DRUG TREATMENT OF HYPERTENSION

S. W. HOOBLER AND A. S. DONTAS

Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan

Although considerable effort has been expended in seeking the mechanisms of human essential hypertension, we still lack knowledge of the cause for the generalized increase in peripheral vascular resistance which appears to be the fundamental abnormality in this condition. Consequently, attempts at therapy with drugs represent treatment of the symptom rather than the underlying disease, a situation comparable to treating hyperpyrexia without knowing the cause. This problem has been discussed in several recent reports in which the place of drugs in the management of hypertensive disease has been considered (5, 26; also 4, 44, 79, 83, 120, 163, 230, 287).

However, just as lowering fever intermittently may permit the patient to tolerate the toxic process more successfully, so reduction of excessive hypertension, even partially, may help the patient withstand the ravages of the disease provided the blood flow to vital organs remains adequate. Therefore, reduction of extremely elevated pressures in the vascular system, even if only for relatively short periods of time, seems rational in an attempt to reduce cardiac work, prevent retinal and cerebral hemorrhages, and possibly to prevent progressive damage to the arteriolar wall.

This school of thought, advocated mainly by research workers in England and New Zealand (214, 255), believes that "whatever the underlying disease, the course of hypertension would be of the malignant type if the arterial pressure was sufficiently raised and of the benign type if the rise was less (214)." Fibrinoid arteriolar necrosis and papilledema are thought to be due to high intra-arterial and cerebrospinal fluid pressure, respectively. They feel that a variety of hypotensive procedures can cause regression of these anatomical lesions and improve prognosis. On the other hand, acute hypotension may precipitate such conditions as cerebral thrombosis, renal failure and coronary thrombosis if regional circulations cannot adapt to the reduced blood pressure by local vasodilatation. That such accidents do not occur more often during hypotensive therapy is probably the result of the intrinsic ability of the regional circulations to adapt to lowered perfusion pressures. For example, reduction in blood pressure by lumbodorsal sympathectomy is not followed by concomitant reduction in cerebral blood flow, and renal blood flow remains relatively constant despite a variety of procedures lowering the blood pressure (115). Consequently, lowering of blood pressure can be tolerated in many instances by the hypertensive patient provided the regional vessels are sufficiently free of sclerosis to be capable of dilatation, and the rate or extent of blood pressure reduction does not exceed their capacity for adjustment. The difference in the response of younger and older patients to hypotensive therapy is a further example of this point. Reduction of pressure in elderly persons often results in cerebral thrombosis, presumably because their sclerotic cerebral vessels are less capable of dilating when systemic

blood pressure is reduced; the decrease in rate of blood flow, in the presence of pathological changes in the vascular walls, leads to thrombus formation.

An ideal anti-hypertensive drug should produce a prolonged reduction of blood pressure in a large percentage of patients through generalized peripheral vasodilatation without side effects or development of tolerance during chronic administration. Such a drug is not available. A drug of limited practical value for chronic administration should meet the following minimum requirements:

1. Development of tolerance should not be marked.
2. The therapeutic dose should be considerably less than the toxic.
3. The side effects of prolonged administration should not be severe enough to interfere with the patient's normal way of living.
4. The diastolic blood pressure should be reduced by 20 mm. Hg or more for one fourth to one half of each day.
5. Cardiac output and cerebral, renal and coronary blood flow should not be reduced substantially.

Unfortunately most of the articles to be reviewed fail to assess one or more of the requirements listed above and in this sense are incomplete. To permit proper evaluation, a report on an anti-hypertensive drug should include the following information: (1) the extent and the significance of blood pressure reduction as compared to adequate control observations, including adequate pretreatment observations or the demonstration of a rise in blood pressure when the drug is replaced by a placebo; (2) the length of the observation period, which should exceed two months because tolerance can often develop after several weeks of drug administration; (3) the number of patients initially rejected because they were unable to tolerate the drug in question (*e.g.*, this information is lacking in certain studies on veratrum derivatives); and (4) the side effects and interference with normal activities, associated with chronic administration.

In the following pages we will review, along the lines of the preceding discussion, the various drugs claimed to be effective in lowering the blood pressure. The progress of experimental pharmacology in the last four years can be judged from the fact that, while reviews on the medical treatment of hypertension in 1948–49 confined themselves almost wholly to thiocyanate therapy (185), recent symposia on the same topic (5) include at least five other anti-hypertensive drugs which for the most part are now under clinical evaluation or accepted as superior to thiocyanates. The data covered in this review are taken from the literature published between 1949 and 1952, but no attempt is made at an exhaustive coverage. Animal investigations are included only when they provide helpful information as to drug action. No attempt is made to review the diagnosis or treatment of pheochromocytoma, or the management of other types of hypertension not ordinarily classified as essential or malignant; nor are surgical, psychological, dietary or physical measures included in this review. Acute treatment of the hypertensive subject is mentioned only where necessary for coverage of the subject. The major purpose of this review, then, is to deal with the mode of action of the anti-hypertensive drugs in the human subject and their applicaiton in the chronic treatment of hypertensive disease.

The drugs to be discussed are classified according to their locus of action, as follows:

I. *Drugs which interfere with sympathetic vasomotor activity.*
   A. *Adrenergic blocking agents:* β-Haloalkylamines (dibenamine, dibenzyline), imidazolines (priscoline, regitine), benzodioxanes (benodaine), yohimbine, ergot alkaloids.
   B. *Ganglionic blocking agents:* Quaternary ammonium compounds (tetraethylammonium, methonium compounds, piperidinium substitutes), thiophanium derivatives (arfonad).
   C. *Centrally-acting inhibitors of sympathetic vasomotor activity:* Hydrogenated ergot alkaloids, pentaquine, 1-hydrazinophthalazine.
   D. *Agents activating afferent vascular reflex arcs:* Veratrum alkaloids.

II. *Drugs acting directly on vascular smooth muscle:* Papaverine, nitrites, adenylic acid.

III. *Drugs exerting unknown or mixed effects:* 1-Hydrazinophthalazine, thiocyanates, sodium nitroprusside, *Rauwolfia Serpentina*, vitamins, dimercaptopropanol, pyrogens, bismuth and cobalt salts, elemental iodine, caffeine.

I-A. ADRENERGIC BLOCKING AGENTS

Mode of Action

An agent which blocks the release or inhibits the effect of the sympathetic mediator at the neuroeffector junction would seem to be ideal for inhibiting sympathetic vasoconstriction since "it is only at this point that the sympathetic nervous system differs sufficiently from other divisions of the autonomic nervous system to allow a good possibility of block of sympathetic vasoconstrictors without complicating cross reactions" (26, p. 503). The agents now available also block circulating epinephrine even more effectively than locally produced norepinephrine, the probable sympathetic mediator of vasoconstriction. For this reason, they are particularly useful in the diagnosis and control of pheochromocytoma, but most are ineffective in clinically suitable doses in blocking sympathetic vasoconstrictor activity. The actions of various agents which compete with epinephrine at the receptor site have been reviewed by Nickerson (195). Many of these are ineffective in essential hypertension either because their action is transient or because they cannot be given clinically in sufficient dosage to modify significantly sympathetic vasoconstrictor tone. Included in this category are the imidazolines (priscoline (41, 196, 276, 282) and regitine (67, 171, 250)) and the benzodioxanes (67). The ergot alkaloids are capable of producing peripheral adrenergic blockade in laboratory animals; but, when employed in doses that can be given safely to man, their primary site of action is central; they are therefore discussed in a subsequent section (I-C).

The beta-haloalkylamines combine irreversibly with the receptors of the effector cell, and thus have the greatest promise because of their long duration of action. Their pharmacodynamic effects in animals have been reviewed by Nicker-

son (195). In dogs no change or a slight increase occurs in renal blood flow, with a decline in renal resistance and no change in glomerular filtration rate and T_m glucose (190). In human studies, oral administration did not change blood pressure, renal blood flow or $T_{m\ PAH}$ in the supine position but did increase glomerular filtration rate (75). In patients tilted head up under influence of the drug, these indices were depressed proportionately with a 25% fall in mean blood pressure. Peripheral blood flow is greatly augmented by intravenous doses (293) and moderately increased by oral therapy (188, 219). No clinical studies of the effects on cardiac output, splanchnic blood flow or cerebral blood flow have been published. A marked blockade of pressor responses to cold (111, 188, 294) and of overshoots following the Valsalva maneuver (188) have been reported.

Human Pharmacodynamic Effects

Numerous studies on the effects of acute intravenous administration of dibenamine (5 mgm./kgm.) (195, 196, 294) or its less toxic and more potent congener, dibenzyline (0.5 to 2 mgm./kgm. intravenously) have been reported (6, 15, 293). In general, the blood pressure of the recumbent hypertensive patient is reduced, and in some cases of malignant hypertension improvement has been reported (111, 294). Side effects, however, limit their usefulness. Severe orthostatic hypotension with distressing reflex tachycardia is prominent. Such symptoms also occur, but with less severity, in other forms of therapy, *e.g.*, ganglionic blocking agents or hydrazinophthalazine, since sympathetic cardio-accelerator pathways are not blocked by these drugs. Subjective weakness, nasal congestion and drowsiness are also apparently unavoidable side effects of dibenzyline; further toxic effects have been reported from dibenamine, including one case in which auricular fibrillation was apparently induced (113).

Oral treatment with dibenzyline has been tried in the management of hypertension (6, 15, 47, 75, 111, 188, 219); the reported results are not uniform either as to blood pressure reduction or side effects. In general, from the limited number of studies reported, it is agreed that the results are not impressive, although there was considerable variation in the oral dosage employed (20 to 480 mgm. per day) and some doubt as to the amount of drug absorbed from the gastrointestinal tract. Furthermore, no systematic effort has yet been made to overcome some of the distressing side effects by prolonged administration, although accommodation to these effects is said to occur.

It is indeed unfortunate that the side effects limit the clinical usefulness of these adrenergic blocking agents. However, their effectiveness in causing epinephrine reversal is most interesting. It has been shown that epinephrine causes considerable hypotension after dibenamine blockade in man (197) and Allen has shown sustained and effective blood pressure reduction in a case of malignant pheochromocytoma with oral dibenzyline (6). This principle has been utilized (60) in chronic oral therapy with revertonal, in which yohimbine is combined with epinephrine as well as phenobarbital and pilocarpine. A reduction in blood pressure, sometimes striking, is reported in 125 out of 250 cases of hypertension.

Unfortunately, few details are given and although the author states that he used an antioxidant with the epinephrine, it is difficult to see how a sufficient dose could have been absorbed for this agent to be a significant factor in the response. No observations of the effect of the mixture after exclusion of epinephrine were reported. The possibility of trying the more effective agents (β-haloalkylamines) with epinephrine by parenteral administration for the treatment of essential hypertension or emergencies deserves further study, although tachycardia might limit its acceptance by the patient. It is perhaps in instances of hypertensive crises, that the adrenergic blocking agents will show their greatest promise.

I-B. GANGLIONIC BLOCKING AGENTS

Since the discovery by Acheson and collaborators (2, 3) of the ganglionic blocking properties of the tetraethylammonium ion, numerous publications on this agent have appeared; the drug has been reviewed extensively (183) and will not be discussed in this report. The search for drugs with the same properties as the tetraethylammonium ion but with a longer or more selective action has resulted in the discovery of a number of active compounds which appear to depend on the presence of the quaternary ammonium ion for their action (211). Lately, compounds possessing a thiophanium or other grouping have been reported and will be discussed separately.

Mode of Action

Paton and his collaborators (201, 206–210), studying the properties of the polymethylene-bistrimethylammonium series, found that the hexa- and pentamethylene derivatives interfere with the transmission of impulses at autonomic ganglia, rendering the post-ganglionic neurone refractory to pre-ganglionic stimulation. These authors showed that the drugs do not interfere with the release of acetylcholine in the ganglion and do not possess any initial "nicotinic" excitatory action. They seem not to affect the post-ganglionic nerve trunks or the vascular system directly, nor to possess histamine-liberating, muscarinic, or curarizing action in the usual dosage. They conclude that these substances act by competition with acetylcholine at the ganglion cell and do not depolarize the post-ganglionic neurone (208). However, the compounds do have certain excitatory actions, for example, contraction of the cat's ileum by hexamethonium (210), and pressor and adrenal-stimulating effects of tetraethylammonium (2, 62, 183, 203, 261) and hexamethonium (62). It is possible to explain such effects of hexamethonium by assuming that it depolarizes certain post-synaptic elements, as does the decamethonium homolog (209). This possibility deserves further investigation.

It is apparent that these agents possess in common the therapeutic disadvantage of blocking parasympathetic as well as sympathetic ganglia. They do not block acetylcholine effects elsewhere than in the ganglia; in fact, the peripheral effects of acetylcholine are prolonged following ganglionic blockade (210). The pressor action of epinephrine is also prolonged and enhanced (210), probably due to the inability of compensatory mechanisms to intervene. This is

common after ganglionic blockade of any kind and appears also after denervation of the carotid sinus.

The observation that ganglionic blockade produces greater reductions in blood pressure in hypertensive than in normotensive subjects has led to the inference of sympathetic over-activity in hypertension. While it is true that tetraethylammonium causes greater increments in regional blood flow when sympathetic tone is artificially elevated (142), that excessive decreases in blood pressure occur in patients with hypertension due to central nervous system disease (126), and that the totally denervated human subject shows no blood pressure decrease after tetraethylammonium, it should be remembered that the magnitude of vasodepressor response to a vasodilating drug is dependent on other factors such as elasticity of the large arteries and cardiac output. This explains the unusually marked reduction in blood pressure following injection of any ganglionic blocking agent in the normotensive elderly subject presumably with normal vasomotor tone, but with reduced ability for non-neurogenic compensation of the arterial tree (126). Likewise, the sensitivity to ganglionic blockade is increased in the subject dehydrated by a low salt diet (255) or by mercurial diuretics. It may be postulated that venous pooling accomplished by the drug, superimposed on the hypovolemic state, so interferes with venous return as seriously to impair cardiac output and thus magnify the hypotensive effects. It can thus be seen that no reasonable relationship between blood pressure decline and extent of inhibition of sympathetic activity can be inferred unless these other factors, difficult to assess in the human subject, are also considered.

Human Pharmacodynamics

The *tetra-* and *penta-methonium* compounds have the same type of action as the *hexamethonium* derivative with which most studies have been performed (207). According to Grob and Harvey (104), pentamethonium has approximately 40 times the depressor effect and 3 to 4 times the duration of action of tetraethylammonium when given intravenously in equimolar amounts. According to Paton and Zaimis (210, 211) hexamethonium appears slightly more active than the pentamethylene derivative as far as hypotensive action is concerned. The *bis-ethyldimethylammonium* substitution product of hexamethonium (used in England under the name of *M. & B. 1863*) is twice as active as *hexamethonium* in lowering blood pressure in the cat (283) and man (152, 254). A closely related compound, *pendiomide*, has similar properties and has been used extensively in Europe (13, 24, 28, 30, 156, 213). According to Smirk, the relationship between subcutaneously injected *hexamethonium*, *pendiomide* and *M. & B. 1863* is 15:17:7.5, for equal hypotensive effects in man (254).

In general, these drugs produce the circulatory effects to be expected from blocking or inhibiting sympathetic vasomotor tone, plus the modifying action of concomitant vagal blockade. Compared to the effects of paravertebral block on blood flow in the foot, 50–100 mgm. of hexamethonium ion intravenously produces an almost complete sympathetic blockade in man (241). The sympathetic vasopressor reflexes in man are likewise suppressed (8, 28, 71, 104, 156).

The total peripheral resistance is lowered in hypertensive man with a resulting reduction in blood pressure. Slight decrease in cardiac output is usually reported (Table I). Associated with these reductions there is a decrease in venous pressure, especially in congestive failure (138, 220), and presumably in right atrial pressure; these reductions are probably the result of inhibition of venous constrictor tone and consequently of venous return to the heart. Total peripheral resistance is decreased and there is a shift of blood from pulmonary to peripheral vessels (280). However, it has been reported (96) that the drug increases cardiopulmonary volume, perhaps by reducing sympathetic tone of the pulmonary vessels. The matter needs further investigation. Regional resistance is lowered in the

TABLE I

*Pharmacodynamic studies of ganglionic blocking agents in man**

FUNCTION	INCREASE	NO CHANGE	DECREASE
Cardiac output	—	85(F), 96(F), 104 (F)	28(W, P), 158(F, P), 220(B), 280(F)
Total peripheral resistance	—	—	28(P), 85, 237(G), 280
Renal blood flow	140	—	9(G), 31, 85(i), 140, 165(i), 192(i)
Foot blood flow	7, 8, 24, 38, 62, 71, 72, 85, 220, 241	—	—
Hepatoportal blood flow	—	85	—
Cerebral blood flow	—	52, 192	—
Glomerular filtration rate	—	140	9(G), 85(i), 140, 165, 193(i)
Urine volume	—	—	9(G), 31, 85, 193
Vasopressor reflexes	—	—	8, 9(G), 28(P), 71, 104, 153(G), 154 (G), 156(P), 237(G)
Heart rate	7, 8, 9(G), 38, 104, 255, 256	13(P), 28(P), 153 (G), 237(G)	138

* Numbers indicate references; parenthetical letters, footnotes as follows: F = direct Fick method; B = Ballistocardiographic determination; W = Wezler-Böger method; i = initially, then return to control values; P = *Pendiomide*; G = other ganglionic blocking agents, besides *hexamethonium* and *Pendiomide*.

extremital, splanchnic and cerebral vessels, and is initially unchanged in the kidneys (Table I). The decreases in regional resistance do not necessarily imply the prior existence of sympathetic tone since the changes may be due to local vascular autonomy, at least in the renal and cerebral circulations. In man, local renal vascular accommodation is suggested by the observation that renal blood flow initially falls when the blood pressure declines, but rises in subsequent periods, despite the continuance of the hypotension (85, 165). Prolonged oral treatment, therefore, does not seriously depress renal function in most cases (193). The glomerular filtration rate, sodium excretion and urine volume are reduced out of proportion to the change in blood flow in most cases; however, despite maintained reductions in the blood pressure, a gradual recovery of these func-

tions to approximately control values is reported (85, 193), except for urine volume which remains depressed. $T_{m\ PAH}$ was not depressed in humans following acute administration, which indicates that the number of functional nephrons did not change during hypotension and that the reduction of glomerular filtration rate results solely from decreased filtration in the active glomeruli (193).

