The Circulatory Effects of Reserpine


The effects of large doses of reserpine have been compared in hypertensive and normotensive patients. The falls of blood pressure are larger in the hypertensives than in the normotensives. In normotensive animals small falls of blood pressure occur. Evidence is presented which suggests that the fall of blood pressure in animals is in part mediated through the sympathetic nervous system. There seems also to be a direct vascular action in animals. In man, evidence is presented which suggests that part at least of the hypotensive action is mediated through the sympathetic nervous system.

The pharmacology of extracts of Rauwolfia serpentina has been studied by Chopra and co-workers,1 Ray and associates,2 and Dasgupta and colleagues.3 Chopra and associates' reported that the alkaloid with which they were working had a marked hypotensive effect which was in part due to depression of central nervous mechanisms, since it was less marked in decerebrate animals; it appeared also to result in part from a direct inhibitory effect on the musculature of the blood vessels. They also demonstrated a fall in the output of the isolated heart. Most subsequent work has suggested that the hypotensive effect of Rauwolfia alkaloids is mediated solely via central nervous mechanisms.

A new alkaloid, now named reserpine, was isolated by Müller and co-workers1 and pharmacologic studies on the action of this alkaloid have been published by Bein and colleagues,5, 6 and Trapold and associates.7 These workers reported that reserpine produced its hypotensive effect through the central nervous system, and they emphasized particularly its capacity to inhibit reflex pressor responses.

Since the falls of blood pressure obtained in normotensive animals with this drug are often inconspicuous, while the falls of blood pressure in hypertensive patients are occasionally very large, it was decided to compare the effects of reserpine on the blood pressure in human subjects with hypertension and in those with normal blood pressures. The action of the drug in laboratory animals has also been studied and evidence as to a mode of action is presented.

Hypotensive Action of Reserpine

(a) In Human Hypertensive Subjects

The acute effects of large doses of reserpine have been studied in 33 hypertensive patients. The type of hypertension varied from grade I to IV.8 The doses given were from 2 to 3 mg, three times daily by mouth.

The extent of the hypotensive response differed widely in individual subjects (table 1). In some, falls of blood pressure were obtained which were within the range commonly noted with the administration of placebo.9 In others very large falls of blood pressure occurred, the blood pressure occasionally reaching normal levels. Although large falls of blood pressure occurred more frequently in those with low basal blood pressures, the lowest pressures recorded after reserpine were usually lower than the basal blood pressure; moreover, some
patients with malignant hypertension and some with high basal blood pressures had large falls of blood pressure with reserpine. Postural hypotension did not occur, the blood pressure being unaltered over periods of up to 15 minutes at a 60 degree tilt with the feet down.

The effect of reserpine on the level to which hexamethonium reduces the blood pressure was observed in five cases. In these hexamethonium was given intravenously in divided doses with the patient recumbent until two successive doses failed to lower the blood pressure further. The test was repeated after large doses of reserpine had been given. The results are given in table 2. It will be seen that in all cases the blood pressure could be reduced to a lower level by hexamethonium after the hypotensive effect of reserpine had become manifest. The falls of blood pressure produced by hexamethonium were smaller, an observation which suggests that part of the neurogenically maintained constriction had been abolished by the action of reserpine.

The blood pressure did not usually begin to fall for three to five hours after a dose of reserpine had been taken by mouth. When the drug was taken thrice daily, the lowest blood pressure was usually noted within 48 hours. The fall of blood pressure with these large doses was preceded by marked blushing of the face and marked conjunctival injection. Miosis and bradycardia were also noted. Some patients complained of diarrhea and in some there was marked shivering and tremor. A few complained of mental depression, nightmares and insomnia, although extreme drowsiness was more commonly noted. With smaller doses such as 0.25 to 1.5 mg. daily, the severe side effects described above do not often occur. With such doses the hypotensive action may not become maximal for about 14 days. Conspicuous falls of blood pressure occur in only about one-fourth of patients tested, particularly those with labile blood pressures.

