ANTIHYPERTENSIVE DRUG ACTION[1,2]

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The increasing availability of drugs which predictably lower blood pressure in hypertensive patients has stimulated the publication of several books and symposia, numerous reviews, and countless individual contributions dealing, totally or in part, with the action of antihypertensive compounds. The pharmacology of substances in this group has been discussed in previous volumes of the *Annual Review of Pharmacology*, and additional data pertinent to their actions are available in another section of this volume. The present review evaluates information from readily available literature sources when it pertains to the mechanism of action of clinically employed antihypertensive agents. The question of therapeutic effectiveness of the diverse compounds is touched upon only incidentally. No attempt is made to classify the different groups of drugs, since such classification would imply bias in what refers to the generally very controversial question of how lowering of blood pressure is achieved.

Chlorothiazide and other diuretic agents.—There is general agreement that CTZ (chlorothiazide) and related diuretic compounds are useful drugs in the treatment of hypertension. They are moderately effective in a significant number of hypertensive patients (1, 2), can potentiate the hypotensive actions of other drugs (3–6), and show a relatively low incidence of side effects, together with minimal toxicity on chronic administration. This can include, as far as is presently known, the risk of hypokalemia; the infrequent appearance of hyperuricemia; the possibility of exacerbating previously controlled diabetes or of provoking hyperglycemia in patients with no previous history of this disease; and the probably more remote danger of jaundice, photosensitivity, skin eruptions, thrombocytopenia, neutropenia, and pancreatitis (4).

The fact that antihypertensive activity has been found with all of the benzothiadiazine diuretic agents, when the action has been adequately sought (7–10), and with many nonbenzothiadiazine diuretics including quinetazone (11, 12), chlorthalidone (13), triamtirene (14), ethacrynic acid (15), aldosterone antagonists (16), mercurials (1), and others (17) has made it seem reasonable to regard the lowering of blood pressure by these compounds as the consequence of their diuretic action. It is significant that the

[1] The survey of literature pertaining to this review was completed in June, 1964.

[2] The following abbreviations will be used: α-MMT (alpha-methyl-*m*-tyrosine); α-methyl DOPA (alpha-methyl dihydroxy phenylalanine); CTZ (chlorothiazide); DOPA (dihydroxy phenylalanine); MAO (monoamine oxidase); and VMA (vanilmandelic acid).

diverse communications mentioned above report antihypertensive action in doses that are roughly equivalent to those at which the different compounds produce clinically useful diuresis. Controlled studies, though few, generally confirm this impression. In one such study (13), it was found that equivalent diuretic doses of cyclopenthiazide, bendrofluazide, and chlorthalidone had similar hypotensive potency; in another (16), hydrochlorothiazide in one tenth the dose by weight was considered to be slightly more effective than CTZ as an antihypertensive agent and as a diuretic; in still another (8), methylclothiazide was about five times more potent as a diuretic than hydrochlorothiazide on a mg-dose basis and showed approximately similar antihypertensive activity when it was compared at 10 mg per day with 50 mg per day of hydrochlorothiazide.

Early in the studies of CTZ, it was discovered that its des-sulfamyl derivative, diazoxide, possessed acute hypotensive properties while showing no diuretic action (18), a pattern shared by other benzothiadiazine dioxides (19). This was initially interpreted as indicating that the two actions of CTZ-like drugs, i.e., diuresis and antihypertensive action, could be separated and were presumably exercised through different mechanisms. The antidiuretic action attributed to diazoxide in initial investigations (18, 20) has been clearly confirmed in experimental animals (21) and in man (22) and is generally accepted to constitute a clear difference with respect to drugs like CTZ. However, it has become apparent that its cardiovascular actions are also very different from those of benzothiadiazine diuretics. Thus, it produced immediate reductions in the arterial blood pressure of normotensive animals (20, 21). The decrease in systemic blood pressure in anesthetized intact dogs and in unanesthetized man was accompanied by a reduction in peripheral resistance and by an increase in cardiac output (23). Similar findings have been reported in the dog (24) and in man (25, 26) by other groups of investigators. It is, then, probable that the chemical relations that exist between diazoxide-like compounds and CTZ-like drugs are intranscendental to the question of whether the antihypertensive and diuretic actions of thiazide diuretics are interrelated.

There is reasonable agreement that the initial lowering of blood pressure following thiazide diuretics in hypertensive patients is accompanied by a decrease in cardiac output and an increase in peripheral resistance (27–30), and that these actions can readily be explained by the drug-induced diuresis which brings about a decrease in plasma and extracellular fluid volumes (31, 32, 33) and a negative sodium balance (31). However, three lines of evidence have been offered against this causal relationship. In the first place, it has been demonstrated that the administration of CTZ to normotensive subjects, in whom the drug produces no lowering of blood pressure, is followed by weight loss and decrease in plasma volume (31, 34) or by changes in renal function (35) which are entirely similar to those observed in hypertensive patients, who have responded well to thiazide therapy. In the second place, it has been pointed out that there is sometimes a poor correlation between

