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Current therapy of essential hypertension

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CURRENT THERAPY OF ESSENTIAL HYPERTENSION

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TABLE OF CONTENTS

INTRODUCTION

High blood pressure affect more than 5% of our adult population today, and is one of the most frequent problems in the practice of medicine.

Until recently, there was little to offer hypertensive patients except encouragement to learn to live with their ailment. The value of any treatment, chiefly sympathectomy, and severe salt depletion, was difficult to determine, when viewed in the perspective of the long, variable, and uncertain natural history of the disease itself. Most physicians feared that lowering the blood pressure would decrease furthur the circulation through vital areas which, had already been altered by the hypertensive process. Also, physicians were not quite certain where normal blood pressure stopped, and high blood pressure began, because critical investigators had challenged the accepted renge of normal values.

Brest, and Moyer state that, "the past decade had seen a resurgence of investigational interest in hypertension with the inevitable result of a better understanding of at least some of the causes of this disease, and with a great expansion of the therapeutic armamentarium available for its treatment."(1)

Clark, and Kaplan state that, "hypertensive vascular disease with its relentless progress resulting in damage to the heart, brain and kidneys constitutes a major medical challenge in which drug therapy has produced good results, although the etiology, and pathogenesis of the disease remain unknown."(2)

Hypertension can be attacked more effectively at the present time, and with a somewhat better understanding of the underlying disease processes. Not only has it been feasible to reduce abnormally elevated blood pressures, but the expected catastrophies in regional circulations did not materialize as experience in judicious patient selection for treatment was gained. "Dividends have seemed to accure from the accompanying reduction in demands on the body as a whole, in the form of reversal or delay of complicating conditions, and prolongation of life."(2)

ETIOLOGY OF HYPERTENSION

Hypertension is only a symptom due to many divirse causes, both known, and unknown.

CLASSIFICATION OF HYPERTENSION:

Hypertension of recognized etiology.

A. Coarctation of the aorta.

B. Unilateral renal disease.

C. Renal arterial or venous thrombosis.

D. Endocrine:

1. Pheochromocytoma.
2. Arrhenoblastoma.
3. Basophil adenoma of the pituitary.
4. Primary hyperaldosteronism.
5. Cushing's syndrome.

E. Glomerulonephritis.

F. Chronic Pyelonephritis.

G. Increased intracranial pressure.

H. Polycystic renal disease.

Hypertension of unknown etiology.

A. Essential (idippathic) hypertension.

B. Malignant hypertension.

When upon routine examination, one finds an elevated blood pressure, it should be checked repeatedly while the patient is at complete rest in the recumbent position. If in excess of 150/90

mm. of Hg. should indicate further investigation. This consists of:

1. Complete history, and physical examination.
2. Urinalysis, and CBC.
3. Chest X-ray.
4. Electrocardiogram.
5. BUN or Creatinine.
6. Blood glucose.

These tests will disclose cases of coarctation of the aorta, glomerulonephritis, many cases of pyelonephritis, and will reveal simple systolic hypertension due to atherosclerosis, and those cases due to thyrotoxicosis.

IVP is then employed to screen out at least the most obvious cases of unilateral renal disease, some cases of chronic pyelonephritis, polycystic renal disease, and obstructions of the upper renal disease. Determination of urinary catechol-amines, and the Regitine test serve best for the exclusion of pheochromocytoma, while cystoscopy with retrograde catheterization of both ureters with a differential study of urinary secretion from each kidney will serve to exclude the more obscure types of unilateral renal disease, and on occasion will reveal an otherwise completely obscure chronic

pyelonephritis. The determination of serum potassium, and bicarbonate serves in the screening for primary hyperaldosteronism, and when suggestive, is followed by a chromatographic measurement of urinary 17-keto, and 17-hydroxycorticosteroid determinations will exclude Cushing's disease. Finally, where indicated, perirenal CO_2 insufflation combined with aortography will pinpoint renal vascular lesions, and adrenal tumors.

In at least 95% of any group of hypertensive patients, after all the above procedures are carried out, one is still left idiopathic, or essential hypertension cases, and constitute the bulk of hypertensive patients.

ESSENTIAL HYPERTENSION

DEFINITION:

A condition about which we know "essentially" nothing. "The term, essential hyperternion, has been employed to indicate those cases of hypertension for which a specific endocrine or renal basis cannot be found, and in which the neural element may be only a mediator of other influences."(3) The predominance of diastolic elevation is a manifestation of increased residual resistance in the peripheral vascular bed after systole, and

probably represents the clinically significant abnormality in the hypertensive syndrome.

Essential hypertension is usually subdivided into two types, benign and malignant. These terms should be employed only as relating to the rapidity and severity of the vascular disease accompanying increased blood pressure levels. The malignant type may be superimposed upon the benign type; occasionally, however, it may be so rapid in onset, and so severe in its course as to appear a separate entity.

PREDISPOSING FACTORS:

Three main predisposing factors leading to essential hypertension are recognized. The first is called the familial factor. Hypertension tends to run in the same family, this does not necessarily mean that a tendency toward high blood pressure is inherited. The second factor is constitutional, that is, some people seem to have a natural weakness or predisposition towards hypertension. The third factor, and perhaps most important of all, essential hypertension is a disease of adaptation, anxiety, overwork, and occupational stress, if they act on the mind for prolonged periods, have an effect on certain parts of the brain which in turn stimulate the

adrenal glands to secrete certain hormones which, in some unknown way, interferes with the mechanism regulating the blood pressure. Ordinarily, it is thought that this interference with the regulating mechanism causes high blood pressure only when a person is continously exposed to emotional disturbance, and stress over a rather long period. Under the rather rapidly changing conditions of life to which most of us are exposed, the risk is much more serious. Other factors may favor the development of high blood pressure such as an unbalanced diet, and over indulgence in certain foods, certain disease of the heart, and kidneys may bring on high blood pressure as an effect rather than a case.

SELECTING HYPERTENSIVE PATIENTS FOR TREATMENT

There is general agreement that all patients with malignant hypertension require treatment since their arteriolar disease is rapidly progressive, and produces death within a year, or at most, two years after the diagnosis has been made. It is in this group that the proper application of antihypertensive drug therapy has produced the most striking results. If treatment can be instituted before the onset of azotemia, it is not at all infrequent to see a marked improvement to the point where

there is reversal of eyeground changes. The EKG, and chese X-ray films show improvement in the usual left ventricular hypertrophy, and albuminuria, and cylinduria disappear.

