Combined Rauwolfia-Hydralazine Therapy of Hypertensive Patients

By Charles F. Naegle, M.D., Ray H. Rosenman, M.D., Charles L. Hoffman, M.D., and Meyer Friedman, M.D.

Controlled blood pressure responses of 13 hospitalized and 33 ambulatory patients with essential or apparent renal hypertension were studied following combined Rauwolfia-hydralazine therapy. Adequate persistent lowering occurred in most instances of mild or moderate, and frequently even severe, hypertension. Prior and concomitant administration of Rauwolfia largely prevented unpleasant effects of hydralazine, permitted smaller dosage and ease of administration and follow-up—often impossible with large dosage of hydralazine used alone.

Despite the present availability of a number of effective hypotensive drugs, none appears to possess the features of the ideal therapeutic depressor agent. An adequate persistent hypotensive response can be induced only in a limited number of patients with the less powerful drugs, and dangerous side effects limit the usefulness of the more powerful depressor agents. Thus, various combinations of such drugs appear to be safer and more effective than any one used alone.

Recently, Wilkins and Judson introduced Rauwolfia serpentina into this country, a drug which appears to be a valuable addition to the therapeutic armamentarium available for the treatment of hypertension and its complications. In preliminary studies we have been able generally to confirm their findings concerning the hypotensive and other effects of this drug. Wilkins and Judson have suggested that the combination of hydrazinophthalazine (hydralazine) and Rauwolfia serpentina appears to be one of the safer depressor combinations, permitting an ease of oral administration and patient follow-up not possible with various other combinations of hypotensive agents. The present study is concerned with determining the clinical usefulness of this particular combination of drugs in the routine treatment of both hospitalized and office patients with hypertension.

Material and Methods

The patients who comprised this study, with few exceptions, had moderate or severe hypertension, usually diagnosed as "essential" hypertension, but in some instances as "renal." There were no cases of "malignant" hypertension, as usually considered. The patients were divided into two series.

The first series consisted of 13 merchant seamen with known persistent severe hypertension for periods of time ranging from at least 6 months to over 10 years. These men had been previously under both outpatient and inpatient medical care. All patients were hospitalized for the purpose of this study and their hypertensive state carefully re-evaluated under routine hospital conditions, while ambulatory and at bed rest. The patients were permitted ambulatory status on the ward while under observation. Each patient had a complete history and physical examination and laboratory studies which included complete blood counts and determination of the sedimentation rate, urinalysis and stain of the urinary sediment for "Sternheimer cells," renal concentration and dilution tests, determination of nonprotein nitrogen, fractional phenolsulfonphthalein test, chest x-ray examination and cardiac fluoroscopy, intravenous pyelography, electrocardiogram and ballistocardiogram. Observations of blood pressure and pulse rate were recorded at least twice daily under standardized conditions, and general symptomatology was noted at each of these periods. There were four instances of apparent "renal" hypertension associated with chronic pyelonephritis.

After usually four or more weeks of control observation, the patients were given Rauwolfia serpentina,* 4 mg. per day by mouth. After one week,

* Rauwiloid (Riker Laboratories, Inc., Los Angeles). The doses of Rauwolfia serpentina are expressed in terms of alkaloids of the alsersoxylon fraction (Rauwiloid, Riker).

From the Medical Service, United States Public Health Service Hospital, and the Harold Brunn Institute, Mount Zion Hospital, San Francisco, Calif.

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hydrazinophthalazine (hydralazine) was added in initial oral dosage of 75 mg. daily, and rapidly increased up to 600 mg. daily given in four divided doses. Observations then were continued for three to seven weeks.

The second series consisted of 33 unselected ambulatory office patients with known persistent hypertension for from six months to 23 years. Seven of these were believed to represent “renal” hypertension. Hypertension occurred in three of these for the first time during toxemia of pregnancy. The hypertension in the remaining four cases appeared to be initiated by a chronic pyelonephritis. In addition to history and complete physical examination, laboratory studies included complete blood counts and determination of sedimentation rate, cardiac fluoroscopy, electrocardiography and ballistocardiography, urinalysis and examination of urine sediment with the Sternheimer stain. Where indicated, renal dilution-concentration tests and intravenous pyelography were performed, and in many instances the blood pressure response to Regitine was tested. During the control observation and treatment periods, blood pressures and pulse rates were obtained in the recumbent position in the afternoon, initially at weekly and, later, usually at monthly intervals. In many instances the patients had been previously observed in private practice over a period of one to five years or during the previous 12-month period while under treatment with hydralazine alone and/or hexamethonium.