the cardiovascular consequences of thiazide administration and fluid and electrolyte balances in patients or experimental animals receiving the drugs (29, 33, 36). Finally, in the hands of some investigators, the administration of sodium or the re-expansion of the extracellular and plasma volumes has not affected the hypotensive response to benzothiadiazine administration (32, 36, 37). The differences between normotensive and hypertensive subjects should not be surprising, if one considers that the latter show clear abnormalities in the handling of salt loads (38) and that their sodium pool is greater, as evidenced by the longer biological half-life of administered Na^{22} (39). The other observations must be judged in the light of the generally accepted coexistence, at the beginning of thiazide therapy, of lowered blood pressure and diuretic response and of numerous results which indicate that there is antagonism between sodium or fluid administration and the antihypertensive action of this group of drugs (5, 34, 40) and, further, that sodium restriction accentuates their effectiveness (5).

On chronic administration of thiazide diuretics to hypertensive patients, there is no longer a decrease in cardiac output, but rather a decrease in peripheral resistance (28, 30) together with a return to control levels of extracellular and plasma volumes (28, 33) and a disappearance of the negative sodium balance. These changes have led to doubts as to the relation between the renal actions of the diuretic agents and their persistent antihypertensive action. It may be that such doubts are only partially justified, since there is evidence of sustained influences on water and electrolyte metabolism during chronic thiazide therapy, as indicated by the persistent reduction in body weight and in total body water in hypertensive patients (28) and by the appearance of increased granularity in juxtaglomerular cells of rat kidney after prolonged treatment with CTZ (41), a situation which is similar to that following diets very low in sodium. It may be that there are small persistent decreases in extracellular fluid or blood volume which are not perceived by the usual types of measurement and that such small changes, as Freis has pointed out (31), can have great influence on blood pressure levels. Moreover, it would seem that, independently of whether such changes exist, insufficient attention has been given to the possibility that chronic diuretic administration may serve a "guardian" function to plasma volume changes following normal dietary variations in sodium and that the efficient handling of electrolyte loads may be sufficient to maintain the antihypertensive action. It is not possible to overlook the fact that dietary sodium deprivation has been found to lower blood pressure with approximately the same frequency as thiazide therapy uncombined with other drugs (38, 42); and that such sodium restriction has been demonstrated to be antihypertensive in animals (42); or that sodium feeding, without necessarily producing hypervolemia or edema, has been shown to produce or to contribute to the production of experimental hypertension (43, 44, 45) and may even be related, in the form of average salt consumption, to the prevalence of hypertension in human populations (46).

It has been suggested that CTZ-like drugs could produce a loss of intracellular electrolytes, either as a consequence of the altered renal handling of cations or as a result of direct actions on the electrolyte content of tissues. Such loss of intracellular electrolytes has not been satisfactorily demonstrated. Though it has been proposed that the decrease in extracellular sodium in rats following hydrochlorothiazide may not be sufficient to account for the marked loss of sodium (47), Freis, in carefully controlled experiments in man (31), found that the sodium content of extracellular fluid lost, following acute CTZ treatment, corresponded surprisingly well with the cumulative negative balance of sodium. Thus, all the sodium lost could be accounted for, and no reduction of intracellular electrolyte had to be postulated. Similarly, indirect evidence of an extrarenal action of thiazide drugs on electrolyte and water balance is available (48, 49), but such an action is put in doubt by the failure of CTZ to modify tissue content of water and electrolytes in nephrectomized hypertensive and normotensive dogs (50).

The facts that the sodium content of arterioles in hypertensive rats is greater than in rats "cured" of previous hypertension by release of the renal artery constriction (51) and that there are important increases in the sodium content of small and large arteries in hypertensive rabbits (52) have suggested a greater water content in vessels from hypertensive subjects and a possible reduction in their internal diameter (51), a condition which could be reversed during the decrease in total body water which persists on chronic treatment with thiazide diuretics after extracellular fluid and plasma volumes have returned to normal (28). It is true that the search for a decreased sodium content of blood vessels of normotensive and hypertensive animals treated with thiazides has been negative (37, 41, 53), but negative findings are difficult to interpret in view of the great heterogeneity in the structure of the vascular wall. Measurements on skeletal muscle, taken by biopsy in hypertensive patients, indicate that long-term treatment with hydrochlorothiazide decreased the sodium and water content of this tissue (54, 55). If these results can have any meaning as an indication of what is happening in smooth muscle, they would support the possibility of changes in the sodium and water content of the vascular wall, which would lead either to a direct decrease in vascular resistance (56) or to the alteration apparently induced by benzothiadiazine substances in vascular sensitivity to catecholamines (57, 58, 59) and to other vasoactive compounds (59). Following up previous observations of significantly higher potassium content in aortas from hypertensive rats (60), and of positive correlation between arterial content of potassium, and the blood pressure in renal hypertensive rats (61), Freed has reported (62) that quinethazone lowers the blood pressure of such rats in association with a decrease in the potassium content of the aorta wall.