Brest and Moyer(1) feel that to date our experience with newer, and more different drugs, is still too limited for us to be able to predict results much beyond five years. It is even more difficult to predict the long-term effects of drug therapy in the management of severe benign essential hypertension since we have not been able to follow the course of this therapy long enough nor to set up adequate controls. It is more difficult to measure accurately the effectiveness of anti-hypertensive drug therapy since this group of patients usually suffer not to much from their arteriolar disease but from the associated arterial disease which produces most frequently complications such as coronary thrombosis, cerebral vascular accidents, dissecting aneurysms, and congestive heart failure, and only infrequently renal failure.

It is wise to treat only those patients with benign essential hypertension who either have

symptoms attribute to their hypertension, progressive hypertension, a poor family history with parents, or siblings who have died prematurely of complications of hypertension, or who belong to the younger age groups at the time of the onset of their disease. The aim of treatment is to reduce hypertension to normal, or to as nearly normal levels as may be compatible with efficient blood supply to vital areas such as the central nervous system, to prevent later arterial degenerative disease.

TREATMENT OF ESSENTIAL HYPERTENSION:

GENERAL MEASURES.

"The clinical literature testifies that skillful drug manipulation may bring about a substantial, and sustained reduction in high blood pressure reading. Many of the outlined programs, useful in expert hands in special clinics, and university centers, are patently unsuitable for the management of the great mass of hypertensive patients because of the delicate adjustment, and therapeutic hazards implicit in their use, as well as the economics of hospitalization for individual dose titration. The truly sucessful treatment should be one which can be carried out

with the patient in his natural environment, rather than in the rigid artificial hospital surroundings."

All patients with high blood pressure, of whatever degree, profit from certain general steps, beginning with a thorough, and leisurely discussion of the nature of hypertension, its effects, the goals of therapy, and the projected program. Reassurance, and encouragement are the two main themes of indoctrination. Most physicians permit moderate use of salt, tobacco, and alcohol. The obese patient should be brought to near-optimal body weight by restriction of calories to 1000, or 1200 daily. Restriction of sodium in the diet is usually unnecessary unless the patient has congestive heart failure, and even then, 2.0 grams of sodium daily can often be tolerated if thiazide diuretics are employed. When hypertension is resistant to treatment, and especially if diuretic agents cannot be used, rigid restriction of sodium in the diet to 0.2 or 0.5 gram daily is sometimes a helpful but certainly unpleasant adjunct. Limitation of protein to 40 grams daily is indicated for most hypertensive patients with azotemia. Appetite suppressants may be helpful in treating patients with poor self-discipline,

and are not contraindicated. Some authors suggest that the fall in blood pressure accompanying weight reduction may be due to the decrease in daily salt intake which automatically accompanies the restriction in total calories.

"Unless the hypertensive patient also has severe heart or renal disease, extra daily rest over, and above that dicated by common sense is not necessary in this age of effective antihypertensive therapy."(5) Daily rest periods and "early to bed" injunctions, more often than not, are constant reminders of illness, and produce more mental turmoil. One should encourage the hypertensive patient to take regular vacations, and to develop hobbies or an advocation of some kind.

As long as cardiac, and renal functions are not impaired, the hypertensive patient needs no restriction in regard to excerise. Strenuous exercise should be permitted to the hypertensive patient who maintains good physical condition. Mild forms of excerise such as golf, bowling, and walking should be encouraged for those who are less athletically inclined.

"Sedation, once the keystone of antihypertensive therapy, is neither an integral nor

desirable part of modern programs of treatment. Sedatives or tranquilizers are sometimes helpful in alleviating the side effects of specific anti-hypertensive drugs, expecially during initiation of treatment, but the objective is to c@nstruct a therapeutic regimen so that side effects will be minimal, and sedation for this purpose can be abandoned."(5) When indicated, phenobarbital, or butabarbital sodium (Butisol Sodium) in doses of 16, to 32 mg. (1/4, to 1/2 grain) three, or four times a day is effective. Meprobamate (Miltown, Equanil) in doses of 0.4 gram three, or times a day is usually as effective, and considerably safer than phenothiazine derivatives.

ANTIHYPERTENSIVE DRUGS.

Even though there is a great array of trade names attached to various hypotensive drugs, either singly or in combination, there are only six classes of hypotensive drugs warranting discussion.

Rauwolfia (Table 1). The action of the rauwolfia products is primarily central. Their effect is predominantly upon the centers at the level of the hypothalamus. This may be a direct

inhibition or a "facilitation" of impulses that normally in hibit the sympathetic activity of the hypothalamus. This sympathetic inhibition is accompained by a relative vagotonia, particulary-if Rauwolfia is used in too large dosage. In usual dosage there is no direct effect upon the arterioles, the humoral pressor substances, or the autonomic mediators such as epinephrine, arterinol, or acetylcholine. There is no blockade at the ganglionic level.

While only a slight or equivocal lowering of blood pressure is found in the normatensive man, in hypertensive patients, large, and prolonged reduction in blood pressure has been observed.

"It may be concluded that the fall in blood pressure is caused by peripheral vasodilatation, unaccompained by reduction in cardiac output. Since the reduction in blood pressure is not affected by atropine or by removal of the vagus nerve, the parasympathetic system is probably not directly involved in the hypotensive effect." (6)

The sedative action of Serpasil, like its effect upon blood pressure, is due to action on the diencephalon, without the depression of the cerebral cortex that is characteristic of the

barbiturates.

After both parenteral, and oral therapy with Rauwolfia, there is a latent period before the hypotensive effect is observed. The effect also persists for some time after therapy has been stopped.

When given intramuscularly or intravenously, the hypotensive effect of Serpasil usually noticed within one to two hours, reaches a maximum in about three hours, and persists for a duration of five to six hours. The larger the dose, the more rapid and prolonged the effect.

