Treatment of Hypertension with Reserpine, with Reserpine in Combination with Penta-pyrroloidinium, and with Reserpine in Combination with Veratrum Alkaloids


The treatment of hypertension with reserpine is described. When used alone it produced adequate falls of blood pressure in ten out of forty patients. The combination of reserpine with veratrum did not increase the hypotensive effects of reserpine alone. The combination of reserpine with pentapyrroloidinium increases the effectiveness of the pentapyrroloidinium and lessens its parasympathetic side effects. The combination of reserpine and pentapyrroloidinium is regarded as the best therapeutic regime for severe hypertension. Some mild cases of hypertension may be managed with reserpine alone.

Extractions of Rauwolfia serpentina have been extensively used in India for several decades in the treatment of a variety of conditions including hypertension. Their value in treatment of the latter condition has recently attracted world-wide interest. The particular activity as a hypotensive agent of reserpine, an alkaloid of Rauwolfia isolated by Swiss workers has been investigated in animals by Bein and associates, Trspold and co-workers, Plummer and colleagues, and McQueen and associates. These studies have indicated that in part at least, the hypotensive action of reserpine is mediated through the sympathetic nervous system. Our own studies have also shown that in rabbits reserpine has a direct vasodilating action on the blood vessels and suggest that there may be some direct effect in man. In a previous report from this department the effects of large doses of reserpine in man were described, and further clinical studies have been published by Löffler and co-workers, Wilkins, Freis and Ari, Hafkenschiel and Sellers, Winsor, and Moyer.

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The use of Rauwolfia alkaloids in combination with other hypotensive agents has been reported on by Wilkins (Serpina and Apresoline), Wilkins and Judson (Serpina and veratrum alkaloids) and Ford and Moyer (Rauwiloid and hexamethonium). A preliminary account has outlined in general terms our own experiences with a combination of reserpine and pentapyrroloidinium. At that time it could be stated that of 40 cases, distinctive benefits had resulted from the use of the combination in 27 (8 classified as very good and 19 as good). Benefit was apparent either in an important decrease of side effects or in improvement in the degree of blood pressure control without increase of side effects, or in a combination of these. Eight were classed as fair, meaning that some specific advantage had been obtained by the combination although this might be of slight degree. In only 5 out of 40 were the results considered poor. It was pointed out that an important advantage of the combination of reserpine and pentapyrroloidinium is that the dose of the latter is smaller than would be needed if it were used alone to produce an equal hypotensive action.

In the present report the results are presented of using reserpine alone in tolerable doses in 40 cases, reserpine in combination with pentapyrroloidinium in 60 cases, with hexamethonium in 9 cases, and in combination with alkaloids of veratrum in 10 cases.
**Results**

*Reserpine Alone*

Reserpine in doses of 9 mg. daily will reduce the blood pressure in most hypertensive subjects. Such large doses are accompanied by side effects of a degree of severity such as to make their use as a form of continuous therapy impractical. In a certain number of cases, however, the blood pressure is substantially reduced at a dosage level low enough to avoid serious side effects (0.5 to 1.5 mg. per day). We have given 40 patients a trial of therapy with reserpine alone in this dosage. In 10 of these blood pressure control was sufficiently good for it to be used as the treatment of choice. In several further patients good falls were obtained with low doses but blood pressure control was not as satisfactory as could be obtained by the addition of small amounts of another hypotensive agent, usually pentapyrrolidinium. Table 1 shows the 10 cases who have been treated with reserpine alone as the therapy of choice. Although in general the cases were relatively mild, several were of considerable severity. The fact that the blood pressure range whilst on reserpine extends well below the basal blood pressure in all cases in which the latter was recorded, suggests that reserpine is exerting an active hypotensive effect and that the blood pressure falls are not merely psychologic or sedative in origin.

**Side Effects.** The side effects of large doses of reserpine have been detailed by Doyle and Smirk; they consist of conspicuous conjunctival injection, nasal blockage, sensations of fatigue and sleepiness, depression, shivering, and occasional restlessness. With doses of the order of 0.5 to 1.5 mg. a day, such as we have used for continued therapy with reserpine alone and in combination with pentapyrrolidinium and veratrum preparations, similar side effects are still frequently encountered, and although of lesser severity, may at times prohibit its use. Other side effects we have encountered with these doses are diarrhea, which is the most troublesome one, undue susceptibility to cold, excessive gains in weight, and nightmares. These side effects, although at times troublesome, are not as a rule sufficiently severe to prevent the use of the drug. We have, however, noticed that in some patients associated conditions not closely connected with the hypertension have been aggravated. This applies particularly to patients with pre-existing depressive states. We have also noticed