It is, of course, possible that reported changes in vascular sensitivity following thiazide diuretics could result from the classical renal actions of the drugs, i.e., volume changes unrelated to intracellular electrolyte concentrations. Thus, the increased vasodilating effects of trimetaphan, induced

by hydrochlorothiazide in hypertensive patients, were lessened by the re-expansion of plasma volume by dextran (32), indicating that extrarenal influences need not be invoked for explaining these actions. In addition, Greene et al. (63) found that the administration of CTZ, in hypertensive and normotensive patients, altered the cardiodynamic actions of phenylephrine only after the diuretic activity had produced hypotension and salt depletion.

Changes in vascular sensitivity following CTZ-like drugs could also be unrelated to renal or electrolyte actions. Thus, Preziosi and co-workers have reported (58, 64) that hydrochlorothiazide depresses responses to stimulation of adrenergic fibers at doses lower than those required to inhibit vascular reactivity to epinephrine and norepinephrine and have attributed this action to depletion of catecholamines, without offering any explanation as to why such depletion does not lower blood pressure in normotensive subjects. A possible influence of benzothiadiazine compounds on the handling of catecholamines is supported by experiments indicating that these drugs inhibit the renal tubular transport of epinephrine (240) and by finding that CTZ lowers the total catecholamine renal excretion in hypertensive patients (241).

Treatment of rats with CTZ was followed by an increase in granularity in the juxtaglomerular cells (41), indicating an increase in the renal content of renin (65). It is interesting to consider that the CTZ-induced increase in renin output could liberate angiotensin within the renal vasculature (66) in sufficient amount to increase vascular resistance and perfusion pressure, thus arousing renal antihypertensive mechanisms of the type suggested by Tobian, Schonning & Seefeldt (67). Increased angiotensin activity is indicated by increased aldosterone secretion during treatment with CTZ-like agents (33, 36, 68). Since pretreatment with aldosterone inhibits the vascular responsiveness to angiotensin (69, 70) and since hypertensive subjects are less responsive than normotensive individuals to the polypeptide (71), increased liberation of angiotensin could proceed without antagonizing the hypotensive actions of the thiazide drugs.

Mecamylamine and other ganglionic blocking agents.—Mecamylamine is generally considered to be the ganglionic blocking agent of choice for the treatment of hypertension. This seems to be the consequence of its smooth and prolonged effects, of its predictable intestinal absorption (2, 72), and of the less frequent development of tolerance during its chronic use (73). These characteristics, some of which are attributed to its tertiary structure, raise the question of whether there are also differences in the intimate mechanism of ganglionic blockade between this compound and the classical quaternary blocking agents. The suggested lack of dependence of mecamylamine blockade on frequency of stimulation is discussed and questioned by Paton (74) and is also put in doubt by the recent publication of McIsaac & Millerschoen (75) who found that mecamylamine and hexamethonium, over a large part of their dose-response curve, were entirely similar in producing a greater blockade of ganglionic transmission at high frequencies of stimulation; after partial blockade by either drug, waning of the nictitating mem-

brane tension followed continued repetitive stimulation; and both drugs produced a similar shift in the dose-response curves to acetylcholine. The greater intracellular penetration of the tertiary amine, which would be offered as a theoretical basis for possible differences in the intimate mechanism of ganglionic action, is put in doubt by the finding (76) that neuromuscular blockade in the isolated nerve diaphragm preparation, following mecamylamine, dimecamine, and pempidine, differed from that following the corresponding methiodides by a factor of less than 2.0, an observation which was interpreted as indicating that the active component of each amine was the cation, acting extracellularly.

An important limitation in the use of ganglionic blocking agents for the treatment of hypertension derives from the lack of specificity among available compounds for pathways involved in maintaining vasoconstrictor tone (2, 77). Comparative studies of the sensitivity of the superior cervical and the ciliary ganglia of cats to diverse ganglionic blocking agents (78) disclosed no significant differences between these two structures, and it was suggested that the development of selective blocking agents was unlikely. In a separate study (79) of the actions of several adrenergic agents on transmission through the superior cervical and ciliary ganglia of cats, again no difference in sensitivity between the two structures could be demonstrated despite the fact that possible variations in the content of catecholamine in sympathetic and parasympathetic structures could indicate that adrenergic mechanisms are of greater significance in sympathetic ganglia. In contrast, differential sensitivity in diverse cell groups within the superior cervical ganglion, to a number of ganglionic blocking agents, has been reported (80), it being accepted by the investigator that the results could be attributed to such conditions as a variable distribution of the drugs within the ganglion and not necessarily to differences in synaptic mechanism among cell groups.

