not play a comparable role in epinephrine toxicity in fowl. Although Dibenamine provides significant protection in fowl, it does not alter the pressor response to injected epinephrine (397).

The role of systemic arterial pressure in death due to epinephrine raises the possibility that any agent with a significant vasodepressor action could provide protection. Several non-specific agents providing no protection under certain experimental conditions (240) may afford protection when administered by selected routes at appropriate time intervals. Care must therefore be employed in interpreting the results of such experiments.

Accumulation of epinephrine of "epinephrine-like" substances in heart muscle was found not to be causally related to epinephrine toxicity in rats (282), although such a relationship has been previously stressed (311, 312). Inasmuch as most of the myocardial effects of epinephrine are unaltered by Dibenamine (see I, A-4), the lack of significance of myocardial accumulation of epinephrine might have been anticipated.

2. Responses to sympatho-adrenal stimulation. The pressor effects of chemically-induced generalized sympatho-adrenal discharge are also inhibited by Dibenamine. Reversal of the nicotinic pressor action of acetylcholine and carbachol in atropinized animals has been regularly observed (286, 408); whereas the response to nicotine has been variously reported to be only inhibited (408) or to be completely reversed (217). Neither of these reports provides sufficient data to allow an adequate explanation of the divergent results. Failure to block completely the pressor response to nicotine may be due to a direct action of nicotine on peripheral vessels (155, 157, 246), which is non-adrenergic in nature and therefore not blocked by Dibenamine or ergotamine (246). An alternative explanation for the difference between the effects of Dibenamine on pressor responses to acetylcholine and nicotine is that sympathetic ganglion cells may differ in their pharmacological responses. It has been suggested that only ganglion cells subserving vasoconstrictor functions are readily stimulated by nicotine, whereas both those with vasoconstrictor and those with vasodilator functions are activated by acetylcholine (366).

Reflex pressor responses to carotid chemoreceptor stimulation (short periods of anoxia or asphyxia) are also reversed (252, 286, 390, 408) but the pressor responses to clamping of the common carotid arteries and to stimulation of the central end of the severed vagus nerve are inhibited without reversal (295, 390, 408, 409). At least part of the residual pressor effect of carotid occlusion after

Dibenamine may be due to a simple mechanical alteration of the vascular bed. Dibenamine has recently been employed as a tool to define other factors involved in the observed differences in the degree of inhibition or reversal by adrenergic blockade of various cardiovascular reflexes (116).

In contrast to the ergot alkaloids (see II, D-2), central nervous system depression does not appear to be a significant factor in the inhibition of vasomotor reflexes by Dibenamine. That the drug is devoid of actions on autonomic ganglia (116, 286, 292) and on reflex pathways in the central nervous system (116) appears to be adequately established. Intra-carotid injection of β-haloalkylamines produces little observable effect, whereas intra-arterial injection produces local vasodilatation (408, 409), presumably by blocking adrenergic vasomotor tone. In addition, reflex cardiac compensation for acetylcholine induced or orthostatic hypotension is unaltered in animals and humans, although responses to compensatory vasomotor reflexes are blocked (158, 432). Dibenamine in doses tolerated by the intact animal has not been shown to have any direct effects on smooth muscle, either of the vascular system, gut, uterus or nictitating membrane.

Several other manifestations of reflex sympatho-adrenal discharge have also been shown to be blocked by Dibenamine (286). The increases in erythrocyte and mononuclear leucocyte counts induced by fright or struggle are abolished, presumably because reflex contraction of the spleen and other blood reservoirs is prevented. The pilomotor response of cats to cold and fright as well as to electrical stimulation of the abdominal sympathetic chain is also abolished. In unanesthetized dogs, excitement may cause a fall in blood pressure for some time after Dibenamine administration (423).

The mydriasis induced in cats by dim light is moderately inhibited and that in response to cervical sympathetic stimulation is largely abolished (286). In man Dibenamine-induced miosis is more marked (see 183), probably because of a larger sympathetic component in the control of the iris. In contrast to the effects of the ergot alkaloids (see II, D-1), the miotic effect of Dibenamine appears to result from adrenergic blockade rather than from direct stimulation of smooth muscle. Except for certain differences in the sweating response, it appears that Dibenamine in adequate dosage may produce a typical Horner's syndrome. The use of Dibenamine offers interesting possibilities for evaluating the role of adrenergic stimuli in other ocular functions. Preliminary observations indicate that Dibenamine does not significantly alter accommodation (75).

Dibenamine blockade of epinephrine stimulation of the nictitating membrane develops more slowly (295, 373) and with small doses of the agent is less complete than blockade of the pressor response (295). This suggests a greater resistance of nictitating membrane than of vascular smooth muscle to blockade, or a poorer penetration of blocking agent into the former. Ocular smooth muscle has been shown to have a similar but much greater resistanee to the effects of Priscol (see III, A-1).

It was early pointed out that Dibenamine more readily blocks responses to circulating epinephrine than those to direct sympathetic nerve activity (286).

However, it has since been contended that the failure of Dibenamine to reverse pressor responses to bilateral occlusion of the common carotid arteries and to electrical stimulation of the central stump of the severed vagus nerve indicates that the agent has little "sympatholytic" effect, *i.e.*, does not block responses to sympathetic nerve activity (408).

Because of the complexity of cardiovascular responses in the intact animal, more convincing evidence regarding the ability of Dibenamine to block sympathetic nerve activity is found in studies on the nictitating membrane of the cat. Such studies have reaffirmed the fact that responses to circulating epinephrine and norepinephrine (292) and to liver sympathin E (373) are more readily inhibited than those to nerve stimulation. However, they have also clearly demonstrated the ability of Dibenamine (292, 373) and several other members of the series (295) to inhibit the response of the nictitating membrane to cervical sympathetic nerve stimulation. The marked inhibition of responses to short periods and low frequencies of stimulation indicates that the responses of directly innervated cells are readily blocked (292). When combined with the many examples of blockade of the effects of reflex sympatho-adrenal discharge mentioned above, these observations warrant the conclusion that the β-haloalkylamine blocking agents are highly effective against most excitatory effects of sympathetic nerve activity as well as against responses to circulating sympathomimetic agents.

3. Other "excitatory" responses. Dibenamine has been shown to block and occasionally to reverse the epinephrine-induced contraction of the non-pregnant rabbit uterus in both *in vitro* and *in vivo* experiments (286). This blocking action has been confirmed by Acheson and Farah (4) who have also studied the quantitative aspects of this inhibition with very instructive results (see I, C-2; C-3). Epinephrine-induced contraction of the isolated seminal vesicle of the guinea pig is similarly inhibited (281).

All the actions of Dibenamine mentioned above involve blockade of so-called E (excitatory) effects of epinephrine or sympathin on smooth muscle. Three points of blockade involving tissues other than smooth muscle have been established. Effective Dibenamine blockade has been demonstrated for adrenergic salivary secretion (404) and sweating (183, 156, 258); for the anti-curare action of epinephrine on the myoneural junction of skeletal muscle (249) and for the arrhythmia-inducing action of adrenergic stimuli on the sensitized myocardium (see I, A–5). The complete blockade of salivary secretion in response to cervical sympathetic nerve stimulation is not surprising in view of the many known pharmacological similarities between smooth muscle contraction and salivary secretion. Dibenamine inhibition of basal sweating (at least in certain areas) and of Neo-Synephrine-induced sweating may provide a useful tool in answering the controversial question concerning the extent to which adrenergic stimulation is involved in the normal sweating pattern (see 156).

Dibenamine prevents the anti-curare action of epinephrine but not that of KCl (249). Some specific, non-vascular action is apparently involved, and a careful study of this phenomenon may help to elucidate the poorly understood role of

adrenergic factors in skeletal muscle and perhaps also in autonomic ganglionic function.

4. Cardiac responses. It was early reported that Dibenamine fails to inhibit the chronotropic and inotropic actions of epinephrine (286, 293, 298, 408), circulating sympathin (286) and reflex and direct sympathetic nerve stimulation (116, 373) on the mammalian myocardium; and these observations have been confirmed *in vitro* (5) and in unanesthetized animals (432) and man (158, 183). The tachycardia induced by epinephrine is usually exaggerated because of the absence of reflex vagal slowing. In contrast to the consistent agreement of the above observations certain reports have suggested that Dibenamine (313) and its 1-naphthylmethyl and 2-biphenoxyethyl congeners (409) inhibit the chronotropic action of stellate ganglion stimulation and epinephrine respectively. No definite explanation of these discrepant observations can be made on the basis of the very limited data supplied in the reports. However, non-adrenergic factors must have been involved. In one series of experiments (313) nitroglycerine and papaverine produced an even greater "blockade" than Dibenamine. In addition, repeated experiments on dogs employing 1-napthylmethyl and 2-substituted-phenoxyethyl derivatives of Dibenamine have uniformly shown these compounds to produce cardiac effects parallel to those of Dibenamine (293, 295). However, two non-specific actions of all active β-haloalkylamines in anesthetized animals have been found to give an apparent inhibition of epinephrine tachycardia. These are (A) a reduction in body temperature due to peripheral vasodilatation, which reduces the tachycardia in response to epinephrine and (B) a decrease in blood pressure which increases the control rate. Both of these factors reduce the extent of the increase in heart rate evoked by epinephrine, but no specific blockade of cardiac responses to adrenergic stimuli is involved.

The increase in cardiac rate after Dibenamine administration in anesthetized (298) or unanesthetized (423, 432) dogs persists for a much shorter period of time than the adrenergic blockade, and can probably be largely, if not entirely, explained on the basis of reflex compensation for the effects of Dibenamine on the peripheral vascular system. However, the marked increase in cardiac rate observed in schizophrenic patients given Dibenamine (258) may be a more complicated phenomenon.

Cardiac acceleration has been widely employed as a test for sympathin E (see 67); however, the failure of Dibenamine to block such acceleration casts doubt on the similarity of this response to the excitatory responses of smooth muscle. Resistance of the myocardium to Dibenamine blockade may be considered as support for the conclusion of Ahlquist (10), that the chronotropic and inotropic responses of the mammalian myocardium to adrenergic stimuli are more properly classed with the inhibitory responses of most smooth muscle.

In contrast to responses of the mammalian myocardium, the chronotropic response of the amphibian heart to epinephrine is blocked and even reversed by Dibenamine and congeners (295). This difference in the response of mammalian and amphibian hearts to adrenergic blockade has also been noted with several other types of adrenergic blocking agents. Its basis is unexplained.

5. Cardiac arrhythmias. Although members of the β-haloalkylamine series of adrenergic blocking agents fail to inhibit the chronotropic and positive inotropic effects of epinephrine on the mammalian myocardium, Dibenamine and all active congeners tested very effectively prevent the cardiac arrhythmias induced either by epinephrine alone in unanesthetized dogs (423) and humans (183) or by epinephrine in the presence of cyclopropane sensitization (299). In comparative studies (298) Dibenamine was found to provide much more effective protection than any of a variety of other agents tested except certain other members of the β-haloalkylamine series (293, 295). Dibenamine also inhibits ventricular fibrillation induced by epinephrine after myocardial sensitization by other volatile hydrocarbons (135) and by D.D.T. (295). Fibrillation after D.D.T. is somewhat more difficult to block with Dibenamine than the arrhythmias induced by epinephrine in the presence of most other sensitizing agents. Dibenamine has also been found to prevent effectively "spontaneous" arrhythmias in surgical patients under deep cyclopropane anesthesia (283) a fact which suggests that endogenous epinephrine or sympathin is the cause of these arrhythmias. In both man and animals complete suppression of arrhythmias was found to require larger doses of blocking agent than are necessary to reverse the pressor response to injected epinephrine.

Studies of the mechanism of Dibenamine protection against cyclopropane-epinephrine cardiac arrhythmias have revealed at least two important components. One is a direct protection of the myocardium which is complete only with doses of Dibenamine larger than those required to reverse the pressor response to injected epinephrine (283, 293, 298), but which may also be dissociated from the peripheral blockade at lower doses (135). The other factor is protection of the myocardium against the stress of increased systemic arterial pressure which would result from the peripheral effects of epinephrine in the absence of blocking agent (269, 293). The sensitizing effect of elevated systemic arterial pressure which permits arrhythmias to occur in the presence of Dibenamine is cumulative and dependent upon the absolute pressure against which the left ventricle must work, rather than upon the magnitude of change in pressure (293); however, the rate of pressure change appears to play a significant role (269).

In addition to its adrenergic blocking action, Dibenamine has certain transient direct effects on the myocardium which are shared by its adrenergically inactive hydrolysis product 2-dibenzylaminoethanol. One of these effects is "quinidine-like." These agents decrease the sinus rate of the isolated rabbit auricle and the maximum rate at which the auricle will follow electrical stimulation (5). A transient increase in the threshold for electrically-induced fibrillation has also been noted (291). Dibenamine (prior to the onset of its adrenergic blocking action) and several adrenergically inactive congeners may actually sensitize the cat myocardium to epinephrine-induced arrhythmias (295). In addition, both Dibenamine and 2-dibenzylaminoethanol sensitize the dog heart to fibrillation after coronary occlusion (295). It is quite possible that these transient non-adrenergic myocardial effects of Dibenamine are involved in the cardiovascular collapse and death which may result from rapid intravenous injection of large doses.

It may be safely concluded that the non-adrenergic actions of Dibenamine on the myocardium are unimportant in protecting the heart against cyclopropane-epinephrine arrhythmias. These non-specific actions last only an hour or two, whereas the major protection against arrhythmias persists for 24 hours (293) and may be detected for as long as 8 days (423). The direct effects are also shared almost equally by 2-dibenzylaminoethanol which provides little or no protection against cyclopropane-epinephrine arrhythmias (293, 298).

6. "Inhibitory" responses. In contrast to its effectiveness in blocking adrenergic excitatory responses, Dibenamine appears to be ineffective against inhibitory, metabolic and central nervous stimulant actions of sympathomimetic agents (286). The relaxation of rabbit, guinea pig and rat ileum produced by epinephrine *in vitro* is unaltered by concentrations of Dibenamine in the same range (1:1,000,000 to 1:15,000,000) as those blocking excitatory responses of smooth muscle (281, 286); this lack of effect has been confirmed by a study of intestinal activity in unanesthetized dogs (335). Much higher concentrations do produce a reduction in the epinephrine-induced relaxation (281), but this effect is probably non-specific; responses to acetylcholine and $BaCl_2$ are almost equally inhibited. Epinephrine-induced *relaxation* of the non-pregnant cat uterus *in situ* is unaltered (286), but epinephrine-induced *contraction* of the rabbit uterus is readily inhibited both *in vivo* and *in vitro* (4, 286). A reported reversal of the bronchodilator actions of epinephrine and norepinephrine (360) is contrary to the usual lack of effect of Dibenamine on inhibitory responses. Unfortunately, the report in question provides no data regarding the concentrations of Dibenamine required or the magnitude of the effect, factors critical for an evaluation of the results.

It is evident that the reversal of the pressor response to epinephrine depends upon the inability of Dibenamine to inhibit adrenergic vasodilatation; this is emphasized by the lack of effect of Dibenamine on the depressor response to Isuprel (N-isopropyl-norepinephrine) (293, 295, 414). As expected, Dibenamine does not alter coronary blood flow or inhibit the increase in flow induced by epinephrine (232). The reported action of di-β-chloroethyl derivatives of Dibenamine in inhibiting the depressor effects of epinephrine and Isuprel (197) is probably a reflection of the greater non-specific toxicity of these compounds which are true nitrogen mustards. Properly selected doses of N-benzyl-N,N-di(β-chloroethyl)amine produce a typical Dibenamine-type reversal of the pressor response to epinephrine but the Isuprel depressor response is unaltered. Larger doses cause a reduction in the depressor response to Isuprel, but the response to methacholine is even more reduced, a fact which indicates a non-specific toxic action (295).

7. Central nervous system and metabolic responses. Dibenamine fails to prevent epinephrine-induced hyperventilation in animals (286) or man (183). The increased activity caused by certain sympathomimetic amines in mice (281) and the "twittering" of chicks evoked by the same agents (78) are also unaltered. Dibenamine causes little reduction in the hyperglycemic response to epinephrine in animals (286, 300) and man (183), but certain congeners, notably those with 1-napthylmethyl substituents, are quite active in this regard (300). It is pos-

sible that a slight glycemic-blocking action, detectable in studies on larger groups of animals (147) may extend through the entire series. Because Dibenamine inhibits local vasoconstriction and thus permits epinephrine to be more rapidly absorbed, small changes in the maximum glycemic response after subcutaneous administration of epinephrine are difficult to evaluate. Studies employing epinephrine administered intravenously will be necessary to determine whether massive doses of Dibenamine specifically inhibit the glycemic response to epinephrine. A report (32) that the BMR is reduced by Dibenamine does not provide adequate evidence upon which to base an interpretation. It is also difficult to evaluate the significance of an increased sensitivity to anoxia noted after Dibenamine administration (101); certain other adrenergic blocking agents have been observed to have an opposite effect (106).

Dibenamine does not prevent the prolonged "lighting" of fireflies induced by amphetamine (365). Whether this response to amphetamine should be classified as metabolic or central is not clear.

8. Specificity. The specificity of the adrenergic blocking action of Dibenamine appears to be greater than that of other classes of adrenergic blocking agents studied to date. Dibenamine is ineffective against non-sympathomimetic smooth muscle stimulants. Cholinergic stimulation of the nictitating membrane (292), acetylcholine and histamine vasodepression (295, 414, 432), morphine stimulation of the intestine in unanesthetized dogs (335), acetylcholine and barium stimulation of rat intestine (281), and the pressor effects of ergotamine (217, 295), angiotonin (284, 432) and posterior pituitary (295, 408, 414, 432) are not blocked by doses of Dibenamine well above those which are effective against most adrenergic excitatory responses. The reported reversal of the pressor effect of KCl in intact animals (241) is best explained as an effect of Dibenamine on the sympatho-adrenal discharge evoked by potassium. Dibenamine also fails to block the direct vasoconstriction elicited by angiotonin and nicotine (155) in the Läwen-Trendelenburg frog-limb perfusion preparation. Dibenamine has a slight antihistaminic action and some congeners are very potent in this regard (239, 290, 292). It is of interest that in a series of over 75 β-haloalkylamines (290) no compound among the most effective antihistaminics failed to show adrenergic blocking activity. An incomplete report of inhibition of the depressor effect of stimulation of the peripheral end of the severed vagus by both Dibenamine and Priscol (255) implies some cholinergic blocking action. However, this action of Dibenamine has not been substantiated. Doses of 20 mgm./kgm. have been found to alter neither the depressor nor the decelerator responses to standardized electrical stimulation of the vagus in dogs (295).

B. Actions other than adrenergic blockade

1. Local actions. The primary side-effects of Dibenamine are local tissue damage after subcutaneous, intramuscular or intraperitoneal administration, and stimulation of the central nervous system (280, 286). The local tissue toxicity is dependent upon the β-haloalkyl grouping and reflects the relationship of these compounds to the nitrogen mustards. Local damage to vital abdominal organs

is largely responsible for the much greater toxicity of Dibenamine after intraperitoneal than after subcutaneous or slow intravenous administration (286). That intraperitoneally administered Dibenamine constitutes a considerable stress is indicated by the sharp drop in adrenal ascorbic acid which has been noted after such administration (394).