### Table 1.—Effects on the Blood Pressure of Reserpine

<table>
<thead>
<tr>
<th>No.</th>
<th>Grade</th>
<th>Age</th>
<th>Basal B.P.</th>
<th>Dose reserpine (mg.)</th>
<th>B.P. range* before reserpine</th>
<th>B.P. range* after reserpine</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>II</td>
<td>53</td>
<td>154/102</td>
<td>0.5 t.i.d.</td>
<td>220/160–190/120</td>
<td>170/100–120/70</td>
<td>Coexisting ulcerative colitis somewhat aggravated, dyspnea</td>
</tr>
<tr>
<td>363</td>
<td>II</td>
<td>37</td>
<td>163/94</td>
<td>1.5 a.m., 0.5 noon, 1.5 p.m.</td>
<td>180/140–170/100</td>
<td>110/70–100/60</td>
<td>Minimal</td>
</tr>
<tr>
<td>733</td>
<td>II</td>
<td>46</td>
<td>144/86</td>
<td>4.0 per day</td>
<td>190/120–170/110</td>
<td>160/90–130/70</td>
<td>Somnolence</td>
</tr>
<tr>
<td>756</td>
<td>(+ angina pectoris)</td>
<td>46</td>
<td>Not recorded</td>
<td>0.5 t.i.d.</td>
<td>Approx. 150/110</td>
<td>120/90–88/70</td>
<td>None</td>
</tr>
<tr>
<td>766</td>
<td>I</td>
<td>50</td>
<td>166/116</td>
<td>1.5 t.i.d.</td>
<td>Clinic casual 214/138</td>
<td>160/80–110/80</td>
<td>Somnolence, nausea</td>
</tr>
<tr>
<td>768</td>
<td>II</td>
<td>46</td>
<td>152/96</td>
<td>0.25 b.d.</td>
<td>175/100–155/90</td>
<td>130/80–120/80</td>
<td>Depression</td>
</tr>
<tr>
<td>776</td>
<td>II</td>
<td>63</td>
<td>196/124</td>
<td>0.5 t.i.d.</td>
<td>210/130–190/140</td>
<td>170/100–130/80</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td>787</td>
<td>III</td>
<td>37</td>
<td>130/90</td>
<td>0.5 t.i.d.</td>
<td>160/110–130/90</td>
<td>150/100–105/75</td>
<td>None</td>
</tr>
<tr>
<td>908</td>
<td>II</td>
<td>46</td>
<td>160/100</td>
<td>0.25 t.i.d.</td>
<td>190/110–160/100</td>
<td>140/100–120/80</td>
<td>None</td>
</tr>
<tr>
<td>915</td>
<td>II</td>
<td>64</td>
<td>Not recorded</td>
<td>1.0 b.d.</td>
<td>230/130–160/120</td>
<td>190/100–140/70</td>
<td>Diarrhea, shivering. Cardiac failure progressed while on treatment</td>
</tr>
</tbody>
</table>

* Range of blood pressure refers to the highest and lowest blood pressure readings recorded during a day spent in the clinic.
### Table 2.—Effects on the Blood Pressure and the Incidence of Side Effects of Reserpine and Pentapyrrolidinium