Effects on Blood Pressure

A. *Acute*

Given parenterally, the ganglionic blocking agents acutely lower the blood pressure, much more so in hypertensive subjects than in recumbent normotensives. The type of hypertension does not appear to be an important determinant of the degree of fall; but excessive reductions may be encountered in the arteriosclerotic and in the short-term treatment of hypertensives with renal insufficiency, in the latter perhaps because the drugs are disposed of through the kidney primarily by glomerular filtration and with minimal tubular excretion (297). When renal function is impaired in severe hypertension the drug is retained in the body (180), especially if the adjustment in glomerular filtration rate, mentioned above, fails to occur. The parenteral dose required for a definite reduction in blood pressure is extremely variable. Some patients respond to doses in the neighborhood of 5 to 10 mgm. of the ion, whereas others are unaffected by as much as 75 mgm. For this reason, the intravenous dose should be administered slowly, with the patient sitting and with constant check on the blood pressure. Gratifying relief of acute hypertensive symptoms such as headache or encephalopathy has been obtained in this manner. Pulmonary edema is also relieved, because sympathetic blockade produces a rapid shift of blood from the pulmonary to the peripheral circulation and thus reduces cardiac work and improves cardiac competence (138, 152, 236, 280).

The hypotension is accentuated markedly by an upright posture or by mechanical devices which increase venous pooling (220, 238). This effect occurs before the reduction in the supine blood pressure and outlasts the latter. It is accompanied by a marked tachycardia in the upright posture, which suggests that chemical ganglionic denervation of the heart is incomplete with these doses. The orthostatic hypotension seems to be due to venous pooling and decreased venous return to the heart, because cardiac output and right atrial pressure fall sharply (104). The venous return and blood pressure can be restored to normal by immersing the lower extremities in a water bath (220). However a reduction in cardiac output occurs normally in the erect position, and Gilmore *et al.* (96) claim that it is not accentuated by hexamethonium. It is probably true, however, that a sharp decline in blood pressure in severely hypertensive patients in the erect position is associated with a more than usual reduction in flow in cerebral, renal and other vascular beds (192). The resulting cerebral ischemia is the basis of the frequently observed dizziness in the upright posture.

B. *Chronic*

No other drug currently provides as certain relief of hypertension for so long a period as the methonium compounds. Both subcutaneous and oral treatment

programs have been devised. By the oral route, it is stated that only 5 to 10% of hexamethomium is absorbed (the usual starting dose is 250 mgm. once or twice a day); if variations in gastrointestinal absorption or motility occur, an innocuous dose may suddenly be transformed into a fatal overdose (103). Because of this, many investigators prefer parenteral administration, even though the patient must be instructed in self-injection of the drug. Some, however, have reported good results with oral therapy (Table II). Kilpatrick and Smirk (139) report that only about 1 in 4 patients can be managed satisfactorily on the oral program alone, owing to variable absorption and unpleasant side effects. Furthermore, when large doses of the drug are administered as the bromide salt, the reduction in pressure may be in part attributable to a bromide effect, and cases of bromidism have been reported (39, 94, 139, 151). Consequently, the drug is usually administered orally as the chloride. Moyer *et al.* have had experience with 120 patients treated for 3 to 18 months with an average dose of 750 mgm. 4 times daily. They report that, after 6 months of therapy, 79% of those patients complaining of headache and 71% of those with precordial pain were improved, and

TABLE II

*Therapy with ganglionic blocking agents**

RESULTS	POOR	MODERATELY GOOD	IMPRESSIVE
Short-term parenteral	28(P)	—	139, 252, 255, 256
Prolonged oral	23, 31, 94, 151, 152(G), 162, 273	29,39, 40, 103, 169, 239	39, 192, [245], [246]
Mixed	—	139, 256	—
Parenteral	28(P), 31, 158(P)	82, [130], [147], 216	251, 254(G), 255

* Numbers indicate references.

[] = combined therapy with 1-*hydrazinophthalazine*. P = *Pendiomide* treatment; G = ganglionic blocking agents other than pendiomide or hexamethonium.

the ocular fundi were improved in 40% of all patients. However, 45% of male patients developed impotence; 38% of patients experienced weakness and dizziness, 22% constipation and 19% anorexia. Patients with combined renal and cardiac involvement were the most difficult to control and, in those with markedly impaired renal function, frank excretory failure occurred even with minimal depression of glomerular filtration rate. Representative of their observations were 49 patients with an average blood pressure of 210/129 mm. Hg, who showed a reduction to 172/107 (recumbent) and 140/91 (standing), after 100 days of treatment (192). They also state that the fall in blood pressure during prolonged hexamethonium therapy in ambulatory cases is more pronounced than the depression of renal function in patients without severely damaged kidneys (76).

Most attempts at therapy have been by means of parenteral injections given 2 to 3 times daily. There is little question that the blood pressure of the hypertensive patient can be effectively reduced by ganglionic blocking agents for short periods of time (Table II). The effects of prolonged treatment (*i.e.*, more than one month) on the blood pressure are a matter of controversy. Smirk, who has had the greatest experience with this form of treatment, reports persisting effects

for 2 to 14 months (255). If one seeks only reduction of the standing blood pressure, the effect can be secured with relatively small daily doses. Smirk, who advocates this technic, recommends it as a means of interrupting the vicious circle whereby hypertension *per se* accelerates vascular disease (251, 255). It is reported, furthermore, that the patient rapidly accommodates to orthostatic hypotension after prolonged treatment, so that it is not a serious problem in the management of the disease (82, 255). A low salt diet potentiates the hypotensive effect of hexamethonium, so that patients on such a diet need smaller amounts of drug.

The greatest obstacles to prolonged treatment are the limitations imposed by the unavoidable side effects of ganglionic blockade and the development of tolerance. Postural hypotension is sufficiently severe at the beginning of treatment to confine the patient to bed for one to two hours after each injection, and since these must be given at least two to three times a day, he is partially incapacitated. If excessive reductions in blood pressure occur, complications such as cerebral or coronary thrombosis may ensue (103, 151). Paralytic ileus (99) may occur if intestinal motility is not stimulated by regular catharsis and/or urecholine therapy (82, 296). Minor annoyances are atony of the bladder and mild disturbances of accommodation. Tolerance may develop, especially during the first 1 to 2 months of treatment, so that the dose must be constantly increased up to a certain point which differs with the individual case (192, 255). It has been reported (254) that cross tolerance occurs between the three commonly used drugs (hexamethonium, M. & B. 1863 and pendiomide). It is probable that significant reductions in blood pressure in the erect posture can ultimately be achieved in most patients; Smirk reports significant reductions over treatment periods of 2 to 23 months, and discusses the problems of such management (251, 256). A summary of results of short-term and prolonged therapy with ganglionic blocking agents is presented in Table II.

It must be recalled that if hexamethonium is given in doses only sufficient to provide a tolerated orthostatic hypotension (the only practical method for long-term management), then during periods of recumbency the blood pressure will not be appreciably lowered. Furthermore, with a practical two dose per day regimen, orthostatic hypotension from the first injection tends to disappear before the next. For this reason Freis and collaborators (77, 130) and Yonkman *et al.* (296) recommend the interval administration of 1-hydrazinophthalazine to reduce the peaks of hypertension. Schroeder (245, 246), observing that sympathectomy enhances the effectiveness of hydrazinophthalazine, has used hexamethonium in combination with the latter drug. Regardless of whether this combination is synergistic, it is perhaps logical to give a drug which produces an increase in renal blood flow along with hexamethonium which may cause renal ischemia.

Attempts to prolong the effects of parenterally injected hexamethonium include a continuous infusion technic (252), and suspension of the drug in polyvinyl pyrrolidone (168, 253) or dextran (253); results with these technics seem encouraging at least in short-term therapeutic trials.

Despite its many disadvantages, it is certain that treatment with methonium compounds is beneficial in some cases of malignant hypertension. The rapid improvement in retinopathy, encephalopathy and cardiac status fully justify its short-term use in such hypertensive emergencies. However, care must be exercised when this acute therapy is proposed for patients with impending cerebral or coronary thrombosis or who are in renal failure with azotemia. It must be remembered that with the exception of the circulation to the hands and feet, the drug produces no significant hyperemia, and the declines in regional resistance compensate exactly, through local vascular adjustments, to the decline in pressure. Thus, if the hypotension is too severe, or if the vessels in some vascular beds are too sclerotic to dilate, regional ischemia may result from therapy with ganglionic blocking agents. This effect is accentuated when the patient assumes the erect posture because reduction of cardiac output is then superimposed.

Other Ganglionic Blocking Agents

In addition to the above drugs, several compounds have been found to possess ganglionic blocking activity; but they have not received extensive clinical trial. As mentioned previously, pendiomide, a ganglionic blocking agent closely related to pentamethonium, has been studied in Europe, mostly by acute administration. Its pharmacological effects are similar to those of pentamethonium (24, 28, 30), and it has approximately the same potency (207). Following parenteral administration of 0.5–1.5 mgm./kgm. in man, a moderate drop in supine blood pressure occurs together with a rise in digital skin temperatures, an inhibition of vasomotor reflexes (cold pressor, carotid sinus) and a marked orthostatic hypotension (13, 28, 156). It has been used with success in the treatment of cerebrovascular emergencies (28, 213, 216). Attempts, however, at chronic parenteral treatment of hypertensives led to rapid tolerance to the drug within a few days (28, 158), despite dosage increases from 5 to 30 mgm./kgm. daily. Tolerance to pendiomide seems to develop faster than that to hexamethonium and M. & B. 1863 (254).

The thiophanium derivative RO 2-2222 (arfonad) (121, 161, 181, 218, 237) can be given only parenterally and has been used to combat cardiac hypertensive emergencies (237). It has the advantage of rapid onset and short duration of action when given by intravenous drip. Its hemodynamic properties in humans have been studied by Assali *et al.* (9) who conclude that its action is closely similar to that of tetraethylammonium. In addition to demonstrable ganglionic blockade, part of its effect may be due to histamine liberation (121, 181). It also possesses a marked direct vasodilator non-histaminic action as measured by McCubbin and Page (161) in the perfused denervated hind-leg of the dog. Interest in this substance is justified by its properties, *i.e.*, short-lasting action, direct vasodilatation and ganglionic blockade not dependent upon a quaternary ammonium group; but it is not suitable for chronic antihypertensive treatment.

Another compound *2,6-dimethyl, diethyl-piperidinium bromide* has been studied in animals and man by Longino *et al.* (153, 154), but no extensive clinical investi-

gations have been reported. It appears to have a ganglionic blocking activity similar to that of tetraethylammonium.

I-C. CENTRALLY ACTING INHIBITORS OF SYMPATHETIC VASOMOTOR ACTIVITY

Dihydrogenated Ergot Alkaloids

The hydrogenated ergot alkaloids were first synthesized by Stoll and Hoffman (260) in 1943 and their pharmacological action in animals has been described by Rothlin (233). They include the dihydrogenated derivatives of alkaloids of the ergotoxine group (ergocryptine, ergocristine and ergocornine). The dihydrogenated product of ergotamine has not had extensive trial in the therapy of hypertension. A mixture containing 0.3 mgm./ml. of each of these three alkaloids has been marketed under the name of hydergine and is sometimes referred to in the literature as "CCK-179." The most widely used single alkaloid of the mixture is dihydroergocornine ("DHO 180"), the effects of which do not differ significantly from those of the mixed alkaloids. Their pharmacological circulatory effects in animal studies are the following: (1) central depression of vasomotor centers, (2) central vagal stimulation, (3) reduction or reversal of pressor effects of sympathomimetic amines without affecting their cardiac or vasodilator properties (adrenergic blocking action), and (4) very weak peripheral constrictor action (134, 232, 233). This latter property is in sharp contrast to the strong vasoconstrictor action of the naturally occurring alkaloids of ergot.

Acute experiments in the human subject confirm some of these findings in animals. A general description of the actions of these alkaloids and a comparison with the veratrum alkaloids has been given by Wilkins *et al.* (288). While proof of the central site of action in the human subject cannot be directly obtained, evidence supports the theory that the major action of these drugs on the blood vessels requires an intact sympathetic innervation. Thus most of the vasodilatation, as will be discussed below, is abolished in sympathectomized extremities (16, 32, 34) and blood pressure is reduced to a lesser extent in patients who have had lumbodorsal sympathectomy (33, 91) or spinal cord transections at D-4 (33). Bradycardia following dihydroergocornine is probably the result of central vagotonic effects and removal of sympathetic cardioaccelerator tone since it is partially blocked by atropine (33, 34, 90, 91). Pressor responses attributed to reflex stimulation of sympathetic activity (cold pressor, Valsalva, postural reflexes and reflex digital vasoconstriction) are usually inhibited (59, 64, 90, 91, 134, 200, 288, 292). Central vagal stimulation is inferred from the observed emesis, bradycardia and yawning when the drug is administered to man. The adrenolytic property can be demonstrated only with difficulty in the human subject because the doses which can be tolerated are considerably smaller than those employed in animals. Crucial experiments have demonstrated failure to block the pressor effects of intravenous epinephrine or norepinephrine (16, 90) or to inhibit epinephrine vasoconstriction in the human extremity (16, 123), although Kappert claims that parenteral administration of these ergot alkaloids can prevent the constrictor effects of epinephrine on the digital circulation (134). Blockade of vasoconstrictor

responses to epinephrine can be demonstrated when sufficiently large intraarterial injections of dihydroergocornine precede intraarterial injection of epinephrine (123, 134).

Human Pharmacodynamics

Reports are at variance on the effects on cardiac output of acute administration of the drug to hypertensive subjects (Table III). Working with the direct Fick method, one group of investigators has shown no change or slight increase in cardiac output, while another group has shown a slight decrease in 5 hypertensive subjects. Total peripheral resistance is generally agreed to fall slightly. With the use of indirect methods for determining cardiac output, the tendency has been to show a decrease in cardiac output and total peripheral resistance (Table III). The regional changes in resistance which may contribute to this reduction in total vascular resistance have been measured only infrequently in the human subject. Cerebral blood flow by the nitrous oxide method is unchanged following dihydroergocornine despite a decrease in blood pressure. Thus there is a decrease in cerebral vascular resistance *pari passu* with the blood pressure drop (109). This may be either a direct action of the drug on the cerebral vessels or an adjustment of regional flow to a reduced pressure. The sympathetic blocking property of the drug can hardly be responsible for such cerebral vasodilatation, since stellate block does not materially alter cerebral flow when measured by the same method (114).

It is generally agreed that, in acute experiments, renal blood flow is reduced initially, but later returns to previous levels despite continued blood pressure reduction (90, 221, 223). Renal vascular resistance is thus usually unchanged or increased, but may later decrease. This is probably the result of an intrinsic renal adjustment, since the same pattern is seen with a variety of other depressor drugs and procedures. After prolonged administration of hydergine, Reubi has found an increase in renal blood flow and a decrease in renal vascular resistance (226). $T_{m\ PAH}$ and $T_{m\ glucose}$ are unchanged after single intravenous injections (225). It therefore appears that prolonged treatment with these drugs will have no harmful effects on the kidney.

According to one group of investigators the splanchnic blood flow shows a marked decrease, proportionally greater than the decline in blood pressure, thus suggesting a slight vasoconstriction in this region (90). Peripheral blood flow is definitely but moderately increased (Table III).

The basal metabolic rate is reported to be reduced by these ergot alkaloids even when the blood pressure is not lowered (118, 128). The effect of these drugs on the electrocardiogram has been reported by a number of authors (32, 33, 134 135, 149, 200, 272). The venous pressure is increased slightly (Table III), perhaps indicative of some residual constrictor properties.