The systemic toxicity of the Dibenamine-type blocking agents is much less than that of the nitrogen mustards (about 1000 times less in the case of Dibenamine administered subcutaneously). Three factors are of importance in reducing the toxicity of these compounds (288), the presence of only a single β-haloalkyl group, a decreased aqueous solubility and a specific action of the aromatic grouping on the reactivity of the β-haloalkyl moiety (see I, D-2). Compounds with a single β-haloalkyl substituent fail to damage hemopoietic tissue even after prolonged administration.

Prolonged daily subcutaneous administration of several times the blocking dose of Dibenamine and several congeners (281, 286) causes only a slight reduction in the growth of young rats and no histologically detectable organ damage (289). Oral administration of doses below about 1 gm./kgm. appears not to produce detectable damage to the gastrointestinal tract. However, doses necessary to produce an adequate block after oral administration may cause nausea and vomiting in humans (183, 337, 379, 424). Local irritation is probably a significant factor in this reaction, as only minimal side effects accompany the production of extensive blockade when the drug is administered intravenously with care (158, 258).

2. Central nervous system. Stimulation of the central nervous system by Dibenamine in animals is manifest in hyperventilation, analepsis and even convulsions (280, 286, 298, 358). In humans, mild stimulation is frequently expressed as a specific loss of time perception (183, 337). This effect has been attributed to temporal lobe excitation (337), but the localization does not appear to be conclusively established. Nausea and vomiting may also occur after intravenous administration (183, 337), particularly if it is rapid, probably on the basis of direct medullary stimulation. Nausea and vomiting are unrelated to the adrenergic blockade. Central nervous system excitation develops earlier and terminates long before the adrenergic blockade. It is elicited even more markedly by the hydroxyl derivatives (hydrolysis products) of various members of the series (280, 286, 287). The central stimulant action of Dibenamine is accentuated by rapid intravenous injection; indeed, the intravenous toxicity may vary by as much as 1000% with variations in the rate of injection (286).

3. Kidney. On the basis of experiments on a single dog, Ogden (303) reported that Dibenamine produced a marked reduction in renal plasma flow and glomerular filtration, and histological evidence of renal cortical necrosis. Histological studies (289) carried out prior to clinical trial of Dibenamine failed to reveal any renal damage in rats, even in animals dying from the chronic administration of massive doses. However, because of the expanding clinical study of Dibenamine, a detailed attempt was made to confirm the reported renal damage in dogs (411). Six weekly intravenous injections of 20 mgm./kgm. Dibenamine

failed to produce any significant renal damage, as measured by glomerular filtration and renal plasma flow, even when each injection was completed within one minute to produce maximum side-effects including prostration of 24 to 48 hours duration. In none of the animals studied were persistent toxic effects of any kind noted. The above discrepancy in results remains unexplained, but the reported toxicity would appear to be most readily accounted for by some factor in the technic employed. The absence of any report of renal damage after fairly extensive clinical use of Dibenamine appears to confirm the lack of renal toxicity.

C. Locus and mechanism of action

1. Locus of blockade. Studies on the locus and mechanism of action of members of the Dibenamine series of blocking agents have revealed certain factors which distinguish this group of compounds from previously studied blocking agents. On the basis of both *in vitro* and *in vivo* experiments it was pointed out that Dibenamine does not affect the alteration or destruction of epinephrine, does not inhibit the release of sympathin E and does not significantly alter the responsiveness of sympathetic nerves to electrical or reflex excitation (286, 292). The agent has also been shown to inhibit adrenergic functions directly rather than by a potentiation of antagonistic cholinergic or histaminergic responses (286, 292).

Quantitative studies on the Dibenamine blockade of the response of the cat nictitating membrane to cervical sympathetic nerve stimulation (292) have indicated that alterations in the permeability of the smooth muscle cells to sympathin is not a significant factor in the blocking action. Inasmuch as Dibenamine-treated cells may contract normally in response to acetylcholine, methacholine, ergotamine, nicotine, barium, posterior pituitary and angiotonin (see I, A-8), it is also apparent that Dibenamine does not paralyze the contractile mechanism of smooth muscle cells. By a process of exclusion it must therefore be concluded that Dibenamine specifically blocks some step in the process of excitation by sympathomimetic agents which is not necessary for stimulation by other substances; this step is interposed between penetration of the cell by the exciting agent and the actual process of contraction. The cellular material or process involved in this step has come to be referred to as the specific "receptor substance" or "receptor process," terms which only thinly disguise the fact that almost nothing is known regarding the true nature of this important step in the activation of effector cells.

2. Type of blockade. Two distinguishing features of the Dibenamine type of blockade are its completeness and its duration. Extensive blockade may persist for three to four days after a single injection (183, 241, 286, 423), and residual effects after even longer periods of time have been reported (183, 423). It has also been observed (4, 281, 290) that the blocking actions of β-haloalkylamines *in vitro* are not reversed even after prolonged washing.

Studies of other series of blocking and exciting agents (acetylcholine-atropine (76), ergotamine-epinephrine (265) and diphenhydramine-histamine (413)) indi-

cate that antagonism occurs at a definite ratio for each pair of agents. This ratio, which varies somewhat with different test objects, implies a dynamic equilibrium of the blocking and exciting agent with some specific grouping or locus in the cell. In blockade of this type "effectiveness" and "potency" are essentially the same.

In the case of Dibenamine, however, it has been shown that once an adequate block has been established it cannot be overcome by massive adrenergic stimulation. This has been demonstrated for contraction of the cat nictitating membrane (292) produced by epinephrine, norepinephrine and cervical sympathetic stimulation; for the pressor action of epinephrine (4, 286) and other sympathomimetic amines (294) in cats; for contraction of the isolated rabbit uterus by epinephrine (4, 281) and for vasoconstriction by epinephrine in the Läwen-Trendelenburg frog-limb perfusion preparation (155). Such findings cannot be explained on the basis of equilibria between mediator and blocking agent for some specific receptor. In this type of blockade "effectiveness" is not a function of "potency."

3. Steps in the production of adrenergic blockade. The prolonged action of the β-haloalkylamine blocking agents might result from persistence of active drug in the body or from some early action of the drug which is only slowly reversed. The blocking action of the β-haloalkylamines is apparently exerted through highly reactive intermediates formed in the body (see I, D-1). These intermediates react rapidly and competitively with thiosulfate, and this reaction has been employed to determine the persistence of active drug in the body. If a high concentration of thiosulfate is maintained *in vivo* during the period of intermediate formation, adrenergic blockade never develops. However, if the thiosulfate concentration is allowed to fall before the completion of the reaction, blockade subsequently develops. In this manner, it has been possible to determine that the sojourn of effective amounts of Dibenamine in the body is approximately 12 to 18 hours (287). This relatively long period is presumably due to the high lipid solubility of the drug, which allows storage in fatty tissue, but it is still far short of the observed duration of blockade. The persistence of blockade beyond the period during which effective concentrations of active drug are present in the body suggests a destruction or prolonged inactivation of something in the cell which is essential for excitation by adrenergic stimuli.

The completeness and "non-equilibrium" character of the adrenergic blockade produced by the β-haloalkylamines also indicates a relatively irreversible inactivation of many or all of the cellular loci at which adrenergic stimulation must occur. However, it has been observed that in the period during which the Dibenamine blockade is developing *in vivo* (a period of at least 1½ hours) an equilibrium between epinephrine and Dibenamine does exist (288). Epinephrine administration at this time definitely reduces the effectiveness of Dibenamine. A similar equilibrium factor, manifested as a decreased sensitivity to epinephrine, has been observed in uterine strips treated with Dibenamine *in vitro* (4). From the above observations it may be concluded that the Dibenamine blockade develops in two stages. First, an approximation of Dibenamine to its site of

action. This is probably at or near the site of action of epinephrine and consequently a state of competitive equilibrium may exist. Second, an actual covalent chemical bonding of the blocking agent to some grouping near its site of action which prevents further equilibration with sympathomimetic agents and accounts for the completeness and duration of the blockade (288).

Acheson and Farah (4) observed occasional rabbit uterus preparations in which only the first step of this sequence appeared to occur, *i.e.*, the maximum control response could still be elicited if high concentrations of epinephrine were employed. These "aberrant" preparations were exposed to Dibenamine for the same period of time as others which exhibited a clear reduction in the maximum possible response (non-equilibrium blockade). The basis for the difference is not clear, but it may well involve factors (tissue pH, etc.) affecting the intermediate reactions of the β-haloalkylamines which are necessary for stable bonding (see I, D-1).

D. Relation of chemical structure to adrenergic blocking activity

1. Blocking reactions. The completeness and duration of the Dibenamine-type blockade are most readily explained on the basis of *in vivo* coupling with sulfhydryl, amino, imidazole or carboxyl groups. Such reactions have been conclusively demonstrated for various β-haloalkylamines in connection with chemical warfare work on the nitrogen mustards (128, 129). They are dependent upon the formation of highly reactive ethylenimmonium or vinyl intermediates (288, 380, 381). The activity of members of the β-haloalkylamine series of adrenergic blocking agents has been shown also to depend upon intermediate formation (287, 296). Thiosulfate reacts rapidly and competitively with both immonium and vinyl intermediates formed from nitrogen and sulfur mustards, but not directly with the parent compounds (see 288). Prior administration of thiosulfate prevents the typical blocking action of even large doses of the β-haloalkylamines, although thiosulfate does not alter the blockade once it is established. This indicates that these agents do not produce their blocking effect before the formation of intermediates. Inasmuch as the final hydrolysis products are uniformly inactive, it may be concluded that the substances immediately responsible for adrenergic blocking activity are the intermediate transformation products. The rather slow production of active intermediates *in vivo* probably also explains the slow onset of action observed even after intravenous administration.

Available information indicates that all tertiary β-haloalkylamines probably undergo qualitatively similar intermediate formation and reaction, but it is also apparent from chemical studies (see 288) that other substituents on the amine may significantly alter the reactions of the β-haloalkyl moiety.

2. Chemical requirements for activity. A detailed study of 190 compounds related to Dibenamine (288) has revealed certain very specific requirements for adrenergic blocking activity. These may be briefly summarized as follows:

(1) The compound must be a tertiary amine. All secondary amines tested were found to be inactive.

(2) The compound must have a β-haloalkyl group capable of the formation

of an active intermediate. All substitutions for the halogen were found to result in inactivation, as does removal of the halogen to the γ-position. β-γ-unsaturation which would also inhibit the formation of intermediates, completely inactivates otherwise active β-haloalkyl compounds.

(3) The compound must include an unsaturated ring structure attached to the nitrogen in such a way that hyperconjugation will act to stabilize the reactive intermediates formed. Substitutions on the unsaturated ring lead to loss of activity in proportion to the extent to which conjugation is inhibited. For example, a 4-chlorine substitution on the phenyl ring of N-benzyl-N-ethyl-β-chloroethylamine results in an 80% loss of activity, whereas a 3-chlorine substitution does not reduce and may even slightly increase activity because it favors hyperconjugation. In the presence of one β-haloalkyl and one suitable unsaturated grouping the nature of the third substituent on the nitrogen usually has only a minor influence on activity.

(4) The unsaturated ring of the compound must satisfy certain steric requirements. The exact limits of these requirements are not clear, but substitutions which would tend to be out of the plane of the ring appear to produce inactivation.

Although the above structural requirements for activity in the β-haloalkylamine series cannot be considered as definitive, they have provided a practical and accurate basis for directing the synthesis of a large number of new compounds. In addition, these requirements point to certain very interesting theoretical considerations. In the past, discussions of structure-activity relationship in series of biologically active compounds have centered almost entirely upon molecular morphology, *i.e.*, steric factors. The general form of the molecules or the distances between particular atoms or radicals have been the usual considerations. In the β-haloalkylamine series of blocking agents, however, attention has been focused upon a very different property of the molecule, *i.e.*, its chemical reactivity. From the evidence presented above it may be concluded that the specific adrenergic blocking reaction, as distinct from whatever other reactions are involved in the toxicity of the nitrogen mustards, requires a stabilization of the reactive intermediate. Why this should be necessary can at the moment be only a matter of speculation, but it is apparent that the hyperconjugation required for activity will supply sufficient stabilization energy to alter markedly the reactions of the intermediates involved in the production of the blockade.

In addition to the large series of β-haloalkylamines discussed above, several members of the group have been reported separately (197, 240). These reports also have included a few compounds with minor alterations of structure (different length alkyl chains as the third (non-critical) substituent and different substitutions in the 2 position of the phenoxyethyl substituent) which were not included in the larger series. When corrected for certain errors due to inadequate testing methods (see I, D-3), the reported activities of these additional compounds in no way alter the above conclusions regarding the structural requirements for activity.

3. Relative potencies. Determinations of the relative potencies of various members of the Dibenamine series are still unsatisfactory. Although the β-haloalkylamines have been shown to exert their blocking action by all routes of administration (286), most routes are not suitable for quantitative tests. Most of the compounds, particularly those with a favorable therapeutic index, are quite insoluble in aqueous media (288). Because of this insolubility and because of varying but quite rapid rates of decomposition (288), oral administration (240) seems to provide an inadequate basis for quantitative comparisons. The factor of solubility also limits the accuracy of tests involving subcutaneous administration; use of this route as well as adherence to a rigid time schedule probably accounts for the reported inactivity (197) of several compounds which are fully active after intravenous administration (288). The varying rates at which blockade develops (288) and the effect of epinephrine in reducing the degree of blockade during its initial stages (see I, C-3) also represent obstacles to accurate comparisons of potency.

However, certain general conclusions may be drawn concerning potency. It is apparent from all tests (197, 240, 288, 295) that Dibenamine is not the most potent member of the series. The compound N-ethyl-N-(1-naphthylmethyl)-β-chloroethylamine possesses a relatively high potency, although much of the observed advantage when administered orally (240) or subcutaneously (197) is undoubtedly due to its high aqueous solubility (which is correlated with a high toxicity (288)). When tested for peak effect after intravenous administration in cats, it appears to be somewhat less than twice as potent as Dibenamine (295). The most active compound studied to date is N-benzyl-N-(2-methylphenoxyethyl)-β-chloroethylamine which is about 5 times as potent as Dibenamine when administered intravenously (295). It is of practical importance that this agent is also one of the least toxic members of the β-haloalkylamine series.

4. Application to other fields. The reactions involved in adrenergic blockade may vary widely from one group of blocking agents to another. It is obvious that the above considerations of the mechanism of blockade cannot apply to members of such series as the ergot alkaloids, benzodioxanes or imidazolines. More subtle distinctions must also occasionally be made. For example, certain primary and secondary phenoxyethylamines without a β-haloalkyl group are adrenergic blocking agents (see VI, B-1). These compounds appeared to represent major exceptions to several of the chemical requirements for activity discussed above until it was noted (288) that the blockade produced is very different in character from that produced by Dibenamine, *i.e.*, it is very much shorter in duration and is essentially unaltered by the presence of thiosulfate.

The demonstration that precise chemical configurations are necessary for adrenergic blocking activity in the β-haloalkylamine series and the insight which this information has provided regarding the chemical reactions involved in the blocking action raise the possibility that other properties of these and related agents may yield to a similar analysis. It may be hoped that comparable studies of other properties, such as the destructive action of the nitrogen mustards on certain neoplasms (139, 144, 201, 332), may provide a theoretical basis for

syntheses leading to much-needed improvements in specificity. Current attempts to improve the specificity of the anti-neoplastic action of certain β-haloalkylamines, *e.g.*, by attaching them to carcinogens (126), have been carried out with only a very limited knowledge of the chemical basis for the desired action and have met with little success.

II. ERGOT ALKALOIDS

Older work on the ergot alkaloids has been excellently reviewed by Barger (20, 21) and will be referred to here only as necessary to clarify more recent results. The first demonstrations of specific adrenergic blockade by any agent were those of Dale (85) and Sollmann and Brown (375) who employed crude or only partially purified ergot preparations. Since then the ergot alkaloids have been extensively investigated, but few basic observations have been made which were not indicated by the classical studies of Dale (86). The alkaloids employed by Dale in these experiments were not completely purified and identified. However, they appear to have been very similar to ergotoxine and his results will be considered as representative of the actions of that agent.

Unfortunately, so much emphasis has been placed on the adrenergic blocking activity of these compounds that their other pharmacological properties frequently have been overlooked with consequent misinterpretation of experimental results. The most important side-effects are direct stimulation of smooth muscle and complex excitant and depressant effects on the central nervous system. Under many experimental conditions these side-effects are prominent with doses smaller than are required to produce significant adrenergic blockade.

A. Alkaloids lacking adrenergic blocking activity

By 1930 the pharmacology of ergotamine and ergotoxine had been extensively studied and it was generally accepted that both the oxytocic and adrenergic blocking activities of ergot resided primarily in these alkaloids. However, in 1932 Moir (27) pointed out that crude extracts of ergot produced a more potent and rapid effect on the parturient uterus than any of the known alkaloids. Investigations designed to clarify this difference in activity resulted in the almost simultaneous isolation of the alkaloid ergonovine in four separate laboratories (see 216). In ergonovine the lysergic acid nucleus is attached to a simple amino alcohol (2-aminopropanol) rather than to a polypeptide chain as in members of the ergotamine and ergotoxine groups of alkaloids (see table I).

The earliest observations on the pharmacology of ergonovine (54, 345, 347) demonstrated it to be essentially devoid of adrenergic blocking activity. A slight reduction in the pressor response to injected epinephrine is observed with large doses (345), but the effect may well be non-specific. Ergonovine is reported to be somewhat more potent than ergotamine in stimulating the guinea pig uterus *in vitro*, but to be a less active vasoconstrictor (345, 347). It has a stronger pressor effect than ergotamine in anesthetized rabbits (345), although it is less pressor than ergotoxine in pithed cats (54). The latter observation is the better index of peripheral vasoconstriction as much of the pressor effect of

this agent, at least in cats, is due to stimulation of spinal vasomotor centers. Under certain conditions ergonovine may actually produce vasodilatation in the perfused cat limb (54). On a weight basis ergonovine has been reported to be twice as potent as ergotamine or ergotoxine in producing cyanosis of the cock's comb (346). The unexpected combination of an *increased* production of cyanosis (probably a rather accurate measure of direct vasoconstriction) accompanied by a *decreased* production of gangrene (54, 345, 347) does not appear to have been adequately studied or explained. Ergonovine is of importance in the field of adrenergic blockade only in control experiments designed to determine the extent to which the effects of other ergot alkaloids are due to side-effects. It has been employed too infrequently for this purpose.

TABLE I

*Composition of the natural alkaloids of ergot**

I. Ergotamine-group		
1. Ergotamine	Lysergic acid	+ l-Phenylalanine
Ergotaminine	NH_3	
2. Ergosine	Pyruvic acid	+ l-Leucine
Ergosinine	d-Proline	
II. Ergotoxine-group		
3. Ergocristine		+ l-Phenylalanine
Ergocristinine	Lysergic acid	
4. Ergokryptine	NH_3	+ l-Leucine
Ergokryptinine	Dimethyl-pyruvic acid	
5. Ergocornine	d-Proline	+ l-Valine
Ergocorninine		
III. Ergobasine**	Lysergic acid	+ d-2-Aminopropanol
Ergobasinine		

* From Rothlin (351).