"The advent of thiazide diuretics has sharply curtailed the use of Rauwolfia. Rauwolfia, when administered orally, has little, if any, place in the treatment of severe or malignant hypertension. Because it tends to produce depression, it is contraindicated for patients who are already depressed or who have been depressed in the past. Many patients experience an unpleasant listlessness and apathy while taking Rauwolfia, although they are not really depressed. For this reason its use should be reserved for patients with mild to moderate hypertension that does not respond adequately to the combination of a thiazide diuretic, and

hydralazine. Sometimes the addition of Rauwolfia to the regimen will prevent the necessity for using a ganglion-blocking drug. When thiazide diuretics are contraindicated, or in the unlikely event that they are poorly tolerated, Rauwolfia may be administered as the initial agent, for like a thiazide diuretic it often reduces the severity of side effects of more potent hypotensive drugs if they are needed subsequently. If hydralazine is poorly tolerated or its use is contraindicated, Rauwolfia may be given in its place in conjunction with a thiazide diuretic if the latter agent alone is not sufficiently effective."(5)

"Syrosingopine, the generic name for carbethozysyringoyl methlreserpate, was synthesized from the reserpine molecule in 1954. It appears to be less sedating than it parent antihypertensive compound. Unlike reserpine, which acts chiefly in the hypothalamic area, and certain medullary centers, syrosingopine acts primary on the peripheral sites, inhibiting sympathetic vasoconstrictor impulses by depleting the mediating chemical norepinephrine from nerve endings. In addition, a central action has also been noted where by serotonin is released in the brain producing increased parasympathetic activity."(7)

Table 1

Preparations of Rauwolfia

Preparation	Size of Tablet (mg.)	Daily Dose* (mg.)
Whole root (Raudixin)	50 100	50-200
Alseroxylon fraction (Rauwiloid)	2.0	2.0-4.0
Single alkaloids Reserpine(Serpasis) Reserpoid, Sandril, Serpiloid and others	0.1 0.25	0.1-0.25
Rescinnamine (Moderil)	0.25 0.5	0.25-0.5
Deserpidine (Harmonyl)	0.1 0.25	0.25-0.5
Syrosingopine (Singoserp)	1.0	0.5-2.0

Side Effects; Troublesome but not serious: nasal congestion, sedation, bradycardia, increased appetite and gain in weight, mild laxation, myalgia, edema. Potentially serious: gastric hyperacidity, nightmares (may herald depression) Serious; require prompt cessation of treatment: depression (often occult), Parkinsonian rigidity.

*Doses in excess of these should be given cautiously and for only short periods. Usually given as single daily dose or divided into two equal doses.(5)

Thiazide Diuretics (Table 2.) These agents are also referred to as "saluretic" drugs. These agents increase the excretion chiefly of sodium, and chloride, of potassium in lesser degree, and increase urinary volume. They are most dramatically helpful with hypertensive heart failure, but are also so effective in the "dry" hypertensive that some investigators believe that they possess hypotensive properties apart from electrolyte, and body water effects.

In a study by Lauwers, and Conway,(8) hypertensive patients took 1 gm. of chlorothiazide, a sulfonamide derivative, for a period between 26, and 60 days. They found that the administration of chlorothiazide to human subjects produces initially an increase in urine volume, and a fall in body weight. Associated with these changes, the blood pressure is frequently reduced in hypertensive patients. In the first week of treatment, it has been shown that a reduction in blood volume, and sodium loss accompany the decline in blood pressure. However, after prolonged therapy, no sodium depletion was found to be present. No consistent changes were seen in plasma or extracellular fluid volume. The fall in body

weight was reflected by a decline in total body water which was believed to come from intracellular water depletion. It is postulated that a reduction in total peripheral resistance is partially due to intracellular dehydration affecting the arteriolar wall. The possibility of changes in the behavior of the muscular elements in the arteriolar wall should also be considered.

"Saluretics should be used cautiously in patients already receiving ganglionic-blocking drugs or following sympathectomy, because the salt, and water depletion produced can unmask postural hypotension or precipitate a variety of vascular insufficiency syndromes."(4)

Hydrochlorothiazide, an analog of chlorothiazide, has approximately ten times greater potency than chlorothiazide. Thus, a starting dose of 50, to 100 mg. daily is average, and 50 mg. of hydrochlorothiazide may be substituted approximately for 500 mg. of chlorothiazide.

"Hydrochlorothiazide belongs to the recently discovered group of heterocyclic compounds which act as potent diuretics by inhibiting carbonic anhydrase, enhancing the excretion of sodium, and chloride, and to a lesser extent, potassium,

and bicarbonate by modifying the reabsorption of these electrolytes."(7)

In addition to its diuretic effect, hydrochlorothiazide has demonstrated hypotensive qualities. Some workers feel that the hypotensive features of the heterocyclic drugs appear to be an action apart from their diuretic effects. Other workers postulate that the hypotensive propensities of the drugs may be due to alterations in plasma volume with resultant changes in the fundamental reactivity of the arterioles to other drugs. The changes are somewhat similar to those produced by adherence to a program of rigid sodium restriction or rice diet.

"A comparison of the nature, severity, and frequency of side effects indicates that it is far better tolerated in most cases. In particular, the freedom from cardiac arrhythmia, and from troublesome gastronintestinal distress, in this series, suggest that hydrochlorothiazide may prove a generally more useful drug than chlorothiazide."(9)

Flumethiazide, a trifluoromethyl derivative of the benzathiadiazine group of diuretic agents, like hydrochlorothiazide, possesses the antihypertensive properties of the parent chlorothiazide

except for individual variations. Four hundred mg. of flumethiazide may be substituted for 500 mg. of chlorothiazide or 50 mg. of hydrochlorothiazide, although individual requirements vary.

Side effects from these two new drugs, hydrochlorothiazide, and flumethiazide, are qualitatively similar to those with chlorothiazide, with two important differences. Although some patients receiving hydrochlorothiazide developed gouty episodes similar to those seen with chlorothiazide, no such articular reactions have been noted to date by patients treated with flumethiazide. Skin reactions, while infrequent with hydrochlorothiazide and chlorothiazide, have not been encountered with the trifluoromethyl derivative. Flumethiazide has been substituted for both other saluretics when skin rashes appeared with subsequent regression of eruptions, and persistence of hypotensive effects. Introduction of the trifluoromethyl group into the chlorothiazide molecule may, therefore, be responsible for decreased toxicity, without loss of potency, resembling produced effects with other pharmacologic agents modified in similar fashion.

"These agents have largely replaced Rauwolfia as the advance guard in the attack on hypertension. They are well tolerated by most patients, and in 40% of the patients with mild to moderate hypertension a thiazide preparation will be the only drug needed to control blood pressure adequately. If more potent agents are needed subsequently, the severity of side effects as well as the dose of these agents is likely to be less if the patient is already taking a thiazide diuretic. In the treatment of severe or malignant hypertension, thiazide diuretics are valuable adjuncts to regimen, for they augment the hypotensive effect of ganglion-blocking agents, thereby permitting better control of blood pressure with smaller doses of the blocking drug. To a lesser degree they also augment the hypotensive response to Rauwolfia, hydralazine, and Veratrum. Because they tend to increase blood urea, thiazide diuretics should be used cautiously, if at all for patients with renal insufficiency, and azotemia."(5)

Table 2

Thiazide Diuretics

Preparation	Size of Tablet (mg.)	Daily Dose* (mg.)
Chlorothiazide (Diuril)	250 500	500-1000
Hydrochlorothiazide (Hydrodiuril, Esidrix, Oretic)	25 50	50-100
Flumethiazide (Ademol)	500	500-1000
Hydroflumethiazide (Saluron)	50	50-100
Benzydroflumethiazide (Naturetin)	2.5 5.0	5-10
Trichlormethiazide (Naqua)	2.0 4.0	8-16

Side Effects: Electrolytic disturbances (usually asymptomatic); hypopotassemia, hyperruricemai (only rarely associated with clinical gout), elevation of blood urea or nonprotein nitrogen, unpleasant taste. Gastrointestinal disturbances (usually mild): bloating, dyspepsia, neusea, abdominal discomfort, diarrhea, weakness, and occasionally syncope (not necessarily associated with hypopotassemia or hypotension), rash or purpura (infrequent), Hematologic dyscrasias (rare): anemis, thrombocytopenia.