Agreement has not been reached as to whether the well known increased pressor responses to catecholamines, which follow the administration of ganglionic blocking agents and could be related to the development of tolerance to these compounds, are the result of direct sensitization of adrenergic tissues by these agents or the consequence of ganglionic blockade itself. There are several recent studies bearing on this point (81–84), but most refer only to the acute administration of ganglionic blocking agents and are probably not pertinent to the problem of tolerance after prolonged use. In a study of the subacute actions of chlorisondamine (85), supersensitivity to norepinephrine was found to develop in the nictitating membrane after 7 days of treatment with the drug, but was not observed in control animals after a single dose. It was suggested that this supersensitivity is of the type which appears whenever the test structure is deprived of the usual influence of tonic impulses for a sufficiently prolonged period and is similar to the decentralization component of denervation supersensitivity. This component was found by Trendelenburg (86) to require 14 days to develop, which corresponds approximately to the time reported previously by Emmelin (87) as necessary

to achieve maximum sensitization following daily treatment with chlorisondamine. Pertinent to this problem are experiments carried out by Vidrio, Gómez & Pardo, on which only a preliminary report has been made (88), which indicate that the chronic administration of mecamylamine to cats over a period of up to three months produces no sensitization to epinephrine and only slight potentiation of norepinephrine, which is maximal at about two weeks of treatment and decreases on more extended administration of the blocking agent. In the studies mentioned (88), the degree of ganglionic blockade following single intravenous doses of mecamylamine was not modified by chronic treatment with the blocking agent. These data indicate that tolerance, on prolonged use of mecamylamine, does not depend on sustained supersensitivity to catecholamines or on the development of refractoriness to ganglionic blockade itself.

Since tolerance to the hypotensive actions of ganglionic blocking agents could be related to a gradual readjustment of the blood-pressure control mechanisms, an exploration was made (89, 90) of the possibility of developing a hypertensive state through the chronic administration of ganglionic blocking agents. A sustained hypertension of the type predicted was obtained following prolonged daily administration of mecamylamine and chlorisondamine, but not following reserpine, CTZ, or phenoxybenzamine. The hypertensive animals were sensitive to the blood-pressure lowering actions of reserpine, CTZ, and phenoxybenzamine. Once developed, the heightened blood pressure decreased only gradually when placebo was substituted for the ganglionic blocking agent. It was suggested that the development of hypertension of this type could depend on the prolonged interruption of the sympathetic pathways believed to regulate baroreceptor sensitivity, resulting in "false" information being delivered continuously to the central vasomotor areas and in a consequent readjustment of blood pressure.

Pargyline and other monoamine oxidase inhibitors.—Of the many MAO (monoamine oxidase) inhibitors that have been used clinically, only pargyline is generally thought of as an antihypertensive agent. It represents at least partial success in the effort (91) to separate MAO inhibition from the toxic effects attributed to the hydrazine group of drugs. It seems established that the compound lowers the blood pressure in experimental animals (92) and in hypertensive human subjects (93–96), and it is generally agreed that the effect is most marked in the orthostatic measurements (95). Side effects, especially central stimulation and orthostatic hypotension, have been a serious drawback to the use of the drug as sole agent in the control of high blood pressure (93, 94, 97). During treatment with the drug, the potency of pargyline as an *in vivo* MAO inhibitor manifests itself by hypertensive reactions, believed to be caused by tyramine or a tyramine-like substance (98), following cheese consumption (97), by potentiation of meperidine (99), and by central nervous system stimulation following α-methyl DOPA (100).

It has seemed natural to consider the vascular actions of pargyline as being in some way related to its influence on amine metabolism. In favor of this

possibility is the similar hypotensive activity shown by other MAO inhibitors, not related chemically to pargyline (101–103). However, it may be important that demethylated pargyline, reported to be as potent a MAO inhibitor as pargyline, showed no significant antihypertensive effects (94). There seems to be some correlation between the intensity of hypotensive action and the degree of measurable *in vivo* MAO inhibition (102, 104).

More crucial to accepting MAO inhibition as the basis for the hypotensive action of pargyline and other inhibitors of MAO would be experiments indicating how hindrance to the metabolic destruction of catecholamines, serotonin, or other biogenic amines would lead to the apparently paradoxical decrease in blood pressure. A situation comparable to the one brought about by MAO inhibition may exist in some patients with pheochromocytoma who have supine hypertension but marked postural hypotension (105), or, experimentally, in animals showing hypotension following discontinuation of infusion of norepinephrine (106). The increased excretion of conjugated metanephrine and normetanephrine in hypertensive patients treated with pargyline (104) might suggest that the products of ortho-methylation are involved in the hypotensive action of the MAO inhibitor. Normetanephrine behaves as a very weak adrenergic stimulant whose action is slightly prolonged after nialamide (107) and could conceivably displace norepinephrine either at storage sites or at receptor sites. This would be similar to the action attributed to α-methyl norepinephrine after treatment with α-methyl DOPA (108). Another possibility is suggested by the finding of Villarreal, Magaña & Pardo (109) that pretreatment of dogs with iproniazid was followed by greater susceptibility of adrenergic receptors to autoinhibitory phenomena, including more rapid tachyphylaxis to certain phenethylamines, and by the similar findings of Day & Rand (110) that, in cats treated with nialamide, the tachyphylaxis induced by tyramine and phenethylamine was much more rapid that that observed in normal animals.