(b) In Normotensive Subjects

The hypotensive effects of reserpine have been examined in 12 subjects with normal blood pressures. The results are presented in table 3. It is evident that the blood pressure falls are much smaller in normotensive subjects than
TABLE 3.—Effects of Large Doses of Reserpine in Normotensive Subjects

<table>
<thead>
<tr>
<th>No.</th>
<th>Daily dose reserpine (mg.)</th>
<th>Casual B.P. before reserpine</th>
<th>Casual B.P. after reserpine</th>
<th>Fall in B.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>128/80</td>
<td>90/52</td>
<td>38/28</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>140/90</td>
<td>130/80</td>
<td>10/10</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>145/90</td>
<td>108/68</td>
<td>37/22</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>145/90</td>
<td>120/75</td>
<td>22/15</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>125/80</td>
<td>112/70</td>
<td>13/10</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>135/80</td>
<td>90/60</td>
<td>45/20</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>140/70</td>
<td>124/66</td>
<td>16/6</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>145/90</td>
<td>140/80</td>
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<td>9</td>
<td>9</td>
<td>135/70</td>
<td>106/60</td>
<td>30/10</td>
</tr>
<tr>
<td>10</td>
<td>9</td>
<td>140/90</td>
<td>106/60</td>
<td>34/30</td>
</tr>
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<td>11</td>
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<tr>
<td>12</td>
<td>9</td>
<td>140/80</td>
<td>124/76</td>
<td>16/4</td>
</tr>
</tbody>
</table>

in hypertensive subjects if the average fall is considered. By contrast the associated symptoms did not differ to any appreciable degree in the normotensive group from those noted in the hypertensives; facial flushing, conjunctival injection, miosis, nasal congestion, shivering, diarrhea and sleepiness were noted by most patients.

EFFECTS OF RESERPINE ON NORMOTENSIVE ANIMALS

(a) Cutaneous Vasodilatation

In rabbits, as in man, reserpine produces cutaneous vasodilatation which can be seen in the vessels of the ear. This action was investigated in the following experiment.

Method

In 18 rabbits the cervical sympathetic trunk on the left side was removed, together with the superior cervical ganglion and as much of the stellate ganglion as could be reached by the anterior approach. After a week had elapsed the animals were placed in boxes over a tray of ice with their heads exposed, and the ears cooled moderately from behind by an electric fan. Both white and gray rabbits were used. Because of the size of the ears and their vessels, the former provided the more striking results. One mg. per kilogram of reserpine was administered intraperitoneally. The size of the central artery of each ear was measured before and after the injection. The measurement was made at corresponding points on the artery using an arbitrary scale inserted into the eye-piece of a low-power dissecting microscope. In control experiments in 13 rabbits similar measurements were made before and after the intraperitoneal injection of 100 mg. of sodium nitrite.

Results

Figure 1 shows the ear vessels of a white rabbit in which the cervical sympathetic chain on the left side had been avulsed one week before. In a the rabbit is seen before and in b one hour after 1.0 mg. of reserpine (rabbit weighed 1 Kg.).

Table 4 shows the results of the measurements. Maximal dilatation of the innervated ear was apparent with reserpine at about three-quarters of an hour to an hour. With nitrite the maximum effect was evident after about 10

<table>
<thead>
<tr>
<th>Reserpine (18 animals)</th>
<th>Artery dilates</th>
<th>No change</th>
<th>Artery contracts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innervated ear</td>
<td>15</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Denervated ear</td>
<td>0</td>
<td>11</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sodium nitrite (13 animals)</th>
<th>Artery dilates</th>
<th>No change</th>
<th>Artery contracts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innervated ear</td>
<td>7</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Denervated ear</td>
<td>6</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>
minutes. Serial measurements in a white rabbit are shown in figure 2.

It will be seen that after sodium nitrite there was no consistent tendency for one or other ear to be especially affected, as might be expected from an agent that acts directly on the vessels. By contrast, reserpine usually produced dilatation in the innervated ear, but either no change or even constriction in the denervated ear. These experiments suggest, therefore, that the cutaneous vasodilatation action of reserpine in conscious rabbits is mediated mainly by the nervous system.

(b) Effects on Blood Pressure

In Rabbits. The blood pressure was measured by the ear method in a number of conscious rabbits before and after reserpine. Although in some there was a fall in blood pressure at about the time of the maximal cutaneous

vasodilatation, there was no significant alteration in the majority. In the anesthetized animal, however, the intravenous administration of similar doses of reserpine produced an immediate effect on the blood pressure which was often transient but which sometimes persisted in some degree for a considerable period. This immediate effect was independent of the anesthetic used, although there was a larger fall from the high pressure usual with chloralose than occurred from the lower pressures recorded with barbiturate anesthesia. The upper record in figure 3 shows the fall in systemic blood pressure in a gray rabbit weighing 1.5 Kg., anesthetized with chloralose (100 mg. per kilogram) after intravenous injection of 1.5 mg. of reserpine in 0.6 ml. of solvent. The effect of a control injection of the solvent* is also shown. Figure 4 shows the effect of 2.5 mg. of reserpine in 2.5 ml. of a solvent consisting of a 1:1:2 mixture of ethyl alcohol, propylene glycol and water on intravenous injection into a 2 Kg. gray rabbit anesthetized with Nembutal-urethane (90 mg. Nembutal and 750 mg. urethane intraperitoneally). The effect of control injection of this solvent is also shown.