*Usually divided, and given twice daily at intervals of approximately twelve hours.(5)

In recent years several new Rauwolfia-Thiazide diuretic combination preparations have been developed, and have become popular. Three such preparations, are: Rautrax (Rauwolfia-flumethiazide), Diupres (Chlorothiazide-reserpine), and Singoserp-Esidrix (Syrosingopine-Hadrochlorothiazide).

For many years, the beneficial effects from depleting stores of sodium in hypertensive patients have been recognized. "Salt restriction is beneficial in patients with hypertension if the NaCl intake is limited to 1 gm. daily, or less."(10)

Salt depletion can be brought about by thiazide diuretics which increase the urinary excretion of sodium. "Chlorothiazide, the first of a number of thiazide compounds to be introduced, possesses specific antihypertensive activity when given alone, and potentiates the action of other antihypertensive drugs when administered concomitantly."(10) It is thought by some authorities that antihypertensive drugs usually work better, and with fewer side effects when used in combination than when given singly.

Each tablet of Rautrax contains Rauwolfia serpentina, whole root, 50 mg.; flumethiazide,

400 gm.; and potassium chloride, 400 mg..
Flumethiazide, a trifluoromethyl of the benzathiadiazine group of diuretic agents, possesses pharmacological activity similar to that of chlorothiazide, without the development of tolerance, and is free of acute toxicity. Potassium chloride has been added for protection against the loss of potassium which may occur during active diuresis. Potassium loss with Rautrax is minimal for two reasons: (1) the preparation contains flumethiazide which is less active than chlorothiazide in potassium excretion, and (2) additional potassium is supplied in the formulation of Rautrax to make up for any loss of potassium that might occur.

Dosage of Rautrax is one tablet twice daily. Maximum blood pressure to Rautrax usually occurs during the first month of administration, and satisfactory blood pressure levels are generally maintained as treatment is continued. This prompt response to Rautrax is of particular benefit in patients with severe hypertension. There is no necessity for discontinueing digitalis therapy of rigid adherence to a salt diet when Rautrax is administered. Rautrax is generally well tolerated, and provides a

satisfactory therapeutic response in the majority of patients treated, even in those with severe hypertension. Extreme or sudden drops in blood pressure which might prove disastrous in those elderly patients with arteriosclerosis or cardiac disease, usually do not occur. Side effects are minimal which is expecially beneficial to the elderly patients. Side effects include: headache, dizziness, blurring of vision, nasal stuffiness, itchiness, increased bowel motility, occasional weakness, and epigastric discomfort. Rarely, purpura, lethargy, and severe diarrhea are encountered. "Rautrax represents a valuable addition to the resources available to the physician for the medical management of hypertensive vascular disease. The combination of a hypotensive saluretic action in a single preparation provides a convenient dosage form in the treatment of the ambulatory patient."(11)

Diupres tablets come in two different sizes; Diupres 500 (500 mg. chlorothiazide and 0.125 mg. reserpine) and Diupres 250 (250 mg. chlorothiazide and 0.125 mg. reserpine). Dosage of Diupres 500 in one tablet one to three times a day (depending on indications and severity). Diupres is used in

hypertension of all degrees of severity. It can be used as total therapy, as primary therapy with addition of other drugs if necessary, or as replacement or adjunctive therapy. Diupres apparently has a potentiated effect, that is an antihypertensive effect greater than either chlorothiazide or reserpine alone. Diupres may bring about arrest or reversal of organic changes of hypertension, allays anxiety, and tension, and usually promptly releives headache, dizziness, and tachycardia. Diupres is well tolerated, and makes the diet more palatable because there is less need for rigid salt restriction.

When syrosingopine, an analog of reserpine, was combined with hydrochlorothiazide, a dramatic potentiating hypotensive effect with excellent reduction in blood pressure was noted. In those instances where patients failed to respond sufficiently to hydrochlorothiazide alone, the addition of syrosingopine helped produce an adequate, and beneficial hypotensive effect.

While the combination is not usually recommended in the more severe grades of hypertension (III & IV) where more potent agents are often required, trial with these compounds is

warranted since successful results have been achieved even among more severely hypertensive patients. The combination may also serve as excellent "background" therapy, permitting smaller doses of such drugs as hydralazine or blocking agents.

Singoserp-Esidrix tablets come in two different sizes; Tablets #1 (0.5 mg. syrosingopine and 25 mg. hydrochlorothiazide.) and Tablets #2 (1 mg. syrosingopine and 25 mg. hydrochlorothiazide). Dosage depends upon individual requirements and severity of the hypertension. Average dosage is one Singoserp-Esidrix tablet #2 three times a day. For patients requiring less Singoserp, Tablet #1 can be substituted. Maximal reduction in blood pressure from a given dosage of Singoserp-Esidrix may not occur for two weeks, since the antihypertensive effects of Singoserp are not immediately apparent. At this time the dosage should be adjusted to the amount necessary to sustain the desired blood pressure response.

"Although combination products are generally frowned upon by the profession, there are times when the synergistic activity of two compounds enchances their effectiveness, and safety, reduces

their dosage, and proves especially advantageous to the patient. Considering our interesting results, we would unhesitantingly recommend this combination of hydrochlorothiazide, and syrosingopine for further trial in all phases of essential hypertension." (7)

Hydralazine (Table 3). It is believed that the principal action of hydralazine (Apresoline) is based upon the ability of the NH_2 group of this compound to combine with the oxygen of the carbonyl group of pherentasin, resulting in loss of vaso-activity of the latter pressor substance.