The possibility that MAO inhibitors reduce blood pressure through blocking sympathetic ganglionic transmission has been considered (111). Such an effect has been demonstrated for certain MAO inhibitors (112) and attributed to the protection of catecholamines at the ganglionic site. However, Urquiaga et al. (113) have shown that this action is unrelated to MAO inhibition and is minimal in those compounds that are not phenethylamine derivatives. Pargyline itself has been shown to produce a very transitory ganglionic blockade with no apparent relation to MAO inhibition (114). The probable lack of significance of ganglionic blockade in the hypotensive actions of MAO inhibitors is generally accepted (115, 116).

Davey, Farmer & Reinert (117) report that in cats, treated with reserpine and then pithed, nialamide prevented the restoration of the pressor effects of tyramine by the slow intravenous infusion of norepinephrine and suggest that MAO inhibitors may exercise their hypotensive effects through hindering the re-entry of norepinephrine into the storage sites in nerve endings. In-

terference with the storage mechanism of catecholamines has also been postulated by other workers to occur after MAO inhibition (92, 118). Gatgounis & Aycock (119), on the other hand, find that several MAO inhibitors reduce the pressor and heart rate responses to stimulation of the adrenal medulla by nicotine and tetramethylammonium and suggest that interference with catecholamine release may be a contributing factor in the hypotension following MAO inhibition. MAO inhibitors can block catecholamine depletion by reserpine (120, 121) and by guanethidine and α-methyl-*m*-tyrosine (121). A bretylium-like action has been found, by Gessa, Cuenca & Costa (122), for a group of MAO inhibitors of diverse structure, including pargyline. Coexistence of MAO inhibition and bretylium-like activity has also been found in a series of benzyl and phenethyl guanidines (123) and in a series of guanidium analogs of bretylium (124).

A possible participation of serotonin in the hypotensive effects of MAO inhibitors was suggested by Hollander & Wilkins (125), who noted that MAO inhibitors enhanced the depressor action of serotonin on blood pressure. This amine seems to act on receptors involved in adrenergic vasodilation, in such a way that these respond with greater intensity to stimulation, with a resulting decrease in total vascular resistance (126).

Alpha-methyl DOPA and other decarboxylase inhibitors.—Interest in methyl DOPA (α-methyl DOPA) derives from early claims for a unique biochemical mechanism of action (127) and from numerous clinical reports indicating effectiveness in lowering blood pressure in a large fraction of hypertensive patients (128–134). These studies indicate that the drug possesses predictability of action comparable to that of substances like guanethidine; that it shows predominant activity on orthostatic but also some effect on supine blood pressure; that it acts through a reduction in peripheral resistance, including renal vascular resistance, without or with only occasional decrease in cardiac output; and that it does not impair renal function. In addition, side effects have been infrequent except for drowsiness and fluid retention. Organ toxicity, reviewed in a recent statement by the American Medical Association Council on Drugs (135), has not been prominent.

The potency initially reported (136) for methyl DOPA as an inhibitor of DOPA-decarboxylase has been confirmed in man (127), but its significance in blood pressure reduction is uncertain. Thus, decreased urinary elimination of VMA (vanilmandelic acid) which would be expected if catecholamine synthesis were depressed, was not found in patients receiving antihypertensive doses of methyl DOPA (129, 137, 138). The similar absence of decreased ortho-methylated catecholamine excretion following methyl DOPA (132) is of less clear interpretation because of the possible presence of ortho-methylated derivatives of methyl DOPA itself (139). When decreased excretion of VMA in hypertensive patients treated with methyl DOPA has been encountered, either a similar influence on VMA excretion was not obtained in a group of normotensive patients with rheumatoid arthritis (140) or there was

no correlation at all between this decrease and the antihypertensive effect (141). Also, against the significance of decarboxylase inhibition in the lowering of blood pressure is the fact that clear antihypertensive activity has not been observed following the administration of other potent decarboxylase inhibitors (129, 137, 142, 143). Acute lowering of blood pressure in hypertensive patients was observed following intravenous doses of 0.5 to 1.0 g of α-MMT (α-methyl-*m*-tyrosine), but this acute action may be unrelated to that observed on chronic administration of methyl DOPA.

Although the generally accepted decrease in catecholamine content of heart and other tissues following administration of methyl DOPA (144–146) could be attributed to a depressed synthesis of mediators, there is abundant evidence to indicate that it is independent of this enzymatic action (144, 145, 147, 148) and could result from a direct action on tissue binding of catecholamines (144, 149).

Depletion of catecholamines by α-MMT has been shown by Gessa et al. (150) to depend on previous decarboxylation to α-methyl-*m*-tyramine, since after pretreatment with potent decarboxylase inhibitors both the conversion of α-MMT to the amine and the release of brain and heart norepinephrine are blocked. Similar inhibition of decarboxylase did not block loss of heart norepinephrine caused by α-methyl-*m*-tyramine. The importance of the amine derivatives of methyl DOPA is supported by other studies (137, 145, 151, 152), but is put seriously in doubt by the finding that α-methyl DOPAmine, itself, produced no lowering of blood pressure in hypertensive patients, at doses of up to 300 mg, considered sufficient for the test, since the amounts of α-methyl DOPAmine recovered in the urine exceeded those appearing when the patients were treated with methyl DOPA (138).