In summary, it appears that these ergot alkaloids produce a moderate decline in total peripheral resistance, particularly evident where sympathetic activity is maximal (hands and especially feet) and least in the regions under minimal autonomic control, such as the cerebral circulation. The vasoconstriction in the

splanchnic area probably indicates the existence of some remaining vasoconstrictor property of the alkaloids.

TABLE III

*Pharmacodynamic studies of dihydrogenated ergot alkaloids in man**

FUNCTION	INCREASE	NO CHANGE	DECREASE
Cardiac output	90(F), 118(W), 134(W)	288(F)	59(W), 118(W), 277(W), 281(F)
Total peripheral resistance	59, 277, 281	281	90, 118, 134
Peripheral blood flow (foot or forearm)	16, 33, 34, 90, 134, 288, 292	277	—
Renal blood flow	—	226	49, 90(i), 221(i), 223(i), 288(i)
Hepatoportal blood flow	—	—	90, 288
Cerebral blood flow	—	109	—
Venous pressure	90, 112, 281, 292	59	—
Vasopressor reflexes	—	—	59, 90, 91, 134, 200, 288, 292

* Numbers indicate references; parenthetical letters, footnotes as follows: F = direct Fick method; W = Wezler-Böger method; i = initially, then return to control values.

TABLE IV

Therapy with hydrogenated ergot alkaloids

RESULTS	POOR	MODERATELY GOOD	IMPRESSIVE
Acute			
Oral/parenteral	—	27, 33, 90, 91, 109, 134, 135, 148, 200, 265, 266, 272	63, 118, 119
Chronic			
Oral	27, 33, 63, 117, 133, 217, 265, 266	95, 118, 131, 132, 134, 148	93
Mixed	133	20, 33, 95, 117, 148, 176, 199, 200	64, 93, 134, 135

Effect on Blood Pressure

A. *Acute*

According to most investigators, the dihydrogenated ergot alkaloids usually reduce moderately the blood pressure in hypertensives and have much less effect in normotensives, when given intramuscularly or intravenously in doses of 0.1 to 0.5 mgm. in acute experiments (Table IV). A moderate bradycardia and orthostatic hypotension (not accompanied by increased heart rate) are observed. The degree of hypotension is variable; after 0.3–0.5 mgm. of intravenous dihydroergocornine, the mean blood pressure falls by 10–20% and the effect lasts between two and three hours; side effects are sometimes present, in the form of

nausea and headaches; also nasal stuffiness is observed by most patients. Oral administration leads to the same results, although the dose required for an equal drop in pressure is said to be about 20 times the intravenous dose (27, 132).

B. *Chronic*

The reports on the effects of chronic oral administration are conflicting. Thus Kappert (134) reports that 57% of 65 patients treated for a mean period of 75 days had a mean blood pressure reduction of −36/−16 mm. Hg in response to oral CCK-179, while the single alkaloids were less effective. The dosage program was as follows: 6–8 drops of the solution of mixed alkaloids (20 drops contain 1.0 mgm.) were given three times daily, with a gradual increase to 80 drops or more daily if tolerated. The author did not control his treatment with placebo administration, although cases pretreated with phenobarbital or bromide exhibited a further drop of −24/−14 mm. Hg on addition of ergot alkaloids to the sedative regimen. Inspection of his graphic records indicates that the blood pressure, initially high, frequently fell on treatment, but often did not rise on discontinuation of medication. Thus an average drop of −36/−16 mm. Hg with CCK-179 was still −28/−13 mm. Hg below the initial blood pressures three months after the drug was stopped. This is interpreted by the author as suggesting a therapeutic effect of the drug outlasting the period of treatment. It has been suggested that it may be the result of accumulation and slow excretion of the drug (33), although pharmacological studies show its rapid inactivation in the body (234). It might be differently explained as due to the concomitant psychological effect of repeated clinic visits. The interpretation of the results is therefore uncertain, but the prolonged blood pressure reduction can certainly benefit the patient. However, it should be noted that this is often inconsequential, *i.e.*, over 40% of patients subjected to this management had no significant reduction, while approximately one half of the remainder must have had less than 16 mm. Hg decline in diastolic blood pressure, a reduction not likely to be of significant long-term benefit to the patient (134). Side effects were not severe, but nasal obstruction and moderate orthostatic hypotension were frequently encountered, while headache and nausea were occasionally observed.

On the other hand, a study by Kaiser and Martini (133) revealed no effect of oral therapy over one to two months' observation, with comparable doses in 8 patients previously controlled by a low sodium diet and in 3 patients without dietary restrictions. Dupuy *et al.* (63) also found no reduction in blood pressure in 23 of 25 patients treated with oral DHO-180 or CCK-179 for periods of 3 weeks to 3 months. Gast *et al.* (93), however, with an average of two months' treatment reduced the blood pressure in 28 out of 50 patients who received daily average oral doses of 1.1 cc. The mean reduction in these patients was −64/−32 mm. Hg. Although periods of placebo medication were interposed in an unstated number of patients, with an attending rise in blood pressure, six months after cessation of all treatment in the 28 patients the pressure had risen only 10/10 mm. Hg.

On the assumption that these alkaloids are not well absorbed (27), most

authors prefer combined oral and parenteral treatment in patients refractory to oral treatment alone. This program consists in the additional administration of one to two doses of 0.3 mgm. of the alkaloids intramuscularly daily for two to three months. Kappert reports reductions of blood pressure on this regimen in 74% of 50 patients, the mean reduction in the successfully treated being −38/−19 mm. Hg (134). On the other hand, the results of Baumgartner (20) in 30 patients treated for two months with combined oral and parenteral therapy are not impressive; the mean blood pressure was 213/115 mm. Hg before treatment and 198/108 after treatment. In most of the studies listed in Table IV, no specific mention is made of the relation of the level of blood pressure during treatment to the time of administration of the drug. It would be presumed, in a drug with a brief period of action, that there would be fluctuations in the blood pressure throughout the day. It is assumed, but not established, that the reduction in blood pressure recorded in the studies is more or less unrelated to the time of administration of the drug.

Certain miscellaneous observations are of interest. (1) All authors agree that the ergot alkaloids are least effective in the more severe cases of hypertension. (2) There is wide variation in the responsiveness of the individual. Some authors prefer a therapeutic trial of chronic therapy, while others (119, 148) believe that the response to a single parenteral dose may serve to predict whether the patient will respond to prolonged treatment. (3) In acute experiments, doses exceeding a certain level, usually 0.5 mgm. intramuscularly, produce no further blood pressure reduction (91) or may even produce an elevation of blood pressure (33). Although no data on chronic administration of high doses are available, it seems possible to overtreat hypertensive patients with the dihydrogenated alkaloids. (4) Oral administration appears less effective than parenteral; the intramuscular dose is approximately ten times as effective as the oral dose, so far as magnitude of vasodepressor action is concerned (119). To avoid the inconvenience of daily injections, some authors advocate sublingual therapy (119) which is approximately one fifth as effective as intramuscular. (5) There is general agreement that, as in many forms of treatment for hypertension, symptomatic relief is often seen in cases where blood pressure reduction is not marked. (6) There is disagreement concerning the development of tolerance to the drug. Two groups of authors (132, 184) claim to have observed it while another author (20) has seen no difference in the depressor effect of a parenteral dose before and after chronic therapy in 30 patients. (7) Although inhibition of pressor reflexes can be demonstrated after acute parenteral administration, oral treatment is not similarly effective, according to our own experience and that of others (292).

In summary, the dihydrogenated ergot alkaloids are presumed to act centrally to inhibit sympathetic vasomotor tone; their effect is to produce a slight decrease in vascular resistance in several areas, particularly in the extremities. In acute experiments the drug usually lowers blood pressure and decreases the vascular lability of the hypertensive patient, while the prolonged oral or combined oral and parenteral therapy usually results in mild and variable reductions in blood pressure, with considerable differences in individual responses. Whereas patients

with severe fixed hypertension may not experience reductions in blood pressure, the drug may be worthwhile in milder cases and has the advantage of being relatively free of distressing side effects.

Pentaquine has been reported by Freis and Wilkins (92) to lower the mean blood pressure of patients by 10–40% after 2–7 days of oral treatment with 120–240 mgm. per day. Their study suggests that it probably acts by central impairment of sympathetic reflexes; orthostatic hypotension, without tachycardia, however, was marked and side effects (abdominal, back and chest pains, nausea, vomiting, weight loss, fever) preceding any blood pressure changes exclude its use in the treatment of hypertension.

1-Hydrazinophthalazine is supposed to act centrally, at least in part; but, since the evidence for this locus of action is weak, the compound is discussed with those drugs which exert mixed effects.

I-D. AGENTS ACTIVATING AFFERENT VASCULAR REFLEX ARCS (VERATRUM COMPOUNDS)

A large number of derivatives of *Veratrum viride* and *album* have been used in the treatment of hypertension. Most of the studies have been done with crude mixtures of the alkaloids of *Veratrum viride* (veratrone, vertavis), but some studies have been made with more purified mixtures (veriloid, anatensol and vergitryl); there have also been a few observations with single alkaloids (germitrine, neogermitrine and protoveratrine). Much of the animal work is confused by the use of various crude mixtures of the alkaloids. We agree with Krayer and Acheson who state, "Only the study of the pure veratrum alkaloids will permit a correct evaluation of their practical usefulness" (144).

Mode of Action

The subject is reviewed extensively by Krayer and Acheson (144) who describe the hypotensive action of the veratrum compounds as due to a cardio-deceleration together with peripheral vasodilatation. In higher doses, probably not attained clinically, these compounds have a pressor and cardio-accelerator effect. Other effects include a positive inotropic action on the heart (145). These drugs act chiefly by increasing the frequency of discharges normally carried by afferent fibres of the vagus from the left ventricle, the so-called von Bezold effect (58, 239A), from the lungs (12, 229) and also from the carotid sinus region (12, 107). A direct action on the central nervous system has also been reported (146). It has recently been reported in cats that emetic, and in minor degree hypotensive effects, have their origin in the stimulation of cells in the nodose ganglion (36, 68), since vagotomy above the ganglion abolishes the emetic and occasionally also the hypotensive (35) effects, while section below this point does not interfere with the typical emetic action of the drug. As the authors of these findings state, the latter observations may explain the fact that administration into the head circulation in cross-perfusion experiments may lower the blood pressure in the body of the animal, in which only aortic-vagal nerve connections with the head exist (228). The anesthetic and the species of experimental animal influence the

results, as it has been shown that dogs do not display these reflexes under pentobarbital anesthesia (58).

The efferent pathway for the veratrum effect includes both components of the autonomic nervous system. Thus vagal stimulation produces bradycardia and vomiting. Atropine or vagotomy abolishes the bradycardia; the vomiting is not relieved because somatic motor nerves to the diaphragm and abdominal muscles are not interrupted. The cardiodecelerating action is especially prominent among the members of the secondary amine group of alkaloids (veratramine and others) which are supposed to act directly on the sinoauricular node ("antiaccelerator" action as a form of negative chronotropic action) and are not antagonized by atropine (143), in contrast to the commonly used tertiary amines. The hypotensive effect of the tertiary amines is not dependent entirely on the vagus nerve, since it is only partially abolished by atropine or vagotomy.

It has been postulated that inhibition of efferent sympathetic activity is chiefly responsible for the vasodepressor action since veratridine-induced hypotension does not occur after tetraethylammonium blockade (182). However, this view has been questioned by the results of studies with doses of TEA as high as 20 mgm./kgm. (136, 263) and of those with bilateral removal of the paravertebral sympathetic chain (160), although in the latter case the veratramine response is reduced. In man, spinal anesthesia up to the level of C-4 with 0.2–1.0% procaine did not eliminate the vasodepressor or cardiodecelerator action of veratrone (11). Therefore the question of the efferent vaso-depressor pathway deserves further investigation; it seems, however, that in blocking experiments the positive are more convincing than the negative results, and that by excluding ganglionic pathways no satisfactory alternative mechanism can be proposed. A direct vasodilating action is also possible, as shown for veratrone in perfused rabbit organs (291), although this possibility is not generally accepted (144).

Pharmacodynamic Effects in Man

There seem to be no qualitative differences between the actions of the different veratrum alkaloids in human and animal experiments (Table V). Studies of the afferent arc cannot be made in man for obvious reasons. Reflex regulation of the circulation is not interfered with, significant orthostatic hypotension does not occur, and the Valsalva overshoot is preserved after administration of relatively large doses of the veratrum alkaloids in man (88, 173). The effect on the cold pressor response is uncertain, some authors claiming partial inhibition (173) and others no effect (88). These results are in contrast to animal studies, where depression of the carotid sinus pressor reflex has been reported, this being due probably to the higher doses of alkaloids injected in the animal experiments (107, 227, 228). This unique property of veratrum alkaloids, namely, lowering of the blood pressure without interfering with vasomotor reflexes, is in sharp contrast to the effect of central depressants or peripheral autonomic blocking agents, and is their greatest advantage in that treatment with them does not affect the postural reflexes required for normal living.

In agreement with animal studies, it has been shown by several authors that

atropine will abolish veratrum-induced cardiodeceleration in man but will not affect appreciably the vomiting or depressor action.

Cardiac output is variably affected by veratrum alkaloids (see Table V), but generally not increased. However, two out of three cases of congestive heart failure reported by Freis *et al.* (88) showed an increase in cardiac output of 20–24% following 0.4–1.0 cc. of veratrone intramuscularly. Abolition of bradycardia with atropine sometimes raises blood pressure from minimum values, perhaps by increasing cardiac output although this mechanism has not been proven. In other cases, atropine has little effect. Venous tone (136, 264) is reported to be increased. A positive inotropic effect may be exerted, as has been shown in the heart-lung preparation of the dog (145). It is obvious, therefore, that the action of the veratrum alkaloids on these factors which indirectly affect cardiac output can result in quite variable results from patient to patient, and it is not

TABLE V

*Pharmacodynamic studies of veratrum alkaloids in man**

FUNCTION	INCREASE	NO CHANGE	DECREASE
Cardiac output	50(B), 88(F)	87(F), 88(F),	53(F), 155(W), 122(F)
Total peripheral resistance	—	155	88, 89, 124
Renal blood flow	155	124	53(i), 87(i), 88(i), 89(i), 172(i), 172a(i)
Muscle blood flow†	89, 124	—	87(i), 88(i)
Hepatoportal blood flow	88, 89	—	—
Cerebrovascular resistance	—	—	50, 51, 179
Urine volume	—	—	10(i), 70(i), 87, 88, 124, 172, 172a
Vasopressor reflexes	—	87, 88, 89, 285	173, 249

* Numbers indicate references; parenthetical letters, footnotes as follows: B = Ballistocardiographic determination; F = direct Fick method; W = Wezler-Böger method; i = initially, then return to control values.

† Forearm or calf blood flow, by plethysmography.

surprising that considerable variation in its effects are reported. Despite this fact, most authors agree that the drug produces a decline in total peripheral resistance and in cardiac work (87, 88, 89, 124). It is our clinical impression, well supported by the observations cited above, that veratrum alkaloids are particularly effective in hypertensive heart disease with decompensation.

Since the total peripheral resistance is reduced, the vascular beds involved in this vasodilatation have to be defined. It seems that, with the possible exception of the extremities and muscles, vasodilatation is only sufficient to retain normal flow at reduced pressure, rather than to permit an active hyperemia, as is the case with hydrazinophthalazine. All major vascular beds appear to dilate equally, to a mild extent. As far as the extremities are concerned, veratrum apparently acts only when sympathetic innervation is intact (88, 122). However, it is unlikely that the uniform vasodilatation seen after veratrum administration is entirely due to decreased sympathetic tone because sympathetic vasomotor

tone is probably not equally distributed throughout the body. Consequently, autonomous readjustments of regional circulations must be an additional factor in the final analysis of the effect of veratrum on local vascular beds.

The effect of veratrum on the kidney deserves further comment. Renal blood flow and glomerular filtration fall concomitantly with the blood pressure but recover despite continued hypotension (88, 124, 172a); during recovery the renal blood flow sometimes exceeds the original level, even while the blood pressure is still low. Urine flow is sharply decreased, out of proportion to the fall in filtration rate. This implies an increase in renal reabsorption of water. Meilman has further shown that tubular reabsorption of sodium and chloride is increased (172). Whether water or electrolyte reabsorption following veratrum is the primary phenomenon is uncertain, although Meilman believes that this is not an antidiuretic-hormone effect. The kidney function does not appear to be seriously affected when the drug is administered over long periods. The nonprotein nitrogen does not usually increase (125), and oliguria is usually overcome when the drug is continuously administered to hypertensives (88) and in cases of toxemia. A rebound polyuria may follow the initial oliguria (10, 70).

The effects on the heart rhythm also deserve comment. Sinus bradycardia has been reported; this is followed by shift of the pacemaker to the AV node or complete dissociation with idioventricular rhythm which is often faster than the auricular rate (50, 66, 157, 173, 264). These effects are accentuated by digitalization (173) and reversed by atropine sulfate (0.5–1.0 mgm. intravenously). The T-waves in the electrocardiogram may become inverted (66, 157); but, if initially inverted, they may become positive in association with a substantial reduction in blood pressure (69, 173). The veratrum compounds have been reported to be of benefit in patients with cardiac decompensation (86, 125, 284).