"The pressor effect of many primary amines is abolished by hydralazine. Hydralazine weakly antagonizes the vasoconstrictor effect of epinephrine and norepinephrine, the cerebral vasoconstrictor substance, and to some extent, angiotonin, and hypertensin. Since it does not reverse the pressor effects of epinephrine, it can hardly be classed as an adrenergic blocking drug." (6)

Hydralazine, if properly used, is one of the safest, and most effective of hypotensive agents available, although this is not a commonly held notion. It rarely, if ever, should be used as the sole antihypertensive agent because, of the high

incidence of unpleasant side effects. These side effects, however, can be avoided or greatly ameliorated, if Rauwolfia, a thiazide diuretic or a ganglion-blocking drug is administered for several days or weeks before treatment with hydralazine is started. It is important, too, to start with small doses of hydralazine (10 mg. three or four times daily), especially for patients who already have headache or palpitations. A total daily dose of 300 mg. should rarely be exceeded, for late toxic effects characterized by a "collagen-like" disorder seldom occur when dosage is maintained at less than 300 mg.. The reactions are completely reversible, however, and are greatly overpublicized, and overfeared.

"The blood pressure of fully 90% of patients with mild to moderate hypertension will be controlled adequately by means of a thiazide diuretic alone or in conjunction with hydralazine. Hydralazine is also a valuable addition to a regimen consisting of a thiazide diuretic, and a ganglion-blocking drug in the treatment of severe hypertension." (5)

Table 3

Hydralazine

Preparation	Size of Tablet (mg.)	Daily Dose* (mg.)
Hydralazine Hydrochloride (Apresoline)	10 25 50 100	40-3000

Side Effects; Early but not serious; headache, palpitations, tachycardia, flushing, unpleasant taste, dry mouth, anxiety, mild depression, nausea, vomiting.

Early and serious; exacerbation of coronary insufficiency, edema of feet, and legs, chills, fever, toxic psychosis, and delirium.

Delayed, and serious; generalized aching, and stiffness, rheumatoid syndrome, "collagen" or lupus-like reaction (hydralazine disease).

* Divided, and given three or four times daily. Start with smaller doses listed, and gradually increase as necessary. Upper limit should be exceeded only rarely, and with caution because of danger of "collagen" reaction.(5)

Ganglion-blocking Drugs (Table 4). The principal pharmacologic action of these drugs is exerted in the autonomic ganglia, both sympathetic and parasympathetic. The various ganglia vary considerably in their sensitivity to blockade, and complete blockade is rarely obtained, even with quite large doses.

These drugs have no significant effect on the effector substances, parasympathetic (acetylcholine) or sympathetic (epinephrine or arterenol). In fact, the vasopressor effects of the latter two are often accentuated during such ganglionic blockade. Of practical importance is the fact that a patient with pheochromocytoma may experience an exacerbation of hypertension if given a ganglionic blocking agent. It has been shown that certain of these drugs, such as tetraethylammonium, may actually stimulate release of adrenalin by direct effect upon cells in the adrenal.

"The antihypertensive effects of ganglionic blocking agents are probably exerted by way of their blockade of the transmission of impulses through the sympathetic ganglia, thus decreasing the postganglionic sympathetic impulses, and output of epinephrine by the adrenal medulla, and leading to

diminution of the total peripheral resistance. The most important sites of such vasoconstriction are in regions, such as the skin, skeletal muscles, and splanchnic viscera."(6)

Trimethidinium methosulfate, an asymmetric bisquaternary amine, is a recently introduced ganglionic blocking agent reported to be orally effective in small daily doses, and to cause fewer, and less severe side effects than the previously used ganglinonic blocking agents such as pentolinium or mecamylamine. The ganglionic blocking activity is of prolonged duration (8 to 12 hours), and has little or no central hypotensive effect. Only 50% of the dose is absorbed from the G.I. tract, and the most marked effects are obtained when it is administered in the fasting state. The usual side-effects are; constipation, postural hypotension, and blurring of vision.

Trimethidinium methosulfate, in dosages ranging from 20 mg. twice daily to 40 mg. three times daily, was very effective in reducing the blood pressure of 21 patients who had either moderate or severe hypertension, in a study by Pelner, and Waldmen.(12) No tolerance to the drug was noted, but some instances the hypotensive

effect was delayed for several weeks. Blood pressure control was consistently better when three doses were taken daily, and absorption was maximal, and most predictable when the medication was taken when the stomach was empty, one hour before meals.

When administered in combination with other medications (reserpine, chlorothiazide) trimethidinium was found to bring about an even more significant decrease in blood pressure.

With the use of a Trimethidinium-Chlorothiazide combination, it is thought that by the oligemia resulting from its diuretic action, chlorothiazide produces an intensification of vasomotor tone which, in turn, induces a neurogenic type of hypertension which is more readily affected by ganglioplegic drugs. With the addition of chlorothiazide, and reduction in trimethidinium the blood pressure has shown less tendency to fluctuate from week to week. There has been a slight reduction in the difference between the standing, and supine blood pressures which may be a factor in the marked reduction of the incidence of postural hypotension, dizziness, and weakness. "Although there probably will always be side effects with the use of effective blood pressure

lowering drugs, the combination of trimethidininium, and chlorothiazide has resulted in an almost total absence of moderate or severe side effects. With the minimum side effects produced by this combination, there is little reason not to use it in patients who have high diastolic blood pressure even without symptoms of complications of hypertension, and therefore are classified as mild or moderate hypertensive patients."(13)

After initiating chlorothiazide in combination with trimethidinium, some workers have been able to reduce the daily dosage of trimethidinium by 40% and still maintain control of the blood pressure.

In a study of the Trimethidinium-Chlorothiazide combination, Janney and Duane[13] found that 75% of the patients became normotensive; 100% were responsive; and side effects were of such minimal severity as to cause very little discomfort to the patient. While on trimethidinium prior to the addition of chlorothiazide, only 50% were normotensive, and 88% responsive, and side effects were more frequent, and severe.

Some of the most potent hypotensive agents available are found within this class of drugs, and their administration requires close supervision, and is attended by a high incidence of unpleasant

and sometimes serious side effects. Some of the best results are obtained when blood pressure is recorded at home as a guide to help adjust the dosage. "This approach to the treatment of hypertension seems to be of value in the majority of patients with hypertension who are financially and intellectually able to cooperate. Intelligence, and satisfactory cooperation by the patient are necessary for a successful therapeutic program. If the blood pressure reports are not reliable, the method has little value. It is the physicians responsibility to decide which patients are good candidates. With effort, suitable recording of blood pressure can be obtained at home for almost all patients. A responsible member of the family can be taught how to take, and record blood pressure readings. In patients in whom severe hypertension has become relatively fixed, and in whom a good therapeutic response is not anticipated, the discouragement which might develop from therapeutic failure must be handled on an individual basis by methods most suitable for the circumstances."(14)

While the patient is sitting, the blood pressure is determined. If the systolic blood pressure is more than 140 mm. of mercury at the

time for a dose, the full maintenance dose is given, if it is between 120 and 140 mm., half the maintenance dose is given, and if it is less than 120 mm. of mercury, the dose is omitted. These arbitrary limits can be raised or reduced depending on the levels at which the physician desires to maintain the blood pressure. Erratic control is the rule, not the exception, when ganglion-blocking drugs are used, for the blood pressure tends to fluctuate widely between doses. This is not inconsistent with a good clinical result, and attempts to eradicate these fluctuations often result in unbearable side effects or hypotension. Use of ganglion-blocking drugs should be reserved for patients with severe or malignant hypertension or for patients with milder hypertension whose blood pressure responds inadequately to combinations of less potent agents.