Doubt as to the significance of catecholamine depletion in the antihypertensive action of methyl DOPA is implied by the absence of sympatholytic actions accompanying such depletion (108, 146, 153). Other direct actions of the metabolites of methyl DOPA therefore have been considered as an alternative explanation for the lowering of blood pressure. Although it is generally accepted that these metabolites are weak pressor substances when injected into the circulation, the suggestion has been made that they may behave differently when introduced into the body via their precursor amino acids (137). Carlsson & Lindqvist (152) suggest that the amine metabolites might enter norepinephrine and DOPAmine storage sites and take over the function of the physiological amines. This is supported by experiments showing that methyl DOPA, presumably through α-methyl norepinephrine, impedes reserpine-induced blockade of tyramine responses (108), and by the fact that, in cats pretreated with reserpine, the action of tyramine on the nictitating membrane is markedly enhanced by methyl DOPA (154). Enhancement of tyramine responses in man, following methyl DOPA, has also been reported (155); and the suggestion has been made that α-methyl amines, not being substrates of MAO, have more likely access to receptors following

release from tyramine sensitive sites at the nerve ending. Fixation of α-methyl norepinephrine in the hearts of rabbits pretreated with methyl DOPA and release of this amine and of the normal mediator by sympathetic stimulation and by dimethylphenylpiperazinium have also been observed (156). The displacement of norepinephrine by α-methyl norepinephrine is also supported by the finding (157) that, following administration of methyl DOPA in hypertensive patients, the excretion of ortho-methylated catecholamines is increased. Against the above "false mediator" action of α-methyl amino acid metabolites are the experiments of Gessa et al. (158) who find that, following the administration of α-MMT, catecholamine depletion was still evident at a time when α-methyl-*m*-tyramine was no longer present.

Guanethidine and other adrenergic neurone blocking agents.—Reserpine, bretylium, and guanethidine are thought of as representing groups of drugs that have in common the capacity of blocking adrenergic transmission at a postganglionic prereceptor site, through influences on either storage or release of catecholamines. Reserpine and the chemically related group of alkaloids have been largely replaced in the long term treatment of mild hypertension by the benzothiadiazine diuretics and currently find only limited application (2, 159–163) as antihypertensive agents. Bretylium has been disappointing when used clinically (164, 165) but has provided leads to the synthesis of additional, possibly interesting, chemically related compounds (166-169). Guanethidine, on the other hand, lacks the central actions of reserpine and, not being subject to the rapid development of tolerance which limits the usefulness of bretylium (164), has become an important antihypertensive agent, as attested by numerous clinical studies confirming its effectiveness when used alone (170–172) or in combination with other drugs (173, 174) and by the active continuing search for antihypertensive agents among chemically related groups (166, 175–179).

The pharmacological actions of this group of drugs have led to new concepts of adrenergic blockade, discussed elsewhere in this volume, and have received special attention in recent reviews of antihypertensive drugs. The data available up to 1962 are carefully evaluated by Greene (180) who concludes, in what refers to mechanisms of action, that, in the case of reserpine, hypotension is probably related to peripheral sympathetic neurone blockade brought about through catecholamine depletion, without it being possible to exclude a central component of action; that, in the case of bretylium, hypotension is produced by sympathetic neurone blockade through interference with mediator release by nerve impulses; and that, in the case of guanethidine, hypotension is again the result of adrenergic neurone blockade, to which catecholamine depletion and interference with mediator release at nerve endings contribute in, as yet, undetermined proportions.

The question of dependence of sympatholysis following guanethidine on catecholamine depletion has remained controversial. Such dependence is accepted by Brodie & Kuntzman (181). Kuntzman et al. (182) find further

evidence for it in the close correspondence of the duration of norepinephrine depletion with the total amount of guanethidine in the body. The evidence against dependence has been reviewed by Zaimis (183) who points out that, in general, after administration of guanethidine, the effects elicited by stimulation of sympathetic nerves are abolished long before significant reduction in tissue norepinephrine content can be demonstrated. This point of view is supported by additional experimental data (184–187). However, a possible fallacy in the line of reasoning is that guanethidine may produce important and persistent changes in the mobile norepinephrine pool of mediator, which would have a profound influence on sympathetic nerve responses, but which would be hardly detectable in measurements of total tissue norepinephrine content. That this is possible is suggested by the fact that guanethidine, in contrast with reserpine, releases norepinephrine via the nerve terminal from the mobile pool like the nerve impulse itself, and not, at least initially, from storage granules (188). It seems interesting to consider that, even should catecholamine depletion not be a prerequisite to sympathetic nerve blockade by guanethidine, such depletion may nonetheless be important for maintaining a persistent hypotensive response in the face of the well documented (189–192) guanethidine-induced sensitization of adrenergic effectors to catecholamines. The hypotensive response to bretylium, which produces sensitization (193) but not depletion, is not well maintained. The suggested bretylium-like action of guanethidine (180) has found support in several recent communications (194–196) and may contribute importantly to its hypotensive effect.

