**SUMMARY OF CURRENT THERAPY**

Antihypertensive Drug Therapy: Current Status*

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During the past decade, a succession of potent antihypertensive compounds have become available for clinical use. The physician can currently choose from a wide spectrum of therapeutic agents with varying pharmacologic attributes. It is the purpose of this review to discuss the antihypertensive abilities and comparative merits of the available hypotensive compounds and to consider their clinical application.

I. Current Drug Armamentarium

Diuretics. Diuretic agents possess antihypertensive abilities which are proportional to their natriuretic potencies. Freis suggested that the hypotensive effect obtained is related to a reduction in plasma volume and a consequent decrease in cardiac output. Subsequently it has been determined, however, that the blood pressure reduction achieved with the diuretic agents is maintained despite the administration of plasma and the consequent correction of the attendant hypovolemia. In addition, it has been found that plasma volumes spontaneously return to pretreatment levels following prolonged (one to two months) administration of the benzothiadiazine drugs. It appears that the administration of thiazide and other diuretic agents affects the gradient of sodium ions existent between the intracellular and extracellular spaces. The latter effect may account for the resultant alteration in vascular responsiveness.

The thiazide and phthlimidine diuretics are particularly suited to the longterm treatment of hypertension. These compounds are extremely potent and orally active. They are effective both in the supine and erect positions, and the incidence of side effects encountered with these compounds is low. In addition, resistance to their natriuretic action rarely occurs; and the usual maintenance dosages do not produce severe electrolyte imbalance despite prolonged administration.

A recent study indicated significant blood pressure reduction in approximately 40 per cent of patients treated with chlorothiazide, hydrochlorothiazide, and flumethiazide. The dosages administered were 100 mg. daily of chlorothiazide (Diurol) or flumethiazide (Ademol) and 100 mg. per day of hydrochlorothiazide (Esidrix, Hydrodiuril, Oretic). Equivalent natriuretic dosages of other thiazide derivatives produce similar antihypertensive responses.

The phthlimidine compounds, like the benzothiadiazine drugs, are potent diuretic agents which are well-tolerated orally. The antihypertensive effectiveness of the phthlimidine, chlorthalidone, is similar to that achieved with the benzothiadiazine drugs. In comparison with chlorothiazide, chlorthalidone has a similar natriuretic potency, but a more prolonged duration of action; i.e., whereas the diuretic effect of chlorothiazide is generally spent within 12-18 hours, the natriuretic action of chlorthalidone may persist for 48 hours or more. Maximum antihypertensive effectiveness can be achieved with chlorthalidone (Hygroton) in a dosage of 100-200 mg. daily.

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for two weeks. Thereafter, the dosage can often be reduced to 100-200 mg. three
days per week (T.I.W.) for maintenance

Equally important to their individual antihypertensive actions, the thiazide and
phthalimidine diuretics also potentiate the effectiveness of the other available hypotensive agents. The combination of diuretic agents with other antihypertensive drugs
will frequently accomplish the desired response in those patients who fail to respond to diuretic therapy alone.

*Rauwolfia.* A variety of rauwolfia compounds are currently available including the single pure alkaloids of rauwolfia serpen tin (reserpine, rescinnamine and deserpidine), various preparations containing multiple active alkaloids (alseroxylon and whole root), and synthetic reserpine-like analogues (syrosingopine). Although there is statistically little difference in the antihypertensive response obtained with these various derivatives, the incidence of associated side effects appears to be least with the alseroxylon fraction (Rauwiloid), the whole root (Raudixin), and syrosingopine (Singoserp).*

The rauwolfia alkaloids have both central and peripheral mechanisms of action.* Earlier investigations indicated that these agents release serotonin from binding sites within the brain; more recently it has been determined that rauwolfia also liberates other catecholamines from the central hypothalamic centers. In addition it has been found that catecholamines are released peripherally from the postganglionic sympathetic nerve fibers as well. The latter