"When ganglion-blocking agents are used, better control of blood pressure is obtained with fewer side effects if a thiazide diuretic with or without hydralazine is given concomitantly. For the 10% of patients with mild to moderate hypertension who do not respond adequately to combination therapy with a thiazide diuretic, and hydralazine,

the addition of small doses of a ganglion-blocking drug may prove more effective, and less objectionable to the patient than the addition of a preparation of Rauwolfia. When hypotension would endanger mycardial, cerebral or renal functions, ganglion-blocking drugs should be used with extreme care and only when less potent drugs in combination fail to produce the desired result."(5)

Table 4

Ganglion-blocking Drugs

Preparation	Size of Tablet (mg.)	Total Daily Dose* (mg.)	Doses Per Day#
Pentolinium Tartrate (Ansolysen)	20 40 100 200	80-2000	3-4
Chloroisondamine Chloride (Ecolid)	10 25 50	40-800	3-4
Mecamylamine Hydrochloride (Inversine)	2.5 10.0	5-120	2-4
Trimethidinium Methosulfate (Ostensin)	20 40	40-5000	3-4

Side Effects: Specific for Drug (Inversine), toxic psychosis, coarse tremors. Nonspecific effects of autonomic blockage; sympatheric blockade, weakness or syncope from hypotension(usually most marked when patient stands),* Parasympathetic blockade; blurring, of vision, dryness of mouth, constipation(May progress to parakytic ileus if neglected). In men: urinary retention, impotence.

* Start with smaller doses indicated here and increase gradually by increments of the size of the smallest tablet, base the increase on the response of the blood pressure. The upper limits of dosage listed here may be exceeded if necessary to control blood pressure adequately, provided that side effects are tolerable. #Give on empty stomach. *Diuretics sensitize patients to ganglion blockade. to prevent orthostatic collapse, the dose of these drugs should be reduced 50% before administering a diuretic.

(5)

Sympatholytic Drugs (Table 5). These recently developed compounds promise to be a great advance in the treatment of hypertension. They depress the sympathetic vasomotor function either by decreasing norepinephrine production by nerve endings or by releasing catecholamines from heart, and blood vessels. They have the advantage over ganglioplegic drugs in that sympathetic function is blocked, while parasympathetic is spared. Early experiences with these drugs suggest that they eventually will replace the ganglion-blocking agents, for their hypotensive effect is as potent, but they do not induce the troublesome side effects of parasympathetic inhibition.

Guanethidine, the most recently synthesized compound, is chemically unrelated to Bretylium tosylate but similar in locus of action.

"The blood pressure is lowered chiefly by reducing cardiac output as result of blocking sympathetic nerves to the veins with consequent dilatation. This in turn results in pooling of blood, especially in the standing position, and failure of return of blood to the heart."(16) Thus, like the ganglion-blocking agents, the sympatholytic drugs reduce blood pressure more when the patient is erect than when he is

recumbent and often the blood pressure in the supine position is not appreciably reduced, even when the patient is normotensive when he stands. Their administration usually is associated with fluctuations in blood pressure as marked as, if not more so than, those produced by ganglionoplegic agents. Diurnal oscillations of blood pressure with lowest readings when the patient first arises in the morning, and highest readings during the afternoon, and evening are frequently produced by treatment with guanethidine, regardless of when or how often the drug is given. Diurnal fluctuations are less marked when bretylium tosylate (Darenthin) is given, and the afternoon elevation can usually be moderated by giving a larger dose of Darenthin before the noon meal than at other times. The indications, and precautions for use of these new agents are similar to those for ganglion-blocking drugs. Best results are obtained if blood pressure is recorded at home, and determinations are used to regulate the dosage.

"Guanethidine would appear to have definite but limited utility, as an antihypertensive agent for the more severely-hypertensive

patient because of its marked postural effect on blood pressure, and the incidence of its side effects. Final conclusion regarding the ultimate usefulness of the drug, administered alone, and in combination with other agents, must await more extended experience." (15)

Table 5

Sympatholytic Drugs

Preparation	Size of Tablet (mg.)	Daily Dose* (mg.)
Guanethidine (Ismelin)	10 25	10-300
Brethlium Tosylate (Darenthin)	200	400-4000*

Side Effects: Weakness with or without syncope from orthostatic hypotension (especially when getting out of bed in the morning), diarrhea, bradycardia, nasal stuffiness, loss of ejaculation but not of potentia, and cutaneous rash. Weakness with or without syncope from orthotatic hypotension (especially when getting out of bed in the morning), pain in parotid glands when starting to eat, nasal stuffiness, drooping of eyelids, conjunctival injection, nausea, and vomiting.

* Start with smallets dose, and increase gradually. The upper limits of dosage listed may be exceeded if necessary to control the hypertension. May be given as one dose or divided into two or three doses.

* Divide and give three or four times a day (half an hour before meals, and at bedtime, the bedtime dose should be kept at low level to prevent orthostatic collapse in the morning).(5)

Veratrum (Table 6). Preparations of Veratrum largely been abandoned in the long-term treatment of hypertension because of the high incidence of unpleasant side effects associated with their administration. Few patients can tolerate effective doses, and even when Veratrum derivatives are used in smaller doses in conjunction with other drugs, they seldom contribute significantly to the regimen. Veratrum to a regimen consisting of a thiazide diuretic, and hydralazine or Rauwolfia or both will yield enough additional hypotensive effect to obviate the use of ganglion-blocking drugs.

Table 6

Preparations of Veratrum

Preparation	Size of Tablet (mg.)	Daily Dose* (mg.)
Alkavervir (Veriloid)	2.0 3.0	8-24
Cryptenamine Tannates (Unitensin)	2.0	8-24
Protoveratrines A and B (Provell, Veralba)	0.2 0.5	0.803.0
Protoveratrine A (Protalba)	0.2	0.8-3.0

Side Effects: Vagotonic symptoms; bradycardia, heartburn, salivation, sour eructation, nausea, vomiting, hypotensive crises.