** Identical with Ergonovine.

Methergine, a partially synthetic alkaloid (385), differs from ergonovine only by the presence of an additional methylene group, and appears to have pharmacological properties almost identical with those of ergonovine (218). This compound was selected for clinical use because it was found to be the most effective uterine stimulant among members of a large series of rather simple amides of lysergic acid (385).

One partially synthetic member of the ergonovine group deserves special mention because of its remarkable effects on the central nervous system (389). The diethylamide of lysergic acid has been descriptively termed "ein Phantastikum." In man oral doses as small as 10 to 30 micrograms cause marked and highly specific psychic responses. These include a state of fluctuating euphoria and depression and alterations in almost all sensory perception. The development of vividly colored and rapidly changing visual hallucinations is particularly characteristic. In view of the fact that the active *l*-isomers of all ergot alkaloids

possess powerful central nervous system actions (see II, D-2), the properties of lysergic acid-diethylamide may be considered merely as extensions of actions common to the group.

In addition to evoking the above psychic effects, lysergic acid-diethylamide stimulates the isolated uterus only slightly less than ergonovine (385, 389) and produces marked analepsis in anesthetized animals. It is probably safe to assume that, in common with all other non-polypeptide ergot alkaloids studied, it is devoid of adrenergic blocking activity.

B. Chemistry

Since the isolation of ergonovine, two major advances have been made in the chemistry of the ergot alkaloids, both in the laboratory of Dr. Arthur Stoll. In 1943 it was reported that ergotoxine is really a complex of three alkaloids (386) which were given the names ergocornine, ergocristine and ergokryptine. Ergocristine had been isolated and characterized in 1937 (384), but at that time it was not recognized as a component of "ergotoxine." In common with ergotamine, but in contrast to ergonovine, these compounds include a polypeptide moiety (see 388). The terminal residue of the peptide chain is *d*-proline in all members of both the ergotamine and ergotoxine groups (see 383). Members of the ergotoxine complex contain dimethyl-pyruvic acid instead of pyruvic acid as in ergotamine and ergosine and differ from each other only in one amino acid residue (388) (table I). However, they do differ very significantly in their adrenergic blocking activity (55, 351, 353). The observed effect of variations in amino acid constitution upon blocking activity suggests that the synthetic substitution of still other amino acids might prove to be a fruitful line of endeavor.

A second major advance in the chemistry of the ergot alkaloids was the partial reduction of all members of the ergotamine and ergotoxine groups to form their dihydro derivatives (387). Hydrogenation decreases the ability to stimulate smooth muscle and increases the adrenergic blocking activity of all natural alkaloids. Specific properties of the reduced alkaloids will be considered together with comparable properties of the parent compounds.

C. Adrenergic blocking action

1. "Excitatory" responses. As noted above, all ergot alkaloids with significant adrenergic blocking activity contain a polypeptide side-chain. Although their potency relationships follow a general pattern in various tests, with ergotamine the least, and ergocristine and ergokryptine the most potent, this order of activity is not inviolable. Ergocornine is significantly more active than ergotamine when tested against epinephrine-induced contraction of the guinea pig seminal vesicle *in vitro* (55, 351), but the relationship is reversed when the agents are tested for their ability to antagonize the effects of epinephrine on the rabbit uterus (351, 353).

The adrenergic blocking potency of the reduced alkaloid is always greater than that of the parent compound. *In vitro* tests on the guinea pig seminal vesicle

and rabbit uterus (55, 351, 353), although not providing identical potency ratios, allow agreement on an order of increasing potency: dihydroergotamine, dihydroergocornine, dihydroergocristine and dihydroergokryptine. No quantitative comparisons of their effectiveness in blocking cardiovascular responses to adrenergic stimuli in intact animals are available, but dihydroergotamine is definitely less active than the derivatives of members of the ergotoxine group (295). Some workers have experienced difficulty in obtaining clearcut reversals of the epinephrine pressor response even with rather large doses of dihydroergotamine (304, 305).

The dihydro ergot alkaloids appear to have a relatively short duration of action *in vivo* when tested for antagonism of the pressor (224, 295, 350, 351) and rabbit uterine responses (351) to epinephrine. This duration of action might have been anticipated from the ease with which these compounds are "washed out" of *in vitro* preparations (55, 353). The adrenergic blocking action of both the natural alkaloids and their dihydro derivatives persists for a considerably shorter period of time than their other pharmacological actions.

Early experiments of Dale (86, 87) demonstrated that large doses of the ergot alkaloids produce a blockade which is effective against strong adrenergic stimuli and this property is shared by their dihydro derivatives (295). With the exception of the β-haloalkylamines, all other series of adrenergic blocking agents produce a less complete and effective blockade. Larger doses of ergotamine and ergotoxine (see 24, 86) are required to inhibit the pressor response to splanchnic stimulation than that to injected epinephrine. In the absence of evidence to the contrary it may be assumed that the dihydro derivatives behave in a qualitatively similar manner. Considerably larger doses of these agents are required to block the response of the cat's nictitating membrane to cervical sympathetic nerve stimulation than to block the response to injected epinephrine (295).

The ergot alkaloids, particularly the dihydro compounds, markedly increase the lethal dose of intravenously administered epinephrine (351). Ergotamine also reduces the amplitude and increases the rate of ureteral peristalsis *in vivo* (148). This effect could be due either to a blockade of adrenergic stimuli or to a direct musculotropic effect of the ergotamine (247). No effort was made to distinguish between these possibilities.

Jang (204) has pointed out that small doses of ergotoxine sensitize the vessels of the rabbit's ear to epinephrine and the smooth muscle of the cat's nictitating membrane to sympathetic nerve stimulation. He emphasized the structural similarity between ergotoxine and cocaine and suggested a common mode of action. However, the functional significance of this comparison may be questioned on the basis that yohimbine, phenoxyethylamines, benzodioxanes and other agents can produce similar sensitization.

Potentiation of pressor responses to sympathomimetic agents by the ergot alkaloids is enhanced by conditions which reduce their adrenergic blocking effectiveness (189). Such sensitization is particularly evident in the presence of barbiturate anesthesia which has long been known to inhibit the adrenergic

blocking action of the ergot alkaloids (see 66). It has been reported (224) that dihydroergotamine, in contrast to ergotamine, is effective in the presence of barbiturate anesthesia. However, the relative reduction in potency in the presence of pentobarbital as compared to urethane anesthesia appears to be roughly the same for a number of natural and hydrogenated alkaloids (295). The blockade produced by dihydroergotamine in the presence of pentobarbital anesthesia thus appears to be merely one expression of the increase in potency induced by hydrogenation.

It has been known for many years (321) that the ergot alkaloids may alter from depressor to pressor the response to amines such as N-ethyl- and N-isopropyl-norepinephrine and 3,4-dihydroxyephedrine; recent interest in Isuprel (N-isopropyl-norepinephrine) has led to a number of confirmatory studies (169, 217, 295). The original explanation for this phenomenon which postulated a greater blockade of inhibitory than of excitatory vascular responses by ergot now appears untenable. The pressor response to depressor amines in the presence of an ergot alkaloid is definitely sympathomimetic in nature because it is reversed by the benzodioxanes and yohimbine and potentiated by cocaine (170). Little else is known regarding its characteristics. Among the various natural and dihydrogenated alkaloids, "depressor reversal" potency is not parallel to adrenergic blocking potency (169, 295). Posterior pituitary produces a similar reversal (171).

2. Cardiac responses. Dale (86) noted that the ergot alkaloids failed significantly to alter responses of the mammalian myocardium to adrenergic stimuli and this observation has been confirmed by many workers. Dihydroergotamine (349) and other dihydro ergot alkaloids (348, 351) also fail to affect adrenergic chronotropic and inotropic cardiac responses in mammals, even when employed in massive doses. In view of the consistent results of well-controlled animal experiments the apparent inhibition of epinephrine tachycardia in a few patients by dihydroergokryptine (121) must be attributed to extraneous factors, perhaps the antagonistic effect of central vagal activation. It has been known for many years that the ergot alkaloids produce a marked cardiac slowing which is due to central vagal stimulation; the bradycardia persists after sympathectomy but not after vagotomy (273, 339). Cardiac slowing probably on the same basis, has been noted in almost all studies on the dihydro alkaloids.

In contrast to their lack of effect on responses of the mammalian heart to adrenergic stimuli, the ergot alkaloids inhibit and even reverse the action of epinephrine on the frog heart (14, 295, 343). Changes in the ionic composition of the perfusion fluid readily alter this antagonism (222), a fact which may explain the failure of some workers to observe it (24, 154). Dihydroergotamine is slightly and dihydroergocornine is considerably more potent than ergotamine in inhibiting the chronotropic response of the isolated frog heart to epinephrine (295). Negative results obtained in experiments employing dihydroergotamine in a single concentration (39) are of questionable significance.

3. "Inhibitory" responses. Dihydro derivatives of the ergot alkaloids antagonize the inhibitory response of the isolated rabbit intestine to epinephrine (351)

in much the same way that ergotamine and ergotoxine antagonize inhibitory responses (277, 308, 343, 344, 396). However, some workers have concluded that the ergot alkaloids do not produce a specific blockade of adrenergic inhibitory responses. This conclusion is based particularly upon the failure of these agents to block adrenergic inhibitory responses of the uteri of various species, particularly that of the non-pregnant cat (265, 344), and of the vascular musculature (86, 213). A report of inhibition of epinephrine-induced uterine relaxation by dihydroergotamine (39) is inconclusive. Only one dose of the blocking agent was employed and this simultaneously eliminated responses to histamine, ergonovine and ergotamine. The report fails to record the species employed. The dihydro derivatives as well as the parent alkaloids fail to block inhibitory vascular responses (349). Blockade of vasodepressor reflexes (343) does not constitute evidence of an antagonism of adrenergic inhibitory responses because of the known central depression of vasomotor reflexes by the ergot alkaloids (see II, D-2).

Intestine represents a much less suitable test object than vascular and uterine smooth muscle upon which to study adrenergic inhibitory responses. The abundance of intramural parasympathetic ganglia in the intestine and the known effect of the ergot alkaloids in potentiating cholinergic responses (86, 188, 237, 342) make it impossible to attribute alterations of epinephrine-induced intestinal relaxation to specific adrenergic blockade. Even the uteri of certain species, *e.g.*, guinea pig (7), show an apparent inhibition and reversal of epinephrine relaxation in the presence of eserine, *i.e.*, after the potentiation of cholinergic effects. Ergotamine definitely enhances the motility of the intact intestine (6, 356, 405). However, doses which alone are completely ineffective markedly potentiate the action of neostigmine (6), cocaine fails to inhibit motility under conditions where ergotamine produces a significant stimulant effect (405) and the response to ergotamine is blocked by atropine (356). Blockade of epinephrine-induced inhibition of the rabbit intestine and of epinephrine-induced contraction of the rabbit uterus is accomplished with essentially the same concentrations of the ergot alkaloids; but adequate data have not been presented to indicate that the potency ratios of the various alkaloids and their dihydro derivatives are the same when tested against excitatory and inhibitory responses. Much more experimental work will be necessary before it can be stated with any assurance that antagonism to inhibitory responses by ergot alkaloids represents a specific adrenergic blockade.

4. Metabolic responses. The ergot alkaloids block epinephrine-induced hyperglycemia more effectively than do other adrenergic blocking agents (see 343). Dihydro derivatives of members of the ergotoxine group also block this response (121, 350, 351), but the potency of this effect is not parallel to adrenergic blocking potency as determined by other tests (351). One report indicates that dihydroergotamine may be twice as effective as ergotamine in blocking the glycemic response to epinephrine in humans (378). It has been reported that adrenergically inactive ergonovine fails to block and may actually enhance the glycemic response to epinephrine (347), but the doses used were not specified.

Ergonovine in doses of 3.0 mgm./kgm. subcutaneously provides effective blockade of the glycemic response to epinephrine in rabbits (300). The specificity and mechanism of the ergot blockade of the glycemic response to epinephrine are questioned by the activity of ergonovine, and by the fact that posterior pituitary causes a comparable reduction in the glycemic response to epinephrine, an effect which is additive with that of ergotoxine (228). As in the case of blockade of inhibitory adrenergic responses, the available evidence is not adequate to allow a definite statement that inhibition of epinephrine-induced glycemia is due to a specific adrenergic blockade comparable to that produced in smooth muscle.

D. Actions other than adrenergic blockade

1. Smooth muscle. One of the most characteristic effects of the ergot alkaloids is a direct stimulation of smooth muscle in many organs (86). This effect was known long before the demonstration of adrenergic blockade by these agents (20, 21) and under most conditions it occurs with smaller doses of the natural ergot alkaloids than are required to produce adrenergic blockade. In the case of ergot alkaloids lacking a peptide substituent, uterine stimulation is prominent in the complete absence of adrenergic blocking activity (see II, A). It has been suggested that the stimulation of smooth muscle by the ergot alkaloids is "sympathomimetic" in nature, but the fact that it is unaltered by Dibenamine (31, 217, 295) is strong evidence against this interpretation.

Hydrogenation produces a marked reduction in the uterine stimulant action of all the ergot alkaloids studied. The dihydrogenated alkaloids not only fail to cause contraction of rabbit or guinea pig uteri *in vitro* (305, 348, 350, 351) or induce labor in pregnant rats (305), but also tend to diminish uterine tone and activity and to inhibit the excitant effects of ergotamine and ergonovine on the uterus (348, 350, 351). Inhibition of the stimulant effect of the natural alkaloids may be related to the previously observed block by ergotamine of its own vasoconstrictor action (24, 237). The mechanism of this effect has not been studied, but it probably does not constitute proof of the "sympathomimetic" nature of smooth muscle stimulation by this agent. Hydrogenation may not completely eliminate oxytocic action, for the induction of labor pains in a pregnant woman given dihydroergotamine for migraine has been reported (398).

Hydrogenation also reduces but does not eliminate the vasoconstrictor actions of the ergot alkaloids, as measured by their pressor action in pithed cats (350, 351). Although dihydroergotamine is less vasospastic than the parent alkaloid it retains considerable constrictor activity in man (37, 38). Dihydroergocornine fails to evoke detectable vasoconstriction in anesthetized dogs (211) and plethysmographic studies (34, 37, 38) indicate that it has little or no direct vasoconstrictor action in unanesthetized man. Only in the pithed cat may a residual vasoconstrictor action of dihydroergocornine be detected (351). Elimination of the prominent vasospastic action characteristic of the natural ergot alkaloids may provide an opportunity to explain certain discrepancies between the actions of different groups of adrenergic blocking agents, *e.g.*, the greater inhibition of the vasopressor action of nicotine by ergotamine (86, 173) than by Dibenamine

(408), 883F, 933F and yohimbine (174, 407). This difference may be unrelated to variations in adrenergic blocking activity and may depend upon differences in the peripheral action of nicotine upon relaxed (after Dibenamine) as compared to constricted (after ergotamine) vessels.

Production of cyanosis and gangrene in the rat's tail or cock's comb is a prominent response to the natural ergot alkaloids, and the production of cyanosis in the cock's comb was for many years the official assay method for extract of ergot (see U.S.P. XII). The early development of a transient cyanosis is probably largely due to a direct vasoconstrictor action, but the basis for the late development of "thromboangiitis" and gangrene (242, 425) is not clear. It is not necessarily related to the extent of the initial cyanosis (see II, A). Although thrombosis is characteristic of the pathological picture in ergot gangrene, it is apparently of limited etiological significance because the incidence of gangrene is completely unaltered by heparin and dicoumarol (16). Hyperthyroidism definitely sensitizes rats and probably also human beings to the production of ergot gangrene (150). It is not clear why gangrene may develop several days after a single injection of ergot although the alkaloids appear to be destroyed very rapidly (223, 352). Dihydroergotamine has very much less tendency than ergotamine to produce gangrene (305), and the other hydrogenated alkaloids appear to have so little direct effect on the peripheral vascular system that thorough tests of their ability to produce gangrene have not been undertaken.

It is well established that ergotamine may act as a direct coronary vasoconstrictor (213). It hastens the development of pain in patients with angina pectoris breathing an atmosphere low in oxygen (138) and may even cause anginal pain in susceptible patients at rest (398). The report of an increased coronary blood flow induced in man by dihydroergotamine (377) is based only upon electrocardiographic changes. No pharmacological or physiological basis for such an action is apparent, and in view of the many other direct and indirect cardiac effects of the ergot alkaloids (see II, C-2; D-2 and VII, E), alterations in the electrocardiogram appear to provide an inadequate basis for adducing changes in coronary blood flow. More reliable testing methods indicate that ergotamine and dihydroergotamine increase cerebral blood flow in the absence of changes in systemic arterial pressure (3), but an evaluation of this effect must await a full report of the observations. It is possible that this effect on cerebral blood flow is involved in the reported protection against anoxia afforded by ergotamine (106). However, adrenergic blockade *per se* does not provide protection against anoxia; Dibenamine has been reported even to produce sensitization (101).

The ergot alkaloids cause mydriasis in rodents, in both sympathetically denervated and normal eyes (98); undoubtedly as a result of direct smooth muscle stimulation (22). The reaction has been well quantitated for ergotoxine and ergonovine (26), and similar tests on the dihydro alkaloids would be of considerable interest. In the cat, miosis is produced by ergotamine and ergotoxine (86, 426), largely on the basis of a direct stimulation of the iris sphincter (426). In this case inhibition of sympathetic dilator tone may also be involved but

appears to be insignificant. The species differences in response of the iris to ergot alkaloids may be due to differences in the relative strengths of the dilator and constrictor muscles. The report that ergonovine produces mydriasis rather than miosis in the cat (345) unfortunately does not include experimental data upon which an evaluation of this unexpected result might be based. However, the evidence of hypothalamic stimulation seen with toxic doses of ergonovine (347) may provide a clue to the mechanism of this response.

The action of the ergot alkaloids in producing perforating gastric ulcers after both oral and intravenous administration (342, 347) has been inadequately studied. Vascular spasm and pylorospasm would appear to be possible etiological factors deserving of careful study. No theoretical basis for the therapeutic administration of ergotamine in peptic ulcer (103) is evident.

2. Central nervous system. The effects of ergot alkaloids on the central nervous system represent a highly complex mixture of stimulation and depression (see 339 for earlier work). Unfortunately, only limited data on the central effects of the dihydro alkaloids are now available. Their acute intravenous toxicity is significantly reduced as compared to the toxicity of the parent compounds (305, 350, 351), but the extent to which this is a measure of central nervous system action is not clear. Somnolence and general sedation are prominent among the signs of acute ergot toxicity in monkeys (420), and injection of ergotamine base into the third ventricle of cats leads to prolonged, and apparently normal sleep (190). The fall in blood pressure regularly noted in intact animals after intravenous administration of the dihydrogenated alkaloids has been attributed to direct depression of the vasomotor center and stimulation of the "vasodepressor" center (351). Elimination of this hypotensive effect by spinal cord section above T_6 (35) provides convincing evidence of its central origin. A marked bradycardia is also produced by relatively small doses of the ergot alkaloids and their dihydro derivatives (36, 38, 121, 342, 348, 350). Ergonovine is about one-half as potent as ergotamine in producing this response (231). This bradycardia is due to a direct stimulation of vagal centers rather than to sympathetic blockade, because it persists after high spinal cord section (35) or sympathetic denervation of the heart and is abolished by vagotomy (273, 339). The central locus and the non-specificity of the depressor effects of the ergot alkaloids is well illustrated by the fact that very small doses of ergotoxine injected intracisternally cause a marked fall in blood pressure and also inhibit the pressor response to KCl administered by the same route (107).