* Vehicle for Serpasil, supplied by Ciba Ltd., Basle; formula not disclosed.
In order to investigate the mechanism of action of this direct effect a series of limb perfusion experiments was carried out according to the method of Gallagher. With this technic the nerve supply to the hind limb is preserved but all vascular communications with the rest of the body are interrupted. A red cell—dextran medium is perfused through the limb via the femoral artery by a pump which delivers the medium at constant rate regardless of pressure. Variations of vasomotor tone are indicated by variations in perfusion pressure. In figure 3 the lower record is the perfusion pressure. Intravenous injection of 1.5 mg. reserpine, as seen previously, caused a marked fall in systemic blood pressure, and this was accompanied by a marked and prolonged rise in perfusion pressure, indicating an increase in nervous tone in the perfused limb.

The effect of injection of 0.125 mg. of reserpine into the perfusion cannula is shown in figure 5. There is an immediate fall in pressure of prolonged duration.

In Cats. The immediate fall in blood pressure which occurred with large doses in anesthetized rabbits occurred also on occasion in cats. However, in cats there was a prolonged hypotensive effect of delayed onset similar to the hypotensive action of reserpine in man. The delayed effect did not occur invariably and appeared to bear a relationship to the level of the initial blood pressure, being marked in animals with a high initial pressure and smaller in animals with lower initial pressures.

Evidence for the central nervous action of Rauwolfia alkaloids has been adduced by Dasgupta and co-workers in the greatly augmented response to a solution of total alkaloids when given intracisternally rather than intravenously. Reserpine is insoluble except in highly acid or irritating solvents and the intracisternal injection of small amounts of either of the above-mentioned solvents produced such manifestations as convulsions, sudden death or extreme rises or falls in blood pressure. Because of the effects of the solvents, those of reserpine could not be studied.

In six experiments using either cats or rabbits, reserpine was injected into the subclavian artery on one side so that all the injected material passed up the vertebral artery. A cannula was inserted into the subclavian artery distal to the origin of the vertebral artery so that injections could be made in a cephalic direction. During injections the subclavian artery was clamped proximal to the origin of the vertebral artery, the clamp being released after the injection had been given. When 0.25 mg. of reserpine was injected in this manner no significant hypotensive effect was produced in any of the six experiments. By contrast, injections of 0.1 mg. of ester alkaloid fraction of veratrum viride* given in the same way produced in some preparations immediate large falls of blood pressure.

(c) Modification of Reflex Cardiovascular Responses by Reserpine

As has been stated in the preceding paragraphs, the prolonged hypotensive effect of

* Anatensol, Squibb.
delayed onset, such as that which occurs with reserpine in hypertensive patients, is frequently not seen to any clearly marked degree in rabbits or cats. A series of further experiments was performed to assess the extent to which reserpine may modify various reflex cardiovascular responses. The effects of occlusion of the carotid arteries, stimulation of the afferent vagus, and the administration of adrenaline were studied in cats. The results are exemplified in figure 6. In this figure is shown the responses in a 3.5 Kg. cat anesthetized with chloralose. Blood pressure was recorded by a cannula in the left femoral artery. Both carotid arteries were isolated and a piece of braided silk looped behind each. Gentle traction on these pieces of silk permitted occlusion of the arteries. The vagus nerve on the right side was isolated and cut and the cephalic end placed over a pair of silver electrodes moistened with saline. Electrical stimuli were applied at a constant rate of eight shocks per second. Adrenaline was administered intravenously in doses of 1.0 μg. It will be seen that the initial marked pressor responses to bilateral carotid occlusion were still present two and eight minutes after 2.5 mg. reserpine intravenously, but were thereafter modified so that the rise in pressure was very much diminished in amplitude and was maintained for only a brief period, being succeeded by a fall. The fall in blood pressure followed a marked slowing of the pulse. Afferent vagal stimulation initially produced a markedly pressor response. At 34 minutes after reserpine the response to the same stimulus was depressor and remained so at 180 minutes. The initial response to adrenaline was biphasic, the initial pressor effect being followed by a marked fall in blood pressure presumably of reflex origin. After reserpine, the reflex depressor element disappeared so that adrenaline produced a purely pressor response.