* Divide into four doses, and five after meals and at bedtime. Start with smaller doses listed and increase gradually.(5)

PLANNING OF DRUG THERAPY:

The general measures for treatment of essential hypertension will alone usually suffice for many patients with uncomplicated mild to moderate essential hypertension. If the blood pressure remains above 160/100 mm. Hg., more active therapy should be started. A successful approach demands persistence of the physician, cooperation by the patient, and gradual titration of drugs singly or in combination, to attain a reasonable blood pressure level. Side effects are best handled by reduction of daily drug rations, and may be prevented by the use of sub-toxic doses of several hypotensives in concert. It is suggested that instead of trying to master the individual properties, and dose forms of the several hundred anti-hypertensive agents, the physician become proficient in the use of one or two preparations within each class of agents, much as he would familiarize himself with one or two digitalis forms for selected situations.

The intelligent choice of drugs, for treatment of hypertension depends upon the presence or absence of cardiac, cerebral, and renal complications as well as the pretreatment level of diastolic blood pressure. Except in emergency

situations, treatment may, and should be deferred until such information is available. When hypertension is mild, and uncomplicated, many determinations of blood pressure over a period of several days or even weeks may be necessary to establish control levels. Home determinations of blood pressure often give valuable information with regard to pretreatment levels of blood pressure.

Specific threatment with drugs for patients with labile diastolic hypertension is not usually indicated. Although the diastolic blood pressure may be 110 mm. of mercury or greater when first recorded by the physician, subsequent readings taken when the patient is more acclimated to his surroundings or recorded in his own home are consistently lower than 100 mm.. Sustained diastolic hypertension eventually will develop in many of these patients, but there is no good evidence that present treatment will alter this natural course of events. Vascular hyper-reactors should be followed carefully, and their blood pressure recorded frequently so that appropriate hypotensive treatment can be instituted before cardiovascular complications develop in the event that the diastolic blood pressure becomes

fixed at higher levels.

As yet, the value of medical treatment for the systolic hypertension that occurs frequently in older people has not been established. As long as the diastolic blood pressure does not consistently exceed 100 mm. of mercury and the systolic pressure does not exceed 200 mm., treatment is probably unnecessary, unless congestive heart failure is present. When the systolic blood pressure is consistently greater than 200 mm., and especially when it exceeds 220 mm., and effort to reduce the systolic levels by specific measures is probably justified, and is usually successful even though the diastolic pressure may be normal. One of the thiazide diuretics (such as hydrochlorothiazide 50 mg. once or twide daily) is frequently the only drug needed.

In my study of the treatment of essential hypertension, I soon realized that there are many different opinions as to the proper method of use of anti-hypertensive drugs. Most workers use the "up-the-steps-, down-the-steps" method whereby one drug after another is added until satisfactory control has been achieved. Than they successively withdraw one drug after another in reverse order to that in which they were added.

The big difference noted was the order in which the drugs were initiated, and successively added to the treatment regimen. Some started with: Rauwolfia to Hydralazine to Ganglionic-blockade. Others started with Rauwolfia to Thiazide diuretics to Hydralazine to Ganglionic-blockade, or Thiazide diuretics to Rauwolfia to Veratrum alkaloids, or Thiazide diuretics to Hydralazine to Rauwolfia to Ganglionic blocking agents. There probably are other ways in which these drugs could be used successfully, such as with the newly developed anti-hypertensive drug combinations.

In the uncomplicated, mild to moderate hypertensive patients (Group 1 or Group 2), Gifford of the Mayo Clinic[5] uses the following method, and suggests that if the average diastolic blood pressure ranges from 100 to 120 mm., if there are no cardiovascular or renal complications, and if the retinas do not contain hemorrhages or exudates, and papilledema is absent, treatment can be undertaken deliberately, allowing time for the effect of each agent to be evaluated before administration of another drug is started. Blood pressure should be recorded at least once or twice a week, but increments in dosage or

addition of new agents should be made only after it is evident that maximal effects have been obtained from the existing regimen. He states that it may take as long as three months to design a satisfactory program of treatment in this manner, but the physician can be certain that his patient is receiving only necessary drugs in minimal doses.

In Step A., Dr. Gifford starts with one of the thiazide diuretics, such as hydrochlorothiazide 50 mg. twice daily. No other drugs will be necessary for approximately 40% of patients with hypertension in this category. If the blood pressure is not in a satisfactory range within three to four weeks proceed to; Step B. Add hydralazine 10 mg. four times daily. Increase each dose by 10 mg. every two or three weeks until blood pressure is controlled or side effects are intolerable or until the maximal dose of 75 mg. four times daily is reached. For approximately 10% of patients it will be necessary to proceed to step C.. If the addition of hydralazine has not had an appreciable effect on the blood pressure or has produced intolerable side effects, treatment with hydralazine should be discontinued before proceeding to step C; if hydralazine has had a benficial though

suboptimal effect, it should be continued. Omit Step B., if hydralazine is contraindicated.

Step C. Add one of the Rauwolfia preparations (such as reserpine 0.24 mg. once daily). If the blood pressure does not respond adequately to Rauwolfia or if this drug is not well tolerated, its administration should be discontinued after a fair trial of three or four weeks, at which time proceed to step D.. Omit step C. entirely if Rauwolfia is undesirable or contraindicated.

Step D. Add a ganglion-blocking agent or a sympatholytic drug, such as, trimethidinium methosulfate which may be given in doses of 20 mg. before each meal, and at bedtime. Each dose can be increased by 10 mg. every two or three weeks until adequate control of blood pressure is achieved or until side effects are unbearable. Instead of a ganglion-blocking agent, bretylium may be added by starting with 100 mg. before each meal, and at bedtime, and increasing the daytime doses by 100 mg. every two or three weeks until the response is optimal. To prevent orthostatic collapse when the patient arises during the night or in the morning, the bedtime dose should not be increased as repidly or as

greatly as the others. If the patient takes his own blood pressure at home, the dose of either of these types of agents can be safely increased more rapidly than this.

In uncomplicated severe hypertension (Group 3 or 4)., Dr. Gifford uses the following criteria: When the diastolic blood pressure is consistently greater than 120 mm., and especially when it is greater than 130 mm., or when there are hemorrhages, exudates, and papilledema in the retinas, the sense of urgency about initiating treatment, and getting the blood pressure under control is greater, even though cardiovascular, and renal complications are absent. In this situation the blood pressure should be recorded every day or two, and increments in dosage, and addition of new drugs should be made more frequently than when hypertension is less severe. It is desirable that the patient or a member of the family take the patient's blood pressure at home two, or three times a day.