Depressant effects on the central nervous system adequately explain the fall in blood pressure, the orthostatic hypotension and the decreased vasomotor reflexes in human subjects given doses of the dihydro ergot derivatives which are inadequate to produce adrenergic blockade (36, 37, 38, 121). These observations suggest that hydrogenation increases the depressant action of the alkaloids on the central nervous system. However, the apparently greater central depressant effect of these derivatives, as measured by cardiovascular indices, may merely be due to their inability to evoke peripheral vasoconstriction. This problem would seem to warrant careful investigation by more direct methods

than have been employed. Ergonovine produces quite significant depression of vasomotor and respiratory centers in anesthetized animals, although it elicits an increase in pressure (347).

It has been reported (350) that hydrogenation reduces the ability of the ergot alkaloids to depress the respiratory center, but that it does not alter their vasomotor depressant action. It is unfortunate that this report does not include or refer to data regarding the extent and significance of this differential effect. Dihydroergotamine and dihydroergocornine produce less respiratory depression in anesthetized dogs than does ergotamine (211). However, all of the derived alkaloids, in the doses required to block responses to sympathetic nerve stimulation do produce marked respiratory depression in anesthetized cats (295).

Ergotoxine produces a marked stimulation of somatic motor neurones (339), but the extent to which this action is shared by the dihydro alkaloids has not been determined. Reports that dihydroergotamine is 6 to 8 times less emetic than ergotamine (348, 350) do not appear to have been substantiated. The ratio has since been observed to be about 1:2 in puppies (305) and not greater than 1:2 in patients with migraine (398). Other dihydro derivatives also appear to have a strong emetic action in man (34, 36, 37, 121, 167); as little as 0.3 mgm. of dihydroergocornine may produce vomiting (34, 36). A report of antagonism to apomorphine emesis in dogs by supra-emetic doses of dihydroergotamine is incomplete (224), but this antagonism appears to be due to brain-stem depression; ergotamine produces an exactly comparable effect (73). Ergotamine raises the electroshock seizure threshold in rabbits (162), an action which is obviously not due to adrenergic blockade because ergonovine has an equal effect.

The ergot alkaloids rather specifically depress certain centers in the brain stem. The effects of CO_2 on blood pressure and respiration are readily inhibited, apparently by decreasing the responsiveness of medullary centers to direct stimulation by CO_2 (235). Depression of the response to CO_2 occurs with doses of ergotamine which do not inhibit chemoreceptor reflexes or prevent the vascular effects of epinephrine or splanchnic nerve stimulation. Dihydroergotamine appears to be somewhat less effective than ergotamine in reducing medullary sensitivity to CO_2 (110, 350). Other dihydro ergot alkaloids have not been tested for this action.

Ergot alkaloids also inhibit vascular responses to carotid baroreceptor (110, 111, 112) and chemoreceptor (137, 252) reflexes in doses which do not significantly alter vascular responses to injected epinephrine or direct splanchnic nerve stimulation. Dihydroergotamine appears to be about as effective as ergotamine in this respect, although it has been stated without the presentation of substantiating data, that dihydroergotamine and dihydroergocornine produce somewhat less depression of carotid sinus reflexes than does ergotamine (350). The complete dissociation of this inhibition of vasomotor reflexes on the basis of brain-stem depression from adrenergic blockade is emphasized by the fact that adrenergically inactive ergonovine is about one-half as potent as ergotamine in depressing responses to carotid sinus nerve stimulation (347).

Electrical recording from the splanchnic nerves has indicated that the flow of

impulses induced by carotid chemoreceptor stimulation is increased rather than decreased by ergotamine (137). This observation is difficult to interpret, but it does not appear to be evidence for a primarily peripheral site of action of the ergot alkaloids in altering cardiovascular reflexes. The frequently observed inhibition of reflex cardiovascular responses by the dihydro ergot alkaloids in man (see VII, A; D-3; E) is undoubtedly due to the central nervous system effects described above and not to a "sympatholytic" action as is so frequently stated.

An increased body temperature evoked by the administration of relatively pure ergot alkaloid preparations was noted early in the study of these compounds (see 22). This effect is probably unrelated to adrenergic blockade because it is also produced by adrenergically inactive ergonovine (26, 54, 345) and Methergine (218). It has recently been reported (348, 350, 351) that ergotamine and ergocristine cause hyperthermia while their dihydro derivatives produce hypothermia. However, the specificity of these differences in action is questioned by experiments which indicate that ergotoxine produces a non-specific impairment of temperature regulation in rats, with hyperthermia observed at environmental temperatures above 28°C and hypothermia at low temperatures (56). Impaired temperature regulation after ergotamine was previously observed in cats (359). The absence of a specific effect of the ergot alkaloids on heat production or dissipation is suggested also by the observation that neither ergotamine nor dihydroergotamine significantly alters the hyperthermic response to dinitrophenol (127). Lack of adequate control of ambient temperature may be responsible for many of the divergent results which appear in the literature on this subject.

3. Miscellaneous effects. The reported diuretic and antidiuretic properties of several ergot alkaloids (434, 435, 436) have not been re-evaluated with modern clearance techniques, and the alleged differences between various ergot preparations are inexplicable on the basis of published data. Ergotamine and dihydroergotamine inhibit both the internal and external secretions of the pancreas (149). The secretory response to secretin, but not that to epinine is inhibited. The reported inhibition of the bronchoconstrictor response to acetylcholine in the guinea pig by ergotoxine (182) is difficult to interpret, particularly because there is evidence (see II, C-3) that the ergot alkaloids potentiate many responses to acetylcholine and vagal stimulation.

E. Fate and excretion. Attempts to elucidate the fate and excretion of the ergot alkaloids by the use of sensitive biological tests (adrenergic blocking action on the rabbit uterus or guinea pig seminal vesicle) (352) have provided primarily negative information. Urinary excretion is insignificant. Parenchymatous organs (particularly the liver) apparently contain larger concentrations of alkaloid than does the circulating blood. However, tests carried out at intervals between 5 and 60 minutes after intravenous injection were never capable of detecting a total of more than 5% of the administered alkaloid. Penetration of significant amounts of the alkaloids into brain and cerebrospinal fluid could not be demonstrated. Studies of ergot metabolism in which a colorimetric assay was employed provided somewhat higher recoveries in several organs (223), and

demonstrated that chloroform or phosphorus liver damage, but not bilateral nephrectomy significantly slows destruction of the alkaloids. Inasmuch as the color test employed is specific for the 2-unsubstituted indol group of the lysergic acid nucleus, these results indicate that the nucleus itself is rapidly degraded in the body.

III. IMIDAZOLINES

The pharmacology of Priscol (2-benzyl-2-imidazoline) was first reported by Hartmann and Isler in 1939 (164) who found it to be the most active depressor agent in a large series of 2-substituted imidazolines. They did not, however, demonstrate adrenergic blockade and compared the actions of Priscol with those of histamine, a comparison probably suggested by the common imidazole radical. Meier and Müller (262) made similar observations, and also noted a number of parasympathomimetic actions. They reported that Priscol did not effectively antagonize epinephrine vasoconstriction in the perfused rabbit ear, or prevent the pressor response to epinephrine unless the two were administered simultaneously.

A. Adrenergic blocking action

1. "Excitatory" responses. The first recognition of the adrenergic blocking action of Priscol appears in the work of Schnetz and Fluch (363), who observed that it blocks the vasoconstrictor action of epinephrine in the Läwen-Trendelenburg frog-leg perfusion preparation. Meyer (266) and Meier and Meyer (261) later observed that Priscol produces marked vasodilatation, not blocked by atropine, in the isolated rabbit limb perfused with epinephrine, and Hermann and coworkers (185) noted that Priscol inhibits and occasionally even reverses the pressor response to stimulation of the peripheral stump of the severed splanchnic nerves.

The adrenergic blocking action of Priscol has been studied on many test objects. Inhibition of epinephrine vasoconstriction in discrete vascular beds or in intact animals has been demonstrated by numerous investigators (11, 71, 145, 164, 226, 261, 276, 363); but in many reports on the depressor and vasodilator actions no real attempt was made to distinguish between the effects of adrenergic blockade and direct vasodilatation. The locus of Priscol vasodilatation, both direct and secondary to adrenergic blockade, is largely peripheral. Vasodilatation occurs after local application (140, 164, 262, 363, 412), iontophoresis (412) and intra-arterial injection or perfusion (11, 262, 266). It has also been suggested (262) that a medullo-spinal vasodilating mechanism is involved, but convincing proof of this contention has not been presented. An important direct action of Priscol on peripheral vessels (see also III, B-1; B-3; VII-A) is suggested by the fact that it causes vasodilatation in some previously sympathectomized limbs (151, 236), induces coronary dilatation (11) and evokes peripheral vasodilatation in doses which do not inhibit responses to even small amounts of injected epinephrine (184). Failure to demonstrate direct vasodilatation in perfused limbs in which the vessels are probably already maximally dilated (266) is not

convincing evidence against such an effect. Vasodilatation caused by a single injection of Priscol in the presence of an epinephrine perfusion (266) or infusion (276) is very transient.

Priscol inhibition of the pressor response to both epinephrine and electrical stimulation of the splanchnic nerves in cats has recently been studied quantitatively (71). It was found that distinctly higher doses of the blocking agent are required to inhibit responses to nerve activity than to block those to circulating epinephrine, a relationship also observed in dogs (185, 187). A similar differential was noted in the inhibition of salivary secretion. It has also been demonstrated that larger doses of Priscol are required to inhibit responses to pressor reflexes than to block pressor responses to epinephrine (187, 254). Epinephrine-induced contractions of the rabbit uterus *in vitro* and the pregnant dog uterus *in situ* are also readily inhibited and reversed (11).

Mydriasis in response to cervical sympathetic nerve stimulation is unaltered and that to injected epinephrine is only slightly reduced by Priscol (71, 187). Epinephrine-induced contraction of iris muscles *in vitro* is also resistant to Priscol blockade (140). In intact animals (140, 187) and man (151) mydriasis rather than miosis may be produced, an effect which has been attributed to inhibition of the response of the iris sphincter to normally prevalent cholinergic stimuli (140). A cholinergic blocking action is also implied in the reported inhibition of the vasodepressor response to stimulation of the peripheral end of the severed vagus (255). These observations are at variance with reports of potentiation by Priscol of cholinergic responses of other organs (145), and require confirmation.

The observation that Priscol transforms epinephrine vasodilatation in the femoral and mesenteric circulations to vasoconstriction (260) has not been repeated or adequately explained. Other workers (145) have noted the expected change in response to epinephrine from vasoconstriction to vasodilatation after treatment with Priscol. A more active congener of Priscol (see III, C) also fails to alter the response to epinephrine from dilator to constrictor in any vascular bed (263).

Orally administered Priscol effectively protects mice against epinephrine toxicity (240). This action probably depends upon both the adrenergic blocking and the direct vasodilating actions of Priscol. The drug also transforms epinephrine apnea to hyperpnea (185). The basis for this action is not clear, but it is not dependent on inhibition of the pressor response to epinephrine because it is evident after denervation of the baroreceptor areas. Priscol does not alter the hyperglycemic action of epinephrine and the drug itself produces an increase in blood glucose (187).

In contrast to the β-haloalkylamines, Priscol has a relatively short duration of action (70, 217, 295) and a limited effectiveness against responses to large doses of epinephrine (145, 295, 298). An "equilibrium" type blockade appears to be involved in the Priscol inhibition of responses to epinephrine (145, 295) and to a large series of other sympathomimetic amines (11). In this respect the imidazolines are comparable to the benzodioxane blocking agents rather than to the β-haloalkylamines.

2. Cardiac responses. The effects of epinephrine on the mammalian heart either isolated or *in situ* are not inhibited by Priscol (11, 145, 259, 298). No explanation for a report of reversal of the cardiac response to stellate ganglion stimulation (313) is available; but the observation probably depends on technical factors (see I, A-4) because nitroglycerin and papaverine also produced apparent adrenergic blockade in these experiments. Priscol potentiates the myocardial stimulation and coronary dilatation evoked by epinephrine (11). In contrast to members of several other series of adrenergic blocking agents Priscol does not effectively antagonize the response of the frog heart to epinephrine (276, 295).

Although Priscol does not inhibit epinephrine-induced tachycardia in dogs, it does provide marked protection against cyclopropane-epinephrine cardiac arrhythmias (298). The protection is essentially the same as that observed with Dibenamine when small challenge doses of epinephrine are employed; but larger doses of epinephrine overcome the Priscol protection whereas the Dibenamine protection remains essentially complete. Larger doses of Priscol are required to protect against epinephrine-induced cardiac arrhythmias than to inhibit the epinephrine pressor response.

3. "Inhibitory" responses. Inhibitory responses (non-pregnant cat uterus, dog, cat, guinea pig and rat intestine) to epinephrine are not blocked by Priscol (11, 187, 276). The agent appears to inhibit slightly the epinephrine-induced relaxation of some rabbit ileum preparations, and of the cat intestine *in vivo* (145) and *in vitro* (276). However, on the rabbit ileum this antagonism is very irregular and no greater than that exerted by ephedrine and Neo-Synephrine. Inhibition of epinephrine-induced relaxation of the cat intestine *in vitro* requires extremely high doses. Responses to vasodepressor amines are not altered by Priscol (11, 295).

4. Specificity. Priscol does not inhibit the pressor response to posterior pituitary, renin or angiotonin (11, 71). Histamine vasoconstriction in the perfused rabbit limb is not altered by doses of Priscol which inhibit the response to epinephrine, and the vasoconstrictor effect of $BaCl_2$ may actually be enhanced (266). However, high concentrations of Priscol can prevent histamine vasoconstriction in the perfused rabbit ear (145). This action is not surprising when one considers the close relationship of Priscol to the active antihistaminic Antistine.

B. Actions other than adrenergic blockade

In addition to their adrenergic blocking action, the imidazoline blocking agents appear to have some direct effect upon almost every organ in the body. These effects are highly varied; they have been assigned to categories such as "sympathomimetic" and "parasympathomimetic" by various investigators primarily as a matter of convenience. Such a classification should not carry implications regarding the intimate mode of action involved.

The lack of specificity of the imidazoline adrenergic blocking agents is not surprising since only slight changes in structure produce compounds with actions which are predominately antihistaminic (Antistine, 2-(N-benzylanilinomethyl-

methyl)imidazoline (123)) or sympathomimetic (Privine, 2-napthylmethyl-imidazoline (82) and Otrivine, 2-phenylaminomethylimadazoline (309)). Under appropriate conditions large doses of Privine may exhibit adrenergic blocking activity by reversing the pressor response to epinephrine (105, 260). N-methyl-substitution of Priscol endows it with pressor properties (145, 164) which are secondary to a nicotinic action on sympathetic ganglia (145). Actions of Priscol other than adrenergic blockade are particularly well illustrated in the observations of Ahlquist and coworkers (11).

1. Sympathomimetic effects. Several properties of Priscol have been described as sympathomimetic. This agent elicits a tachycardia and increased stroke volume in intact dogs (25, 298) and tachycardia, coronary dilatation and increased cardiac output in isolated mammalian hearts (11, 23, 145, 333). Priscol-induced cardiac stimulation has also been reported with therapeutic doses in man (11, 184, 276), although other workers (151) have observed only minimal tachycardia with tolerated doses. Tachycardia is a prominent sign of Priscol toxicity in man (272). Reasons for the failure of earlier workers to demonstrate significant coronary dilatation and myocardial stimulation in isolated mammalian hearts (262) and heart-lung preparations (166) are not apparent, although recent observations (145) indicate that some species differences may have been involved. Stimulation of the isolated guinea pig heart is such a sensitive test for Priscol that it has been employed as an assay in experiments designed to determine the fate of this agent in the body (333). Priscol is less effective in stimulating the frog heart and higher concentrations depress it (25, 164, 276, 295).

In dogs the net cardiovascular response to Priscol may actually be an increase in systemic arterial pressure (11, 185, 254, 262), probably because of dominance of an increased cardiac output (frequently more than doubled by moderate doses) over the peripheral vasodilatation (11). Therapeutic doses of Priscol also have been noted to cause an alarming hypertension in man (28), probably on the same basis. Increased peripheral resistance is probably not a significant factor in the hypertensive action of Priscol in the dog, although it may occur in the rabbit (11) (see III, B-3).

Priscol potentiates the myocardial stimulation and coronary dilatation caused by epinephrine (11). It may also produce transient relaxation of the gastrointestinal musculature (11). Whether the pilomotor response to Priscol which is prominent in both animals (262, 276) and man (52, 151, 184, 427), is direct or reflex in nature cannot be stated on the basis of the published data.

Evidence for the sympathomimetic nature of the above enumerated effects of Priscol is largely indirect and negative. In general, inclusion in this category has been based upon the similarity of the responses to those evoked by epinephrine, and upon the failure of atropine to block them.

2. Parasympathomimetic effects. Priscol may be compared chemically to pilocarpine on the basis of the imidazole grouping, and this radical may be important for its parasympathomimetic properties. Parasympathomimetic actions of Priscol include cardiac slowing (observed only in rabbits (11)) and stimulation

of the intact gastrointestinal tract (11, 145, 184, 276, 428). The responses are blocked by atropine, a property which is usually considered to be evidence for their cholinergic nature. A miotic effect (71) and stimulation of salivary (71, 187), pancreatic (187) and respiratory tract (298) secretion have also been reported, but the influence of atropine on these effects has not been studied. An overdose of Priscol was noted to produce profuse sweating in man (272).

Priscol evokes submaxillary secretion by a direct action in the gland cells because it is observed even after denervation (187). Priscol potentiates the responses of a number of organs to acetylcholine (145) perhaps through an inhibition of cholinesterase (266, 361).

3. Histamine-like effects. Certain responses to Priscol have also been attributed to histamine-like properties. These include vasoconstriction in the rabbit (11, 276), stimulation of the isolated gut not blocked by atropine (11, 266), stimulation of the uteri of dogs, cats, guinea pigs and rabbits *in vivo* and *in vitro* (11, 276) and stimulation of the intestine and nictitating membrane of the intact cat (145). Priscol potentiates the effects of histamine on several of these structures. Peripheral vasodilatation is prominent (11, 71, 164, 261, 262), is not blocked by atropine and appears with doses of the drug which do not inhibit the pressor response to small amounts of epinephrine (184). Some workers have classified this action as sympathomimetic (11). Priscol-induced vasoconstriction in the dog spleen and kidney (185, 187) may belong in this category, but other workers have failed to confirm these effects (145). No attempt has yet been made to employ antihistiminic drugs in analyzing the above "histamine-like" actions of Priscol.

Priscol stimulates gastric secretion of both acid and pepsin in man and animals (52, 145, 364, 395). It is only slightly less effective than histamine, and has been substituted for the latter as a test for gastric secretion in man with apparent success (52, 278, 364, 395).