At the beginning of the present study other drugs were withdrawn and Rauwolfia serpentina* was administered orally in a total daily dosage of 4 to 8 mg. After one week to three months, hydralazine was added in 27 instances, in initial daily dosage of 75 mg. and, where necessary, rapidly increased up to a total of 300 mg. daily, except in four patients who received a somewhat larger dosage. The patients subsequently were observed for 3 to 12 months.

### Results

Table 1 depicts the blood pressure responses of the hospitalized group of nine patients with essential hypertension. The blood pressures were taken twice daily and recorded on a graph. The control values listed in table 1 represent the highest, lowest and approximate median blood pressure observed during the initial period of observation. Each patient of this series had severe hypertension, generally of known or obviously long-standing duration. The recorded blood pressures after therapy represent the approximate median blood pressures, as well as the highest and lowest levels recorded during the last 10 days of the therapeutic trial period. When response to therapy was observed, the blood pressures usually fell rapidly and remained stabilized at their lowered levels with only minor fluctuations and an occasional transient rise of greater magnitude. No significant response occurred in case 1 or case 9 despite 600 mg. daily dosage of hydralazine, although the highest and lowest diastolic values were somewhat diminished in case 9. Both of these patients exhibited severe hypertensive cardiovascular disease, with a failure of the blood pressure to fall during the preliminary control period of bed rest. Each of the other patients also exhibited severe chronic hypertension, but some reduction of blood pressure occurred in each instance during therapy. The fall in blood pressure observed in cases 3 and 8 might have been more marked had larger dosage of hy-

### Table 1.—Effect of Rauwolfia-Hydralazine in Hospitalized Patients with “Essential” Hypertension

<table>
<thead>
<tr>
<th>Case</th>
<th>Pt.</th>
<th>Age</th>
<th>Duration (wks.)</th>
<th>Control Observation</th>
<th>Observation on Rauwolfia-Hydralazine Therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>OL</td>
<td>49</td>
<td>4</td>
<td>224/124 230/160 180/100</td>
<td>400 220/120 230/130 150/110</td>
</tr>
<tr>
<td>2.</td>
<td>JW</td>
<td>73</td>
<td>5</td>
<td>190/120 230/140 180/110</td>
<td>500 140/85 160/103 130/70</td>
</tr>
<tr>
<td>3.</td>
<td>CD</td>
<td>40</td>
<td>4</td>
<td>165/115 180/120 150/90</td>
<td>280 150/100 160/110 140/80</td>
</tr>
<tr>
<td>5.</td>
<td>MC</td>
<td>49</td>
<td>2</td>
<td>170/100 200/130 150/90</td>
<td>600 150/90 185/103 140/60</td>
</tr>
<tr>
<td>6.</td>
<td>JD</td>
<td>54</td>
<td>3</td>
<td>170/116 205/120 160/110</td>
<td>400 140/90 150/109 130/70</td>
</tr>
<tr>
<td>7.</td>
<td>DL</td>
<td>24</td>
<td>5</td>
<td>190/140 230/140 180/110</td>
<td>600 170/90 180/130 160/80</td>
</tr>
<tr>
<td>8.</td>
<td>JS</td>
<td>55</td>
<td>2</td>
<td>190/120 200/130 180/110</td>
<td>300 170/98 183/110 150/93</td>
</tr>
<tr>
<td>9.</td>
<td>JS</td>
<td>38</td>
<td>2</td>
<td>180/110 210/160 170/130</td>
<td>600 180/107 195/110 160/90</td>
</tr>
</tbody>
</table>

* Last 10 days of therapy.

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Rauwolfia-Hydralazine Therapy of Hypertensives

Table 2.—Effect of Rauwolfia and Hydralazine in Hospitalized Patients with “Renal” Hypertension

<table>
<thead>
<tr>
<th>Case</th>
<th>Pt.</th>
<th>Age</th>
<th>Control Observation</th>
<th>Observation on Rauwolfia-Hydralazine Therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration (wks.)</td>
<td>Blood Press. (mm. Hg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median</td>
<td>High</td>
</tr>
<tr>
<td>1. AW</td>
<td>49</td>
<td>4</td>
<td>220/130</td>
<td>230</td>
</tr>
<tr>
<td>2. CR</td>
<td>62</td>
<td>4</td>
<td>222/120</td>
<td>260</td>
</tr>
<tr>
<td>3. AL</td>
<td>58</td>
<td>4</td>
<td>200/110</td>
<td>260</td>
</tr>
<tr>
<td>4. AB</td>
<td>61</td>
<td>3</td>
<td>160/90</td>
<td>180</td>
</tr>
</tbody>
</table>

* Last 10 days of therapy.