The possibility of a direct influence of guanethidine on vascular tone is suggested by experiments in which the compound produced vasodilation in the perfused forelegs of dogs pretreated with reserpine (197). The action became more pronounced as catecholamine depletion developed and did not seem mediated through release of catecholamines, histamine, or acetylcholine. It was partially blocked by dichloroisoproterenol. Increases in blood flow, induced by guanethidine at the perfused femoral bed of reserpine-pretreated animals, have also been reported (198), together with positive inotropic and chronotropic action on the heart. In this study, the cardiac effects were more sensitive to blockade by pronethanol than the peripheral action. In cardiac-denervated dogs, guanethidine produced only a small decrease in myocardial contractile force and a small increase in heart rate (199).

Phenoxybenzamine and other alpha-adrenergic blocking agents.—The compounds in this group are generally considered to be of minimal utility in the treatment of hypertensive disease, except possibly in combination with substances like hydrochlorothiazide (200) or with reserpine (201, 202). In regards to the latter possibility, Pickering (201) suggests that low doses of phenoxybenzamine might contribute to the effectiveness of treatment by antagonizing the increased sensitivity to catecholamines which results from chronic administration of the Rauwolfia alkaloids. It is possible that this

suggestion might bear consideration in relation to other antihypertensive agents which produce vascular hyper-reactivity to catecholamines.

The action of phenoxybenzamine and similar compounds on adrenergic mechanisms seems more complex than initially supposed. Thus, the increase in the venous outflow of catecholamines produced by phenoxybenzamine during stimulation of the splenic nerve (203), the increased excretion of norepinephrine after diverse antiadrenergic compounds (204), the increased catecholamine-related vasopressor activity of blood plasma which follows the intravenous administration of phenoxybenzamine, piperoxan, and dihydroergotamine (205), the increase by phenoxybenzamine in catecholamine output and in background pressor activity following stimulation of the splanchnic nerve to the adrenal medulla (206), and the increase by phenoxybenzamine in the catecholamine concentrations in arterial plasma following hemorrhage (207) have been interpreted as a drug-induced displacement of transmitter from receptor sites or as decreased destruction due to the lack of uptake by adrenergic receptors, these being involved in the inactivation of neurally released transmitter. However, it is possible that all of these effects could also be due to a reserpine- or guanethidine-like action on catecholamine storage or release. For example, Stafford (208) finds that phenoxybenzamine shares with guanethidine the capacity to increase the rate and force of contraction of isolated rabbit atria following epinephrine and norepinephrine and suggests that this might be due to an inhibition of uptake of the catecholamines into storage sites; Furchgott & Kirpekar (209) report that dibenamine and phenoxybenzamine increased the contractile force of electrically-driven guinea pig atria and interpret the results as indicating liberation of endogenous catecholamines, the action being minimal in preparations from animals pretreated with reserpine; Benfey (210) finds that the inotropic, chronotropic, and hypertensive effects of phenoxybenzamine after ganglionic blockade were avoided by previous treatment with reserpine. More direct evidence of this type of action is provided by D'Iorio & Laguë (211) who found that phentolamine, benzodioxane, dibenamine, and phenoxybenzamine released catecholamines from isolated ox adrenal chromaffin granules. The significance of these results is limited by the high concentrations of drug which were necessary to demonstrate the effect. However, von Euler, Stjärne & Lishajko (212) also found that phenoxybenzamine, at slightly lower concentrations, produced liberation of catecholamines together with adenosine triphosphate from adrenal medullary granules. Likewise, Axelrod, Hertting & Potter (213) report that phenoxybenzamine, like reserpine and tyramine, decreased tissue levels of administered H^3-norepinephrine, whether given before or after administration of the marked mediator. More recently, Hertting (214) reports that phenoxybenzamine, like reserpine and guanethidine, interfered with the binding mechanism of catecholamines. Boshart et al. (215) found that phentolamine and, to a lesser degree, tolazoline inhibited the weight gain of rat epididymal tissue and interpret the results as indicating either

drug-induced release of norepinephrine from sympathetic nerve endings or reflex liberation of the mediator by the drug-induced hypotension. The fact that pretreatment with reserpine, but not with ganglionic blocking agents, antagonized this phentolamine-induced fatty acid mobilization (216) would offer evidence in favor of the first of the two mechanisms. Finally, it seems interesting that DaCosta & Spector (217) found that adrenolytic and catecholamine depleting activities exist together in 1-[5,6-dimethoxy-2-methyl-(3-indole)-ethyl]-4-phenylpiperazine, an α-adrenergic blocking agent.