Effects on Blood Pressure

A. *Acute*

Given intravenously and in sufficient doses, the veratrum alkaloids and their mixtures produce a sharp decrease in the systolic and diastolic blood pressure and in the pulse rate; but they are clinically ineffective until a certain dose, characteristic for each individual, is exceeded. Presumably this is the threshold necessary to initiate a repetitive discharge in the afferent nerves concerned in the depressor reflex arc. The effects occur after a certain unexplained period of delay and the dose-response relationship in the human is fairly constant when the minimal effective dose is exceeded, as is well described by Meilman and Krayer (173). Duration of action is approximately 1 to 3 hours following a single intravenous dose. Normotensive patients and hypertensive individuals, regardless of the etiology of their hypertension, show a fall of blood pressure following intravenous injection of these alkaloids, provided the critical dose is exceeded. The bradycardia is variable in degree, occurs at the time of minimum blood pressure, and may be abolished by intravenous atropine with only partial or no restoration of initial blood pressure levels (124).

The side effects of the intravenous injection of veratrum alkaloids include the rapid appearance of paresthesias of lips and tongue, a sense of warmth over

face and chest and, with a decline in blood pressure, relaxation and drowsiness. Substernal choking sensations followed by nausea and vomiting occur rarely after intravenous injections of the crude or more purified derivatives. Vomiting cannot be alleviated by any drug, but is said to be prevented by barbiturates.

Injections may be repeated in 3 to 4 hours, and under these conditions tachyphylaxis to the hypotension does not occur (173, 249). Attempts to prolong the action of these alkaloids by intravenous drip has resulted in sustained blood pressure reductions, complicated more or less frequently by nausea and vomiting (14, 70, 73, 259, 286). The critical dosage and the delay in maximal hypotensive effect leads to difficulty in controlling the level of the blood pressure by this method. Meilman and Krayer (174), who have particular experience with protoveratrine, describe excellently the technical precautions necessary. Subcutaneous and intramuscular injections have been tried by some investigators, but here also nausea and vomiting attend continued hypotension. The alkaloids are local irritants and must be mixed with procaine before injection. The following is a partial list of veratrum preparations which have been given parenterally to hypertensive patients, together with references to the literature.

Veratrone	(10, 11, 66, 88, 248, 249)
Verenteral	(14)
Veraflex	(14)
Anatensol	(286)
Veriloid	(129, 136, 179, 259, 286)
Vergitryl	(70, 73)
Protoveratrine	(50, 51, 53, 124, 155, 157, 172, 173, 174)

Prolonged Treatment

Although some parenteral preparations have been advocated for prolonged treatment by self-administration, no clinical studies have been reported with this technic. The discussion will therefore deal with oral administration of the veratrum preparations. A considerable number of preparations have been made available for this purpose. The following is a partial list of available hypotensive products with the average daily dose necessary to produce a significant depression of the blood pressure. They are listed according to their degree of purification.

NAME OF DRUG	APPROXIMATE DAILY DOSE	DESCRIPTION	REFERENCES
Vertavis	30–80 Craw units*	Mixed alkaloids from *Veratrum viride*	45, 69, 86, 88, 164, 170, 256, 284
Veriloid	8–16 mgm.	Purified mixture from *Veratrum viride*	78, 105, 129, 137, 178, 179, 259, 264, 284, 286, 289
Anatensol	2–10 mgm.	Highly purified mixture from *Veratrum viride*	19, 78, 129, 179, 256, 286
Protoveratrine	1–1.5 mgm.	Protoveratrine A and B from *V. album*	53, 125, 174, 256

* A "Craw unit" is the amount of alkaloids necessary to stop the contractions of the heart of *Daphnia magna* under standard conditions.

The process of the purification of these alkaloids is expensive and complicated, and it is not certain that the emetic side-effects are reduced since, as noted previously, pharmacological investigation tends to indicate that reflex emetic and reflex hypotensive actions are parallel effects from activation of the same afferent pathways. However, certain observations tend to suggest some differentiation of emetic and hypotensive effects. (1) The presence of the nodose ganglion is necessary for the occurrence of the emetic action but is questionably necessary for the hypotensive action (35). (2) Veratridine has a prominent emetic effect without vasodepressor activity (173). Consequently, crude mixtures may contain alkaloids which increase toxic side effects without contributing to reduction in blood pressure. This agrees with the clinical observation that, for the same reduction of blood pressure, frequency of side effects is greatest with vertavis, less with veriloid and least with protoveratrine (122). Therefore, apart from the theoretical but highly questionable possibility that purified derivatives will differ in

TABLE VI

Therapy with veratrum alkaloids

RESULTS	POOR	MODERATELY GOOD	IMPRESSIVE
Acute			
Oral	264	86, 286	—
Parenteral	—	136, 157, 173, 179, 256	51, 124, 131, 174, 248, 249, 259, 264, 286
Short-term			
Oral	—	105, 174	78, 86, 129
Parenteral	—	259	10, 14, 73, 249
Prolonged			
Oral	19, 45, 105, 129, 164, 179	69, 78, 86, 137, 170, 178, 250, 256, 289	125, 284, 286

their ratio of hypotensive to emetic effect, purification would seem to be justified on the basis of clinical observation, probably because of the removal of emetically active substances.

Veriloid and anatensol have been given orally, with a moderately satisfactory ratio of hypotensive to emetic effect (see Table VI). Thus Wilkins estimates that he obtained a 20 mm. Hg reduction in diastolic blood pressure in 70% of patients on short-term therapy, but acknowledges that hypotensive effects became less prominent as treatment was prolonged (284). The number of patients refusing to continue treatment and the control periods prior to treatment are not adequately described. He states, however, that there is a striking feeling of increased strength and endurance associated with a decrease of heart size (286). Gropper *et al.* (105) gave increasing doses of veriloid sufficient to lower the blood pressure by 25/15 mm. of Hg or to cause the appearance of toxic effects. On this program, no patients were significantly benefited when compared to the results from placebo administration on observation periods up to two months. McNair and

Griffith (164) approached the problem somewhat differently by treating 22 patients for from 2 to 5 months with the maximum dose of vertavis which they could tolerate without side effects (mean dose, 82 Craw units daily). They observed a mean blood pressure reduction of 7/6 mm. Hg, comparable to the reduction achieved with placebos.

No purified derivatives have been studied by chronic oral administration with the exception of *protoveratrine*. This substance is highly potent, and appeared on single oral doses to be better tolerated than the semi-purified mixture, veriloid (125). However, repeated administration of hypotensive doses 2 to 3 times daily led to emetic effects (53, 125). The emetic action seems to require more prolonged exposure to the alkaloid than does the hypotensive effect. Thus, subcutaneous administration of doses which produce a depressor effect equal to that of an intravenous dose is associated more often with nausea. Similarly, oral doses are still more prone to induce emesis for an equal drop in blood pressure. If the drug is given in equal doses 3 to 4 times daily, this undesirable side effect becomes more prominent, eventually necessitating discontinuation of drug administration. This line of reasoning led Hoobler *et al.* (125) to propose single large daily doses with the limited objective of producing short periods of hypotension not exceeding 6 to 8 hours in each day. Clinically, this dosage program is infrequently associated with emesis and does appear to have therapeutic value despite its intermittency, in that heart size has been shown to decrease and retinopathy and encephalopathy have been ameliorated. An interesting observation was that on this regimen no tolerance could be observed even after many months of treatment.

The number of patients who can accept this intermittent type of therapy also is somewhat restricted since, as in the other reports, those who show intolerance to initial doses are invariably excluded from consideration. However, it has been observed that if a patient responds satisfactorily and without severe side effects to initial attempts at management with this regimen, then persistence in treatment is often rewarded by clinical improvement without serious side effects as a necessary accompaniment of therapeutic success. Furthermore, it is comforting to know that no deaths directly attributable to veratrum have been reported, despite accidental administration of large overdoses (53), although acute myocardial insufficiency is said to have occurred during veratrum-induced hypotension (141).

II. DRUGS ACTING DIRECTLY ON VASCULAR SMOOTH MUSCLE

Few such agents are known which are clinically effective. Among reports published during the period 1950–52, the following may be mentioned.

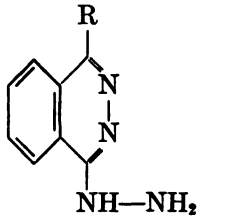
Hexaminomesoinositol has been reported to lower blood pressure for 2 to 3 hours after oral ingestion of 10 to 20 mgm., presumably by slow release of nitrate. No chronic studies have been reported (61, 262). A parenteral *tissue extract* (embran) containing adenylic acid has been reported to be beneficial in essential hypertension. It is said to be a good cerebral and coronary vasodilator. Moderate acute reductions in blood pressure (up to a $-30/-20$ mm. Hg) have been reported (43). Intravenous infusions of *papaverine* (0.12 gram per hour for 3

hours) in toxemia of pregnancy and in essential hypertension complicating pregnancy are said to control satisfactorily the acute hypertensive state (159). The average blood pressure dropped from 192/125 to 139/90 mm. Hg on this regimen, although a secondary rise occurred within a few hours after stopping the infusion. No side effects were noted.

III. DRUGS WITH UNCERTAIN OR MIXED EFFECTS

1-Hydrazinophthalazine

A new group of substances containing a phthalazine ring with the structure



in which R has been varied have been initially studied by Gross, Druey and Meier (106) and found on animal testing to possess hypotensive activity with a mode of action "not common to other blood pressure depressing substances" The following discussion concerns the hydrochloride of 1-hydrazinophthalazine (apresoline) in which an H atom is substituted for R in the formula. The blood pressure drop in animals following intravenous administration of 0.1–2.5 mgm./kgm. occurs slowly after a 10-minute latent period, is not profound and is accompanied by a marked tachycardia; it is associated with increased cardiac output (191) and increased femoral (106), renal (106, 189, 191) and coronary (18, 25, 106) blood flow. It has further been shown that the drug partially antagonizes the pressor action of epinephrine (37, 48, 102, 106, 191, 279) more than that of nor-epinephrine (37, 106, 279) and some reports suggest it may reverse the pressor effect of epinephrine (37, 191). In normotensive animals, the total peripheral resistance is therefore decreased; blood pressure reduction also occurs in neurogenic (101, 102) and renal hypertensive animals (202), although the drug is less effective in the latter. Several modes of action have been postulated, but the evidence appears to be inconclusive to us. It has been claimed that it acts by central inhibition of vasomotor reflexes. However, the pressor effect of carotid clamping is variously reported, as being reduced or blocked by Grimson *et al.* (102), and not blocked or unaffected by Walker *et al.* (278, 279) and Britton *et al.* (37). The pressor reflex to anoxia is not inhibited (37, 102). The rise in blood pressure following central vagal stimulation is said to be inhibited by Taylor *et al.* (269), but it is unaffected according to other investigators (37, 102). The drug does not further lower the pressure of the hypotensive spinal cat; but, when the blood pressure is raised to normal by ephedrine or ergotamine, the drug reduces it more markedly than in the anesthetized normal animal (106). It would appear that this latter observation supports a peripheral rather than a central action of 1-hydrazinophthalazine in animals.

It has been claimed that the drug acts by blocking or reversing certain physiologically occurring pressor substances such as epinephrine, serotonin, or angiotonin (269). The drug, however, possesses only weak adrenolytic potency; furthermore, the role of these pressor substances in maintaining the blood pressure of the normal or hypertensive animal is disputed. There is no evidence of peripheral ganglionic blockade in animals; no studies on pre- and post-ganglionic stimulation have been reported and the failure of the drug to enhance the pressor effects of norepinephrine argues against a ganglionolytic mode of action. The possibility of direct action on the blood vessels cannot be excluded; intra-arterial injections in man in a few instances have produced a rise in temperature of the skin of the corresponding area (290). No studies of changes in blood flow in the denervated extremity have been reported. These aspects need further investigation.

TABLE VII

*Pharmacodynamic studies of 1-Hydrazinophthalazine in man**

FUNCTION	INCREASE	NO CHANGE	DECREASE
Cardiac output	80(F), 240(W), 290(F)	—	—
Total peripheral resistance	—	—	240, 290
Renal blood flow	65, 222, 223, 224, 240, 275, 290	—	—
Foot blood flow	240, 275	—	—
Muscle blood flow	—	80	—
Hepatoportal blood flow	80	—	—
Cerebral blood flow	—	110	—
Glomerular filtration rate	224	222, 223, 275, 290	—
Urine volume	222, 223, 224. 290	275, 290	—
Vasopressor reflexes	—	—	81, 84, 102

* Numbers indicate references; parenthetical letters, footnotes as follows: W = Wezler-Böger method; F = direct Fick method.

Clinical studies on the mode of action are even less definite. The following observations are cited as evidence for central sympathetic inhibition: (1) incomplete inhibition of cold pressor, Valsalva (81, 102) and tiltback overshoots (81); (2) slight postural hypotension (81, 244); and (3) inhibition of the bradycardia in response to norepinephrine despite persistence of its pressor action (81, 84). That this interference is not the result of peripheral sympathetic or ganglionic blockade is inferred by the lack of other evidence of autonomic paralysis, such as pupillary changes, nasal congestion and alteration of pressor effects of norepinephrine (81). In man as in animals the possibility of a direct vascular action has not been excluded; in fact, it seems a likely possibility in view of the generalized vasodilatation and cardioexcitatory effects which resemble more the actions of imidazolines such as priscoline than those of the central nervous system depressants such as the dihydrogenated ergot alkaloids.

Regional Blood Flows

Table VII presents the few clinical studies on the regional circulations. Study of cardiac output and peripheral flow in the human suggests an increase, as in the animal studies cited above. A recent abstract by Hecht and coworkers (290, also 80) confirms that an increase in cardiac output of approximately 100 % occurs. It seems possible that such cardiac stimulation exceeds any potential coronary dilatation, since it has been reported that anginal attacks were induced by the drug (268). The T waves are reported to be flattened or inverted (81, 223). The renal effects of the drug are of special interest since the increase in renal blood flow exceeds that reported with any other agent, except pyrogens (Table VII). The drug decreases the renal extraction of para-aminohippurate in animals (191).

The glomerular filtration rate is not changed despite increases in renal blood flow. Thus it is not likely that the drug will improve excretion of metabolites in hypertensives with uremia or lower the non-protein nitrogen, since these functions depend particularly on glomerular filtration rate and tubular reabsorption. Tubular function as measured by $T_{m\ glucose}$ is not affected in dogs (189, 191), and has not been studied in man. Insufficient studies of other regional circulations in man have been reported, but those which have been completed are presented in Table VII. Cerebral blood flow is maintained as with dihydrogenated alkaloids or protoveratrine, despite the pressure decrement (110), but there is no true cerebral hyperemia as might be expected from the development of headache or from the concomitant renal hyperemia. Splanchnic blood flow appears to be increased to almost twice control levels (80). It would thus appear that this drug is a potent vasodilator which stimulates cardiac output and increases splanchnic and renal blood flow very considerably. The extent of the reduction in blood pressure will be the result of the summation of the effects of the drug on these various circulations and on the cardiac output.

Effects on the Blood Pressure

A. *Acute*

The intravenous or intramuscular administration of 10–30 mgm. of 1-hydrazinophthalazine in man is usually accompanied by moderate to marked reduction in blood pressure, particularly diastolic, after a lag of about 10 minutes (81, 102, 110, 223, 290) (Table VIII). The reduction lasts about 1 to 2 hours; but tachycardia, severe generalized headache, and nausea often accompany the reduction, and this method of administration is therefore not particularly useful in treating the hypertensive patient.

B. *Chronic*

The extent to which chronic oral administration of the drug lowers the blood pressure is a matter of uncertainty from published observations. The report by Johnson and collaborators (130) is the least encouraging. Thus, in 16 patients, single oral doses of 50 to 150 mgm. reduced supine blood pressure an average of

10% systolic and 16% diastolic, and the reduction lasted one to three hours. Prolonged treatment of 17 patients for 2 weeks to 3½ months did not result in lowering the initial daily pre-treatment blood pressure. Eight patients showed no blood pressure reduction at dosage levels free of side effects, 6 failed to respond after a period of time, and only 3 who took the drug daily had "significant" blood pressure reduction.

In contrast, a recent report by Taylor *et al.* (268), based on a study of 97 patients treated for 3 to 12 months with a "usual" dose of 200 mgm. four times daily, records a reduction of diastolic pressure to normal levels in one third of the cases and to less than 110 mm. Hg in another one third. Unpleasant side effects occurred in two thirds of the patients but receded on continued treatment in most instances. Improvement was most apparent in the cerebrovascular cases, and least in the cardiac cases presumably on account of the increase in heart rate. Progression of nephrosclerosis was said to have been checked, but the residues persisted.