4. Miscellaneous effects. Priscol inhibits oxidative metabolism in kidney slices and is destroyed by liver slices (23, 333). The pharmacological significance of these observations is not clear. Priscol is also an active inhibitor of monoamine and diamine oxidases (361), but this property appears to be unrelated to adrenergic blockade. The sympathomimetic imidazolines Privine and Otrivine produce a similar inhibition.

C. Other imidazolines with adrenergic blocking activity. Although many congeners of Priscol have been synthesized, the adrenergic blocking properties of only 2-(N,p-tolyl-N-(m'oxy-phenyl)-aminomethyl)-imidazoline (#7337) has received detailed attention (263). This agent is more potent than Priscol in blocking the pressor response to epinephrine and the salivary secretion induced by epinephrine and cervical sympathetic nerve stimulation. It is also a very effective antagonist of epinephrine-induced contraction of the guinea pig seminal vesicle *in vitro*. In contrast to Priscol, #7337 blocks mydriasis in response to cervical sympathetic stimulation. However, large doses are required and this effect may only be a reflection of quantitative differences in potency. The ad-

renergic blockade produced appears to be quite similar to that of Priscol in that it is not effective against large doses of epinephrine and its duration is relatively short (295). Metabolic responses to epinephrine are not blocked by #7337, and limited studies have not demonstrated antagonism of inhibitory responses.

Unfortunately, insofar as #7337 has been studied, it appears to possess only slightly greater specificity than Priscol. The direct depressor effect is only slightly decreased and appears with doses which produce little alteration of carotid sinus pressor reflexes. Cardiac stimulation in the dog is only slightly reduced. Stimulation of the guinea-pig ileum *in vitro* is much less than observed with comparable doses of Priscol (295), but the intestine *in situ* is stimulated and diarrhea is prominent after the administration of relatively small doses to unanesthetized animals (263).

IV. BENZODIOXANES

The past decade has produced few fundamental changes in our understanding of the adrenergic blocking activity of members of the benzodioxane series (see 47, 407). Coumarane derivatives (see 18, 47, 49) have been studied much less thoroughly and have received little recent attention. Most of their properties are similar to those of the benzodioxanes and they will not be discussed separately.

A. Adrenergic blocking action

1. "Excitatory" responses. Since the first report of the adrenergic blocking action of the benzodioxanes (118, numerous experiments have demonstrated blockade of excitatory adrenergic responses of the general circulation, renal vascular bed, nictitating membrane, iris and certain uteri. Some members of the series are effective primarily against responses to circulating sympathomimetic agents (933F type) while others are effective against responses to both circulating mediators and sympathetic nerve activity (883F type) (see 19). However, all combinations of intensities of these two properties are present within the series (47). Responses to circulating mediator (including sympathin (17, 192, 238) and norepinephrine (264)) are always blocked more readily than responses to sympathetic nerve stimulation, even in the case of the salivary glands where nerve endings are supposed to be extracellular (275). Even 933F produces significant blockade of responses to sympathetic nerve stimulation (17, 18, 338) and to carotid cardiovascular reflexes (252, 407). Conversely, 883F is quite ineffective against the excitatory responses of some organs (*e.g.*, the iris) to sympathetic nerve stimulation (369). Low concentrations of 933F potentiate the effects of epinephrine and sympathetic nerve stimulation on the perfused rabbit ear (204). Here also, higher concentrations are required to alter the response to nerve stimulation than that to injected epinephrine. Efforts to localize the action of certain benzodioxanes and other agents at the cell surface on the basis of quantitative differences in effectiveness against responses to circulating mediator and sympathetic nerve activity lack convincing support (see 275, 292).

The adrenergic blockade produced by the benzodioxanes is rather weak, in that it is readily overcome by large doses of epinephrine (295) and rapidly disappears in the presence of a continuous epinephrine infusion (186). The *l*-form of 883F is about six times as potent in producing adrenergic blockade, and twice as toxic as the *d*-isomer (46). Other members of the series have not been resolved.

It has recently been reported (240) that orally administered 883F or 933F fails to protect against epinephrine toxicity in mice, and 933F was also found to be ineffective when administered in large doses subcutaneously one hour prior to the epinephrine. Inasmuch as 933F provides definite protection in rats when a shorter time interval is employed (312), and in mice (see 47), the only immediate explanation for the reported negative results appears to be that the animals were not tested soon enough after administration to detect the rather transient blockade produced by these agents. Unfortunately, no attempt has been made to determine the time of peak effect.

Stimulation of the central nervous system by sympathomimetic amines is not blocked by 933F or 883F (78).

Responses of the isolated frog heart to epinephrine and sympathin are inhibited or reversed by the benzodioxanes (204, 238, 367, 368), although some workers (194) have failed to confirm this action. Changes in the composition of the perfusion medium may greatly modify the ability of the ergot alkaloids to block adrenergic responses of the frog heart (see II, C-2), and it is possible that a similar factor may explain the divergent results obtained with the benzodioxanes. The effects of epinephrine on the mammalian myocardium are not specifically inhibited (194, 253, 407).

Benzodioxane derivatives have been reported in common with ergotamine and certain phenoxyethylamines, to prolong significantly the bleeding time, presumably by inhibiting reflex sympathetic vasoconstriction (95). This action is not shared by related compounds (such as 933F) which are relatively ineffective in blocking responses to sympathetic nerve activity. The fact that benzodioxanes fail to alter the hemostatic effect of injected epinephrine (94) appears to be good evidence that an altered conversion of epinephrine or sympathin to adrenochrome is not involved in the prolongation of bleeding time reported above. Although 933F has been reported to promote the inactivation of epinephrine *in vitro* (275), there is no evidence that this adrenolytic action is involved in the production of adrenergic blockade. Yohimbine and phenoxyethylamines (which produce an adrenergic blockade very similar to that of the benzodioxanes) have been shown not to alter the disappearance of epinephrine from the blood stream (63).

2. "Inhibitory" responses. Studies of the effect of benzodioxanes on inhibitory responses to adrenergic stimuli have not yielded conclusive results. Epinephrine-induced coronary artery dilatation is not altered by 933F (213); an apparent reduction in epinephrine-induced coronary artery dilatation by 883F (89) may be largely a passive effect of inhibition of the pressor response to epinephrine, although direct coronary artery constriction by 883F (see IV, B-1)

cannot be ruled out as a contributing factor. It has been observed that 933F inhibits epinephrine-induced relaxation of rat and rabbit intestine only in concentrations which also inhibit the myotropic action of $BaCl_2$ or directly affect the tonus of the test object (136, 180, 274). Epinephrine-induced relaxation of the guinea pig intestine may be somewhat more readily inhibited (178, 180), but in the required concentrations 933F itself induces a very marked relaxation of the test object.

The non-pregnant cat uterus provides a somewhat more reliable test object than intestine upon which blockade of adrenergic inhibitory responses may be studied. The benzodioxanes have never been shown to produce more than minor alterations in the response of this organ to epinephrine (83, 341), and some studies have failed to demonstrate any blockade of the epinephrine inhibition (18, 84). Indeed, at times 933F may actually potentiate the epinephrine-induced relaxation. The benzodioxanes act directly to stimulate the uteri of several species (18, 83), a property which seriously complicates the interpretation of subsequent responses to epinephrine. The evidence for a specific blockade of adrenergic inhibitory responses by the benzodioxanes is not conclusive. Variations in experimental conditions as well as in the species and organs employed may be involved in the discrepancies reported. A comprehensive, well controlled study of the entire problem is needed.

3. Specificity. Benzodioxanes have been reported not to block pressor responses to nicotine, KCl, $BaCl_2$, posterior pituitary and β-tetrahydronaphthylamine (see 407). In addition, the pressor response of both normal and renal hypertensive dogs to renin is unaltered by 933F (212). Observations indicating a reduced response of the nictitating membrane of the cat to acetylcholine, KCl, and $CaCl_2$ after the administration of 933F (340) have not been explained or repeated.

B. Actions other than adrenergic blockade

1. Smooth muscle. The benzodioxanes directly stimulate many different types of smooth muscle including those of uteri, gut, bronchi and nictitating membrane (18, 47, 83). Coronary vessels are strongly constricted (89, 213), and it is impossible to find a theoretical basis for the trial of 883F in the therapy of angina pectoris (77). The agents also exert a potent direct constrictor action on peripheral vessels which is responsible for the pressor effect in dogs after pithing (206) or complete spinal anesthesia (208).

2. Cardiac muscle. Effects of 883F and other benzodioxanes on the mammalian heart appear to be best explained on the basis of a direct myocardial depression (207, 382); indeed, 933F has been found to be approximately 3 times as active a myocardial depressant as quinidine (92). Isolated cat, rat and guinea pig hearts are directly depressed by lower concentrations of 933F than are required to alter the response to epinephrine (253). Specific blockade of adrenergic cardiac acceleration by these agents in mammals is very limited or absent. Doses of 883F or 933F which reverse the pressor effects of epinephrine in anesthetized animals do not alter epinephrine-induced tachycardia (407).

The non-specificity of the cardiac effects of these agents on the mammalian heart is emphasized by the fact that electrically-induced fibrillation and $BaCl_2$-induced ectopic rhythms are inhibited as readily by 933F as epinephrine arrhythmias (96), and the fact that the response to vagal stimulation is reduced almost parallel to that to accelerator nerve stimulation (407).

Chloroform-epinephrine ventricular fibrillation is prevented by 933F and 883F (370). Inhibition of the pressor response to epinephrine has been advanced as the basis for this protection, although some of the published records indicate that the pressure may rise as much in the presence of 883F as in unprotected animals prior to the onset of arrhythmias. Corynanthine also affords marked protection despite epinephrine-induced pressure rises of as much as 140 mm. Hg (372). Pressure is probably a factor in the induction of cardiac arrhythmias, but the absolute pressure rather than the magnitude of the rise appears to be the primary sensitizing factor (see I, A-5). Fibrillation induced by digitalis overdosage in cats is not inhibited by 883F or 933F (104).

3. Central nervous system. Stimulation of the central nervous system by the benzodioxanes appears to affect particularly the lower brain stem. At least among piperidine derivatives of benzodioxane, this effect is roughly parallel to adrenergic blocking activity (47). Central nervous system stimulation is probably involved in the production of hypertension in unanesthetized animals (29, 47, 172) and man (143).

Administration of the benzodioxanes to anesthetized dogs may produce a vagus-mediated bradycardia even in the presence of a systemic hypotension (172, 407). This response is followed by a secondary cardiac acceleration which is prevented by ganglionic blockade or cardiac denervation but not by removal of the adrenal glands (172, 407). The hyperglycemic response to the administration of the benzodioxanes (47, 177) is also probably due to a central action mediated through the sympatho-adrenal system, although the same compounds have been reported to inhibit the hyperglycemic action of epinephrine (33, 47; contrast 177). Antidiuresis, presumably induced by hypothalamic stimulation, has also been noted (434).

Although the reported central nervous system effects of the more commonly employed members of the benzodioxane series are primarily excitatory, elements of brain-stem depression are also present. The hypotension induced by these agents in anesthetized animals is at least partially due to a depression of central vasomotor tone (206, 208; compare 407). Inhibition of responses to carotid reflexes, and to stimulation of the central stump of the severed vagus, by doses of 883F which do not inhibit responses to splanchnic nerve stimulation (407), also indicates brain-stem depression. Although a local anesthetic action of the benzodioxanes on carotid receptors represents another possible mechanism of action (421), concentrations adequate to produce this effect (0.15%) are probably not attained in intact animals. Other manifestations of central nervous system depression are analgesia, suppression of vomiting due to digitalis or apomorphine, and prolongation of the action of other central nervous system depressants (49). An adrenergic-blocking benzodioxane derivative with predominately anesthetic

properties has been reported, and large doses of 933F may also produce anesthesia (160).

When applied locally the benzodioxanes also block ganglionic transmission (17). Whether this is a true "nicotinic" ganglionic blockade or merely a local anesthetic effect (49) is not apparent from the published results.

It is unfortunate that the central nervous system actions of the benzodioxanes have not been studied by more direct neurophysiological technics. At the present time it is impossible to evaluate clearly the relative contributions of peripheral adrenergic blockade and central nervous system stimulation and depression to the over-all pharmacological properties of members of this series.

V. YOHIMBINE

Despite the fact that its adrenergic blocking action has been known since 1925 (314), yohimbine has had only limited use as a laboratory tool and has not been employed therapeutically as a blocking agent.

A. Adrenergic blocking action

1. "Excitatory" responses. Yohimbine and ethyl-yohimbine block certain responses to both circulating epinephrine and sympathetic nerve activity, but sympathetic blockade is produced only by doses two to five times greater than those required to prevent responses to epinephrine (24, 430). Failure of some investigators to demonstrate blockade of the pressor effects of splanchnic nerve stimulation by yohimbine (225) is probably due to the use of inadequate doses. Very low concentrations of yohimbine sensitize the perfused rabbit's ear to epinephrine (204), an action shared by several other adrenergic blocking agents. In the cat, pressor responses and salivary secretion are more readily inhibited than ocular smooth muscle responses (430), a fact which may largely explain the lack of "sympatholytic" activity reported on the basis of tests on the nictitating membrane and iris (17, 369). Yohimbine adrenergic blockade has also been demonstrated on ocular smooth muscles, arterial strips and rabbit uteri *in vitro* (69, 198, 355). Orally administered yohimbine provides significant, but not marked, protection against the lethal effects of epinephrine in mice (240). Greater protection would probably be provided by parenteral injection. Yohimbine blockade of cardiovascular responses to epinephrine is not altered by any of a considerable number of anesthetic agents (198, 225).

Yohimbine readily reverses the pressor response to acetylcholine in anesthetized, atropinized animals, but only reduces the response to nicotine (366). This difference in action is similar to that noted with Dibenamine, and the same possible explanations apply (see I, A-2). The glycemic response to epinephrine is inhibited (161).

Yohimbine blockade of the responses of arterial strips to epinephrine *in vitro* is much less complete in the presence of cocaine (69). The adrenergic blocking action of the benzodioxanes is also antagonized by cocaine (19), but that of the β-haloalkylamines is not significantly altered by this agent (295). The difference is probably due to the fact that yohimbine and the benzodioxanes produce an

"equilibrium" blockade which may be overcome by increased doses of epinephrine (295, 327), while the β-haloalkylamines produce a "non-equilibrium" blockade (see I, C-2). Although the exact mechanism of the sympathomimetic action of cocaine is unknown, the drug potentiates many responses to epinephrine. This potentiation provides an adequate basis for explaining the above effects of cocaine on "equilibrium" blockade.

The fact that yohimbine reversal of the nicotinic pressor response to acetylcholine is enhanced rather than depressed by cocaine (366) may be reconciled with the observations discussed in the preceding paragraph on the basis that both excitatory and inhibitory effects of epinephrine are potentiated by cocaine and that inhibitory factors play a much more important role in responses of the intact vascular system than in responses of arterial strips. Yohimbine actually slightly potentiates responses to vasodepressor amines (168).

Yohimbine has been shown to suppress carotid cardiovascular reflexes in animals (24, 252, 403). In one of the few reported administrations of yohimbine to man (62), the agent significantly reduced orthostatic vasoconstriction. Central actions, such as are prominent in the case of ergot preparations (see II, D-2), may be involved in the depression of vasomotor reflexes by yohimbine. The pressor effects of carotid occlusion and of stimulation of the central end of the severed vagus nerve are inhibited by smaller doses than are required to block the effects of splanchnic stimulation (24). However, other observations (403) indicate that ordinarily effective doses of yohimbine do not inhibit carotid sinus initiated vasoconstriction when the drug is in contact only with the central nervous system and is excluded from both the sinus and the reacting limb. The possibility that yohimbine acts to block afferent impulses from the carotid area on the basis of its known local anesthetic action (317) must therefore be considered. Experiments involving perfusion of the vascularly isolated carotid sinus have demonstrated a local action by concentrations of yohimbine which may be attained *in vivo* (402). It is possible that adrenergic blockade, inhibition of central reflex pathways and local anesthesia of carotid receptors are all involved in the inhibition of vasomotor reflexes by yohimbine. A critical reexamination of this problem might be most rewarding.

2. Cardiac responses. In common with other adrenergic blocking agents, yohimbine does not inhibit the chronotropic and inotropic effects of epinephrine on the mammalian heart (315). It has been reported that the rabbit heart is a qualitative exception to this general resistance to blockade (45), both in its response to yohimbine and that to several other blocking agents. However, more data on possible complicating experimental factors (see I, A-4) would seem desirable before this is accepted as a major exception to the generalization that chronotropic and inotropic responses of the mammalian myocardium are resistant to specific adrenergic blockade.

Yohimbine and corynanthine (an isomer of yohimbine) provide significant protection against chloroform-epinephrine ventricular fibrillation (370, 372). Yohimbine has also been reported to reduce but not to reverse the response of the frog heart to epinephrine (204), but other workers have failed to confirm

the observation (24). As in the case of observations on the blockade of adrenergic stimulation of the frog heart by the ergot alkaloids (see II, C-2), differences in technic may account for these divergent observations. It has also been reported that yohimbine may depress the frog heart in lower concentrations than those required to inhibit the response to epinephrine (198), an observation which must be kept in mind in an evaluation of the reported inhibition of adrenergic cardiac responses.

3. "Inhibitory" responses. Yohimbine has been reported to antagonize epinephrine relaxation of rabbit and cat intestine (198, 431), but very high concentrations (1:1000) are required to block responses of the latter. Rat intestine is relaxed by yohimbine (198). The limited number of observations make any definite conclusion regarding the blockade of adrenergic inhibitory responses by yohimbine impossible. In view of the limited specificity of enteric organs as test objects (see II, C-3), it must be concluded that specific blockade of adrenergic inhibitory responses by yohimbine has not been established.

4. Specificity. Ethyl-yohimbine, even in large doses, does not alter the vascular or ocular smooth muscle responses to angiotonin and posterior pituitary (429), nor does yohimbine suppress the pressor effect of KCl in adrenalectomized dogs (179). The actions of histamine, barium chloride and nitrite on arterial strips *in vitro* are also unaffected (69). The significance of a reported reduction by yohimbine of responses of the cat nictitating membrane to KCl, $BaCl_2$ and acetylcholine (340) is not clear.

B. Actions other than adrenergic blockade

1. Central nervous system. Yohimbine has several well-established effects on the central nervous system. Anti-diuresis is prominent (130, 437), and appears to be due to the release of posterior pituitary hormone in response to hypothalamic stimulation. It does not occur after section of the hypophyseal stalk (130). Corynanthine and yohimbine also induce melanophore expansion in intact but not in hypophysectomized frogs (393). This effect appears not to involve nervous mediation from the hypothalamus because it is not prevented by the application of local anesthetics to the hypophyseal stalk (371). However, proof that local anesthetics adequately penetrate the hypophyseal stalk after topical application would make this interpretation more certain.

Yohimbine inhibits epinephrine- (141) and ergotamine-induced (176) apnea in anesthetized dogs, despite the fact that the drug itself can produce apnea. However, the reports provide little or no evidence regarding the significance of these phenomena, or of the failure of rabbits to respond in a comparable manner (175). Although nicotine apnea is apparently unaffected (141) the above alterations in respiration are probably manifestations of non-specific stimulation of the central nervous system by yohimbine. There is no reason to believe that they are related to the protection against anoxia which this agent is reported to provide (106).