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\begin{array}{|c|c|c|}
\hline
\text{Severity of Hypertension} & \text{Initial Therapy} & \text{Adjunctive Therapy When Not Adequately Responsive to Initial Therapy} \\
\hline
\text{Diastolic blood pressure} & \text{Hydrochlorothiazide*} & \text{Rauwolfia} \\
>100 \text{ mm. Hg & <120 mm. Hg} & \text{Hydrochlorothiazide*} & \text{Hydralazine} \\
\text{Diastolic blood pressure} & \text{Hydrochlorothiazide*} & \text{Hydralazine} \\
>120 \text{ mm. Hg & <140 mm. Hg} & \text{and rauwolfia} & \text{or ganglion blocking agent} \\
\text{Diastolic blood pressure} & \text{Hydrochlorothiazide*} & \text{Hydralazine} \\
>140 \text{ mm. Hg} & \text{and guanethidine} & \text{or ganglion blocking agent} \\
\hline
\end{array}
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*May use other thiazide or phthalimidine diuretics with equally good results.
Adjunctive Dose Pentolinium infusion

Hydralazine. Hydralazine (Apresoline) is a rather unique peripheral vasodilator agent which produces prolonged dilatation of constricted vascular smooth muscle. In addition, hydralazine depresses the outflow of sympathetic impulses from the hypothalamus and vasomotor center within the medulla. It is of interest that there is a maximum dose response curve beyond which further dilatation cannot be achieved even by huge doses of the drug.  

The recommended initial dosage is 100 mg. daily (25 mg. Q.I.D.). Thereafter, the daily dosage may be doubled at weekly intervals until an adequate reduction of blood pressure has been accomplished or the incidence of side effects becomes prohibitive. Total dosage of hydralazine generally should not exceed 400 mg. per day (100 mg. Q.I.D.) since the use of larger doses may be associated with the development of severe side effects and, particularly, a mesenchymal lupus erythematosus-like syndrome. Although uncommon, a few case reports of iatrogenic lupus have been reported in patients receiving as little as 100 mg. per day.

The major untoward reactions observed with hydralazine include headache, palpitations, and tachycardia (due to the associated cardiostimulatory effect of this compound). The latter effect may aggravate coronary insufficiency, and actual instances of myocardial infarction have been precipitated. Hence, hydralazine is preferably avoided in patients with angina pectoris or coronary artery disease. In addition, hydralazine should probably never be used as the sole antihypertensive agent. Instead, it is advantageous to use this drug in combination with other hypotensive compounds, especially rauwolfia or guanethidine. The latter two agents have bradycrotic actions which tend to lessen the cardiostimulatory effect of hydralazine.

Guanethidine. Guanethidine (Ismelin) is the most useful of the newer antihypertensive agents. The drug possesses a hypotensive potency similar to that of the ganglion blocking compounds, but with a rather unique mechanism of action. The latter consists of an inhibition of the peripheral release of catecholamines from the postganglionic sympathetic fibers. The blood pressure reduction obtained is predominantly a postural one; however, in contrast with the ganglioplegic drugs, guanethidine produces a significant hypotensive response

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**Table 2—Outline for the Treatment of Hypertensive Emergencies**

<table>
<thead>
<tr>
<th>Emergency</th>
<th>Initial Therapy</th>
<th>Adjunctive Therapy When Initial Drug Inadequate</th>
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<tbody>
<tr>
<td>Encephalopathy</td>
<td>Reserpine or rescinnamine 2.5 to 10 mg. 5 to 15 mg. I.M.* I.M.</td>
<td>Pentolinium. If inadequate response, then Veriloid by I.V.** infusion Reserpine I.M. or Veriloid by I.V. infusion</td>
</tr>
<tr>
<td>Fulminating heart failure</td>
<td>Pentolinium 5 to 50 mg. I.M. 30 minutes to 8 hours</td>
<td>Reserpine I.M. or Veriloid by I.V. infusion</td>
</tr>
<tr>
<td>Intractable angina with severe hypertension</td>
<td>Pentolinium 5 to 50 mg. I.M. 30 minutes to 8 hours</td>
<td>Reserpine I.M. or Veriloid by I.V. infusion</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>Reserpine or rescinnamine 2.5 to 10 mg. 5 to 15 mg. I.M. I.M.</td>
<td>Pentolinium. If inadequate response, then Veriloid by I.V. infusion</td>
</tr>
<tr>
<td>Toxemia of pregnancy</td>
<td>Reserpine or rescinnamine 5 to 10 mg. 7.5 to 15 mg. I.M. I.M.</td>
<td>Hydralazine 5-20 mg. I.V. or 10-25 mg. I.M.</td>
</tr>
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</table>

*Intramuscular; **Intravenous

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*Intravenous; **Intravenous
without the associated side effects due to parasympathetic blockade. The only untoward reaction of consequence is diarrhea, which manifests itself as frequency of bowel habit (three to five times daily) rather than loose stools. If necessary, the latter effect can be improved with anticholinergic drugs.