TABLE VIII

*Therapy with 1-Hydrazinophthalazine**

RESULTS	POOR	MODERATELY GOOD	IMPRESSIVE
Acute			
Oral	—	102, 244	—
Intravenously	—	81	102
Intramuscularly or subcutaneously	—	223	110
Chronic			
Oral	102, 130, 275	[130], 147, 244	202, [245], [246], 268

* Numbers indicate references.

[] = combined therapy with hexamethonium.

The experience of the authors with this drug has led to the conclusion that with carefully-regulated dosage certain patients have definite improvement of retinopathy with repeated transient lowering of blood pressure. We have not seen the development of marked tolerance to the drug, nor have we observed changes in resting blood pressure during the course of treatment such as to suggest a long-standing reversal of the underlying disorder.

Schroeder (242, 243, 244) and Freis (77) have studied this drug alone and in combination with hexamethonium (245). The former author reported a reduction of 20 mm. Hg or more in the diastolic pressure in 35 out of 50 cases treated with hydrazinophthalazine for 1 to 40 weeks in and out of the hospital (control consisted of 1 week of observation of the patients in the hospital prior to starting treatment). Despite these apparently good results, the author states: "This drug does not provide any therapeutic answer to the pressing problem of hypertension." The drug was most effective in malignant hypertension, with or without uremia, and after low salt diet or sympathectomy. The latter observation suggested the use of ganglionic blockade with hexamethonium to augment the

depressor action of apresoline (245, 246); it would seem rational also to try to relieve the apresoline-induced tachycardia by means of ganglionic blockade.

Although no proof for their synergistic action exists, the vasodilator effect of the drug on the renal circulation may counteract the reduction in renal blood flow which accompanies orthostatic hypotension produced by ganglionic blockade. Furthermore, pressor overshoot in the wake of hexamethonium injections may be counteracted by interval oral administration of hydrazinophthalazine (130, 147). This also avoids many of the side effects of hydrazinophthalazine since only one or two doses per day are given.

Blood pressure reduction would probably be more frequent if development of side effects did not limit the dosage. These side effects, which come on abruptly at a different dosage level for each patient, consist of headache, nausea, nervousness and palpitation. While nothing is known of their origin, it has been presumed that the headaches represent the effect of cerebral vasodilatation since they can be relieved by vasoconstrictors such as ergotamine (295, 296). The palpitation and nervousness are the effects of increase in cardiac output and central nervous system stimulation. The development of edema in some cases is unexplained, but may represent a type of "high-output failure." Nausea and urticaria also occur. The similarity of many of these symptoms to the effects of histamine suggests that in some way the drug has a histamine-like action or results in histamine release (244). Moderate but not usually disabling orthostatic hypotension accompanies the maximum action of the drug. The hydrazine grouping might suggest the possibility of a toxic effect on bone marrow, but no anemia in animals or man has been demonstrated, despite careful observations.

Because of side effects, the drug should be given orally only in very gradually increasing dosage, starting with 10 to 25 mgm. three to five times daily, and increasing by very small amounts until a maximum tolerated dose is reached. Even with doses up to 450 mgm. daily, our experience indicates that many patients do not respond. Consequently, therapeutic usefulness of the drug is limited to those patients who obtain a reduction in pressure from dosages which they can tolerate.

In summary, the pharmacological effects of 1-hydrazinophthalazine are not well understood, but appear to be related to direct vascular and histamine-like effects and perhaps also to changes in central vasomotor regulation. The drug stimulates cardiac output and, uniquely among hypotensive drugs, it appears to increase markedly renal blood flow in the human subject. It is effective in transiently lowering the blood pressure when given in adequate dosage, but there are many patients who prove resistant or who cannot tolerate effective levels because of side effects. There is no evidence that the drug will permanently alter the status of the hypertensive patient, but it clearly deserves further clinical trial in individuals with severe hypertension.

Thiocyanates

Since the popularization of thiocyanate treatment in the United States by Barker (17), several critical reviews comparing its effectiveness with that of

nitrite, barbiturate, bromide and iodides have been published (235, 258). The major addition to our knowledge of thiocyanate consists in the observations of Davis and collaborators who have shown a reversible depletion of the lipid granules in all three layers of the adrenal cortex in rats, dogs and man after intravenous administration of thiocyanate (57). Clinical tests, however, on patients treated for long periods of time with large doses (15–20 mgm.% blood levels) do not show any measurable depression of adrenal function (150). It is interesting that acute intravenous administration is well tolerated and that high blood levels and greater effect on blood pressure and headache can be achieved than by the prolonged use of the oral route (150). Davis *et al.* suggest that, by conversion of small amounts of thiocyanate into cyanide which may render the adrenal cortex anoxic, this ion acts to lower the blood pressure (56). The increased efficacy of the drug after sympathectomy (common to other agents) is recognized by others (212) and is reported by Davis *et al.* (57) to be due to prior adrenal denervation by the sympathectomy. It should be pointed out, however, that the evidence of sympathetic inactivation by this method is entirely morphologic, not functional, and that even total adrenalectomy often does not appreciably lower the blood pressure (271). Pines *et al.* (215), on the other hand, have shown that the SCN ion enhances excretion of sodium in hypertensives and they believe that its action may be explained on this basis. It has been shown by Gubner (108) that thiocyanate inhibits carbonic anhydrase and thus interferes with sodium reabsorption in the distal tubule. This drug has been advocated for plethoric hypertensives because it is said to lower the hematocrit in such individuals (55). A few recent reports evaluating this agent in chronic treatment have also appeared; but, with some exceptions (231, 235, 258), the data published are insufficient to permit comparative evaluation (1, 46, 205, 212, 270). In reasonably well controlled studies, the effect of thiocyanate was only slightly superior to placebo administration (1, 175, 231, 235, 258). In addition to the well recognized toxic effects (weakness, dyspnea, rash, joint pain, hypothyroidism), the drug may produce hypophosphatemia and hypercalcemia associated with renal loss of electrolytes (108). Nickerson *et al.* (198) have shown that chloride ion will hasten excretion of thiocyanate when intoxication occurs. Therapy with this drug requires periodic estimation of blood levels which should be between 8 to 12 mgm.% to affect the blood pressure. Some authors reserve this agent for symptomatic treatment of headache only, for which purpose smaller daily doses and lower blood levels may be successful.

Other Agents

Sodium nitroprusside is reported by Page (202) to possess some of the properties of thiocyanate; it is stated that the nitroprusside ion *per se* is required for the hypotensive effect, that it does not produce tachyphylaxis or refractoriness in acute or chronic animal experiments, and that its hypotensive activity is associated with renal vasodilatation. Administration is oral (30 mgm. four times daily) and, as with the SCN ion, the nitroprusside blood levels have to be checked frequently. (They should not exceed 12–20 mgm./100 cc. serum.)

Rauwolfia serpentina, a drug from India, has been used empirically in that country for many centuries. A recent report indicates moderate hypotensive properties (274). It appears to have few toxic side effects, but slows the pulse, and allays anxiety and tension, features which may be useful in treatment of certain forms of hypertension. It seems to require several days of administration before appearance of effects. Mueller *et al.* (193a) have recently reported the isolation of the active alkaloid, which has a strong central sedative action. Active interest in this agent in the United States has arisen recently (287,288a); Wilkins reports good results with *R. serpentina* (serpina) in combination with small doses of either hydrazinophthalazine or veratrum alkaloids or both. It is stated that the small doses of each of these drugs produce a greater hypotensive action with fewer side effects than does either drug alone. He believes this combination is superior to the more dangerous hexamethonium-hydrazinophthalazine treatment (287).

Vitamins continue to be reported on for the treatment of hypertension, although only modest therapeutic claims are made. Fat-soluble vitamins have been investigated, mostly with unfavorable or uncritical reports (vitamin A: 98, 100, 267; vitamin K: 177, 194; vitamin E: 97). The parenteral use of these compounds has sometimes lowered the blood pressure of experimental animals, perhaps, as suggested by Gounelle *et al.* (100), in proportion to the extent of the local reaction at the site of injection, as a non-specific pyrogenic effect.

Dimercaptopropanol (BAL) has been found by Schroeder (242) to be an antihypertensive of theoretical importance because it contains active SH-radicals which can inactivate CO-groups in the alleged pressor substance extracted from human plasma, pherentasin. Unfortunately for this theory, the observations could not be confirmed (21).

Pyrogen therapy has been tried mainly by Page *et al.* (202, 204) in cases of malignant hypertension without severely impaired kidney function. The mode of action of intravenously injected bacterial protein is not well understood; but, associated with a substantial elevation of body temperature (101°–103°F.), there appears to occur a generalized drop in total peripheral resistance with an especially prominent increase in renal blood flow. The cardiac output is increased; however, the blood pressure drops because the reduction in peripheral resistance exceeds and outlasts increases in cardiac output. The injections have to be repeated almost every day for several weeks before definite improvement occurs in the form of prolonged blood pressure reduction, regression of retinopathy and improvement in renal function. Admittedly, the treatment is unpleasant, to say the least, and expensive. Malignant hypertension is, however, more than unpleasant; it is a rapidly fatal disease.

Among other agents which have been advocated to lower blood pressure, but concerning which insufficient data are available, are *bismuth* and *cobalt salts* (42, 127), elemental *iodine* (116) and, surprisingly, *caffeine* (0.05 to 0.1 gm. orally) which, according to Sebök (247), lowered the systolic pressure in 32 patients by an average of 45 mm. Hg. If coffee is not a good therapeutic agent, at least it does not appear that an occasional cupful is harmful to a hypertensive!

SUMMARY AND CONCLUSIONS

Attempts to lower the blood pressure in hypertension are not necessarily harmful, since hypertension can be shown to be the cause of many complications of the disease and its reduction by a number of recently available drugs can be demonstrated to be fraught with few serious consequences except for occasional coronary or cerebral thrombosis or renal failure. Of the recent effective agents, the veratrum alkaloids and hexamethonium are the most potent, but their use is attended by many undesirable side effects closely associated with therapeutic efficacy, whereas hydrazinophthalazine and dihydrogenated ergot alkaloids are less effective, but cause fewer side effects. There is no question that these drugs often have very satisfactory effects when administered in acute hypertensive emergencies. On the other hand, none is able to maintain a persistently normal blood pressure over many months, and all suffer the disadvantage of requiring continuous administration, probably throughout the life of the patient. This represents in itself a very major problem. Until more is known of the varied etiology of hypertension, these therapeutic agents are far from ideal, although they represent a remarkable advance from the therapeutic nihilism present only a few years ago. The reviewers would like to recall that older methods of management by psychotherapy, diet and sympathectomy, while not always effective, are still to be preferred, the first two in the less severe cases, and the last when other methods have proven unsuccessful. The report of Smithwick (257) on the greatly improved survival rates of sympathectomized as compared to medically treated patients, in spite of the fact that the reduction in blood pressure is often not permanent, makes us recall the saying of Hippocrates: "What drugs cannot cure, surgery can." However, we have now reached a stage, with the aid of experimental pharmacology, where we can choose from among several ways to combat hypertensive disease. We may conclude with Professor J. McMichael (163) that, "The desire to find benefit for our patients and enthusiasm for the 'latest' must be tempered with critical insight. The present mood, however, is one of quiet optimism."

REFERENCES

1. Aas, K. and Thingstad, R.: Thiocyanate therapy of hypertension. Acta med. Scandinav., 139: 229-241, 1951.
2. Acheson, G. H. and Moe, G. K.: The action of tetraethylammonium ion on the mammalian circulation. J. Pharmacol. & Exper. Therap., 87: 220-236, 1946.
3. Acheson, G. H. and Pereira, S. A.: The blocking effect of tetraethylammonium ion on the superior cervical ganglion of the cat. J. Pharmacol. & Exper. Therap., 87: 273-280, 1946.
4. Adams, W. R.: The medical aspects of hypertension. Postgrad. Med., 9: 408-411, 1951.
5. Allen, E. V.: Symposium on the treatment of essential hypertension. Proc. Staff Meet., Mayo Clin., 27: 473-500, 1952.
6. Allen, E. V., Bannon, W. G., Upson, M., Jr., Huizenga, K. A., Bastron, J. A. and Waugh, J. M.: A new sympatholytic and adrenolytic drug. Clinical studies on pheochromocytoma and essential hypertension. Tr. A. Am. Physicians, 64: 109-120, 1951.
7. Arnold, P., Goetz, R. H. and Rosenheim, M. L.: Effect of pentamethonium iodide on peripheral circulation. Lancet, 2: 408-410, 1949.
8. Arnold, P. and Rosenheim, M. L.: Effect of pentamethonium iodide on normal and hypertensive persons. Lancet, 2: 321-323, 1949.
9. Assali, N. S. and Douglass, R. A., Jr.: The hemodynamic properties of a thiophanium compound (RO 2-2222) in human subjects. Am. J. Med. 14: 492, 1953.
10. Assali, N. S., Kistner, R. W. and Garber, S. T.: The effect of veratrum viride on the urine volume, blood pressure and pulse rate in normal and toxemic pregnancy. Am. J. Obst. & Gynec., 58: 90-100, 1949.

11. Assali, N. S. and Prystowski, H.: Studies on autonomic blockade. III. Effect of high spinal anesthesia on the vasodepressor action of veratrum in human subjects. J. Pharmacol. & Exper. Therap., 100: 251–257, 1950.
12. Aviado, D. M., Jr. and Pontius, R. G.: Reflex respiratory and circulatory action of veratridine on cardiac, pulmonary and carotid receptors. Federation Proc., 8: 5–6, 1949.
13. Baikie, A. G. and Smith, J. R.: A new ganglion-blocking agent—Trial of 'Ciba 9295' in man. Lancet, 1: 1144–1145, 1952.
14. Baird, W. W. and Assali, N. S.: The use of new veratrum preparations in the treatment of toxemia of pregnancy. Am. J. Obst. & Gynec., 62: 1093–1099, 1951.
15. Bannon, W. G.: A new sympatholytic and adrenolytic drug. Clinical studies on essential hypertension. Proc. Staff Meet., Mayo Clin., 27: 475–481, 1952.
16. Barcroft, H., Konzett, H. and Swan, H. J. C.: Observations on the action of the hydrogenated alkaloids of the ergotoxine group on the circulation in man. J. Physiol., 112: 273–291, 1951.
17. Barker, M. H.: The blood cyanates in the treatment of hypertension. J. A. M. A., 106: 762–767, 1936.
18. Barrett, W., Reitze, W., Plummer, A. J. and Yonkman, F. F.: Coronary dilating action of 1-hydrazinophthalazine (BA-5968) (Apresoline) in the canine heart-lung preparation. Federation Proc., 11: 320–321, 1952.
19. Barrow, J. G. and Sikes, C. R.: The use of purified veratrum viride alkaloids in the treatment of essential hypertension. Am. Heart J., 41: 742–748, 1951.
20. Baumgartner, P.: Erfahrungen bei der Hyderginbehandlung der Hypertonie mit besonderer Berücksichtigung des i.v. Injektionstestes. Ztschr. f. Kreislauff., 40: 453–463, 1951.
21. Baylis, J. W. and Kauntze, R.: The effect of dimercaprol on hypertension. Lancet, 1: 1092, 1952.
22. Beaconsfield, P.: Dangers de l'emploi de l'hexaméthonium en médecine et en chirurgie. Presse méd., 60: 811, 1952.
23. Bechgaard, P., Iversen, T. and Nielsen, A. L.: Hexamethoniumbehandling af essentiel hypertension. Ugesk. f. laeger, 113: 1335–1340, 1951.
24. Bein, H. J. and Meier, R.: Zur Pharmakologie des N, N, N¹, N¹-3-Pentamethyl-N, N¹-diäthyl-3-aza-pentan-1, 5-diammonium-dibromid (Ciba 9295) einer ganglionär hemmenden Substans. Experientia, 6: 351–353, 1950.
25. Bein, H. J., Tripod, J. and Meier, R.: Zur Kreislaufwirkung des l-Hydrazinophthalazin. Experientia, 8: 74–75, 1952.
26. Bell, E. T.: Hypertension, a Symposium. Univ. of Minnesota Press, Minneapolis, 573 pp., 1951.
27. Bello, C. T., Moss, W. G. and Weiss, E.: Effect of orally administered Dihydroergocornine (DHO 180) on hypertension. Am. J. Med., 8: 634–639, 1950.
28. Bernsmeier, A., Esser, H. and Lorenz, W.: Klinisch-experimentelle und therapeutische Beobachtungen mit Pendiomid, einer neuen ganglienblockierenden Substans. Schweiz. med. Wchnschr., 81: 452–456, 1951.
29. Bertrand-Fontaine and Schneider, J.: Traitement de l'Hypertension artérielle par les derivés du méthonium. Bull. méd., Paris, 67: 466–468, 1951.
30. Binet, L., Burstein, M. and Damoiseau, B.: Recherches expérimentales sur un ganglioplégique de synthèse. Presse méd., 60: 801–803, 1952.
31. Blainey, J. D.: Hexamethonium compounds in the treatment of hypertension. Lancet, 1: 993–996, 1952.
32. Blüntschli, H. J.: Clinical observations on the sympathetic inhibitory effects of a new ergot alkaloid. South African M. J., 21: 21–23, 1947.
33. Blüntschli, H. J. and Goetz, R. H.: The effect of a new sympathicolytic drug (dihydroergocornine) on the blood pressure with special reference to hypertension. South African M. J., 21: 382–401, 1947.
34. Blüntschli, H. J. and Goetz, R. H.: The effect of ergot derivatives on the circulation in man, with special reference to new hydrogenated compounds (dihydroergotamine, dihydroergocornine). Am. Heart J., 35: 873–894, 1948.
35. Borison, H. L.: Studies on peripheral factors in the hypotensive action of veratrum alkaloids. J. Pharmacol. & Exper. Therap., 106: 374, 1952.
36. Borison, H. L. and Fairbanks, V. G.: Nodose ganglion as receptor site for emetic and vasodepressor actions of veratrum. Federation Proc., 11: 325, 1952.
37. Britton, J. P., Taylor, J. P. and Ahlquist, R. P.: Cardiovascular actions of 2,3-benzodiasine-4-hydrasine (C-5968). Federation Proc., 10: 282, 1951.
38. Burt, C. C. and Graham, A. J. P.: Pentamethonium and hexamethonium iodide in investigation of peripheral vascular disease and hypertension. Brit. M. J., 1: 455–460, 1950.
39. Campbell, A. J. M., Graham, J. G. and Maxwell, R. D. H.: Treatment of hypertension by oral methonium compounds. Brit. M. J., 1: 251–254, 1952.
40. Campbell, A. and Robertson, E.: Treatment of severe hypertension with hexamethonium bromide. Brit. M. J., 2: 804–806, 1950.
41. Caplowitz, C. D. and Moyer, J. H.: Imidazoline as a hypotensive agent. Am. J. Med., 11: 617, 1951.
42. Carini, R.: Sull'asione ipotensiva del bismuto. Gass. med. Ital., 110: 127–130, 1951.
43. Cecchi, E.: Observations cliniques sur l'emploi de l'"Embran" dans les affections de l'appareil circulatoire. Schweiz. med. Wchnschr., 81: 287–288, 1951.
44. Chisholm, R.: The investigation and treatment of high blood pressure. New Zealand M. J., 50: 114–118, 1951.
45. Coe, W. S., Best, M. M. and Kinsman, J. M.: Veratrum viride in the treatment of hypertensive vascular disease. J. A. M. A., 143: 5–7, 1950.
46. Connell, W. F., Wharton, G. K. and Robinson, C. E.: Thiocyanate therapy. Canad. M. A. J., 62: 20–27, 1950.
47. Corcoran, A. C., Taylor, R. D. and Harrison, M.: Ineffectiveness of 688A in treatment of essential hypertension. Proc. Soc. Exper. Biol. & Med., 80: 265–268, 1952.