<table>
<thead>
<tr>
<th>No.</th>
<th>Previous dose pentapyrrolidinium (mg.)</th>
<th>Present dose pentapyrrolidinium (mg.)</th>
<th>Dose reserpine after reserpine</th>
<th>B. P. control</th>
<th>Previous side effects pentapyrrolidinium</th>
<th>Present side effects pentapyrrolidinium</th>
<th>Side effects reserpine</th>
<th>Classification of results</th>
<th>Range* before reserpine</th>
<th>Range after reserpine</th>
<th>Range before reserpine</th>
<th>Range after reserpine</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>400 daily orally</td>
<td>180 daily orally (Later maintained on reserpine alone)</td>
<td>0.5 t.i.d.</td>
<td>Improved</td>
<td>Nausea</td>
<td>Diminished</td>
<td>None</td>
<td>Good</td>
<td>220/160-190/150</td>
<td>152/102-116/80</td>
<td>220/170-140/100</td>
<td>124/80-76/?</td>
</tr>
<tr>
<td>17</td>
<td>Hexamethonium 200 i.d. t.i.d.</td>
<td>Hexamethonium 200 i.d. t.i.d.</td>
<td>0.5 t.i.d.</td>
<td>Improved</td>
<td>Dry mouth, blurred vision</td>
<td>No change</td>
<td>Somnolence</td>
<td>Fair</td>
<td>206/120-122/90</td>
<td>189/72-136/80</td>
<td>204/120-160/110</td>
<td>188/72-122/68</td>
</tr>
<tr>
<td>25</td>
<td>4.8 b.d. subcutaneously</td>
<td>4.8 b.d. subcutaneously</td>
<td>0.5 t.i.d.</td>
<td>Much improved</td>
<td>Vomiting, severe dryness of mouth, severe constipation</td>
<td>No vomiting, less dry mouth, constipation relieved</td>
<td>None</td>
<td>Very Good</td>
<td>200/130-134/80</td>
<td>152/82-100/72</td>
<td>180/110-110/90</td>
<td>120/68-80/60</td>
</tr>
<tr>
<td>22</td>
<td>920 daily orally</td>
<td>920 daily orally</td>
<td>0.5 b.d.</td>
<td>Improved</td>
<td>Dryness of mouth</td>
<td>Unchanged</td>
<td>Flushing of face, lassitude</td>
<td>Poor</td>
<td>206/130-120/75</td>
<td>152/82-110/90</td>
<td>192/130-120/75</td>
<td>192/130-110/70</td>
</tr>
<tr>
<td>24</td>
<td>34 b.d. subcutaneously</td>
<td>26.5 b.d.</td>
<td>1.0 b.d.</td>
<td>Improved</td>
<td>Diarrhoea, constipation</td>
<td>None</td>
<td>None</td>
<td>Good</td>
<td>198/130-146/104</td>
<td>149/80-146/104</td>
<td>194/130-146/104</td>
<td>152/110-146/104</td>
</tr>
<tr>
<td>25</td>
<td>28 b.d. subcutaneously</td>
<td>26 b.d.</td>
<td>3.0 t.i.d.</td>
<td>Unchanged</td>
<td>Dry mouth</td>
<td>Unchanged</td>
<td>Somnolence</td>
<td>Poor</td>
<td>206/130-120/75</td>
<td>152/82-110/90</td>
<td>192/130-120/75</td>
<td>192/130-110/70</td>
</tr>
<tr>
<td>26</td>
<td>15.5 b.d. subcutaneously</td>
<td>11 b.d. subcutaneously</td>
<td>0.5 b.d.</td>
<td>Improved</td>
<td>Dryness of mouth, blurred vision, constipation, occasional slight shivering 2 hours after injection</td>
<td>Constipation improved, otherwise no change. Duration side effects less</td>
<td>Shivering unassociated with sensations of coldness</td>
<td>Poor</td>
<td>200/130-120/75</td>
<td>152/82-110/90</td>
<td>192/130-120/75</td>
<td>192/130-110/70</td>
</tr>
<tr>
<td>28</td>
<td>230 daily orally</td>
<td>80 daily orally</td>
<td>0.5 t.i.d.</td>
<td>Improved</td>
<td>Dryness of mouth</td>
<td>None</td>
<td>Billary colic necessitating withdrawal</td>
<td>Poor</td>
<td>198/130-146/104</td>
<td>149/80-146/104</td>
<td>194/130-146/104</td>
<td>146/104</td>
</tr>
<tr>
<td>29</td>
<td>Hexamethonium 100 i.d. t.i.d.</td>
<td>Hexamethonium 100 i.d. t.i.d.</td>
<td>1.5 t.i.d.</td>
<td>Improved</td>
<td>Dry mouth, blurred vision</td>
<td>None</td>
<td>None</td>
<td>Poor</td>
<td>238/160-152/110</td>
<td>200/130</td>
<td>200/130</td>
<td>200/130</td>
</tr>
<tr>
<td>10</td>
<td>50 b.d. subcutaneously</td>
<td>780 daily orally</td>
<td>3.5 at night</td>
<td>Improved</td>
<td>Extreme dryness of mouth, blurred vision</td>
<td>Diminished</td>
<td>None</td>
<td>Very Good</td>
<td>248/142/106/74</td>
<td>192/110-92/60</td>
<td>194/120-110/90</td>
<td>110/110</td>
</tr>
<tr>
<td>11</td>
<td>Hexamethonium 20 b.d. (Subsequently well managed on reserpine-pentapyrrolidinium)</td>
<td>1.5 b.d. subcutaneously</td>
<td>Unchanged</td>
<td>Dryness of mouth, blurred vision, constipation</td>
<td>Unchanged</td>
<td>None</td>
<td>Poor</td>
<td>240/130-160/116</td>
<td>220/142-160/116</td>
<td>204/116-148/98</td>
<td>148/98</td>
<td></td>
</tr>
</tbody>
</table>

* Range of blood pressure refers to the highest and lowest blood pressure readings recorded during a day spent in the clinic.

† Except where indicated figures in these columns refer to pentapyrrolidinium.