In order to achieve maximum antihypertensive effectiveness with guanethidine (as with the ganglion blocking compounds), careful dosage titration is required. Because of the predominant orthostatic response, the blood pressure must be titrated with the patient in the erect position. The drug may be started in an initial dosage of 20 to 25 mg. daily and then increased by 10 mg. increments at seven to 14 day intervals until a significant response has been achieved. The concomitant administration of thiazide derivatives lessens the dosage requirement of guanethidine, improves the supine response, and reduces the incidence of accompanying side reactions.

The antihypertensive effect of guanethidine is usually delayed for two to three days following oral administration, but the ensuing blood pressure reduction is generally prolonged (for seven to 14 days) once an effective response has been obtained. Therefore, the drug can be administered effectively in a single daily dose.

In summary, the lesser incidence of side reactions, lack of parasympatholytic effects, and prolonged therapeutic response constitute significant clinical advantages for guanethidine. This agent is particularly effective in those patients with the more severe degrees of diastolic blood pressure elevation.

**Ganglionic-Blocking Agents.** With the availability of guanethidine, the clinical indications for ganglioplegic therapy have lessened. Nevertheless, these compounds remain among the most potent antihypertensive drugs available and hence they continue to offer clinical usefulness. Their hypotensive mechanism of action is due to the pharmacologic blockade of neurogenic transmission within the sympathetic ganglia. Multiple preparations are available including pentolinium (Ansolysen), chlorisondamine (Ecolid), and mecamylamine (Inversine). The approximate equivalent dosages of these drugs are 20 mg. pentolinium, 12.5 mg. chlorisondamine, and 2.5 mg. mecamylamine.

Determination of optimum drug dosage is dependent upon effective drug titration. It is important to start with a small dose of ganglion blocking agent, and then the dosage can be increased gradually until the standing blood pressure is reduced to the desired level. As a further guide to proper dose titration, the therapist should also question the patient concerning the occurrence and incidence of orthostatic hypotensive episodes. Thus, if the patient complains of attacks of dizziness occurring at specific times during the day, this indicates that he is obtaining an excessive hypotensive effect at that particular time and the dosage of the drug must be adjusted accordingly. Mecamylamine appears to be the ganglioplegic drug of choice, primarily because its absorption from the gastrointestinal tract is complete and therefore the daily hypotensive response is more nearly uniform than that achieved with the other ganglion blocking compounds.

Side effects encountered with these agents are due to the simultaneous inhibition of neurogenic transmission within the parasympathetic ganglia. These untoward effects should be anticipated and properly treated; however, they need not be feared. Constipation is the most common side effect and can usually be controlled with milk of magnesia (30 ml.) or cascara sagrada (10 to 30 ml. elixir) or prostigmine (15 to 30 mg. before meals). Likewise, impaired visual accommodation and dry mouth usually improve with pilocarpine (5 mg. T.I.D.) and urinary retention can generally be controlled with urecholine (5 mg. T.I.D.).

The incidence of side effects differs with the various ganglion blocking agents. 18 Constipation and dryness of the mouth are
more frequent and of greater severity following the administration of mecamylamine. Blurring of vision and photophobia are more severe with chlorisondamine. Thus, it may be helpful to shift to a different ganglion blocking drug if a particular side effect is too severe or cannot be otherwise controlled.

*Veratrum alkaloids and adrenergic blocking agents.* Multiple veratrum alkaloids and adrenergic blocking compounds are available. However, the use of the former group is limited by the development of nausea and vomiting which frequently accompanies effective dose levels and the use of the latter agents has been disappointing because of the numerous associated side effects and the rapid developments of tolerance. Therefore, the oral administration of these compounds is currently of limited value.