48. Craver, B. N. and Yonkman, F. F.: Some pharmacological properties of 1-hydrazinophthalazine, a hypotensive agent. Federation Proc., 9: 265–266, 1950.
49. Crosley, A. P., Jr., Cummins, A. J., Barker, H. G. and Clark, J. K.: The renal hemodynamic effects of dihydroergocornine (DHO-180) in man. J. Pharmacol. & Exper. Therap., 98: 138–143, 1950.
50. Crumpton, C. W., Friedland, C. K., Kuo, P. T., Schnabel, T. G., Folts, E. L., Page, R. G., Alanis, J. and Hafkenschiel, J. H.: The hemodynamic actions of Protoveratrine in essential hypertension. J. Clin. Investigation, 30: 634, 1951.
51. Crumpton, C. W., Klingensmith, W. C., Keffer, N. J. and Hafkenschiel, J. H.: Effects of Protoveratrine on cerebral hemodynamics and oxygen metabolism in hypertensive subjects. Federation Proc., 10: 32, 1951.
52. Crumpton, C. W., Murphy, Q. R., Whitmore, J. J., Capps, R. T. and Orth, O. S.: Cerebral circulatory and metabolic changes following intramuscular hexamethonium bromide (C–6) in subjects with severe hypertensive retinopathy. Federation Proc., 11: 335, 1952.
53. Currens, J. H., Myers, G. S. and McGinty, J. S.: Observations on the use of Protoveratrine in hypertensive vascular disease. J. Clin. Investigation, 31: 623, 1951.
54. Davis, L.: Treatment of high diastolic type of essential hypertension. Combined use of thiocyanates and sympathectomy. Postgrad. Med., 9: 321–324, 1951.
55. Davis, L.: Physiological principles underlying the treatment of high diastolic essential hypertension by thiocyanates and sympathectomy. Lancet, 1: 1171–1174, 1952.
56. Davis, L., Tanturi, C. A. and Tarkington, J. A.: The combination of sympathectomy and thiocyanates in the treatment of experimental and essential, or high diastolic hypertension. Tr. Am. S. A., 68: 74–90, 1950.
57. Davis, L., Tarkington, J. and Anderson, R. K.: Physiologic principles underlying the treatment of high diastolic hypertension by thiocyanates and sympathectomy. Ann. Surg., 133: 867–873, 1951.
58. Dawes, G. S., Mott, J. C. and Widdicombe, J. G.: The depressor action of the veratrum alkaloids. Brit. J. Pharmacol., 6: 675–681, 1951.
59. Delius, L., Hammerschmidt, D. and Odenthal, F.: Klinische-experimentelle Untersuchungen über die kreislaufdynamischen Wirkungen der dihydrierten Mutterkornalkaloide. Klin. Wchnschr., 27: 33–34, 1949.
60. Dennemark, H. G.: Die Adrenalin-Umkehr und ihre therapeutische Verwertbarkeit für die Senkung des Blutdrucks. Medizin. Klin., 45: 1558–1560, 1950.
61. Donatelli, L., Spigliati, P., Zabban, M. and Selleri, R.: L'essestere nicotinico della m-inosite (Esantene), nuovo farmaco ipotensivo sintetico ad azione protratta. Minerva med., 1: 1117–1125, 1951.
62. Dontas, A. S. and Hoobler, S. W.: Pressor effects of TEA and hexamethonium in man after partial ganglionic blockade. Federation Proc. 12: 34, 1953.
63. Dupuy, H. J., Signorelli, J. and Attyah, A. M.: Dihydrogenated ergot alkaloids in the treatment of essential hypertension. Circulation, 5: 285–286, 1952.
64. Duret, R. L.: Action des dérivés di-hydrogénés de l'ergot dans l'hypertension artérielle. Acta clin. belg., 6: 85–106, 1951.
65. Dustan, H. P., Corcoran, A. C., Taylor, R. D. and Page, I. H.: Renal vasodilator effects of l-hydrazinophthalazine in hypertensive patients. Am. J. Med. 14: 502, 1953.
66. Elek, S. R., McNair, J. D. and Griffith, G. C.: Cardiac effects of intravenous veratrum viride. Am. J. Med., 8: 532–533, 1950.
67. Emlet, J. R., Gemmon, K. S. and Metcalf, B. H.: Comparison of adrenolytic blocking effects of Regitine (C-7337) and Benodaine. Am. J. Med., 11: 241, 1951.
68. Fairbanks, V. F. and Bohlson, H. L.: Studies on emetic action of veratrum alkaloids in cats. J. Pharmacol. & Exper. Therap., 103: 343, 1951.
69. Faust, F. B.: Veratrum Viride in the treatment of essential hypertension. Journal Lancet, 71: 65–68, 1951.
70. Finnerty, F. A., Jr.: Hypertensive toxemias of pregnancy. A simplified method of management using a purified extract of Veratrum Viride. New England J. Med., 246: 646–651, 1952.
71. Finnerty, F. A., Jr. and Freis, E. D.: Experimental and clinical evaluation in man of Hexamethonium, a new ganglionic blocking agent. Circulation, 2: 828–836, 1950.
72. Finnerty, F. A., Jr. and Freis, E. D.: Clinical appraisal of hexamethonium (C-6) in peripheral vascular diseases. New England J. Med., 245: 325–328, 1951.
73. Finnerty, F. A., Jr. and Freis, E. D.: Clinical evaluation of vergitryl, a new, highly purified extract of veratrum viride. M. Ann. District of Columbia, 21: 75–76, 1952.
74. Folts, E. L., Page, R. G., Crumpton, C. W. and Alanis, J.: Circulatory and cardiac metabolic changes following intravenous injections of protoveratrine. Federation Proc., 10: 296, 1951.
75. Ford, R. V. and Moyer, J. H.: Renal hemodynamics as effected by posture and by sympathoadrenal blockade. Federation Proc., 11: 346, 1952.
76. Ford, R. V., Moyer, J. H. and Spurr, C. L.: Hexamethonium in the chronic treatment of hypertension, its effects on renal hemodynamics and excretion of water and electrolytes. J. Clin. Investigation (in press).
77. Freis, E. D.: Methonium compounds in hypertension. Lancet, 1: 909, 1951.
78. Freis, E. D.: Veratrum Viride and Hexamethonium in the treatment of severe diastolic hypertension. M. Ann. District of Columbia, 20: 297–304, 1951.
79. Freis, E. D.: An approach to the treatment of severe essential hypertension. Med. Illustrated, 5: 53–58, 1951.
80. Freis, E. D.: Unpublished observations (personal communication).
81. Freis, E. D. and Finnerty, F. A.: Suppression of vasomotor reflexes in man following l-hydrazinophthalazine (C-5968). Proc. Soc. Exper. Biol. & Med., 75: 23–24, 1950.

82. Freis, E. D., Finnerty, F. A., Jr., Schnaper, H. W. and Johnson, R. L.: The treatment of hypertension with hexamethonium. Circulation, 5: 20-27, 1952.
83. Freis, E. D., Finnerty, F. A., Jr., and Walsh, W. B.: The treatment of severe essential hypertension. M Clin. North America, 34: 1741-1750, 1950.
84. Freis, E. D., McKay, J. C. and Oliver, W. F.: The effect of "sympatholytic" drugs on the cardiovascular responses to epinephrine and norepinephrine in man. Circulation, 3: 254-259, 1951.
85. Freis, E. D., Ross, J. C., Higgins, T. F., Kelley, R. T., Schnaper, H. W. and Johnson, R. L.: The hemodynamic effects of hexamethonium in man. J. Clin. Investigation, 31: 629, 1952.
86. Freis, E. D. and Stanton, J. R.: A clinical evaluation of veratrum viride in the treatment of essential hypertension. Am. Heart J., 36: 723-738, 1948.
87. Freis, E. D., Stanton, J. R., Culbertson, J. W., Litter, J. and Halperin, M. H.: The hemodynamic effects of veratrum viride in hypertensive man: Studies of arterial pressure, cardiac output, renal and hepatic clearances, peripheral blood flow, "venous tone" and vasomotor reflexes. J. Clin. Investigation, 27: 535, 1948.
88. Freis, E. D., Stanton, J. R., Culbertson, J. W., Litter, J., Halperin, M. H., Burnett, C. H. and Wilkins, R. W.: The hemodynamic effects of hypotensive drugs in man. I. Veratrum viride. J. Clin. Investigation, 28: 353-368, 1949.
89. Freis, E. D., Stanton, J. R., Litter, J., Culbertson, J. W., Halperin, M. H., Moister, F. C. and Wilkins, R. W.: Hemodynamic effects of hypotensive agents in man. Am. J. Med., 7: 414-415, 1949.
90. Freis, E. D., Stanton, J. R., Litter, J., Culbertson, J. W., Halperin, M. H., Moister, F. C. and Wilkins, R. W.: The hemodynamic effects of hypotensive drugs in man. II. Dihydroergocornine. J. Clin. Investigation, 28: 1387-1402, 1949.
91. Freis, E. D., Stanton, J. R. and Wilkins, R. W.: The effects of certain dihydrogenated alkaloids of ergot in hypertensive patients. Am. J. M. Sc., 216: 163-171, 1948.
92. Freis, E. D. and Wilkins, R. W.: Effect of Pentaquine in patients with hypertension. Proc. Soc. Exper. Biol. & Med., 64: 455-458, 1947.
93. Gast, W. and Hueber, E. F.: Über die Behandlung der Hypertension mit Hydergin. Wien. klin. Wchnschr., 62: 900-903, 1950.
94. de Gennes, L., Courjaret, J. and Bricaire, H.: Résultats obtenus par l'emploi de l'hexaméthonium chez 17 malades. Bull. méd., Paris, 67: 982-485, 1951.
95. Gibbs, D. F.: Dihydrogenated alkaloids of ergot in the investigation and treatment of diastolic hypertension. Brit. Heart J., 14: 77-86, 1952.
96. Gilmore, H. R., Kopelman, H., McMichael, J. and Milne, I. G.: The effect of hexamethonium bromide on the cardiac output and pulmonary circulation. Lancet, 2: 898-902, 1952.
97. Glauner, W.: Blutdrucksenkende Wirkung des Vitamin E bei essentieller Hypertension. Deutsche med. Wchnschr., 77: 627, 1952.
98. Goldring, W.: Recent advances in the medical and surgical management of hypertension. Connecticut M. J., 11: 87-97, 1947.
99. Goldstone, B.: Death associated with methonium treatment. South African M. J., 26: 552-554, 1952.
100. Gounelle, H., Teulon, H. and Cheroux, R.: Recherches sur la vitamine A et les huiles de poisson; la réaction locale dans les états hypertensifs. Bull. méd., Paris, 67: 814-821, 1951.
101. Grimson, K. S. and Chittum, J. R.: Effectiveness of several adrenolytic, sympatholytic or ganglionic blocking drugs against acute and chronic neurogenic hypertension. Am. J. Med., 7: 251, 1949.
102. Grimson, K. S., Chittum, J. R. and Metcalf, B. H.: Actions of l-hydrazinophthalazine (C-5968) on vasomotor reflexes and hypertension in dogs and man. Federation Proc., 9: 279, 1950.
103. Grimson, K. S., Orgain, E. S., Rowe, C. R., Jr. and Sieber, H. A.: Caution with regard to use of hexamethonium and "Apresoline". J. A. M. A., 149: 215-220, 1952.
104. Grob, D. and Harvey, A. M.: Observations on the effects of the autonomic blocking agent, bis-trimethylammonium pentane dibromide (C_5) in normal subjects and in patients with peripheral vascular disease and hypertension, and comparison with tetraethylammonium chloride. Bull. Johns Hopkins Hosp., 87: 616-639, 1950.
105. Groffer, A. L., Surtshin, A. and Hedrick, J. T.: Effects of veriloid on essential hypertension. Arch. Int. Med., 87: 789-794, 1951.
106. Gross, F., Druey, J. and Meier, R.: Eine neue Gruppe blutdrucksenkender Substanzen von besonderem Wirkungscharakter. Experientia, 6: 19-21, 1950.
107. Gruhzit, G. and Moe, G. K.: Mechanism of hypotensive action of "Veraloid". Federation Proc., 11: 352, 1952.
108. Gubner, R.: Hypercalcemia, hypophosphatemia and salt loss caused by thiocyanate. Am. J. Med., 10: 236, 1951.
109. Hafkenschiel, J. H., Crumpton, C. W., Moyer, J. H. and Jeffers, W. A.: The effects of dihydroergocornine on the cerebral circulation of patients with essential hypertension. J. Clin. Investigation, 29: 408-411, 1950.
110. Hafkenschiel, J. H., Friedland, C. K., Yobaggy, J. and Crumpton, C. W.: Effects of l-hydrazinophthalazine on cerebral hemodynamics and oxygen metabolism in hypertensive subjects. J. Pharmacol. & Exper. Therap. 103: 345, 1951.
111. Haimovici, H., Moser, M. and Krakauer, H.: Effect of oral 688 A (N-phenoxyisopropyl-N-benzyl-β-chloroethylamine HCl) on blood pressure in normotensive and hypertensive subjects. Proc. Soc. Exper. Biol & Med., 77: 477-480, 1951.
112. Halmagyi, D., Felkai, B., Ivanyi, J. and Hetenyi, G., Jr.: The role of the nervous system in the maintenance of venous hypertension in heart failure. Brit. Heart J., 14: 101-111, 1952.