Hydralazine.—Despite the high incidence of toxic reactions which have followed the clinical use of hydralazine (218, 219) and which limit its recommended application to combined use with other antihypertensive agents (77), the study of its yet undetermined mechanism of action has continued. Most recent statements regarding this point (2, 220, 221) accept that the cardiovascular effects of the drug depend on mixed central and peripheral actions, and that the latter are possibly related to direct modification on smooth muscle activity, to inhibition of responses to vasoactive agents, to chelation of trace metals, or to inhibition of diverse enzymes. The ganglionic blocking action reported for hydralazine, initially investigated because of chemical similarity to iproniazid (222), should probably be interpreted in the light of the fact that the compound seems to stimulate, rather than to depress, MAO (220), and that the significance of the ganglionic actions of iproniazid itself have been put seriously in doubt (113).

The preponderant peripheral action of the drug is strongly supported by the experiments of Åblad (223) who found that when hydralazine was injected intravenously to man, at relatively low doses, it produced an increase in blood flow in one of the forearms, which was left with intact circulation during and after the administration of the drug, but only a pronounced and persistent decrease in blood flow in the other forearm which had been excluded from the circulation during and for 10 min after the injection of the drug. This seems a reasonable indication that any central action of the drug consists of vasoconstriction rather than vasodilation. In additional experiments (224), the injection of hydralazine into the brachial artery produced a slowly developing increase in blood flow in the injected side, whereas the blood flow in the contralateral side was unchanged. The known antiadrenergic action of hydralazine was confirmed, but it was found that vasodilation could be obtained on intra-arterial injection at doses which did not modify the vasoconstrictor effects of norepinephrine or of a cold pressor test (225). The above data are reviewed by Åblad (226) who cites additional results indicating that the pattern of action of hydralazine against vasoconstriction, induced by norepinephrine and by the cold test, is different from the corresponding patterns for phenoxybenzamine and guanethidine. The only relatively recent evidence of a central site of action, presented by Tangri & Bhargava (227), is not unequivocal in interpretation. The reported greater activity of hydralazine on neurogenic, as opposed to renal, hypertension does

not necessarily indicate central activity, since potency in neurogenic hypertension is typical of drugs which like phenoxybenzamine are generally accepted to have a peripheral site of action (228). Further, the fact that a dose of hydralazine which did not produce adrenergic blockade could inhibit the vasomotor response to stimulation of the medullary centers speaks of a central action only if direct vascular effects, separate from adrenergic blockade, can be excluded. Such is not the case with hydralazine.

Veratrum ester alkaloids.—Recent work on the vascular actions of the hypotensive veratrum ester alkaloids is not abundant. In studies by West & Foltz (229) of diverse hemodynamic parameters in the renal hypertensive dog, protoveratrine was shown to decrease the work of the heart and the coronary vascular resistance while maintaining coronary blood flow and cardiac output. This effect, which could be beneficial in therapy, stresses the potential interest of compounds that lower blood pressure through central and reflex actions and "should enhance the depressor components in the cybernetic regulatory systems of vasomotor control" (77). The structure-activity relationships for hypotensive action which have become apparent from the study of a large group of veratrum ester alkaloids are discussed by Kupchan (230). Since the greatest limitation in the clinical use of the veratrum alkaloids for the chronic treatment of hypertension is the pronounced emetic effects which they provoke at near therapeutic doses and which are poorly controlled by standard antiemetic medication, work has continued in search for hypotensive derivatives without this serious drawback. The measurement in unanesthetized dogs of the comparative hypotensive and emetic activities of a large number of synthetic esters would seem to indicate that only minimal dissociation between these two actions is possible (231).

Mebutamate.—The expectations in clinical usefulness, which should pertain to a centrally acting blood-pressure-lowering agent (232) reported (233) to produce "selective inhibition of spinal vasoconstrictor tracts", have not generally been fulfilled. Together with reports indicating some effectiveness as an antihypertensive agent (234, 235), others have indicated minimal or no activity (236–238). Most investigators, whether reporting favorable or unfavorable results, are in agreement that useful dose schedules produce serious central nervous system depression. The compound would seem to possess antihypertensive actions similar to those reported for meprobamate (239) and to those generally attributed to sedative drugs like phenobarbital (2). It is possible that the minimal degree of effectiveness could have been predicted from data in the first extensive publication (232) on the pharmacology of the compound: the lowering of blood pressure in the rat was reported to occur after oral doses of 120 mg per kg; and the most significant effect, i.e., inhibition of pressor responses induced by central stimulation, was found also with pentobarbital, except for qualitative differences of uncertain significance. The selectivity of the compound as an inhibitor of vasoconstrictor tracts was defined (233) on the basis of experiments on "spinal vasomotor

reflexes" which consisted of the administration of the drug intrathecally and the demonstration of a subsequent fall in blood pressure and an increase in peripheral blood flow. The action reported lasted only approximately 20 min, whereas the blood pressure responses attributed to the drug lasted several hours (232). The very unique central action might thus be unrelated to the observed clinical actions and might be thought of, not as an indication of the mechanism of action of mebutamate, but rather as a lead to be pursued in the search for new and possibly more useful compounds.

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