‡ Classification is based on the extent to which addition of reserpine has improved management with pentapyrrolidinium. "Very good" and "good" signify a distinctive benefit from the combination, apparent either in an important decrease in side effects or in improvement in the degree of blood pressure control without increase in side effects, or in a combination of these. "Fair" means that some specific advantage was obtained by adding reserpine. "Poor" means that management was no better or was worse after adding reserpine.
<table>
<thead>
<tr>
<th>Time</th>
<th>Treatment Details</th>
<th>Symptoms/Effects</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 200 a.m.</td>
<td>40 noon, 100 p.m., orally</td>
<td>Unchanged</td>
<td>Poor</td>
</tr>
<tr>
<td>153 100 b.d.</td>
<td>100 b.d., orally</td>
<td>Improved</td>
<td>Fair</td>
</tr>
<tr>
<td>164 18 b.d.</td>
<td>subcutaneously</td>
<td>Improved</td>
<td>Good</td>
</tr>
<tr>
<td>171 30 b.d.</td>
<td>subcutaneously 300 orally</td>
<td>Improved</td>
<td>Good</td>
</tr>
<tr>
<td>194 180 daily</td>
<td>orally</td>
<td>Improved</td>
<td>Good</td>
</tr>
<tr>
<td>195 7 b.d.</td>
<td>subcutaneously</td>
<td>Unchanged</td>
<td>Fair</td>
</tr>
<tr>
<td>204 24.5 b.d.</td>
<td>subcutaneously</td>
<td>Unchanged</td>
<td>Fair</td>
</tr>
<tr>
<td>207 920 a.m.</td>
<td>880 a.m., 400 p.m., orally</td>
<td>Improved</td>
<td>Good</td>
</tr>
<tr>
<td>222 25 a.m.</td>
<td>37.5 p.m. subcutaneously</td>
<td>Unchanged</td>
<td>Poor</td>
</tr>
<tr>
<td>236 Hexameth-</td>
<td>Onionium 200 t.d. subcutaneously 40 a.m., 20 noon, 40</td>
<td>Dryness of mouth, blunted vision, constipation</td>
<td>Very Good</td>
</tr>
<tr>
<td>242 Hexameth-</td>
<td>onium tabs. 5 t.i.d.</td>
<td>Improved</td>
<td>Poor</td>
</tr>
<tr>
<td>243 Hexameth-</td>
<td>onium 160 b.d. subcutaneously and 4 tabs. orally</td>
<td>Dryness of mouth</td>
<td>Good</td>
</tr>
<tr>
<td>246 380 daily</td>
<td>120 daily orally</td>
<td>All improved</td>
<td>Poor</td>
</tr>
<tr>
<td>No.</td>
<td>Previous dose pentapyrroloidinium (mg.)</td>
<td>Present dose pentapyrroloidinium (mg.)</td>
<td>Dose reserpine (mg.)</td>
</tr>
<tr>
<td>-----</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>261</td>
<td>Hexamethonium 100 mg.</td>
<td>Hexamethonium 100 mg.</td>
<td>0.25 b.d.</td>
</tr>
<tr>
<td>264</td>
<td>220 a.m., 260 p.m. orally</td>
<td>220 a.m., 260 p.m. orally</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>273</td>
<td>9 a.m., 10 p.m. subcutaneously</td>
<td>9 a.m., 10 p.m. subcutaneously</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>294</td>
<td>120 a.m., 120 noon, 220 p.m. orally</td>
<td>120 a.m., 120 noon, 220 p.m. orally</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>334</td>
<td>7 a.m., 9 a.m. subcutaneously</td>
<td>7 a.m., 9 a.m. subcutaneously</td>
<td>0.25 t.i.d.</td>
</tr>
<tr>
<td>357</td>
<td>120 a.m.</td>
<td>120 a.m.</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>308</td>
<td>140 a.m., 140 noon</td>
<td>140 a.m., 140 noon</td>
<td>0.5 t.i.d.</td>
</tr>
<tr>
<td>313</td>
<td>15.5 a.m., 16.0 p.m. subcutaneously</td>
<td>15.5 a.m., 16.0 p.m. subcutaneously</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>329</td>
<td>6 a.m., 10.0 p.m. subcutaneously</td>
<td>6 a.m., 10.0 p.m. subcutaneously</td>
<td>0.75 b.d.</td>
</tr>
<tr>
<td>336</td>
<td>8 a.m., 17 p.m. subcutaneously</td>
<td>8 a.m., 17 p.m. subcutaneously</td>
<td>0.5 t.i.d.</td>
</tr>
<tr>
<td>339</td>
<td>440 a.m., 460 noon</td>
<td>440 a.m., 460 noon</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>344</td>
<td>33 b.d.</td>
<td>33 b.d.</td>
<td>0.5 t.i.d.</td>
</tr>
<tr>
<td>359</td>
<td>12.8 b.d. subcutaneously</td>
<td>12.8 b.d.</td>
<td>1.5 b.d.</td>
</tr>
<tr>
<td>354</td>
<td>30 b.d. orally</td>
<td>30 b.d. orally</td>
<td>0.5 t.i.d.</td>
</tr>
<tr>
<td>361</td>
<td>189 a.m., 189 noon, 40 p.m. orally</td>
<td>189 a.m., 189 noon, 40 p.m. orally</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>No.</td>