113. Hanno, H. A.: Auricular fibrillation following administration of dibenamine hydrochloride. J. A. M. A., 141: 1144–1145, 1949.
114. Harmel, M. H., Hafkenschiel, J. H., Austin, G. M., Crumpton, C. W. and Kety, S. S.: The effect of bilateral stellate ganglion block on the cerebral circulation in normotensive and hypertensive patients. J. Clin. Investigation, 28: 415–418, 1949.
115. Hartmann, H., Øskov, S. L. and Rein, H.: Die Gefässreaktionen der Niere im Verlaufe allgemeiner Kreislauf-Regulationsvorgänge. Pflüger's Arch. f. d. ges. Physiol., 238: 239–250, 1937.
116. Häusler, H. P., Lauda, E. and Siedek, H.: Über die Behandlung der Hypertonie mit elementarem Jod. Wien. Klin. Wchnschr., 63: 623–626, 1951.
117. Hauss, W. H. and Kreuziger, H.: Über die Wirkung neuer Sympatholytica bei Hypertonikern. Wien. med. Wchnschr., 101: 544–556, 1951.
118. Hauss, W. H., Kreuziger, H. and Asteroth, H.: Über die Wirkung neuer sympathicolytischer Substanzen. Klin. Wchnschr., 27: 690–697, 1949.
119. Heni, F. and Nieth, H.: Vergleich der Hyderginwirkung bei enteraler und sublingualer Zufuhr. Klin. Wchnschr., 30: 354–357, 1952.
120. Hill, I. G. W.: The drug treatment of hypertension. Practitioner, 166: 541–547, 1951.
121. Holman, J. and Goth, A.: Histamine release in the human skin and the effect of cortisone. Federation Proc., 11: 358, 1952.
122. Hoobler, S. W.: Unpublished observations (see also 125).
123. Hoobler, S. W. and Avera, J. W.: Unpublished results.
124. Hoobler, S. W. and Corley, R. W.: The hypotensive action of Protoveratrine. Univ. Mich. M. Bull., 16: 362–368, 1950.
125. Hoobler, S. W., Corley, R. W., Kabra, T. G. and Loyke, H. F.: Treatment of hypertension with oral protoveratrine. Ann. Int. Med., 37: 465–481, 1952.
126. Hoobler, S. W., Moe, G. K. and Lyons, R. H.: The cardiovascular effects of tetraethylammonium in animals and man with special reference to hypertension. M. Clin. North America, 33: 805–831, 1949.
127. Jacquet, M.: Le benzène sulfonate de cobalt, hypotenseur artériel et hypoconstrictant périphérique. Arch. mal. Coeur, 45: 633–635, 1952.
128. Jakob, R.: Der Gasstoffwechsel von Hochdruckkranken unter der Behandlung mit hydrierten Mutterkorn-Alkaloiden. Ztschr. f. Kreislaufforsch., 39: 729–736, 1950.
129. Johnson, I. and Mills, L. C.: Response of essential hypertension to semi-purified extracts of veratrum viride (Veriloid) using oral and intramuscular routes of administration. Federation Proc., 11: 360, 1952.
130. Johnson, R. L., Freis, E. D. and Schnaper, H. W.: Clinical evaluation of l-hydrazinophthalazine (C-5068) in hypertension, with special reference to alternating treatment with hexamethonium. Circulation, 5: 833–841, 1952.
131. Josephs, I. L.: Therapy of hypertension. The use of veratrum viride alone and combined with certain dihydrogenated alkaloids of ergot. Ann. West. Med. & Surg., 4: 789–794, 1950.
132. Josephs, I. L.: Clinical observations on the hypotensive effect of certain dihydrogenated alkaloids of ergot in human beings. Am. Pract., 4: 71–74, 1949.
133. Kaiser, K. and Martini, P.: Über die Wirkung der Dihydroalkaloide des Mutterkorns bei der Hypertonie. Deutsche med. Wchnschr., 75: 1516–1519, 1523–1524, 1566–1568, 1950.
134. Kappert, A.: Untersuchungen über die Wirkungen neuer dihydrierter Mutterkorn-alkaloide bei peripheren Durchblutungsstörungen und Hypertonie. Helvet. Med. Acta, 16: Suppl. 22, 1949.
135. Kappert, A., Baumgartner, P. and Rupp, F.: Über die blutdrucksenkende Wirkung neuer dihydrierter Mutterkornalkaloide. Schweiz. med. Wchnschr., 78: 1265–1269, 1948.
136. Kauntze, R. and Trounce, J.: The hypotensive action of veriloid (veratrum viride). A clinical investigation. Lancet, 1: 549–555, 1951.
137. Kauntze, R. and Trounce, J.: Treatment of arterial hypertension with veriloid. Lancet, 2: 1002–1008, 1951.
138. Kelley, R. T., Higgins, T. F. and Freis, E. D.: Effect of acute reduction of arterial pressure using hexamethonium on the manifestations of congestive heart failure in man. Am. J. Med., 13: 103, 1952.
139. Kilpatrick, J. A. and Smirk, F. H.: Comparison of oral and subcutaneous administration of methonium salts in the treatment of high blood pressure. Lancet, 1: 8–12, 1952.
140. Kirkendall, W. M. and Culbertson, J. W.: Some effects of hexamethonium (C-6) and l-hydrazinophthalazine on kidney circulation. J. Lab. & Clin. Med., 40: 818, 1952.
141. Koenigsberg, M.: Unheralded hypotension and coronary insufficiency following the use of veratrum viride in the treatment of primary (essential) hypertension. W. Va. M. J., 47: 203–206, 1951.
142. Kowalski, H. J., Hoobler, S. W., Malton, S. D. and Lyons, R. H.: Studies on vasomotor tone. II. Measurement of vasoconstrictor tone in the extremities in hypertension. Circulation, 1953 (in press).
143. Krayer, O.: Antiaccelerator cardiac agents. J. Mt. Sinai Hosp., 19: 53–69, 1952.
144. Krayer, O. and Acheson, G. A.: The pharmacology of the veratrum alkaloids. Physiol. Rev., 26: 383–446, 1946.
145. Krayer, O. and Mendes, R.: Studies on veratrum alkaloids. I. The action of veratrine upon the isolated mammalian heart. J. Pharmacol. & Exper. Therap., 74: 350–364, 1942.
146. Krayer, O., Wood, E. H. and Montes, G.: Studies on veratrum alkaloids. IV. The sites of heart rate lowering action of veratridine. J. Pharmacol. & Exper. Therap., 79: 215–224, 1943.
147. Kvale, W. F.: Hexamethonium and Apresoline (l-hydrazinophthalazine). Proc. Staff Meet., Mayo Clin., 27: 489–494, 1952.

148. Lasch, F.: Zur Frage der Blutdruckwirkung des Hydergins. München. med. Wchnschr., 26: 1325–1331, 1952.
149. Leik, D. W. and Elek, S. R.: Cardiac effects of dihydroergocornine. Am. J. Med., 8: 539, 1950.
150. Lindberg, H. A.: Personal communication.
151. Lockett, S., Swann, P. G. and Grieve, W. S. M.: Methonium compounds in the treatment of hypertension. Brit. M. J., 1: 778–784, 1951.
152. Lockett, S., Swann, P. G., Grieve, W. S. M. and Player, H. P.: M. & B. 1863, a homologue of hexamethonium, in treatment of hypertension. Brit. M. J., 1: 254–258, 1952.
153. Longino, F. H., Grimson, K. S., Chittum, J. R. and Metcalf, B. H.: Effects of a new quaternary amine and a new imidasoline derivative on the autonomic nervous system. Surgery, 26: 421–434, 1949.
154. Longino, F. H., Chittum, J. R. and Grimson, K. S.: Effects of a quaternary amine on functions of the autonomic nervous system. Am. J. Med., 7: 256, 1949.
155. Losse, H., Heintz, R., Kiefer, K. and Göbelitz, F.: Die Kreislauffunktion unter Veratrin-Gaben bei Hypertonikern. Verh. Dtsch. Ges. Kreislauff., 17 Tag: 307–309, 1951.
156. Lottenbach, K.: Die Wirkung des N, N, N′, N′, 3-Pentamethyl-N, N′-diäthyl-3-aza-pentan-1, 5-diammonium dibromid (Ciba 9295), auf die Kreislaufreflexe beim Carotissinussyndrom. Schweiz. Med. Wchnschr., 81: 310–312, 1951.
157. Lovejoy, F. W., Yu, P. N. G., Bruce, R. A., Nye, R. E., Welch, G., Brody, B. B. and Muxworthy, J.: The effects of intravenous protoveratrine on hemodynamics and exercise tolerance in patients with hypertension. Am. J. M. Sc., 222: 129–137, 1951.
158. Lynn, R. B., Sancetta, S. M. and Simeone, F. A.: A new ganglionic blocking agent. Angiology, 3: 241–248, 1952.
159. McCall, M. L.: Acute hypertension in toxemia of pregnancy treated with papaverine hydrochloride infusion. Quart. Rev. Obstet. & Gynec., 10: 67–70, 1952.
160. McCubbin, J. W. and Page, I. H.: Effect of veratramine on arterial pressure and heart rate in normal and hypertensive dogs. Am. J. Physiol., 167: 714–720, 1951.
161. McCubbin, J. W. and Page, I. H.: Nature of the hypotensive action of a thiophanium derivative (RO 2-2222) in dogs. J. Pharmacol. & Exper. Therap., 105: 437–442, 1952.
162. McKey, W. A. and Shaw, G. B.: Oral hexamethonium bromide in essential hypertension. Brit. M. J., 2: 259–265, 1951.
163. McMichael, J.: The management of hypertension. Brit. M. J., 1: 933–938, 1952.
164. McNair, D., Griffith, G. C. and Elek, S. R.: A prolonged study of oral veratrum viride in the treatment of essential hypertension. Am. Heart J., 40: 382–389, 1950.
165. Mackinnon, J.: Effect of hypotension-producing drugs on the renal circulation. Lancet, 2: 12–15, 1952.
166. Maison, G. L., Goth, E. and Stutzman, J. W.: Relative hypotensive activity of certain veratrum alkaloids. J. Pharmacol. & Exper. Therap., 103: 74–78, 1952.
167. Marocco, F.: L'uso del tiocianato di potassio nella terapia della ipertensione arteriosa. Omnia therap. (Pisa), 1: 333–342, 1950.
168. Masini, V. and Rossi, P.: Preparato di metonio in solusione ritardante nella cura dell'ipertensione arteriosa. La Riforma Med., 65: 898–900, 1951.
169. May, E., Lamotte-Barrillon, Dubreissay, J. and Heyblon, R.: Note préliminaire sur l'emploi des méthoniums chez les hypertendus. Bull. méd., Paris, 67: 440–445, 1951.
170. Meador, C. B., McKee, K. T. and Boone, J. A.: Veratrum viride in hypertension. J. South Carolina M. A., 46: 313–315, 1950.
171. Meier, R., Yonkman, F. F., Craver, B. N. and Gross, F.: A new imidasoline derivative with marked adrenolytic properties. Proc. Soc. Exper. Biol. & Med., 71: 70–72, 1949.
172. Meilman, E.: The mechanism of protoveratrine-induced oliguria. J. Clin. Investigation, 31: 649, 1952.
172a. Meilman, E.: Clinical studies on veratrum alkaloids. III. The effect of protoveratrine on renal function in man. J. Clin. Investigation, 32: 80–89, 1953.
173. Meilman, E. and Krayer, O.: Clinical studies on veratrum alkaloids. I. The action of Protoveratrine and Veratridine in hypertension. Circulation, 1: 204–213, 1950.
174. Meilman, E. and Krayer, O.: Clinical studies on veratrum alkaloids. II. The dose-response relations of Protoveratrine in hypertension. Circulation, 6: 212–221, 1952.
175. Melchinger, G., Sarre, H., Wale, L. and Zimmerman, G.: Über die Behandlung der Hypertonie mit Rhodan. Deutsche Med. Wchnschr., 77: 990–993, 1952.
176. Méndez, L. and Chávez, I.: El tratamiento simpáticolítico de la hipertensión arterial esencial. Arch. Inst. Cardiol. Méx., 20: 595–609, 1950.
177. Merli, A.: Trattamento degli stati ipertensivi con vitamina K. Osped. Maggiore, 38: 65–68, 1950.
178. Merritt, W. A.: The treatment of essential hypertension with veratrum. Proc. Staff Meet., Mayo Clin., 27: 481–485, 1952.
179. Mills, L. C. and Moyer, J. H.: Treatment of hypertension with orally and parenterally administered purified extracts of veratrum viride. Arch. Int. Med., 90: 587–601, 1952.
180. Milne, G. E. and Olbrsky, S.: Excretion of the methonium compounds. Lancet, 1: 889, 1951.
181. Mitchell, R., Newman, P. J., McGillivray, D. and Clark, B. B.: Evaluation of histamine liberator activity, illustrated by a thiophanium compound RO 2-2222. Federation Proc., 10: 325–326, 1951.
182. Moe, G. K., Capo, L. R. and Peralta, R. B.: The action of tetraethylammonium on chemoreceptor and stretch receptor mechanisms. Am. J. Physiol., 153: 601–605, 1948.
183. Moe, G. K. and Freyburger, W. A.: Ganglionic blocking agents. Pharmacol. Rev., 2: 61–95, 1950.

184. Moister, F. C., Stanton, J. R. and Freis, E. D.: Observations on the development of tolerance during prolonged oral administration of dihydroergocornine. J. Pharmacol. & Exper. Therap., 96: 21–30, 1949.
185. Mosenthal, H. O.: Medical (conservative) treatment of essential hypertension. M. Clin. North America, 33: 687–701, 1949.
186. Moser, M., Walters, M., Master, A. M., Taymore, R. C. and Metraux, J.: Chemical blockade of the sympathetic nervous system in essential hypertension. Arch. Int. Med., 89: 706–723, 1952.
189. Moyer, J. H. and Handley, C. A.: Renal function and systemic blood pressure changes following the administration of hydrazinophthalazine. J. Lab. & Clin. Med., 36: 969, 1950.
190. Moyer, J. H. and Handley, C. A.: Renal hemodynamic and blood pressure response to N-phenoxyisopropyl-N-benzyl-B-chloroethylamine (SKF 688A). J. Pharmacol. & Exper. Therap., 104: 329–333, 1952.
191. Moyer, J. H., Handley, C. A. and Huggins, R. A.: Some pharmacodynamic effects of l-hydrazinophthalazine (C-5968) with particular reference to renal function and cardiovascular response. J. Pharmacol. & Exper. Therap., 103: 368–376, 1951.
192. Moyer, J. H., Miller, S. I. and Snyder, H.: Hexamethonium chloride administered orally for the treatment of hypertension. J. A. M. A. (in press); also personal communication.
193. Moyer, J. H. and Mills, L. C.: Hexamethonium—its effects on glomerular filtration rate, maximal tubular function and renal excretion of electrolytes. J. Clin. Investigation, 33: 172–184, 1953.
193a. Muller, J. M., Schlitter, E. and Bein, H. J.: Reserpin, der sedative Wirkstoff aus "Rauwolfia serpentina" Benth. Experientia, 8: 338, 1952.
194. Nasello, J. and Camponovo, P. B.: Accion de la vitamina K sobre la hipertension arterial y la colinesterasa serica. Prensa Med. Argent., 37: 2864–2870, 1950.
195. Nickerson, M.: The pharmacology of adrenergic blockade. Pharmacol. Rev., 1: 27–101, 1949.
196. Nickerson, M.: Sympathetic blockade in the therapy of hypertension, in "Hypertension, a Symposium". Edited by E. T. Bell, Univ. of Minnesota Press, Minneapolis, 410–421, 1951.
197. Nickerson, M.: Personal communication.
198. Nickerson, M. and Thomas, J. J.: Renal excretion of thiocyanate. J. Lab. & Clin. Med., 38: 194–198, 1951.
199. Nuzum, F. R.: The dihydrogenated ergot alkaloids in the treatment of essential hypertension. Ann. West. Med. & Surg., 4: 781–788, 1950.
200. Odenthal, F.: Über die Behandlung der Hypertonie mit Hydergin. Deutsche Med. Wchnschr., 76: 1107–1112, 1951.
201. Organe, G., Paton, W. D. M. and Zaimis, E. J.: Preliminary trials of bistrimethylammonium decane and pentane diiodide (C 10 and C 5) in man. Lancet, 1: 21–23, 1949.
202. Page, I. H.: Treatment of essential and malignant hypertension. J. A. M. A., 147: 1311–1318, 1951.
203. Page, I. H. and McCubbin, M. W.: Increased resistance to autonomic ganglionic blockade by tetraethylammonium chloride and pentamethonium iodide in experimental neurogenic hypertension. Am. J. Physiol., 168: 206–217, 1952.
204. Page, I. H., Taylor, R. D. and Corcoran, A. C.: Pyrogens in the treatment of malignant hypertension, in "Hypertension, a Symposium". Edited by E. T. Bell, Univ. of Minnesota Press, Minneapolis, 524–533, 1950.
205. Parsonnet, A. E., Simon, F. and Bernstein, A.: Low dosage potassium thiocyanate in the treatment of hypertension. J. M. Soc. New Jersey, 47: 504–510, 1950.
206. Paton, W. D. M.: Paralysis of autonomic ganglia; with special reference to the therapeutic effects of ganglion-blocking drugs. British M. J., 1: 773–778, 1951.
207. Paton, W. D. M.: Ganglionic blocking agents; with special reference to the effect of hexamethonium on the cardiovascular system. Brit. M. Bull., 8: 310–315, 1952.
208. Paton, W. D. M. and Perry, W. L. M.: Depolarisation and transmission block in the cat's superior cervical ganglion. J. Physiol., 112: 48–49P, 1951.
209. Paton, W. D. M. and Zaimis, E. J.: The pharmacological actions of polymethylene bistrimethylammonium salts. Brit. J. Pharmacol., 4: 381–400, 1949.
210. Paton, W. D. M. and Zaimis, E. J.: Paralysis of autonomic ganglia by methonium salts. Brit. J. Pharmacol., 6: 155–168, 1951.
211. Paton, W. D. M. and Zaimis, E. J.: The methonium compounds. Pharmacol. Rev., 4: 219–253, 1952.
212. Pesant, L.: Hypertension artérielle a minima élevée; sensibilisation au thiocyanate de potasse après splanchnicectomie bilatérale. U. Medic. Canad., 80: 316–322, 1951.
213. Petit-Dutaillis, D., Guiot, G. and Damoiseau, B.: Premiers essais d'application de certains ganglioplégiques aux accidents vasculaires aigus du cerveau. Presse méd., 60: 657–659, 1952.
214. Pickering, G. W., Wright, A. D. and Heptinstall, R. H.: The reversibility of malignant hypertension. Lancet, 2: 952–956, 1952.
215. Pines, K. L. and Perera, G.: Effect of thiocyanates on sodium excretion in normotensives and hypertensives. J. Clin. Investigation, 31: 654, 1952.
216. Plechet, A.: Le traitement de l'hypertension artérielle par les sels de penta- et hexa-méthonium. Presse méd., 59: 893–894, 1951.
217. Popkin, R. J.: Dihydrogenated alkaloids of ergot in the treatment of peripheral vascular diseases. California Med., 72: 108–112, 1950.
218. Randall, L. O., Peterson, W. G. and Lehmann, G.: The ganglionic blocking action of thiophanium derivatives. J. Pharmacol. & Exper. Therap., 97: 48–57, 1949.