Brain-stem depression also appears to be involved in the anti-emetic action of yohimbine (72). Toxic doses of yohimbine first stimulate and then depress

respiration (433). Because of the subcortical central nervous system effects of yohimbine (and also of the benzodioxanes, see IV, B-3), the reported prevention of decerebrate rigidity by yohimbine and 933F (268) provides an inadequate basis for the conclusion that an "epinephrine-like" substance is involved in this phenomenon.

It has been claimed that yohimbine causes prolonged estrus or pseudopregnancy in intact adult female rats but not in hypophysectomized or castrate animals (131); however, other work failed to confirm these results (391). It is clear that yohimbine exerts no endocrine effect in immature or castrate animals, but the claim that yohimbine activates the anterior pituitary has not been established. The ejaculation elicited by yohimbine in mice treated with Pernoston (244) is inhibited by high section of the spinal cord (245). Present evidence provides no endocrine basis for the "aphrodisiac" effects of yohimbine and corynanthine. The observed responses appear to depend entirely upon circulatory changes (322) and central nervous system stimulation.

2. Miscellaneous actions. Yohimbine hastens muscle fatigue and reduces skeletal muscle sensitivity to acetylcholine (401), but no evidence has been adduced to indicate that these effects involve adrenergic blockade, as in the case of Dibenamine inhibition of the anti-curare effect of epinephrine (see I, A-3). Yohimbine also produces mydriasis in mice by inhibiting cholinergic pupillary constriction (44). Both of these effects are probably related to the local anesthetic property of the agent.

It appears that no physiological significance can be attached to the potentiation of phenol sulfur esterase activity by very high concentrations (5%) of yohimbine and ergotamine (399), or the inhibition by yohimbine, corynanthine and 933F of the potentiation of acetylcholine synthesis from choline by adrenochrome and cocarboxylase (267).

C. Yohimbine congeners

Except for ethyl-yohimbine, which has attracted attention because of its low toxicity (433), derivatives of yohimbine have received only superficial study. Although adequate comparative data are not available, the ethyl, allyl, butyl, phenyl, diethylamine, ethylene glycol and diethylene glycol derivatives of yohimbine appear to have very similar pharmacological properties (69, 431, 433). Diacetylation, which presumably blocks the secondary amine and alcohol groupings, also has been reported not to alter significantly the activity of yohimbine and corynanthine (327), although others have reported that diacetylation increases by several fold the activity of corynanthine and certain other congeners (205, 307). The quaternary methyl-iodide of yohimbine is almost completely inactive (328). A number of other derivatives have been reported, but their properties do not appear to be unusual.

Corynanthine, an isomer of yohimbine, possesses properties very similar to those of the latter. Although it is less toxic (209, 354, 437) and appears to be a more active adrenergic blocking agent than yohimbine (44, 209, 354; contrast 205), this agent and its derivatives have been little studied.

VI. MISCELLANEOUS ADRENERGIC BLOCKING AGENTS

In addition to the various groups of agents discussed above, a large number of miscellaneous compounds have been reported to exhibit adrenergic blockade. Few of these agents have been adequately studied with regard to the specificity of the blockade produced, and some of the published reports seemingly substantiate the dictum that "enough of anything will block anything." Only rarely have the compounds been compared quantitatively with more thoroughly studied agents, and therefore, an accurate evaluation of many of the substances to be discussed below is almost impossible.

A. Natural products

A variety of compounds occurring in nature have been reported to possess adrenergic blocking activity. The pharmacological properties of the alstonia alkaloids (215) and purified alstonine (410), obtained from the bark of Australian trees of the genus *Alstonia*, very closely resemble those of quinine. Like quinine, they have very weak adrenergic blocking activity. Hydrocinchonidine appears to be the most active of the "quinine-like" alkaloids (323), but it is still far from being a potent adrenergic blocking agent. A quaternary derivative of hydrocinchonidine (329) is active although a similar derivative of yohimbine is inactive (328). Extracts of *Galium aparine* (93) and several species of *Rauwolfia* (see 316, 324, 325) have been reported to possess detectable adrenergic blocking activity, but their properties do not appear to be remarkable. It is possible that the active agents in extracts of *Rauwolfia* are closely related chemically to yohimbine.

Bulbocapnine (318) and boldine (320) are said to differ significantly from other adrenergic blocking agents in their ability to block inhibitory vascular responses to adrenergic stimuli as readily as excitatory responses. However, studies employing N-ethyl-norepinephrine (319) have demonstrated that inhibitory cardiovascular responses are largely unaffected by bulbocapnine. No proof of the specificity of the adrenergic blocking action of these compounds has been presented, and the published observations are most readily explained by the assumption that they are simply weak adrenergic blocking agents with a high non-specific toxicity for smooth muscle.

B. Synthetic compounds

The first demonstration of adrenergic blocking activity by synthetic agents was that of Loewe in 1927 (243). He observed that a number of polyphenolethylamines inhibited and reversed the vasopressor and rabbit uterus responses to epinephrine. These agents received little additional attention, but this early work did much to stimulate the search for adrenergic blocking activity in synthetic compounds.

1. Phenoxyethylamines. Interest in the phenoxyethylamine adrenergic blocking agents has been revived by reports of Lévy and coworkers on a series of primary and secondary phenoxyethylamines (57, 59, 210, 219, 220, 221, 234). Phenoxyethyl compounds first attracted attention about two decades ago because

of the marked uterine stimulation which they produce (see 15), and a number of compounds of this type are included in the Fourneau series. They may be considered to be chemically related to the benzodioxanes (compare structure and activity of 928F, 930F, etc., (18, 47)). These compounds appear to have many and varied pharmacological properties (see 40 for the details of older work). Several members of the series possess a hypotensive action and antagonize the pressor and renal vasoconstrictor actions of epinephrine (57, 210). Whether the hypotensive action is due entirely or even in major part to adrenergic blockade has not been determined. The adrenergic blocking action is very weak and many members of this series reduce, but do not reverse the pressor response to epinephrine. In low concentrations, many phenoxyethylamines sensitize to adrenergic stimuli. The blocking action of even the most active phenoxyethylamines is of short duration and exhibits tachyphylaxis (295).

Various members of this series have been shown to exert antidiuretic (434), central nervous system depressant (49, 210), direct vasopressor (50, 57, 210) and ganglionic effects (17, 50). They also produce dilatation or constriction of the bronchi (234), stimulate the isolated intestine (41), and inhibit epinephrine-induced relaxation of bronchi (234) and of isolated rat intestine (219). The effects of acetylcholine on bronchi (234) and of acetylcholine and barium on isolated intestine are also inhibited (41, 220, 221). Compounds which most effectively antagonize responses to barium and acetylcholine are not necessarily the most potent inhibitors of responses to epinephrine, but responses to acetylcholine and barium *in vitro* appear to be antagonized by lower concentrations than are required to block epinephrine-induced intestinal relaxation (57).

The phenoxyethylamines (929F and 1081F), both with disubstituted phenyl radicals, have been reported to block epinephrine relaxation of the dog intestine and the nonpregnant cat uterus and to reduce only slightly the pressor response to epinephrine (43, 48). Although it is true that the non-pregnant cat uterus provides a test of adrenergic inhibitory responses involving fewer complications than the intestine; 1081F directly stimulates the uterus. In the absence of experiments with non-adrenergic agents to determine the specificity of the above inhibition, these observations cannot be considered as proof of specific blockade of an adrenergic inhibitory response. Although phenoxyethyl substitutions in the β-haloalkylamine series usually yield highly active blocking agents (288), all compounds with double substitutions on the aromatic ring are inactive (281). Although this evidence is indirect, it suggests that disubstituted phenoxyethyl radicals do not favor the production of adrenergic blockade.

The glycemic response to epinephrine may be blocked by phenoxyethylamines (233), but this effect does not parallel the potency of members of this series in blocking vascular responses to epinephrine (33).

Phenoxyethylamines also have a negative inotropic action on the frog heart and have been reported to antagonize, but not to reverse the action of epinephrine thereon (59). The important role of direct myocardial depression in determining the cardiac effects of phenoxyethylamines is indicated by the fact that a member of this series, 1262F, suppresses arrhythmias due to electrical stimula-

tion, $BaCl_2$ and aconitine as readily as it does arrhythmias due to adrenergic stimuli (41, 51, 97). Indeed, careful measurements on the rabbit auricle *in vitro* (92) indicate that 1262F is 4 times as depressant as quinidine to the myocardium.

The many non-specific inhibitory effects of the phenoxyethylamines are probably related to a strong local anesthetic action (49, 50, 57, 210). Within the series, the most effective adrenergic blocking agents are among those with the strongest local anesthetic action (the secondary amines). The local anesthetic action of these agents has been directly implicated in their mydriatic action (44).

In general, phenoxyethylamines with a substitution in the 4, 3 or 2 position of the phenyl ring possess increasing adrenergic blocking activity in the order named. Di(2-methylphenoxyethyl)amine is the most active member of this series (210).

Substitution of the 2-methylphenoxyethyl radical for one or both of the benzyl groups of Dibenamine produces compounds with very high adrenergic blocking activity (288) (see I, D-3). In these compounds the presence of a β-chloroethyl moiety provides both a marked increase in potency and in duration of action. The high activity of members of both the β-haloalkylamine and the above primary and secondary amine series containing the 2-methylphenoxyethyl radical, implies some special role for this grouping. In view of the very different chemical mechanisms involved in the blocking action of members of the two series (see I, D-1; D-4), it may be postulated that the 2-methyl- and certain other 2-substituted-phenoxyethyl radicals are effective on the basis of some structural (steric) relationship to the locus of blockade. Whether anything is to be gained by a comparison of the structure of the phenoxyethylamines to that of the phenylethylamine sympathomimetics is debatable. There are many points, such as the high effectiveness of the 2-substitution, whch weigh against the pharmacodynamic significance of such a comparison (see summary).

Mercapto homologs of several of the above phenoxyethylamines have also been reported to possess adrenergic blocking activity (58). The sulfur containing compounds are somewhat weaker and have a shorter duration of action than the oxy-congeners. A similar potency relationship was found for phenoxyethyl and phenylthioethyl derivatives of Dibenamine (288).

2. Sympathomimetic amines. The first demonstration of inhibition of the effects of one sympathomimetic amine by another probably was the observation of Abderhalden and Slavu (1) in 1909 that *d*-epinephrine protected mice against the lethal effects of *l*-epinephrine. Since that time many workers have reported competitive interactions between various sympathomimetic amines (see 159, 250). The weak adrenergic blocking activity of several phenylethylenediamines and phenylhydrazines (27, 42) has been attributed to a similar action on the basis of a "structural relationship" to phenylethylamine. Recently, apparently specific inversions of the pressor response to Vonedrine (β-phenyl-N-propylmethylamine) by Paredrine (β-(*p*-hydroxyphenyl)-isopropylmethylamine) (9), and of the response to several aliphatic amines by ephedrine (8) have been reported. These reversals apparently involve a true peripheral vasodilatation not detectable in the absence of the inverting amine. Most observations indicate

that Dibenamine and Priscol do not unmask significant vasodilator responses to Vonedrine and the aliphatic amines (9, 294), although slight depressor activity was observed when relatively large doses were administered to cats pretreated with a Dibenamine congener (81).

In common with many adrenergic blocking agents, most sympathomimetic amines appear to potentiate adrenergic stimuli at low concentrations and to inhibit such stimuli at high concentrations (133, 203). Whether or not the interactions between sympathomimetic amines mentioned above involve a mechanism similar to that involved in adrenergic blockade by such agents as Priscol and Dibenamine cannot be stated at the present time.

3. Isoquinolines. An extensive series of tetrahydroisoquinolines has been studied recently and certain members found to produce inhibition and reversal of the pressor response to epinephrine (60, 113, 195, 196). Many of the compounds also produce a considerable fall in blood pressure, apparently due to direct vasodilatation. Other members of the series, particularly the secondary amines, have a pressor action (113). N-aliphatic substituted compounds appear to have maximal adrenergic blocking activity. Such compounds may be considered to represent N-benzyl-N-alkyl-β-chloroethylamines in which the β-haloalkyl group has condensed with the 2-position of the aromatic ring. However, this structural comparison appears to have no pharmacodynamic significance, because the activity of tetrahydroisoquinolines is completely abolished by N-benzyl or N-β-chloroethyl substitutions (288). These substitutions yield compounds related in the same way to other active members of the β-haloalkylamine series (N,N-dibenzyl-β-chloroethylamine and N-benzyl-di(β-chloroethyl)amine). The blocking action of the tetrahydroisoquinolines is also entirely different from that observed in the β-haloalkylamine series. The former is much shorter in duration and is unaltered by thiosulfate (288, 295). Structural comparison of these reduced isoquinolines with cyclized β-phenylethylamines is possible (113), but probably of no greater pharmacodynamic significance than the above comparison with the β-haloalkylamines.

4. Miscellaneous synthetic compounds. Morphothebaine-dimethylether (an aporphine derivative related to bulbocapnine) appears to have quite specific adrenergic blocking activity (154). The pressor response to epinephrine in anesthetized cats and the epinephrine-induced contraction of the isolated rabbit uterus and spleen are readily reversed, although the effects are very transient. The chronotropic action of epinephrine on both the frog and rabbit heart is also inhibited. However, the agent is a strong myocardial depressant and the cardiac blockade may be non-specific. It is also a relatively strong central nervous system stimulant. Morphothebaine-dimethylether does not effectively block adrenergic inhibitory responses. Epinephrine-induced relaxation of the non-pregnant cat uterus and of the rabbit ileum *in vitro* is not significantly altered by concentrations well above those shown to block excitatory responses to epinephrine.

Pyridine (326) and β-ionone (99) have been reported to possess adrenergic blocking activity, but their actions are quite weak. The orthostatic hypotension

induced by pentaquine (122, 334) appears to be due to depression of the central nervous system similar to that demonstrated for pamaquine (270), rather than to a "sympatholytic" effect; the latter is ruled out by failure of the drug to alter responses to epinephrine (334).

A group of unrelated drugs including atropine, diphenhydramine, meperidine, procaine and quinidine has been shown to antagonize both the vasoconstrictor and vasodilator (after Priscol) responses to epinephrine in the perfused rabbit ear (61). However, most of these agents are equally or more effective against responses to acetylcholine and histamine. Their adrenergic blocking action therefore appears only at concentrations which suppress the over-all reactivity of the effector cells.

VII. CLINICAL AND EXPERIMENTAL APPLICATIONS OF ADRENERGIC BLOCKING AGENTS

A number of clinical and experimental uses of the adrenergic blocking agents were discussed in the preceding sections for the information they provided regarding the basic pharmacology of the compounds under consideration. In this section several additional applications will be discussed briefly. Particular attention will be paid to those which involve or might be expected to involve actual adrenergic blockade. However, certain uses which appear to depend primarily upon actions other than adrenergic blockage will be included in order to place them in proper perspective.

A. Human pharmacology

The rational clinical use of any drug is dependent upon a clear understanding of its pharmacological actions in man. In the field of adrenergic blockage, qualitative differences between the responses of man and laboratory mammals have not been demonstrated. However, certain important quantitative differences exist. These arise particularly from the fact that unpleasant and even dangerous side-effects prevent the administration of many agents in doses adequate to produce the effects commonly seen in animal experimentation. Unfortunately, few clinical investigators have actually tested for adrenergic blockage in man. Consequently, many observations have been attributed to adrenergic blockade or "sympatholysis" even though the doses of blocking agent employed appear to be completely inadequate to produce such an effect. Only Dibenamine (183) and Priscol (151) have been conclusively demonstrated to produce significant adrenergic blockade in man.

In the majority of subjects Dibenamine inhibits or reverses the pressor effects of injected epinephrine and Neo-Synephrine, of apnea, and of the cold pressor and Flack tests. The orthostatic hypotension, nasal congestion and miosis commonly observed after Dibenamine administration must also be due to adrenergic blockade as they can be accounted for by no other known properties of the agent.

Troublesome side-effects, particularly nausea and vomiting, may occur in the clinical use of Dibenamine (183, 337, 424), but some reports indicate that they

may be largely eliminated by slow administration of the agent (158, 258) or by prior sedation (281). A reported sedative action of Dibenamine (281, 379, 424) is probably secondary to the psychic effects discussed elsewhere (see I, B-2 and VII, F-2). The direct effect of Dibenamine on the central nervous system is primarily stimulant. Orthostatic hypotension is always observed, but cannot be considered as a side-effect because it is merely one expression of the desired adrenergic blockade. It may be overcome by the use of leg and abdominal binders and preliminary observations (281) indicate that patients may compensate for postural changes in the presence of continued blockade. Presumably this adjustment is similar to that occurring after extensive sympathectomy. However, a more thorough study of the problem is warranted.

The hydrogenated ergot alkaloids have not been demonstrated to produce any extensive adrenergic blockade in man. Plethysmographic studies (37, 38, 167) have demonstrated increases in limb and digit volume and pulse, and an augmented peripheral blood flow after dihydroergocornine; but central vasomotor depression rather than adrenergic blockade appears to be the most plausible explanation for the observed changes. A central site of action is also strongly suggested by the fact that reversal of the pressor response to injected epinephrine has been demonstrated only with difficulty (large doses of dihydroergokryptine vs. very small doses of epinephrine), whereas orthostatic hypotension is readily produced (121). Inasmuch as responses to circulating epinephrine are always more readily inhibited by the ergot alkaloids than are those to sympathetic nerve activity, inhibition of vasomotor reflexes cannot be considered as proof of the establishment of adrenergic blockade if responses to epinephrine are unaltered.

Nausea, vomiting and general malaise are the most commonly observed toxic responses to the dihydro alkaloids (34, 36, 37, 121, 167) and seriously limit the dose which may be administered. These reactions appear with total doses as low as 0.3 mgm. of dihydroergocornine (34, 36). This observation suggests a stronger emetic action than is observed with dihydroergotamine which is employed in considerably larger doses in the therapy of migraine.

Adrenergic blockade produced in man by Priscol (151) appears to be less complete than that produced by Dibenamine, but greater than that observed with the ergot alkaloids. The pressor response to moderate doses of epinephrine is reversed, but pressor responses to the cold-pressor and breath-holding tests are only partially inhibited and rarely reversed. Mydriasis rather than miosis may develop. The orthostatic hypotension observed after administration of Priscol is not necessarily due to adrenergic blockade, although this factor is probably involved. It is well known that orthostatic hypotension may be produced by many "non-sympatholytic" effects of drugs including central or galglionic interruption of vasomotor reflexes and direct peripheral vasodilatation. The fact that peripheral vasodilatation is elicited in man with much smaller doses of Priscol than are necessary to reverse the pressor responses to even small doses of epinephrine (184), and that dilatation may occur in some sympathectomized limbs (151, 236) suggest that direct non-adrenergic dilatation of blood

vessels is a very important factor in the action of Priscol in man. Although the case records reported are incomplete, sympathetic regeneration could hardly have occurred in some of the cases in which dilatation was observed after Priscol. Failure to demonstrate similar vasodilatation in other sympathectomized extremities appears to be due, at least in many cases, to a high degree of pretreatment dilatation. Also, reductions in the blood pressure of extensively sympathectomized, but still hypertensive patients in response to Priscol are essentially the same as observed in non-sympathectomized hypertensives (151). The response to Priscol after sympathectomy warrants further study.