<td>Dosage</td>
<td>Time</td>
<td>Frequency</td>
</tr>
<tr>
<td>-----</td>
<td>--------</td>
<td>------</td>
<td>-----------</td>
</tr>
<tr>
<td>355</td>
<td>30 b.d. subeutaneously</td>
<td>16 b.d.</td>
<td>0.5 t.i.d.</td>
</tr>
<tr>
<td>356</td>
<td>12.5 a.m., 13.5 p.m. subeutaneously</td>
<td>12.5 a.m., 13.5 p.m.</td>
<td>0.5 t.i.d.</td>
</tr>
<tr>
<td>357</td>
<td>120 a.m., 80 noon, 160 p.m. orally</td>
<td>120 a.m., 80 noon, 160 p.m. orally</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>358</td>
<td>200 a.m., 400 noon, 400 p.m. orally</td>
<td>200 a.m., 400 noon, 400 p.m. orally</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>359</td>
<td>12 b.d. subeutaneously</td>
<td>5 b.d.</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>360</td>
<td>84 b.d. subeutaneously</td>
<td>88 b.d.</td>
<td>2.0 b.d.</td>
</tr>
<tr>
<td>361</td>
<td>200 a.m., 240 p.m. orally</td>
<td>170 a.m., 200 p.m. orally</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>362</td>
<td>28 b.d. subeutaneously</td>
<td>200 a.m., 80 noon, 240 p.m. orally</td>
<td>0.5 t.i.d.</td>
</tr>
<tr>
<td>363</td>
<td>210 b.d. orally</td>
<td>100 a.m., 120 p.m. orally</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>364</td>
<td>340 a.m., 80 noon, 340 p.m. orally</td>
<td>340 a.m., 80 noon, 340 p.m. orally</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>365</td>
<td>220 b.d. orally</td>
<td>220 b.d. orally</td>
<td>0.25 b.d.</td>
</tr>
<tr>
<td>366</td>
<td>65 b.d. subeutaneously</td>
<td>60 b.d. subeutaneously became resistant</td>
<td>3.0 t.i.d.</td>
</tr>
<tr>
<td>367</td>
<td>35.5 b.d. subeutaneously</td>
<td>33 b.d.</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>368</td>
<td>15 b.d. subeutaneously</td>
<td>10 b.d.</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>369</td>
<td>Hexamethonium</td>
<td>100 a.m., 40 noon, 190 p.m. orally Pentapotassium nitrate</td>
<td>0.5 t.i.d.</td>
</tr>
<tr>
<td>370</td>
<td>100 b.d. subeutaneously</td>
<td>100 b.d. subeutaneously</td>
<td>0.5 t.i.d.</td>
</tr>
<tr>
<td>371</td>
<td>Hexamethonium</td>
<td>2.0 b.d.</td>
<td>0.5 t.i.d.</td>
</tr>
<tr>
<td>372</td>
<td>Hexamethonium</td>
<td>0.5 daily</td>
<td>0.5 daily</td>
</tr>
<tr>
<td>373</td>
<td>190 b.d. orally</td>
<td>180 b.d. orally</td>
<td>0.5 daily</td>
</tr>
<tr>
<td>No.</td>
<td>Previous dose pentapyropridinium (mg.)</td>
<td>Present dose pentapyropridinium (mg.)</td>
<td>B. P. control after reserpine</td>
</tr>
<tr>
<td>-----</td>
<td>--------------------------------------</td>
<td>--------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>775</td>
<td>26 b.d. subcutaneously</td>
<td>19 b.d.</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>780</td>
<td>12.5 b.d. subcutaneously</td>
<td>19 b.d.</td>
<td>0.5 t.i.d.</td>
</tr>
<tr>
<td>781</td>
<td>12.5 b.d. subcutaneously</td>
<td>8 b.d.</td>
<td>0.5 t.i.d.</td>
</tr>
<tr>
<td>785</td>
<td>15 b.d. subcutaneously</td>
<td>200 a.m., 40 noon, 200 p.m. orally</td>
<td>0.5 t.i.d.</td>
</tr>
<tr>
<td>790</td>
<td>22 b.d. subcutaneously</td>
<td>14 b.d.</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>795</td>
<td>8 b.d. subcutaneously</td>
<td>8 b.d.</td>
<td>0.5 t.i.d.</td>
</tr>
<tr>
<td>796</td>
<td>22 b.d. subcutaneously</td>
<td>6 b.d. subcutaneously, Now on 120 b.d. orally</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>797</td>
<td>120 a.m., 40 noon, 200 p.m. orally</td>
<td>240 a.m., 40 noon, 200 p.m. orally</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>810</td>
<td>600 a.m., 40 noon, 200 p.m. orally</td>
<td>120 a.m., 40 noon, 200 p.m. orally</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>812</td>
<td>200 a.m., 40 noon, 40 p.m. p.m.</td>
<td>200 a.m., 40 noon, 200 p.m. orally</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>916</td>
<td>120 b.d. orally</td>
<td>120 b.d.</td>
<td>0.5 b.d.</td>
</tr>
<tr>
<td>912</td>
<td>40 b.d. orally</td>
<td>40 b.d.</td>
<td>0.5 b.d.</td>
</tr>
</tbody>
</table>