II. COMPREHENSIVE THERAPEUTIC REGIMENS

*Ambulatory Management.* An overall therapeutic regimen for the ambulatory patient with diastolic hypertension is outlined in Table 1. It is recommended that one of the thiazide derivatives be utilized as basic therapeutic agents because of their: (1) individual antihypertensive attributes, (2) relatively low incidence of accompanying side reactions, and (3) ability to potentiate all of the other available antihypertensive drugs. If the oral diuretic fails to achieve the desired response, a rauwolfia drug should be added to the therapeutic regimen after two weeks. Thereafter, if the blood pressure remains elevated after two or more weeks of combination therapy, hydralazine should be started according to the dose schedule described above. In those instances of severe progressive hypertension, it is recommended that guanethidine be added to the therapeutic regimen without delay.

Most patients with moderate or severe diastolic hypertension require a double or triple-drug regimen in order to accomplish significant blood pressure reduction. The combination of thiazide derivative, rauwolfia, and hydralazine is particularly effective in the subject with moderate blood pressure elevation. A regimen consisting of thiazide derivative, guanethidine, and hydralazine may be required if the hypertension is severe or rapidly progressive.

*Hypertensive Emergencies.* There have not been any significant recent additions to the parenteral antihypertensive drug armamentarium. Hence, the management of hypertensive emergencies has changed little during the past several years. An overall therapeutic regimen for the treatment of hypertensive emergencies is outlined in Table 2.

Many of the preparations which are commonly used orally in the treatment of essential hypertension are also available for parenteral administration. These include reserpine, hydralazine, several veratrum preparations (including alkavervir [Veriloid] and protoveratrine [Veralba]), and a number of ganglion blocking compounds (including pentolinium [Ansolysen] and mecamylamine [Inversine]). Parenteral reserpine appears to be the drug of choice in most hypertensive emergencies associated with essential hypertension. However, hydralazine is very dependable in the therapy of toxemia of pregnancy and acute glomerulonephritis; ganglion blocking agents are particularly useful in the patient with fulminating heart failure; and parenteral veratrum extracts are effective in all types of hypertension (except pheochromocytoma).

**Summary**

At present, there are few patients whose blood pressure cannot be reduced to normotensive levels with the available hypertensive agents. Often a double or triple-drug regimen is required. The ultimate goal of the therapist will be accomplished, however, only when the underlying etiology of essential hypertension is discovered.

**References**

1 Freis, E. D.: "The Effects of Salt and Extracellular Fluid Depletion on Vascular Responsiveness with Particular Reference to Chloro-

HEMOPTYSIS WITHOUT APPARENT CAUSE

D'Alfonso, Melillo and Scala studied 102 subjects with hemoptysis without apparent cause. Bronchoscopic examinations revealed diffuse or circumscribed bronchitis in 37 per cent. Other conditions found in order of frequency were: diffuse or circumscribed hypervascularized type hemorrhagic bronchitis; spastic circumscribed bronchitis; bronchiectasis and, of rarer occurrence, bronchial diverticula, benign tumors, and inflammatory granulomas.


PARADOXICAL RESPIRATION

Pendelluft, the pendulum-like movement of air from one lung to the other, is generally accepted as the cause of respiratory distress in the presence of paradoxical respiration. Despite the wide acceptance of this theory, no evidence has ever been presented in its support.

In an experimental study, simultaneous recordings of endobronchial carbon dioxide concentration, air flow, right and left pleural pressures and chest wall motion were made before and after extrapleural thoracoplasty. The analysis of data from these experiments shows no evidence of pendelluft, despite the presence of paradoxical motion of the chest wall. These experimental studies are on clinical situations. On the basis of their findings, the authors recommend that the concept of pendelluft in the presence of a closed chest be abandoned.


SURGICAL TREATMENT OF CONGENITAL LOBAR EMPHYSEMA

Congenital lobar emphysema of the lung resulting from the impaired bronchial patency leads to grave respiratory disturbances which usually manifest themselves in early childhood and mostly result in fatality. The author has observed congenital lobar emphysema in three patients. All of them were subjected to surgical treatment. Resection of the affected portions of pulmonary tissue provided good results in every patient.