219. REDISCH, W., TEXTER, E. C., JR., HOWARD, R. M., STILLMAN, P. H. AND STEELE, J. M.: The action of SKF 688A upon certain functions of the sympathetic nervous system in man. Circulation, 6: 352-358, 1952.
220. RESTALL, P. A. AND SMIRK, F. H.: Regulation of blood pressure levels by hexamethonium bromide and mechanical devices. Brit. Heart J., 14: 1-12, 1952.
221. REUBI, F.: L'action de quelques dérivés de l'ergot de seigle sur la circulation rénale. Experientia, 5: 296-297, 1949.
222. REUBI, F.: Influence de quelques vasodilatateurs périphériques sur le flux sanguin rénal. Helvet. med. acta, 16: 297-301, 1949.
223. REUBI, F.: Le flux sanguin rénal. Aspects physiopathologiques, cliniques et thérapeutiques. Helv. med. acta, 17: Suppl. 26: 9-108, 1950.
224. REUBI, F.: Renal hyperemia induced in man by a new phthalasine derivative. Proc. Soc. Exper. Biol. & Med., 73: 102-103, 1950.
225. REUBI, F.: L'Hydergine modifie-t-elle l'activité tubulaire rénale? Helv. med. acta, 19: 1-8, 1952.
226. REUBI, F.: Les fonctions rénales des hypertendus au cours d'un traitement prolongé par les dérivés dihydrogénés de l'ergot de seigle (Hydergine). Helv. med. acta, 19: 29-41, 1952.
227. RICHARDSON, A. P., FARRAR, C. AND WALKER, H. A.: Effect of veratrine alkaloids on the carotid sinus pressor reflex. Federation Proc., 10: 331, 1951.
228. RICHARDSON, A. P., WALKER, H. A., FARRAR, C. B., GRIFFITH, W., POUND, E. AND DAVIDSON, J. R.: The mechanism of the hypotensive action of veratrum alkaloids. Proc. Soc. Exper. Biol. & Med., 79: 79-85, 1952.
229. RICHTER, H. AND AMANN, A.: Ist die Lunge chemosensibel? Arch. f. exper. Path. u. Pharmakol., 196: 274-279, 1940.
230. ROSENHEIM, M. L. AND KAUNTZE, R.: Discussion on the medical treatment of hypertension. Proc. Roy. Soc. Med., 45: 269-276, 1952.
231. ROSS, P. S.: Hypertension and arterial disease. Ohio State M. J., 47: 639-644, 1951.
232. ROTHLIN, E.: Über die adrenergischen Funktionen am Herz und an Gefässen. Bull. Schweiz. Akad. d. med. Wissensch., 1: 194-206, 1945.
233. ROTHLIN, E.: The Pharmacology of the natural and dihydrogenated alkaloids of ergot. Bull. Schweiz. Akad. d. med. Wissensch., 2: 249-273, 1947.
234. ROTHLIN, E.: Über das Schicksal der natürlichen und dihydrierten Mutternkornalkaloide im Organismus. Schweiz. med. Wchnschr., 77: 1161-1163, 1947.
235. RUSKIN, A. AND MCKINLEY, W. F.: Comparative study of potassium thiocyanate and other drugs in the treatment of essential hypertension. Am. Heart J., 34: 691-701, 1947.
236. SARNOFF, S. J.: Massive pulmonary edema of central nervous system origin: hemodynamic observations and the role of sympathetic pathways. Federation Proc., 10: 118, 1951.
237. SARNOFF, S. J., GOODALE, W. T. AND SARNOFF, L. C.: Graded reduction of arterial pressure in man by means of a thiophanium derivative (RO 2-2222). Circulation, 6: 63-73, 1952.
238. SAUNDERS, J. W.: Negative-pressure device for controlled hypotension during surgical operations. Lancet, 1: 1286-1288, 1952.
239. SAVILLE, S.: Pentamethonium in hypertension. Lancet, 2: 358-360, 1950.
239a. SCHAEFER, H.: Elektrophysiologie der Herznerven. Ergebn. Physiol., 46: 71-125, 1950.
240. SCHMID, A. AND REUBI, F.: Hämodynamische Eigenschaften zweier neuer Phthalasinderivate. Helv. med. acta, 17: 543-546, 1950.
241. SCHNAPER, H. W., JOHNSON, R. L., TUOHY, E. B. AND FREIS, E. D.: The effect of hexamethonium as compared to procaine or metycaine lumbar block on the blood flow to the foot of normal subjects. J. Clin. Investigation, 30: 786-791, 1951.
242. SCHROEDER, H. A.: Effects on hypertension of sulfhydryl and hydrazine compounds. J. Clin. Investigation, 30: 672-673, 1951.
243. SCHROEDER, H. A.: The effect of l-hydrazinophthalasine and hexamethonium in hypertension. J. Lab. & Clin. Med., 38: 949, 1951.
244. SCHROEDER, H. A.: The effect of l-hydrazinophthalasine in hypertension. Circulation, 5: 28-37, 1952.
245. SCHROEDER, H. A.: Control of hypertension by hexamethonium and l-hydrazinophthalasine. Arch. Int. Med., 89: 523-540, 1952.
246. SCHROEDER, H. A. AND MORROW, J. D.: Further observations on the control of hypertension by "Hyphex." J. Lab. & Clin. Med., 40: 941, 1952.
247. SEBÖK, I.: Koffeinwirkung bei Hypertonikern. Deutsche med. Wchnschr., 75: 1067-1070, 1950.
248. SHAPIRO, A. P., BRUST, A. A. AND FERRIS, E. B.: A comparative study of the effects of veratrum viride and tetraethylammonium chloride in hypertension. Ann. Int. Med., 36: 807-810, 1952.
249. SHAPIRO, A. P. AND FERRIS, E. B.: The effects of intravenously administered veratrum viride in hypertensive and normotensive subjects. Ann. Int. Med., 36: 792-806, 1952.
250. SIKES, C. R. AND BARROW, J. G.: Drug therapy of hypertension. Am. J. Med., 11: 616-617, 1951.
251. SMIRK, F. H.: Practical details of the methonium treatment of high blood pressure. New Zealand M. J., 49: 637-643, 1950.
252. SMIRK, F. H.: Blood pressure reduction to a selected level by continuous injection of methonium halides (C_8 and C_6) and the use of an electrically operated syringe. Am. Heart J., 42: 530-537, 1951.
253. SMIRK, F. H.: Prolongation of action of hypotensive drugs. Lancet, 2: 695-699, 1952.
254. SMIRK, F. H.: Hypotensive actions of hexamethonium bromide and some of its homologues; their use in high blood-pressure. Lancet, 2: 1002-1005, 1952.

255. SMIRK, F. H. AND ALSTAD, K. S.: Treatment of hypertension by penta- and hexa-methonium salts. Brit. M. J., 1: 1217–1228, 1951.
256. SMIRK, F. H. AND CHAPMAN, O. W.: Comparison of the effects of veratrum alkaloids and of hexamethonium bromide upon the blood pressure in arterial hypertension. Am. Heart J., 43: 586–605, 1952.
257. SMITHWICK, R. H.: The effect of sympathectomy upon the mortality and survival rates of patients with hypertensive cardiovascular disease. In "Hypertension, a Symposium" edited by E. T. Bell, Univ. of Minnesota Press, Minneapolis, 429–448, 1950.
258. SOLAR, A. DEL, DUSSAILLANT, G., BRODSKY, M. AND LEVY, M.: A critical study of the medical treatment of hypertension. Rev. méd. de Chile, 73: 293, 1945. Abstract in Am. Heart J., 31: 523, 1946.
259. STEARNS, N. S. AND ELLIS, L. B.: Acute effects of intravenous administration of a preparation of veratrum viride in patients with severe forms of hypertensive disease. New England J. Med., 246: 397–400, 1952.
260. STOLL, A. AND HOFFMAN, A.: Die Dihydroderivate der natürlichen linksdrehenden Mutterkornalkaloide. Helvet. chim. acta, 26: 2070–2081, 1943.
261. STONE, C. A., ENTWISLE, G. E. AND LOEW, E. R.: Effect of tetraethylammonium chloride on the adrenal medulla of cats. J. Pharmacol. & Exper. Therap., 101: 34, 1951.
262. STROBBIA, R.: Ricerche cliniche e sperimentali sull'esanitromesoinosite nella ipertensione arteriosa e negli spasmi vasali. La Riforma Medica, 64: 956–960, 1950.
263. STUTZMAN, J. W. AND MAISON, G. L.: Hypotensive action of veriloid, an extract of veratrum viride. Federation Proc., 9: 318–319, 1950.
264. STUTZMAN, J. W., MAISON, G. L. AND KUSSEROW, G. W.: Veriloid, a new hypotensive extract of veratrum viride. Proc. Soc. Exper. Biol. & Med., 71: 725–727, 1949.
265. SUTTON, G. C., BUCKINGHAM, W., BROWN, R. D. AND SUTTON, D. C.: A clinical evaluation of the treatment of hypertension with dihydrogenated ergotoxine alkaloids. Am. Heart J. 44: 622–628, 1952.
266. TANDOWSKY, R. M.: The clinical effect of dihydroergocornine methanesulfonate (DHO-180) in arterial hypertension: a preliminary report. Circulation, 1: 686–691, 1950.
267. TAYLOR, R. D., CORCORAN, A. C., SCHRADER, J. C., YOUNG, W. C. AND PAGE, I. H.: Effects of large doses of a vitamin A concentrate in normal and hypertensive patients. Am. J. M. Sc., 206: 659–667, 1943.
268. TAYLOR, R. D., DUSTAN, H. P., CORCORAN, A. C. AND PAGE, I. H.: Evaluation of l-hydrazinophthalazine ("Apresoline") in the treatment of hypertensive disease. Arch. Int. Med., 90: 734–749, 1952.
269. TAYLOR, R. D., PAGE, I. H. AND CORCORAN, A. C.: A hormonal neurogenic vasopressor mechanism. Arch. Int. Med., 88: 1–8, 1951.
270. THOMAS, C. B.: What is the mode of action of thiocyanate compounds in essential hypertension? Ann. Int. Med., 37: 106–122, 1952.
271. THORN, G. W., HARRISON, J. H., MERRILL, J. P., CRISCITIELLO, M. G., FRAWLEY, T. F. AND FINKENSTAEDT, J. T.: Clinical studies on bilateral complete adrenalectomy in patients with severe hypertensive vascular disease. Ann. Int. Med., 37: 972–1005, 1952.
272. THORNER, M. C., STOLPESTAD, C. T. AND GRIFFITH, G. C.: The effect of the dihydrogenated ergot alkaloids (CCK-179) on the electrocardiogram. Ann. West. Med. & Surg., 4: 795–798, 1950.
273. TURNER, R.: "Medical sympathectomy" in hypertension. A clinical study of methonium compounds. Lancet, 2: 353–358, 1950.
274. VAKIL, R. J.: A clinical trial of Rauwolfia Serpentina in essential hypertension. Brit. Heart J., 11: 350–355, 1949.
275. VANDERKOLK, K., DONTAS, A. S. AND HOOBLER, S. W.: The hypotensive and renal effects of chronic oral treatment with l-Hydrazinophthalazine. (Unpublished results.)
276. VAN ITALLIE, T. B. AND CLARKE, C. W., JR.: The effect of Priscoline on peripheral blood flow in normal subjects and patients with peripheral vascular disorders. Circulation, 3: 820–829, 1951.
277. VÖLKER, R. AND KACZMAREK, E.: Die Kreislaufwirkungen des Hydergins (CCK-179) beim Hochdruck. Zeitschr. f. Kreislauff., 39: 85–96, 1950.
278. WALKER, H. A., WILSON, S., ATKINS, E. C., GARRETT, H. E. AND RICHARDSON, A. P.: The effect of l-hydrazinophthalazine (C-5968) and related compounds on the cardiovascular system of dogs. J. Pharmacol. & Exper. Therap., 101: 368–378, 1951.
279. WALKER, H. A., WILSON, S. AND RICHARDSON, A. P.: Effect of l-hydrazinophthalazine (C-5968) on cardiovascular system of unanesthetised dogs. Federation Proc., 9: 323, 1950.
280. WERKÖ, L., FRISK, A. R., WADE, G. AND ELIASCH, H.: Effects of hexamethonium bromide in arterial hypertension. Lancet, 2: 470–472, 1951.
281. WERKÖ, L. AND LAGERLÖF, H.: The effect of dihydroergotamine and dihydroergocornine on cardiac output and blood pressure in hypertension. Cardiologia, 15: 120–126, 1949.
282. WHEATLEY, D.: Relief of acute left ventricular failure by "Priscol". Brit. M. J., 1: 1174, 1952.
283. WIEN, R. AND MASON, D. F. J.: Some actions of hexamethonium and certain homologues. Brit. J. Pharmacol., 6: 611–629, 1951.
284. WILKINS, R. W.: Veratrum viride and essential hypertension. New England J. Med., 242: 535–538, 1950.
285. WILKINS, R. W.: The hemodynamic effects of various types of therapy in hypertensive patients. In "Hypertension, a Symposium," edited by E. T. Bell, Univ. of Minnesota Press, Minneapolis, 400–409, 1951.
286. WILKINS, R. W.: Recent experiences with the pharmacologic treatment of hypertension. In "Hypertension, a Symposium," edited by E. T. Bell, Univ. of Minnesota Press, Minneapolis, 492–501, 1951.
287. WILKINS, R. W.: New drug therapies in arterial hypertension. Ann. Int. Med., 37: 1144–1155, 1952.
288. WILKINS, R. W., FREIS, E. D. AND STANTON, J. R.: Essential hypertension. J. A. M. A., 140: 261–264, 1949.

288a. WILKINS, R. W. AND JUDSON, E.: The use of rauwolfia serpentina in hypertensive patients. New England J. Med., 248: 48–53, 1953.
289. WILKINS, R. W., STANTON, J. R. AND FREIS, E. D.: Essential hypertension. Therapeutic trial of veriloid, a new extract of veratrum viride. Proc. Soc. Exper. Biol. & Med., 72: 302–304, 1949.
290. WILKINSON, E. L., BACKMAN, H. AND HECHT, H. H.: Cardiovascular and renal adjustments to a hypotensive agent (C-5968). J. Clin Investigation, 31: 872–879, 1953.
291. WILLSON, J. R. AND SMITH, R. G.: The peripheral circulatory action of veratrum viride. J. Pharmacol. & Exper. Therap., 79: 208–214, 1943.
292. WINSOR, T.: Effects of hydrogenated alkaloids of ergot on vasomotor reflexes. Am. J. M. Sc., 224: 42–52, 1952.
293. WOODWARD, D. J., HOOBLER, S. W. AND NICKERSON, M.: Effect of Dibensyline (SKF 688A) on peripheral blood flow in man. Federation Proc., 11: 404–405, 1952.
294. WUNSCH, R. E., WARNER, R. D. AND MYERS, G. B.: The effects of dibenamine on severe hypertension. Ann. Int. Med., 33: 613–628, 1950.
295. YONKMAN, F. F.: Neurogenic hypertension; chemical approaches to its amelioration. J. Michigan State M. Soc., 50: 160–167, 1951.
296. YONKMAN, F. F. AND FREIS, E. D.: Rational elimination of side reactions and/or tolerance in the development of potentially valuable drugs. Angiology, 3: 36–41, 1952.
297. YOUNG, I. M., DE WARDENER, H. E. AND MILES, B. E.: Mechanism of the renal excretion of methonium compounds. Brit. M. J., 2: 1500–1501, 1951.