Side-effects, including some severe reactions, are relatively common with what are now considered to be effective doses of Priscol (28, 151, 236, 363, 427). The most commonly observed side-effects are piloerection, chills, nausea, vomiting, apprehension and palpitation. A severe tachycardia is noted with overdosage (272).

B. Peripheral vascular disease

Among the most obvious clinical indications for adrenergic blockade are peripheral vascular conditions involving a component of sympathetically mediated spasm. Members of the β-haloalkylamine, ergot and imidazoline series have been employed in such conditions and all appear to produce beneficial vasodilatation. However, a precise evaluation of the relative effectiveness of these agents and their relation to other methods of therapy is impossible at this time. Most of the reported series are small, and controls and placebos have rarely been employed. From the standpoint of interpretation of results, an almost equally serious omission in most studies is the absence of evidence that significant adrenergic blockade was achieved and was responsible for the observed results.

Dibenamine has been reported to produce peripheral vasodilatation and clinical improvement in Buerger's and Raynaud's disease, acute peripheral arterial occlusion and frostbite (2, 79, 183, 379). Results with this agent appear to be due to true adrenergic blockade, but the number of cases reported to date are too few to give a clear picture of its clinical usefulness. The prolonged action of members of the β-haloalkylamine series may prove to be a distinct advantage in their therapeutic use.

The vasoconstrictor action of the naturally occurring ergot alkaloids is too strong for these agents to be useful in peripheral vascular insufficiency. However, their dihydro derivatives have had preliminary trial. Dihydroergotamine has been reported to produce beneficial results in peripheral vascular disease (199, 230), but its effectiveness has been questioned by some (379). Pharmacological data (see II, C-1; D-1) indicate that derivatives of members of the ergotoxine complex should have a considerable advantage over dihydroergotamine because of their lower vasospastic and greater adrenergic blocking potencies. However, it has been reported (34) that dihydroergocornine does not benefit "pathological spasm" such as that observed in Raynaud's disease, whereas dihydroergotamine has been reported to give excellent results in the treatment of this condition (230). Discrepancies such as this should emphasize

the necessity for caution in evaluating reports of the clinical effects of adrenergic blocking agents which do not include rigorous controls.

Priscol has been employed by many investigators in Europe to produce vasodilatation in a variety of peripheral vascular conditions including cerebral vascular accidents (see 52, 236, 336, 363, 412, 438), with some beneficial results reported in all series. However, many of the reports are rather uncritical and placebos and controls are rarely included. It is not clear why migraine should be included in the list of conditions benefited by this vasodilator (412) (see VII, F-1). Only one full report of the clinical use of Priscol (151) has appeared in the American literature. In this study the agent was found to produce significant peripheral vasodilatation, much of which appears to be independent of adrenergic blockade. The results indicate that larger doses than employed in many of the earlier studies are necessary to achieve significant effects. Patients with Raynaud's, Buerger's and arteriosclerotic peripheral vascular disease, with acute vascular occlusion and with "causalgia" were reported to be benefited by Priscol. The most favorable results were observed in Raynaud's disease and the least favorable results in causalgia.

C. Pheochromocytoma

The diagnosis and preoperative therapy of pheochromocytoma are obvious, although rare, indications for the use of adrenergic blocking agents. The benzodioxanes have been employed successfully in the diagnosis of several cases, and in the detection of unsuspected multiple tumors either during or after operation (64, 134, 143). However, blockade produced by the benzodioxanes is much too short to permit these agents to be used therapeutically; also, unpleasant side-effects are not uncommon. Dibenamine has been employed effectively in the diagnosis and in the rather prolonged preoperative maintenance of patients with pheochromocytoma (376, 379). The results reported have been excellent with injections at 72 hour intervals providing complete symptomatic relief. During the period of Dibenamine administration the Roth-Kvale histamine test was found consistently to be negative, although it was highly positive prior to treatment with Dibenamine.

D. Hypertension

Many workers studying adrenergic blocking agents have entertained the thought that these compounds might be of value in the treatment of "essential" hypertension. In the absence of any reliable information regarding the etiology of essential hypertension this approach is without theoretical basis. However, reports of partial, although highly variable, relief obtained from surgical sympathectomy in this condition have kept alive the hope that chemical adrenergic blockade might provide similar benefits.

1. Experimental neurogenic hypertension. The role of adrenergic blockade in the therapy of neurogenic hypertension is obvious. Consistent, though transient, lowering of blood pressure has been observed in hypertensive dogs administered ergotamine (191), 883F and 933F (29, 192). However, central inhibition of

vasomotor activity as well as adrenergic blockade may be involved in the observed results. Compounds 1071F and 1072F, adrenergic blocking agents with little effect on the central nervous system, are not effective in decreasing pressure in chronic neurogenic hypertension (29).

2. Experimental renal hypertension. The role of adrenergic factors in experimental renal hypertension is vague. The sequence of events by which interference with renal hemodynamics leads to elevation of the systemic blood pressure has been carefully studied and has been shown to be independent of nervous mechanisms (53, 142). However, the many similarities between experimental renal hypertension and human essential hypertension (see 306, 234a) have prompted extensive investigation of the former. Renal hypertensive animals respond to sympathectomy by a limited reduction in blood pressure (13), but prior sympathectomy does not prevent the development of renal hypertension (13, 119, 193, 406). There is no reason to believe that, in either experimental renal or human essential hypertension, adrenergic blockade can accomplish more than surgical excision of the sympathetic nervous system.

Adrenergic blocking agents produce a significant, but highly variable reduction in systemic arterial pressure in animals with experimental renal hypertension. Yohimbine administered orally for periods up to 35 days elicits some reduction of the blood pressure in dogs with chronic renal hypertension (200). However, the pressure is not consistently returned to normotensive levels. Dibenamine administered intravenously at three-day intervals to dogs with chronic renal hypertension has been observed to produce some reduction in pressure, but not to lower it consistently into the normal range (423). Wide fluctuations in pressure were noted during the period of treatment. In these experiments with Dibenamine the degree of adrenergic blockade was tested at intervals and the failure of Dibenamine to lower the pressure consistently to normotensive levels does not appear to be due to inadequate adrenergic blockade. Daily oral administration of Dibenamine to renal hypertensive rats in doses adequate to produce partial, but not complete, adrenergic blockade produced similar results (284). All hypertensive animals (and also normotensive controls) responded to each administration with a rapid but limited reduction in blood pressure. However, only 65% of the hypertensive and none of the normotensive animals showed a cumulative effect. Pressures of the animals which responded favorably were lowered to essentially normotensive levels which were irregularly maintained during 10 days of drug administration and for three to five days thereafter. The observed effects were shown to be due to adrenergic blockade because they could not be duplicated with 2-dibenzylaminoethanol (the hydrolysis product of Dibenamine) which has many pharmacological properties in common with Dibenamine but lacks adrenergic blocking activity.

Single injections of 883F and 933F (29, 100, 212) produce only irregular vasodepression in dogs with chronic renal hypertension, a response very similar to that seen in normotensive controls. Single injections of pentobarbital or yohimbine (330), and 883F, but not 933F (357), have been reported to produce a transient depressor response in renal hypertensive rats, which appeared to be

greater in animals hypertensive for more than two months. These observations on rats, particularly the difference in response to 883F and 933F, have been interpreted to indicate that neurogenic factors are of importance in late, but not in early renal hypertension. Fewer rats with prolonged renal hypertension (over two months duration) responded to Dibenamine with a persistent lowering of the blood pressure than did those with a shorter period of hypertension (284). Observations demonstrating an almost equal effect of 933F and 883F in neurogenic hypertension (see VII, D-1) have apparently been overlooked in this interpretation. It has been noted that single injections of ethyl-yohimbine cause a marked reduction in the blood pressure of renal hypertensive dogs under pentobarbital anesthesia (68). The reductions in pressure induced by pentobarbital and yohimbine therefore appear to be due to cumulative factors and attributing them to a common inhibition of sympathetic vasoconstrictor activity does not appear to be warranted at the present time.

The above observations, particularly those obtained with single injections of blocking agent, are extremely difficult to evaluate. However, their marked irregularity, compared with the consistent depressor response to adrenergic blockade seen in animals with neurogenic hypertension, argues against derangement of sympatho-adrenal function as a major factor in renal hypertension. It must be concluded that the contention that nervous factors are of importance in late but not in early renal hypertension (302, 330, 357) has not received convincing support from experiments employing adrenergic blocking agents.

It is known that the blood pressure can be maintained within normal limits after complete sympathectomy (152, 257), presumably by autonomous vascular tone. The possibility must therefore be considered that the rate and extent of peripheral vascular compensation rather than the level of sympathetic activity may determine the magnitude and duration of the depressor response to drug-induced sympathetic blockade.

3. "Essential" hypertension. The clinical application of adrenergic blockade to the study and treatment of hypertension has been very limited. Therapy with Dibenamine has been reported to produce significant benefit in severe, particularly malignant, hypertension (424). The drug was found to lower significantly the blood pressure in most cases, and relief of symptoms such as hypertensive encephalopathy was even more prominent. Other workers (158) have observed a significant depressor response to Dibenamine, lasting 24 to 72 hours, in early benign hypertension, but not in patients with advanced organic changes in the cardiovascular system. On this basis it has been suggested that the response to this drug be determined prior to sympathectomy as a measure of the role of the sympatho-adrenal system in a given case of hypertension. On theoretical grounds, an agent with the specificity of Dibenamine would be expected to be ideal for this purpose; indeed, attention has been called to the similarity between the effects of Dibenamine medication and those of surgical sympathectomy (423). However, the same arguments regarding possible misinterpretation of depressor responses to sympatho-adrenal blockade apply here as in the above discussion of responses to adrenergic blockade in experimental renal hypertension. Results obtained with Priscol, the ergot alkaloids, tetra-

ethylammonium and spinal anesthesia where factors in addition to blockade of the sympatho-adrenal system are involved would seem to have even less diagnostic specificity. It has been reported that Dibenamine is superior to tetraethylammonium as a test for predicting the results of sympathectomy in acute peripheral vascular conditions (79), but the same worker questions its prognostic value in hypertension. Lack of knowledge concerning the etiology of essential hypertension makes the interpretation of any prognostic test extremely hazardous.

Dihydroergotamine (377) and dihydro derivatives of members of the ergotoxine complex (36, 37, 121, 167) have recently been studied in a few cases of hypertension. Parenteral administration appears to produce a significant reduction in blood pressure and an orthostatic hypotension, but the response of different patients varies widely and as yet unpredictably. Reduction in the elevated blood pressure was not found to parallel suppression of experimentally initiated vasomotor reflexes, and in many cases (36, 38) an increase in the dose of dihydroergocornine caused an increase rather than a decrease in pressure. A similar pressor response to large doses of dihydroergocornine has been noted in normotensive individuals (36). This alteration in response with increasing dosage is compatible with a central site of action. Systolic pressure is often significantly reduced without any change in diastolic pressure (see 37), a fact which questions relaxation of peripheral arteriolar constriction as a significant factor in the depressor response. More than 10 times the parenteral dose must be employed when the dihydro ergot alkaloids are administered orally and they appear to produce even more irregular responses when administered by this route (36, 121).

The hypotension and depression of cardiovascular reflexes observed in man are undoubtedly due to central nervous system rather than "sympatholytic" effects. Central depression of vasomotor reflex pathways and central vagal stimulation may both be involved. Bradycardia is usually observed.

Nausea and vomiting are common after the administration of dihydro ergot alkaloids to hypertensive patients (36, 121, 167) and are not necessarily associated with blood pressure changes. Total doses as low as 0.3 mgm. dihydroergocornine have been reported to produce rather severe side-effects (34, 36). It has been stated that nausea and vomiting result from lower doses of dihydroergocornine in hypertensive than in normotensive individuals (36).

Priscol has been critically tested in only a small number of hypertensive patients (151); even large doses were found to produce very little reduction in blood pressure. The extent to which adrenergic blockade is involved in the cases showing some reduction is called into question by the fact that essentially equal responses occurred in patients who had remained hypertensive after extensive sympathectomy. Even a massive overdose of Priscol fails to reduce the blood pressure (272), presumably because cardiac stimulation balances peripheral vasodilatation. Some blood pressure reduction has been reported to result from the administration of Priscol to a few hypertensive patients (363) but this observation has not been substantiated.

The few observations which have been made indicate that the benzodioxanes

933F and 1164F tend to raise the blood pressure in human essential hypertension (143), probably due to central vasomotor stimulation (see IV, B-3).

E. Cardiac effects

Although Dibenamine, Priscol, yohimbine, corynanthine, the ergot alkaloids and several benzodioxanes have all been shown to inhibit adrenergically induced cardiac arrhythmias in hearts sensitized by anesthetics and other hydrocarbons (12, 96, 135, 269, 293, 298, 299, 305, 370, 372), only Dibenamine has been studied clinically (283). This agent proved to be very effective in preventing "spontaneous" arrhythmias in surgical patients under deep cyclopropane anesthesia, a fact which indicates an etiological role of adrenergic stimuli in these arrhythmias.

The effects of various blocking agents on cardiac arrhythmias induced by procedures or conditions not involving adrenergic stimuli is quite variable. Both 883F and 933F have been found to be completely ineffective in preventing cardiac arrhythmias caused by digitalis overdosage in cats (104), but to prevent those due to electrical stimulation and $BaCl_2$ (96). A phenoxyethylamine derivative (1262F) protects against fibrillation caused by several non-adrenergic stimuli (51, 97), apparently on the basis of direct myocardial depression. Ergotamine and dihydroergotamine provide significant protection against fatal ventricular fibrillation after acute coronary occlusion in dogs (251, 295). However, the protection provided by the dihydro ergot alkaloid does not increase in proportion to its adrenergic blocking potency and Dibenamine is ineffective (295). These observations strongly suggest that the protection observed is dependent upon non-specific myocardial effects of the ergot alkaloids rather than upon adrenergic blockade. In addition, dihydroergotamine is less than one-half as potent as ergotamine in preventing epinephrine-cyclopropane arrhythmias (305), a fact which suggests that the limited protection afforded by the ergot alkaloids against this type of arrhythmia (12, 298, 305) is also largely independent of adrenergic blockade (see discussion, 298).

Other cardiac effects of ergotamine and dihydroergotamine observed with doses obviously too small to produce adrenergic blockade must be dependent upon direct myotropic or central nervous system actions. In small doses these alkaloids cause an increase in the T waves of the human electrocardiogram (165, 301, 378, 416) and also inhibit changes which appear when the subject is standing (362, 418). They have been used diagnostically to enhance disturbances in cardiac rhythm in acute rheumatic fever (417), and to differentiate between organic and functional heart disease, particularly by preventing ECG changes in the latter in response to exercise or anoxia (30, 256, 301, 378). It has been argued that ergotamine or dihydroergotamine affects the ECG by a "sympatholytic" action which alters "autonomic balance." However, in the absence of tests to indicate the presence of adrenergic blockade it must be assumed that such small doses act through some mechanism other than "sympatholysis." This interpretation is strengthened by excellent evidence of the inability of the ergot alkaloids, even when administered in adequate blocking doses, to alter

most responses of the mammalian myocardium to adrenergic stimuli or to block adrenergic dilatation of the coronary arteries (see II, C-2; C-3). If any action of the ergot alkaloids on the autonomic nervous system is involved in the observed ECG alterations it is probably central inhibition of vasomotor reflexes or central vagal stimulation. The latter factor would seem to be particularly important as alterations in the ECG are frequently accompanied by some bradycardia. To claim that the effect of 0.5 mgm. of ergotamine tartrate in man is "primarily sympatholytic in character" is to ignore the accumulated data on the human and animal pharmacology of this agent.

F. Miscellaneous clinical uses

1. Migraine. The statement that adrenergic blockade is involved in the beneficial effects of the ergot alkaloids in migraine recurs even in recent clinical literature; this misunderstanding is probably involved in attempts to employ Priscol in the treatment of migraine (412). Many diverse observations provide strong evidence against this interpretation. Careful studies by Wolff and associates on the vascular mechanisms in migraine (146, 400) have demonstrated that vasodilatation rather than vasoconstriction predominates during an attack and that ergotamine acts by promoting vasoconstriction rather than vasodilatation; the latter would result if sympathetic blockade were the predominant effect. This mechanism of action of ergotamine is supported by the fact that epinephrine (146) and other sympathomimetic amines (248) may also provide relief. Furthermore, the doses of the ergot alkaloids employed in migraine, are much too small to produce adrenergic blockade. Ergonovine is effective in a considerable percentage of cases despite its lack of adrenergic blocking activity (231). Finally, hydrogenation of the ergot alkaloids, which decreases direct vasoconstrictor and increases adrenergic blocking activity, reduces their effectiveness in migraine. For example dihydroergotamine must be employed in doses about double those of ergotamine (see 124, 125, 398) and dihydroergocornine, one of the most potent adrenergic blocking agents in the series, has only questionable value in migraine (124). One report (377) claiming that dihydroergotamine has a greater potency than ergotamine in the treatment of migraine is not in agreement with most observations.

2. Psychoses. Reports of benefit from the use of ergotamine (181, 214, 310; contrast 153) and Dibenamine (258, 337) in psychiatric conditions are very difficult to interpret. In most cases the criteria of improvement are nebulous. However, Medinets and coworkers (258) have made a laudable attempt to quantitate the responses of schizophrenic patients to Dibenamine and have reported significant improvement.

It is probable that any benefit derived from these agents in psychoses is due to factors other than adrenergic blockade, but unfortunately these have been largely overlooked in a tendency to attribute the results to autonomic "balancing" or "unbalancing" by adrenergic blockade. All adrenergic blocking agents reported to be of value in these conditions have at least transient direct effects on the central nervous system. The role of direct central effects is particularly

clear in the case of the ergot alkaloids. These agents always produce brain-stem depression with smaller doses than are necessary for adrenergic blockade; somnolence and sedation are among the most prominent signs of acute toxicity in primates (420), and an adrenergically inactive alkaloid (ergonovine) has been found to produce essentially the same psychic response as ergotamine (214). The extremely potent effects of the ergonovine congener lysergic acid diethylamide on the central nervous system (see II, A) may provide a useful point of departure for a critical study of the non-adrenergic psychic effects of the entire series of ergot alkaloids.

A second consideration in evaluating the role of adrenergic blockade in the psychic responses to blocking agents is that, insofar as they have been studied, adrenergic blocking agents do not inhibit responses of the central nervous system to adrenergic stimuli. This factor has been considered in only one of the reports on the subject (258). Finally, with the exception of certain studies on Dibenamine (258, 337) there is little evidence that the doses employed produce significant adrenergic blockade. In one series (310), huge doses of dihydroergotamine (to 200 mgm./day) were administered orally, but little is known of the blocking action of the ergot alkaloids when administered by this route, and no attempt was made to show that adrenergic blockade was achieved. Studies with the hydrolysis product of Dibenamine which retains the central stimulant, but is devoid of adrenergic blocking activity (see I, B-2) would be of interest in determining the mechanism involved in the production of the reported beneficial psychic effects of Dibenamine.

3. Other uses. Although it does not alter the pressure in normal eyes, Dibenamine has been reported to reduce very effectively the intraocular pressure in cases of acute glaucoma refractory to other therapy (75). It is known that cervical sympathectomy causes some lowering of intraocular pressure in animals (202), but the mechanism of the Dibenamine action is far from clear. The reduction in pressure is much greater than can be accounted for on the basis of the miosis produced.