TREATMENT OF HYPERTENSION WITH RESERPINE.

Table 2.—(Continued)
the occurrence in three patients of paroxysmal dyspnea of the type described by Winsor. In two of these cases bronchospasm had been previously noted and we attributed their attacks to precipitation of bronchial asthma. In one patient with gallstones the administration of reserpine was followed by typical biliary colic which subsided after the reserpine was withdrawn. In two further patients pain of a similar character occurring after reserpine is under investigation. One patient with chronic ulcerative colitis noted a distinct exacerbation of her symptoms while taking reserpine. Where side effects are prominent within the therapeutic range, small reductions in dosage may appreciably relieve them without sacrificing more than a small part of the hypotensive effect contributed by the reserpine.

The Combination of Pentapyrrolidinium with Reserpine

In table 2 results in 66 cases under treatment with a combination of reserpine and pentapyrrolidinium are presented. A further nine are on a combination of reserpine and hexamethonium. Data showing the extent to which reduction of pentapyrrolidinium or hexamethonium dosage was possible with equally good or better blood pressure control before and after the addition of reserpine is given in 69 cases. The same system of grading results has been used as in the previous report and is based as before on the extent to which therapy with the methonium compound has been improved by the concurrent administration of reserpine. Low doses of the latter were used as shown in the table.

Preparations of pentapyrrolidinium included 4, 5 and 10 per cent solutions in polyvinyl pyrrolidone (P. V. P.), 20 per cent with ephedrine, 0.5 or 1.0 per cent for injection, and a 2 per cent solution and 40 and 200 mg. tablets* for oral use. Preparations of hexamethonium bromide included 10 and 20 per cent solutions in polyvinyl pyrrolidone, 20 per cent, with ephedrine, 0.5 per cent, for injection and hexamethonium bitartrate tablets, each 375 mg., for oral use.

The "Range of Blood Pressure" refers to the highest and lowest readings recorded during a day spent in the clinic. The cases were of all degrees of severity including cases of malignant hypertension. Of the 69 cases, the result of introduction of the combined therapy is now considered very good in 15 cases and good in 20 cases, distinctive benefits having resulted from the addition of reserpine either in an important decrease of side effects or in improvement in the degree of blood pressure control without increase of side effects, or in a combination of these. In 18 the result is classed as fair, some specific advantage having been gained, though this might be of slight degree. Thus, in 53 of the 69 cases the addition of reserpine to the methonium compound in use is considered to have improved the treatment. Sixteen were no better or were worse.

An important advantage from the use of reserpine in combination with pentapyrrolidinium is the extent to which the dose of the latter may be diminished for an equal or greater hypotensive effect on addition of reserpine. Patients stabilized on pentapyrrolidinium usually remark on an increased hypotensive effect from their usual dose within 48 hours of the addition of reserpine. They are warned to expect this and told to reduce the dose of pentapyrrolidinium by progressive decrements (see table 4) until they reach that at which the hypotensive effect at its maximum is tolerable. The severity of parasympathetic side effects is usually reduced proportionally to the fall in methonium dosage. Additionally, in many cases the maximum blood pressure readings permitted by the regimen are significantly lowered. Although the extremes of variation of blood pressure seen with hexamethonium are better controlled with pentapyrrolidinium, some effect of the latter usually still being manifest even 12 hours after the last dose, high peaks may still be encountered. These high (and undoubtedly dangerous) peaks are notably diminished after addition of reserpine.

Side effects from the reserpine are frequent but with the small doses used are seldom a source of serious inconvenience. They have already been detailed in the section on reserpine.

*Ansolysen, May and Baker.
Table 3.—Effects on the Blood Pressure and the Incidence of Side Effects of Reserpine and Veratrum

<table>
<thead>
<tr>
<th>No.</th>
<th>B. P. range* before reser-</th>
<th>Dose reser-</th>
<th>B. P. range* after reser-</th>
<th>Side effects reserpine</th>
<th>Dose veratrum</th>
<th>B. P. after addition veratrum</th>
<th>Side effects veratrum</th>
<th>Definitive form of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>220/120–190/110</td>
<td>0.5 t.i.d.</td>
<td>185/100–145/80</td>
<td>Negligible. Does not relieve dyspnea completely</td>
<td>2 tabs. Veriloid</td>
<td>210/110–150/90</td>
<td>Nausea and vomiting precluding further elevation of dose</td>
<td>No</td>
</tr>
<tr>
<td>192</td>
<td>0.5 t.i.d.</td>
<td>180/140–150/110</td>
<td></td>
<td>Negligible</td>
<td>2 tabs. Ver. a.m.</td>
<td>1½ tabs. Ver. noon</td>
<td>2 tabs. Ver. p.m.</td>
<td>170/120–140/100</td>
</tr>
<tr>
<td>285</td>
<td>0.5 t.i.d.</td>
<td>180/100–160/90</td>
<td></td>
<td>Negligible</td>
<td>2½ tabs. Ver. a.m.</td>
<td>1½ tabs. Ver. noon</td>
<td>2½ tabs. Ver. p.m.</td>
<td>160/100–130/80</td>
</tr>
<tr>
<td>376</td>
<td>220/140–180/130</td>
<td>3.0 t.i.d.</td>
<td>220/130–210/120</td>
<td>Somnolence</td>
<td>1 tab. Veriloid t.d.s.</td>
<td>220/120–170/80</td>
<td>Not significant at this dosage level</td>
<td>No</td>
</tr>
<tr>
<td>379</td>
<td>2.5 daily</td>
<td>200/130–180/120</td>
<td></td>
<td>Negligible</td>
<td>2½ tabs. Ver. a.m.</td>
<td>1½ tabs. Ver. noon</td>
<td>2½ tabs. Ver. p.m.</td>
<td>190/130–130/90</td>
</tr>
<tr>
<td>794</td>
<td>Clinic casual</td>
<td>0.5 t.i.d.</td>
<td>Clinic casual</td>
<td>Nasal congestion, coryza, depression</td>
<td>1 tab. Veriloid t.d.s.</td>
<td>Clinic casual</td>
<td>200/100</td>
<td>Vomiting if dose increased above this</td>
</tr>
<tr>
<td>903</td>
<td>220/150–200/130</td>
<td>0.5 t.i.d.</td>
<td>220/130–170/90</td>
<td>Somnolence</td>
<td>2 tabs. Ver. a.m.</td>
<td>1½ tabs. Ver. noon</td>
<td>2 tabs. Ver. p.m.</td>
<td>180/100–130/70</td>
</tr>
<tr>
<td>904</td>
<td>0.5 h.d.</td>
<td>210/110–140/100</td>
<td></td>
<td>Negligible</td>
<td>4 mg. mixed alkaloids t.d.</td>
<td>140/90–120/70</td>
<td>Nil significant</td>
<td>Yes</td>
</tr>
<tr>
<td>910</td>
<td>240/140–220/140</td>
<td>0.5 t.i.d.</td>
<td>220/120–170/110</td>
<td>Negligible</td>
<td>4 tabs. Ver. a.m.</td>
<td>200/110–145/90</td>
<td>Vomiting</td>
<td>No</td>
</tr>
<tr>
<td>912</td>
<td>Casuals before order</td>
<td>3.0 t.i.d.</td>
<td>170/100–160/90</td>
<td>Somnolence</td>
<td>2 tabs. Veriloid t.d.s.</td>
<td>190/140–140/90</td>
<td>Vomiting if dose increased above this</td>
<td>No</td>
</tr>
</tbody>
</table>