Step A. Start with a thiazide diuretic such as hydrochlorothiazide 50 mg., twice daily. Since use of a thiazide agent alone seldom, if ever, suffices to control severe hypertension, it is wise to proceed to step B., within a few days.

Step B. Add hydralazine 25 mg. three or four

times daily. Increase each dose by 25 mg. every three or four days until the blood pressure is controlled. If side effects are unbearable or the maximal dose of 75 mg. four times daily is reached without producing optimal hypotensive effect, proceed to step C..

Step C. Add a ganglion-blocking agent or a sympatholytic agent as outlined in step D., of the previous section. Increments in dosage should be made every two or three days until hypertension is controlled. When hypertension is severe, guanethidine may be effective when a ganglion-blocking agent and bretylium may fail. The initial dose of guanethidine is 25 mg. given at bedtime. The dose should be increased by 25 mg., but not oftener than every three or four days, since the onset of hypotensive effect is delayed. The total dose can be given at one time each day. Gifford feels that one should not discontinue effective measures because hypertension will only recur.

Special precautions in managing hypertension are indicated when hypertension is complicated by impairment of cerebral, cardiac, or renal functions. For instance, after acute myocardial or cerebral infarction, anti-hypertensive treatment is

contraindicated for four to six weeks unless hypertension is severe, and is embarrassing myocardial function. Thereafter, regimens such as those already outlined are indicated. Treatment also is indicated for hypertensive patients who have angina pectoris or cerebral vascular insufficiency without actual infarction of the myocardium or brain. Hydralazine should be used with extra caution for patients with coronary disease because it sometimes aggravates coronary insufficiency, although this is not common. Also, ganglion-blocking drugs, and sympatholytic drugs must be admininstered charily to avoid sudden hypotension that might aggravate ischemia, or precipitate infarction of heart or brain. Long-term treatment with anticoagulants should be initiated before attempts are made to reduce blood pressure for patients with severe angina pectoris or re-curring episodes of cerebrovascular insufficiency.

When the values for urea are between 50 and 100 mg. per 100 ml. of blood thiazide diuretics, ganglion-blocking drugs, and sympatholytic agents must be used cautiously, and treatment should be stopped if the concentration of blood urea increases significantly. When values for

blood urea are greater than 100 mg. per 100 ml., thiazide diuretics should be omitted from the-regimen, and ganglion-blocking drugs or sympatholytic agents should be used only if the blood pressure cannot be controlled by combinations of reserpine, and hydralazine. If reduction in blood pressure results in further significant increase in blood urea, all attempts at hypotensive therapy should be abandoned.

SURGICAL TREATMENT:

Thoracolumbar sympathectomy is indicated only in two instances; 1. for patients with severe hypertension which cannot be controlled adequately by combinations of hypotensive drugs, and 2. for those patients who cannot or will not adhere to a medical regimen.

EMERGENCY SITUATIONS:

Urgent situations include (1) the accelerated or malignant phase of hypertension (2) hypertensive encephalopathy (3) hypertensive heart failure; (4) acute nephritis (5) toxemia of pregnancy and (6) cerebral hemorrhage. These potential threats to life require prompt, and energetic action.

Step A. Since reserpine is easy to administer is effective in most cases regardless of the cause

of the hypertension and does not require constant attendance by trained personal during administration, it is usually the drug of choice. Give 2.5 or 5 mg. intramuscularly. Do not repeat the injection for two or three hours, for it may take this long to obtain the maximal hypotensive effect. If it is imperative to reduce the blood pressure more promptly, pentolinium tartrate (Ansolysen) 5 mg. oralkavervir (Veriloid) 0.8 mg. may be given intramuscularly when reserpine is given. A more reliable method to achieve prompt control of hypertension is slow intravenous injection of a solution of pentoliunim tartrate (5 mg. per cent 20cc.) or of alkavervir (2 mg. per cent 20cc.). Thereafter the blood pressure usually can be controlled by repeating the injection of reserpine at appropriate intervals, increasing the dose if necessary. If reserpine is ineffective, or if by inducing so much drowsiness it confuses the clinical picture (as in cerebral hemorrhage or hypertensive encephalopathy), or if the dose of reserpine required is in excess of 20 mg. in 24 hours, proceed to step B.

Step B. Administer 5 mg. of pentolinium tartrate by intramuscular injection. If trained

personnel can be in constant attendance, it is preferable to give pentolinium by continuous intravenous infusion. Catheterization is usually necessary for men who receive ganglion-blocking agents parenterally for more than a few hours, and paralytic ileus is not infrequently observed as a result of prolonged therapy. Better hypotensive effect is achieved if the head of the bed is elevated.

If paralytic ileus ensues, treatment with reserpine can be resumed, or one the preparations of Veratrum can be given by intramuscular or continuous intravenous injection. If side effects are troublesome or hypertension cannot be controlled by parenteral administration of any of the drugs mentioned, proceed to step C..

Step C. Start an intravenous infusion containing 60 mg. of sodium nitroprusside per liter at a rate that does not exceed 10 drops per minute at first. This requires careful, and close supervision to prevent hypotension. The rate of administration of the infusion must be skillfully adjusted to keep the blood pressure at desired levels, for this is a potent hypotensive agent and it is effective when all other drugs fail. If

its administration did not require such close, and constant supervision, it would be the treatment of first choice in most cases of hypertensive crisis.

Once the acute exacerbation of hypertension is controlled, an effort should be made to switch from the parenteral to the oral route of administration as soon as feasible.

SUMMARY

With the review of recent medical literature, material concerning the treatment of essential hypertension has been compiled, and presented. The causes of hypertension, and methods of diagnosing these causes are discussed.

Emphasis is especially placed upon anti-hypertensive drugs, and their usage in uncomplicated mild, moderate, and severe hypertension. Management of complicated hypertension, and emergency hypertensive situations are included.

CONCLUSION

The past decade has seen a dramatic change in the management of high blood pressure. A program consisting of sedatives, diets, and surgery has gradually been replaced by one that is based on the use of antihypertensive medications, either singly or in various combinations.

Hypertension is a chronic illness which requires observation, and management over a great many years. The hypertensive patient requires the diligent, sincere, and persistent interest, and attention of a sympathetic personal physician prepared to view the problem in the familiar setting of the everyday world. This concern by the family physician is fundamental treatment in itself. The first line of attack on the problem of high blood pressure must be launched in the daily office schedule of the family doctor, and only by means of a vigorous therapeutic approach to the management of diastolic hypertension can the physician expect an arrest of the anticipated vascular damage, and a significant reduction in the associated morbidity, and moratlity.

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