Hydralazine has been employed. Some reduction of the resting pulse rates occurred in every case, but this effect was not marked, perhaps because the pretreatment values were already lowered secondary to prolonged bed rest during the preliminary control period of observations.

Table 2 shows the blood pressure responses of the four hospitalized patients with hypertension occurring in association with chronic pyelonephritis. This diagnosis was based upon a history of pyelonephritis and/or the findings of persistent albuminuria, pyuria and urinary Sterneheimer “motility” cells in the urine. Although none of these patients exhibited azotemia, diminished renal function was present in most. Each patient had a severe hypertension and, except in case 4, it was fixed at a level not altered by the preliminary period of rest. In the patient whose blood pressure fell during bed rest alone (case 4), therapy with Rauwolfia alone further depressed the blood pressure to normotensive levels. In the other three cases, satisfactory lowering of the blood pressure could not be induced even by daily dosage of 600 mg. of hydralazine.

Table 3 presents the blood pressures observed in the 26 ambulatory office patients with essential hypertension. Less significance can be attached to these observations and to the recorded blood pressures since the blood pressures were obtained under necessarily variable circumstances and at intervals varying up to one month. The values listed in the table represent the final blood pressures obtained during the control and, posttreatment periods. During the treatment period of the ambulatory patients, the dosage of hydralazine was adjusted in an attempt to achieve or to maintain satisfactory blood pressure reductions. In some instances this required later increase of dosage, and on occasion the daily dosage could be reduced. As a result some variation of the blood pressure was observed. The blood pressure values in tables 3 and 4 represent the final values observed during therapy with the recorded dosage of hydralazine. In general, these patients exhibited less severe hypertension than those in the hos-
pitalized group, and a smaller dosage of Rauwolfia and of hydralazine was employed with few exceptions. Some blood pressure reduction occurred in every case. Six patients received only Rauwolfia, which lowered the blood pressure to normotensive levels in three patients (cases 13, 22, 23), and almost to normal in one (case 24). In another instance, (case 21), the diastolic pressure fell to normal, and the systolic remained elevated, possibly because of advanced sclerotic changes in the aorta. No hydralazine was given to case 2 because of the presence of advanced coronary artery disease. A reduction of the blood pressure to normal levels (150 systolic, 90 diastolic) occurred in many of the remaining patients on combined therapy. The blood pressure response was not entirely satisfactory in three patients (cases 7, 20, 25). Each of these patients had severe hypertension, known to be present for many years. Side effects prevented administration of a larger and perhaps more effective dosage of hydralazine in case 7 and case 20.

The effects of combined therapy in the ambulatory series of seven patients with "renal" hypertension are presented in table 4. This diagnosis was based on the fact that hypertension either began with a toxemia of pregnancy or was present in association with apparent chronic pyelonephritis, based on the criteria described for the hospitalized group. Hypertension began in cases 1, 4, and 5 with toxemia of pregnancy, but severe hypertension was observed only recently in cases 1 and 4. It is of interest that therapy was effective in these two patients, but was less effective despite a larger dosage of hydralazine in case 5 where severe, fixed hypertension, known for many years, had failed to respond to a sympathec-tomy performed five years ago. The remaining patients presented evidence of chronic pyelonephritis. The results of therapy were excellent in case 2 and Rauwolfia alone served to reduce the blood pressure effectively in cases 3 and 7. Patient 6 had only a fair result, which was not improved by further increasing the dosage of hydralazine.

A reduction of the pulse rate, often to brady-cardiac levels, occurred in many of the ambulatory groups of patients. Nasal congestion was observed in some of the patients but was troublesome in only one instance. Significant increase of bowel frequency occurred in one patient who had a history of "irritable colon" syndrome. No serious side effects occurred in any patient, although increased angina was observed in one instance, preventing a larger and probably more effective dosage of hydralazine. In contrast to an earlier experience with hydralazine used alone, it was observed that the prior administration of Rauwolfia markedly reduced the incidence and severity of palpitation, tachycardia, and "headache" commonly observed when initiating treatment with hydralazine, and permitted administration of the latter in an initial dosage of 25 to 50 mg. given three times daily. Finally, although precise comparative studies were not performed in this group of patients, it is our definite impression that the concomitant administration of Rauwolfia and hydralazine induces a degree of blood pressure reduction which would require substantially larger doses of hydralazine if used alone, doses more prone to induce serious side effects and more difficult to control. We have also been impressed with the favorable effects of Rauwolfia upon the anxiety, general tension and other symptoms prone to occur in hypertensive patients.