Dibenamine has been observed to provide marked symptomatic relief in cardiospasm, accompanied by roentgenographic evidence of relaxation of the cardia and rapid emptying of the esophagus (281). However, more extensive observations are necessary to determine the duration of relief and the incidence of favorable responses. It has been reported that dihydroergotamine also may relieve cardiospasm (199), but these observations are complicated by the simultaneous administration of physostigmine.

Dibenamine also induces a significant diuresis and an increased urea clearance in patients with malignant hypertension (424). Priscol has been reported to produce a similar response in acute nephritis (227).

G. Miscellaneous experimental applications

1. Shock. Early in the study of the β-haloalkylamine blocking agents it was noted that less hemorrhage is required to induce a fall in blood pressure in Dibenamine-treated animals than in controls, but that equal or larger withdrawals

of blood could be made from the former before shock supervened (297). More detailed experiments (331, 422) have now demonstrated that adrenergic blockade with Dibenamine provides marked protection against both hemorrhagic and traumatic shock. Careful hemodynamic measurements in control and Dibenamine-treated dogs subjected to hemorrhagic and traumatic shock indicate that the observed protection is largely due to the elimination of reflex vasoconstriction which ordinarily sustains blood pressure at the expense of blood flow (331). The protection afforded by Dibenamine under these conditions might have been anticipated on the basis of older experiments (120) demonstrating a marked resistance of sympathectomized dogs to hemorrhagic shock.

2. Inhibitory properties of sympathomimetic amines. Adrenergic blocking agents have been employed as tools in several studies designed to evaluate the relation between the chemical structure of sympathomimetic amines and the depressor component of their activity. The effect of a Dibenamine congener (N-benzyl-N-β-phenylisopropyl-β-chloroethylamine) on the pressor response to 20 pressor amines and catechol has recently been reported (81). All agents except Neo-Synephrine, Privine and Paredrinol elicited some depressor response after blockade. Maximum adrenergic blockade may not have occurred in these experiments. Two-thirds of the preparations showed only partial inhibition of response of the nictitating membrane to epinephrine. Other workers, most of whom have studied only a few amines, have observed much less depressor response after adrenergic blockade, particularly with non-catechol, aliphatic and imidazoline sympathomimetic agents (11, 105, 114, 259, 260, 408, 409). However, one report indicates epinephrine-like reversal even of Privine and Neo-Synephrine by a β-haloalkylamine (414). The relatively large doses of pressor amines employed by Coret (81) may have been a factor in the production of the observed depressor responses, for it has been noted that large doses of several amines are reversed more readily than small doses (114, 294, 414) and that repetition of small doses produces a similar increased depressor effect (294). A standardization of methods and doses will be necessary before the above divergent results can be quantitatively interpreted.

Another study of cardiovascular responses to an extensive series of sympathomimetic amines administered after large doses of Dibenamine (287, 294) has indicated that four structural factors are of importance in eliciting a depressor response: alkyl substitution on the amine, hydroxyl substitutions (especially 3,4-) on the aromatic ring, β-aliphatic substitutions and α-oxy substitutions. The importance of these factors tends to decrease in the order listed, but at least two of the mentioned substitutions are necessary for any considerable depressor activity, and the alkyl groupings are relatively ineffective in the absence of the phenolic hydroxyls. Qualitative confirmation of the significance of these constituents is found in several of the series of experiments discussed in the preceding paragraph when they are reevaluated with these factors in mind.

A study of cardiovascular responses to graded doses of epinephrine in cats before and after the administration of Dibenamine has provided data for the construction of dose-effect curves for pressor and depressor responses (286).

Differences in the shape of these curves may provide an explanation for recognized differences in the response of untreated animals to large and small doses of epinephrine and perhaps other sympathomimetic amines.

3. Identification of adrenergic mediators. A number of workers have employed adrenergic blocking agents as tools to unmask the depressor component of the response to epinephrine and thus to differentiate this agent from norepinephrine which has little or no vasodepressor action. Studies have been carried out particularly in efforts to identify the sympathetic mediator and the sympathomimetic agents extracted from various tissues. The ergot alkaloids have been most commonly employed (108, 132, 419), probably because of their availability; benzodioxanes have also been used (264). However, Euler has recently employed Dibenamine for this purpose (109) with more reproducible results and fewer complicating side-effects. The depressor responses noted after ergotamine, and more recently after Dibenamine, also have been studied as one step in the characterization of newly synethesized series of sympathomimetic agents (*e.g.*, 392).

After confirming the specificity of the adrenergic blocking action of Dibenamine, Folkow and coworkers have employed this agent in several extensive studies of the mechanisms of certain cardiovascular reflexes and of the relative roles of cholinergic and adrenergic factors in sympathetic vasodilatation (114, 115, 116, 117).

4. Other uses. The β-haloalkylamines have also been utilized by a number of investigators to determine whether the effects of various agents and procedures are adrenergically mediated. This question has been answered in the affirmative for the pressor effect of certain anticholinesterases (80), the secondary pressor response to epinephrine (229), sweating in certain areas (palms of hands, etc.) (156, 183, 258) and the hyperthermic response to typhoid toxin (415). The inhibition of hyperthermia by N-1-naphthylmethyl-N-ethyl-β-bromoethylamine was similar to, but somewhat less than, the inhibition by corynanthine and 883F of dinitrophenol hyperthermia reported many years ago (374). Dibenamine (157) and ergotamine (246) have also been employed in experiments demonstrating a direct peripheral vasoconstrictor action of nicotine.

Priscol has been used as a vasodilator to facilitate blood pressure readings in the rat's tail (74), but the validity of such determinations may be questioned.

Rapid intravenous administration of large doses of Dibenamine has been shown to prevent post-coital ovulation in the rabbit (358). It was concluded that this inhibition indicated adrenergic mediation to the anterior pituitary. However, the marked central nervous system excitation which occurred and the short time intervals involved in these experiments strongly suggest that direct central nervous system stimulation rather than adrenergic blockade was important in the observed inhibition (280). Dibenamine failed to prevent the release of adrenocorticotrophin in response to stress in experiments in which adequate time was allowed for side-effects of the agent to be dissipated (394).

SUMMARY

Members of the various series of adrenergic blocking agents differ widely in the blockade they produce and even more widely in the nature of their side-effects. However, a general pattern of activity emerges if the components of specific adrenergic blockade are extricated from complicating side-effects, often a difficult process because of the limited nature of many reports.

The data listed in table II summarize the pharmacological properties of the more important series of adrenergic blocking agents. This tabulation is certainly not definitive and some exceptions to almost every statement in the table have been reported. Aberrant results in the field of adrenergic blockade have been frequently attributed to species differences or to qualitative differences in the activities of a few members of a series. Such differences may exist (*e.g.*, absence of significant adrenergic vasodilatation in the rabbit); but in explaining conflicting results they should be invoked only as a last resort. Whenever well-controlled experiments with a group of related agents have been carried out in parallel on several species, many apparent exceptions have disappeared. Side-effects, use of an inadequate dose range or factors of experimental technic frequently may be the basis for apparent exceptions, and must be rigorously ruled out before observations which conflict with a general pattern of activity can be accepted.

The contraction of smooth muscle and the secretion of exocrine glands in response to adrenergic stimuli are inhibited by all adrenergic blocking agents and blockade of these responses has been tacitly accepted as the basis for defining adrenergic blocking activity. The most thoroughly studied manifestations of this action are inhibition of the pressor response to injected epinephrine and inhibition of the epinephrine-induced contraction of various smooth muscle structures *in vitro*. However, the elimination of such responses does not constitute proof of specific adrenergic blockade; many substances in adequate dosage are capable of destroying the ability of smooth muscle to contract. Reversal of the pressor response, as distinct from its depression, is more adequate evidence of specific blockade because such reversal indicates that the vascular system is still capable of physiological responses. In experiments on smooth muscle *in vitro*, reactions to several activating agents must be studied in parallel in order to establish the specificity of alterations in the response to epinephrine.

All specific adrenergic blocking agents inhibit responses to circulating mediator more readily than those to adrenergic nerve stimulation. Some agents show a much greater differential than others in their activity against these two types of stimuli, but all gradations occur and the difference is therefore unreliable as a basis for classifying blocking agents. Inhibition of vasomotor reflexes cannot be considered as proof of "sympatholytic" activity. The ergot alkaloids inhibit vasomotor reflexes more readily than responses to injected epinephrine, but the mechanism involved is depression of the brain stem rather than inhibition of responses to sympathetic nerve activity.

Specific blockade of adrenergic "inhibitory" responses does not appear to have been conclusively established for any blocking agent. Epinephrine-induced

Table II

Summary of properties of major series of adrenergic blocking agents

Properties \ Agents		β-Haloalkylamines	Ergot Alkaloids[1]	Imidazolines	Benzodioxanes	Yohimbine Corynanthine	Phenoxyethylamines
Adrenergic blocking actions							
Specificity[2]		Very hi h	Natural—very low DHA—low	Low	Low	High	Very low
Effectiveness[3]		Very high	High (DHA—more potent)	Low	Low	Low	Low
Duration of action		Very long	Intermediate	Intermediate	Short	Short	Short
Type of blockade		Non-equilibrium	Equilibrium	Equilibrium	Equilibrium	Equilibrium	Equilibrium
"Excitatory" responses	Organs	All	All	Ocular smooth muscle resistant	Iris resistant	All	All ?
	Stimuli	Sympathomimetics > nerve impulses	Sympathomimetics > nerve impulses	Sympathomimetics > nerve impulses	Sympathomimetics > nerve impulses	Sympathomimetics > nerve impulses	Sympathomimetics > nerve impulses
Cardiac responses	Mammalian	Unaltered, but arrhythmias prevented	Unaltered	Unaltered, but arrhythmias prevented	Unaltered	Unaltered, but arrhythmias prevented	Unaltered
	Amphibian	Blocked or reversed	Blocked or reversed	Little effect	Blocked	Blocked ?	Blocked ?
"Inhibitory" responses	Observations	Little effect	Intestine and some uteri blocked or reversed; vasodilatation unaltered	Intestine moderately inhibited; uteri and vasodilatation unaltered	Intestine blocked; cat uterus and vasodilatation unaltered	Intestine slightly inhibited	Intestine and some uteri blocked and reversed
	Status		Specificity not demonstrated; cholinergic stimuli potentiated	Specificity not demonstrated	Specificity not demonstrated	Specificity not demonstrated	Specificity not demonstrated
Glycemic response		Unaltered or moderately inhibited	Strongly inhibited	Unaltered	Moderately inhibited	Moderately inhibited	Moderately inhibited
C.N.S. Responses (to symp. amines)		Unaltered	?	?	Unaltered	?	?

	Actions other than adrenergic blockade					
Smooth muscle[1]	Little effect	Natural—many organs strongly stimulated DHA—slightly stimulated or relaxed	Parasympathomimetic and histamine-like stimulation; sympathomimetic relaxation; peripheral vasodilatation	Moderately stimulated (direct and secondary to sympatho-adrenal discharge); some organs relaxed	Slightly relaxed	Strongly stimulated and relaxed (series varies widely)
Heart	Myocardium slightly and transiently depressed	Myocardium strongly depressed; ECG altered; inhibited through the vagus; arrhythmias prevented	Strongly stimulated (sympathomimetic); coronaries dilated	Myocardium strongly depressed; inhibited through vagus; stimulated through sympathetic; arrhythmias prevented	Not significantly affected	Myocardium very strongly depressed; arrhythmias prevented
Central nervous system	Strongly but transiently stimulated	Strongly and complexly stimulated and depressed; vasomotor reflexes depressed; vasomotor center depressed; vagus stimulated; vomiting induced; respiration depressed	Not significantly affected	Strongly stimulated and depressed; vagus and sympathetics stimulated; vasomotor reflexes depressed; antidiuresis produced	Mildly stimulated and depressed; antidiuresis produced	Strongly stimulated and depressed; antidiuresis produced
Miscellaneous	Histamine blocked by some compounds; local tissue irritation	Cholinergic stimuli potentiated; pancreatic secretion inhibited	Gastric, pancreatic, salivary secretion stimulated; glycemia produced	Glycemia through sympathetics; local anesthesia	Local anesthesia	Some cholinergic responses blocked; powerful local anesthesia

[1] Properties of natural and dihydrogenated (DHA) alkaloids similar unless stated otherwise.
[2] Factors such as central nervous system depression roughly weighted on the basis of the complications and limitations of adrenergic blocking action produced.
[3] Ability to block responses to strong adrenergic stimuli.

relaxation of certain organs is inhibited by a number of compounds. However, the interpretation of this effect is complicated by the presence of intramural parasympathetic ganglia in many organs which respond to adrenergic stimuli by relaxation, the known parasympathomimetic and direct musculotropic actions of many adrenergic blocking agents, and the ganglionic effects of epinephrine. In sharp contrast to the uniformity of blockade of excitatory responses, antagonism of inhibitory responses varies widely with different species, organs, blocking agents and experimental conditions. Two general observations regarding the inhibition of adrenergic relaxation of smooth muscle weigh against the conclusion that this is an expression of specific adrenergic blockade. (A). The responses of organs most subject to complicating reactions, (*e.g.*, intestine) are most frequently reported to be inhibited. In contrast, relaxation of the non-pregnant cat uterus by epinephrine is relatively uniform and dependable; responses of this organ are much less frequently reported to be inhibited and only partial blockade is usually observed. Finally, blockade of adrenergic inhibition of the vascular musculature has never been clearly demonstrated. Vascular smooth muscle represents the most reliable object upon which to test blockade of adrenergic inhibitory responses because of the absence of ganglia, the absence of constrictor responses to cholinergic stimuli, etc. (B) Blockade of adrenergic inhibitory responses is reported most frequently as a property of those drugs (ergot alkaloids, phenoxyethylamines, benzodioxanes) which possess many important side-effects and least frequently as a property of those agents (β-haloalkylamines, yohimbine) which exhibit the greatest specificity of action. It must be concluded that blockade of adrenergic inhibitory responses by members of any of the known series of adrenergic blocking agents has not been conclusively established.

It is generally agreed that no adrenergic blocking agent specifically inhibits the chronotropic and inotropic responses of the mammalian heart to adrenergic stimuli. Even those agents which profoundly depress the myocardium have rarely been reported to depress in equal measure its response to epinephrine. In contrast to the responses of the mammalian heart, stimulation of the amphibian heart by epinephrine appears to be subject to inhibition by several agents. This inhibition may be markedly altered by the composition of the perfusion fluid, a fact which may account for a number of contradictory reports which have appeared.

In contrast to their ineffectiveness against the chronotropic and inotropic responses of the mammalian heart to epinephrine, adrenergic blocking agents are quite effective in preventing epinephrine-induced arrhythmias both in the presence and in the absence of sensitizing hydrocarbons. Some agents (β-haloalkylamines, yohimbine, imidazolines) apparently protect by virtue of their adrenergic blocking activity, whereas others (ergot alkaloids, benzodioxanes, phenoxyethylamines) protect by directly depressing the myocardium. Compounds of the latter type are also effective against arrhythmias evoked by non-adrenergic stimuli (electric current, $BaCl_2$, etc.) whereas the former are not.

Many adrenergic blocking agents inhibit the glycemic response to epinephrine; but other potent agents, notably Dibenamine and Priscol, have little effect on this response. Among agents for which adequate data are available it is obvious

that inhibition of the glycemic response is very poorly correlated with the inhibition of excitatory responses of smooth muscle. In addition substances other than adrenergic blocking agents (*e.g.*, posterior pituitary) are able to inhibit the hyperglycemic response to epinephrine. The fact that the antiglycemic action of ergotoxine is additive with that of posterior pituitary suggests that specific adrenergic blockade is not the basis for the observed inhibition.

The blockade produced by all major series of adrenergic blocking agents is relatively specific for adrenergic stimuli. Lack of specificity is manifested primarily by direct actions on various tissues. Such direct actions may seriously interfere with the use of these agents both in experimentation and in therapy, by producing effects which cannot be readily differentiated from those of adrenergic blockade or by preventing the administration of doses adequate to establish adrenergic blockade. Direct actions of the natural ergot alkaloids, the benzodioxanes and the phenoxyethylamines on smooth muscle not infrequently complicate experiments or produce toxic reactions. However, the most serious side-effects are those involving the central nervous system. For example, all ergot alkaloids depress vasomotor centers and inhibit transmission of vasomotor reflexes through the brain stem in smaller doses than are required to produce sympathetic blockade. In addition, stimulation of the emetic center by the ergot alkaloids is responsible for the fact that "sympatholytic" doses of these agents cannot be tolerated by man. Central nervous system stimulation is also the most prominent side-effect of the β-haloalkylamines. However, this has much less serious consequences than in the case of the ergot alkaloids because the adrenergic blockade produced by the β-haloalkylamines far outlasts the central effects and the latter do not significantly interfere with vasomotor tone or reflexes.

Little is known regarding the finer mechanisms of action of any of the adrenergic blocking agents. Evidence is available to indicate that the β-haloalkylamines act through an alkylating reaction with cellular constituents, but nothing is known concerning the nature of these constituents or why their alkylation should prevent the contraction of smooth muscle or the secretion of exocrine glands in response to specific stimuli.

Present data indicate that alterations in the destruction or transformation of the mediator *in vivo*, and alterations in cell permeability are not important factors in adrenergic blockade. A dynamic equilibrium between mediator and blocking agent is characteristic of at least certain stages in the action of all types of compounds producing adrenergic blockade. However, the question why certain chemical structures and not others produce effective blockade remains unanswered.

The steric antagonism of a pharmacologically active compound by a relatively inactive congener is a common observation and such a mechanism may be involved in the antagonism of one sympathomimetic amine by another. However, almost insurmountable obstacles are encountered in efforts to explain the action of the more effective blocking agents on the basis of a molecular similarity to the basic phenylethylamine structure of sympathomimetic agents.

All the most active and specific blocking agents are found in series (β-halo-

alkylamines, yohimbine, ergot) where the relationship to phenylethylamine is the least obvious. In the β-haloalkylamine series, benzyl and phenoxyethyl derivatives are active, but the phenylethylamine derivatives are almost completely inactive. The relationship of the benzodioxanes to phenylethylamine is much less obvious than that of the phenoxyethylamines, and yet the former blocking agents are much more effective and specific than the latter. Some workers have considered the presence of a phenylalanine residue in ergotamine to allow a structural comparison with phenylethylamine. However, replacement of this radical by a non-aromatic amino acid residue may increase rather than decrease blocking activity, *e.g.*, ergokryptine. Additional objections to the acceptance of structural similarity to phenylethylamine as a basis for most adrenergic blocking activity may be found in the preceding sections. At the present time little is gained by attempts to squeeze blocking molecules into the phenylethylamine mold.

Discovery of the adrenergic blocking activity of the β-haloalkylamines and imidazolines, and preparation of dihydroderivatives of the ergot alkaloids have done much to renew interest in the field of adrenergic blockade. No ideal blocking agent is yet available, but compounds with improved specificity and potency are rapidly being developed in all three series. Future experimental and clinical applications of these agents may be expected to yield new and valuable information on the normal and pathological physiology of the sympathoadrenal system.

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