* Range of blood pressure refers to the highest and lowest blood pressure readings recorded during a day spent in the clinic.
alone. Occasionally side effects from reserpine may cancel out those of an opposite character resulting from the ganglionic blocking agents.

The Combination of Reserpine with Veratrum

In 10 cases an extended trial was undertaken of reserpine combined with veratrum. In two of these this mixture is being used as the definitive form of treatment, but in only one has it seemed to give optimum results. In the others the degree of blood pressure control at dose levels at which side effects of the veratrum (nausea and vomiting) were tolerable was inferior to that which could be obtained either with reserpine and pentapyrrolidinium or with the latter alone. The results of the reserpine–veratrum regimen are shown in table 3.

DISCUSSION

Our object in treating hypertensive patients is to reduce the blood pressure to as near normal as possible, for as much of the 24-hour day as can be achieved, and our assessment of the therapeutic value of hypotensive drugs is an assessment of the degree of safe blood pressure reduction which can be obtained without intolerable side effects. We have used these criteria in examining the efficacy of reserpine, alone and in combination with pentapyrrolidinium and with veratrum alkaloids.

Reserpine alone sometimes produces large blood pressure falls but usually only in doses which are accompanied by severe side effects. When smaller doses are used, the side effects are generally less conspicuous, but with such doses we have been able to obtain an adequate hypotensive action in only one-fourth of our patients. Those in whom an adequate control could be achieved by the use of reserpine alone were generally the milder cases, and often, though not invariably, they had low basal blood pressures. Even with the low doses used we have encountered some difficulties from side effects, particularly in the aggravation of symptoms in subjects with bronchial asthma, ulcerative colitis, gallstones and pre-existing mental depression. Further, we have found that in patients with hypertensive heart failure blood pressure reduction by reserpine does not improve breathlessness as with a corresponding reduction by pentapyrrolidinium.

We have examined the effects of combining reserpine with various preparations of veratrum. Our particular interest was to determine whether the addition of reserpine enabled a greater degree of blood pressure reduction to be obtained without the development of vomiting or other side effects of veratrum. The results have been disappointing. In 10 patients the addition of reserpine did not alter the dose of veratrum which led to vomiting, and sub-toxic doses of veratrum were not found to exert any distinctively greater hypotensive effect after the addition of reserpine than they did before. We have concluded that the combination of reserpine with veratrum is not a satisfactory means of treating hypertension.

The combination of reserpine with pentapyrrolidinium has also been studied. Pentapyrrolidinium is a substance chemically related to hexamethonium, but, unlike hexamethonium, it can be safely and effectively given by mouth in most patients. It shares with hexamethonium the disadvantage that blockade of the sympathetic ganglia sufficient to induce a useful blood pressure fall cannot usually be obtained without parasympathetic ganglionic blockade also occurring. Although the hypotensive action of pentapyrrolidinium is more prolonged than that of hexamethonium, the blood pressure usually rises to hypertensive levels by the time that the next dose is due to be taken. We have examined the result of combining reserpine with pentapyrrolidinium, with special reference to the incidence of parasympathetic side effects, and also to determine whether the combination of drugs gave a more consistent and smooth hypotensive effect. The results of combining the two drugs have been encouraging. In 53 out of 69 cases in whom the combination was examined, it was possible to produce a better control over the blood pressure with less side effects. In those previously taking pentapyrrolidinium alone, the addition of reserpine made it necessary to reduce the dose of pentapyrrolidinium. In some instances the dose of pentapyrrolidinium required was less than half that previously needed. The greater the reduction in dose of pentapyrrolidinium
the greater was the reduction of side effects due to parasympathetic blockade. In a few it had been difficult to maintain fully effective hypotensive therapy with pentapyrroloidinium alone because of the severity of the side effects, and in these, a striking improvement in the degree of control has usually been obtained by the combination with reserpine.