**Discussion**

*Rauwolfia serpentina* has been used in India for over 10 years in the treatment of hypertension. Wilkins and Judson (3) introduced the drug into the United States and found that it had a mild hypotensive effect, caused
bradycardia frequently, and had a sedative effect occasionally, but did not result in postural hypotension or vagal stimulation. They observed that it was well tolerated by hypertensive patients over prolonged periods, with hypotensive effects slow both to appear and to disappear. Wilkins¹ ² has suggested that rauwolfia is most useful as an adjunct to more powerful hypotensive agents. The logical use of Rauwolfia in conjunction with other hypotensive agents³ led to this study of combined Rauwolfia and hydralazine therapy in an attempt to determine the clinical usefulness of this drug combination. Our results with this combination of drugs confirm in general those previously presented by Wilkins and Judson.⁴

Thus, in a small series of hospitalized patients followed carefully over relatively long periods of time, control of hypertension was achieved in those with mild or moderate, and occasionally severe hypertension. Failures occurred in some patients with long-standing, fixed, severe hypertension, or those with apparent "renal" hypertension. This experience was confirmed in a larger number of unselected ambulatory office patients with hypertension.

In the dosage used, side effects attributable to Rauwolfia were significantly few and included only bradycardia, observed frequently, nasal congestion, and a sedative effect observed infrequently. The prior administration of Rauwolfia appeared to prevent the commonly encountered headache, tachycardia, and palpitation which frequently occur when initiating therapy with hydralazine, and permitted initial hydralazine therapy in moderate dosage. Moreover, concomitant administration of Rauwolfia appeared to permit effective therapy with hydralazine in significantly smaller dosage of the latter, doses which avoid the more serious side effects of hydralazine administration which can occur with large doses given over long periods.⁵ ⁶ Finally, the safety and ease of administration of this combination of drugs permitted an ease of patient follow-up which, following stabilization, required only bimonthly or monthly routine check. Thus, combined Rauwolfia-hydralazine therapy appears to us to be a preferable combination of drugs for most patients with hypertension who fail to respond to Rauwolfia used alone, although other drug combinations have been shown to be advantageous.¹¹ As shown by Wilkins,¹ ² ³ the substitution or addition of a third hypotensive agent may be required to control the blood pressure of selected patients with severe, chronic, fixed hypertension or “renal” hypertension.

Summary

Blood pressure responses of 33 ambulatory and 13 hospitalized patients with hypertension were studied under controlled conditions during combined therapy with Rauwolfia serpentina and hydralazine. Adequate lowering of the blood pressure was achieved in most patients with mild or moderate hypertension, and frequently in those with severe hypertension. With the dosage used in this study, an inadequate response occurred only in patients with severe, chronic, fixed hypertension or with hypertension of apparent renal origin.

Prior administration of Rauwolfia largely prevented untoward effects prone to occur when initiating therapy with hydralazine, and permitted initial administration of hydralazine in larger dosage than ordinarily tolerated. With combined Rauwolfia-hydralazine therapy, adequate lowering of the blood pressure was achieved in a high incidence, using moderate dosage of hydralazine which permitted an ease of administration and patient follow-up often not possible with larger dosage of hydralazine used alone.

Summario in Interlingua

Le reactiones del pression sanguinee a un therapia combine de Rauwolfia serpentina e hydralazina esseva studiate sub conditiones controle in 46 patientes hypertensive inter le quales 13 esseva hospitalizate e 33 ambulatori. Satisfacentemente reductiones del pression sanguinee esseva effectuate in le majoritate del patientes con leve o moderate hypertension e frequentemente etiam in patientes con hypertension sever. Le dosages usate in iste studio resultava in reactiones inadequate solo in patientes con sever e chronic hypertension fixate o in patientes con hypertension de origine apparentemente renal.
Le pre-administration de rauwolfia preveniva in grande messura le effectos nocive que occurre facilmente quando le therapia es comenciate per le administration de hydralazina. Iste pre-administration de rauwolfia etiam rendeva possibile un administration initial de hydralazina in dosages plus grande que illos normalmente tolerate. Le therapia combinate de rauwolfia e hydralazina resultava in un adequadte reduction del pression sanguinee in un alte procentage del casos ben que le dosages usate esseva satis moderate pro evitar omne difficultates in le administration del drogas e le supervigilantia posterior del paciente, lo que es frequentemente impossibile quando on usa plus grande dosages de hydralazina isolate.

ACKNOWLEDGMENT
We wish to express our appreciation to Dr. Norman W. Karr of the Riker Laboratories, Inc., Los Angeles, for the generous supplies of Rauwiloid, the preparation of Rauwolfia serpentina used in this study.

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