Over the past four and one-half years we have studied the therapeutic value of the methonium compounds, the veratrum alkaloids, 1-hydrazinophthalazine (Apresoline), the hydrogenated ergot alkaloids, the adrenolytic agents such as Dibenzyline, and reserpine. Of these the combination of reserpine and pentapyrroloidinium appears to be distinctively the most effective means of controlling the blood pressure. Where there is no special urgency about the institution of hypotensive therapy, we now give reserpine in doses of 0.5 mg. thrice daily for a period of about 14 days. No special observation is required during this period since reserpine has the advantage that the dose in the therapeutic range is not immediately critical, in contrast to the extreme accuracy of the dose required when the methonium compounds or the veratrum alkaloids are used. This obviates the need for the close control of dosage so necessary with the latter drugs. In the small dose range, variations in the dose of reserpine of up to 0.5 mg. daily are not accompanied by noticeable variations in the immediate hypotensive effect. At the end of this time a few will be found to have a satisfactorily controlled blood pressure. In our experience these amount to about one in four and are generally the milder cases. In the remainder it is necessary to use pentapyrroloidinium as an additional measure, and this is added under close control. Initial doses and increments of pentapyrroloidinium for oral and parenteral use are shown in table 4. The use of pentapyrroloidinium is described in detail elsewhere.20, 21

For patients with hypertensive heart failure, or for those with malignant hypertension, reserpine is never adequate alone, and in these patients we commence treatment with pentapyrroloidinium and reserpine in combination.

The duration of treatment with the combination of reserpine and pentapyrroloidinium has been less than six months in all our patients, so that there has been insufficient time to determine whether the long-term effects of treatment will be better than with pentapyrroloidinium alone.

**SUMMARY AND CONCLUSIONS**

The clinical use of the alkaloid reserpine in the treatment of hypertension has been studied in 85 hypertensive subjects.

In doses with few side effects, the hypotensive action of reserpine alone produced therapeutically useful falls of blood pressure in 10 out of 40 patients.

The administration of veratrum alkaloids to patients already taking reserpine did not produce any further significant hypotensive effects except in toxic doses.

The administration of reserpine in combination with pentapyrroloidinium to subjects previously taking the latter substance alone, led to an improvement in the hypotensive action, with a reduction in the severity of side effects due to parasympathetic blockade.

It is concluded that the combination of reserpine and pentapyrroloidinium is the most satisfactory means at present available of treating severe hypertension, although some mild hypertensives may be managed with reserpine alone.

**SUMMARIO IN INTERLINGUA**

Le uso clinico del alcaloi de reserpina in le tractamento de hypertension eseva studiate in 85 subjectos hypertensive.

In dosas calculate a producir pauc efectos accessori le action hypotensive de reserpina in

---

**Table 4.—Initial Doses and Dosage Increments of Methonium Compounds**

<table>
<thead>
<tr>
<th>Initial dose (mg.)</th>
<th>Dose may be raised or lowered by increments or decrements of (mg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>As salt</td>
<td>As methonium ion</td>
</tr>
<tr>
<td></td>
<td>As salt</td>
</tr>
<tr>
<td>Pentapyrroloidinium bitartrate oral . . .</td>
<td>20</td>
</tr>
<tr>
<td>Pentapyrroloidinium bitartrate &quot;retard&quot; subcutaneous . . .</td>
<td>3</td>
</tr>
</tbody>
</table>
administration isolate se manifestava in 10 inter 40 patientes per un reduction del pression sanguine a grados therapeuticamente benefic.

Le administration de alcaloides de veratro a patientes jam sub tractamento a reserpina non resultava in ulle significative effects hypotensive additional, excepte quando illos esseva usate in dosages toxic.

Le administration de reserpina in combination con pentapyrrolidio a patientes previemente tractate per pentapyrrolidio isolate resultava in un melioration del action hypotensive con un reduction del severitate de effects accessori causate per blocage parasympathic.

Nos conclude que le combination de reserpina con pentapyrrolidio es le plus satisfacentemente medio nun disponible pro le tractamento de hypertension sever. Certe leve casos hypertensive pote esser tractate con reserpina isolate.

ACKNOWLEDGMENTS

We wish to thank Messrs. Ciba Ltd., Basle, for generous supplies of reserpin, and Messrs. May & Baker Ltd., Dagenham, England, for supplies of pentapyrrolidinium. We are most grateful to Miss N. Richardson for secretarial assistance.

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Treatment of Hypertension with Reserpine, with Reserpine in Combination with Pentapyrrolidinium, and with Reserpine in Combination with Veratrum Alkaloids
A. E. DOYLE, E. G. MCQUEEN and F. H. SMIRK

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