In rabbits the effects of electrical stimulation of the cephalic end of the cut vagus and of injection of adrenaline before and after reserpine were studied in similar fashion. There is marked difference in species response between rabbits and cats. However, the capacity of reserpine
to modify the responses was again demonstrated. Blood pressure was recorded from one carotid artery, and the vagus nerve of the same side isolated and cut low in the neck. Electrical stimulation before reserpine produced a minimal effect with slight rise in blood pressure. After reserpine there was a marked rise. Extreme tachycardia accompanied the rise in blood pressure. These results are illustrated in figure 7 which shows the effect of stimulation of the cephalic end of the cut vagus before and after reserpine (1.5 mg. intravenously), in a 1.5 Kg. gray rabbit anesthetized with chloralose. The rabbits invariably responded to adrenaline by a rise of pressure, but following reserpine the rise was of considerably greater magnitude (fig. 7).

**Discussion**

One of the difficulties of assessing the site of action of reserpine in normotensive animals is that in these, as in normotensive man, the falls of blood pressure are often inconspicuous or absent. In both normotensive and hypertensive man, however, the facial flushing which precedes the fall of blood pressure occurs to a similar degree, and in rabbits a similar flushing of the ears occurs. Our results seem to indicate that the vasodilatation observed in the rabbit’s ear is mediated through the sympathetic nervous system since in the denervated ear the vasodilatation seen in the innervated ear did not occur. There is, therefore, strong evidence that part at least of the peripheral vasodilating action of reserpine is mediated through the sympathetic nervous system.

Prolonged hypotensive effects from reserpine, such as are seen in hypertensive man are, in experimental animals as in normotensive man, of small order and inconsistent. It is thus difficult to demonstrate that the hypotensive effect of reserpine is similarly mediated via the sympathetic nervous system. Reserpine was found, however, to produce a profound modification of certain reflex vasomotor responses. In cats the effect of occlusion of the carotid arteries was abolished or even reversed; the pressor response to electrical stimulation of the cephalic end of the cut vagus was converted to a depressor response and the reflex (depressor) sequel of adrenaline injection abolished so that the action of adrenaline became purely pressor.

In rabbits also the effect of electrical stimulation of the proximal end of the cut vagus was greatly modified as was also the effect of an injection of adrenaline, the latter it seems reasonable to suggest, by suppression of the reflex nervous mechanism tending to minimize the pressor effect.

Modification of reflex vasomotor responses of various kinds by Rauwolfia derivatives has been demonstrated by most workers, and it is considered by Trapold and associates that the hypotensive effect of reserpine is due to central inhibition of reflex pressor sympathetic activity. The present series of experiments gives further evidence of an inhibitory effect on reflex vasomotor activity.

It has thus been shown that reserpine acts through the sympathetic nervous system to produce cutaneous vasodilatation and also modification of vasomotor reflex responses. It seems reasonable to assume, therefore, that reserpine produces its hypotensive action in part through the mediation of the sympathetic
nervous system. There is, however, evidence that the hypotensive effect cannot be solely ascribed to this action. In the limb-perfusion experiments performed by us the fall of systemic pressure which occurred immediately after the intravenous injection of reserpine was accompanied by a marked rise of pressure in the perfused hind limb, indicating an increase in vasomotor tone. Were the fall of systemic blood pressure solely the result of inhibition of the sympathetic nervous system, it would have been expected that the perfusion pressure in the limb would also have fallen. The fact that the perfusion pressure rose suggests that compensatory nervous mechanisms had become active in response to a fall of blood pressure resulting from a nonnervous cause.\(^2\)

The production of vasodilatation by injection of reserpine directly into the perfused innervated hind limb demonstrates that reserpine has a direct action on the vessels in the rabbit.

In man, ganglionic blockade with hexamethonium produced a lower blood pressure after reserpine had been given than before. Unless there are autonomic nervous pathways unaffected by hexamethonium in man, this seems to suggest that the hypotensive effect of reserpine does not occur exclusively through the sympathetic nervous system. It seems that in man, as in rabbits and possibly cats, reserpine may have a peripheral vasodilating effect in addition to an effect mediated through the sympathetic nervous system.

**Summary**

The hypotensive effects of large doses of reserpine have been studied in 33 hypertensive patients and in 12 subjects with normal blood pressure. In the hypertensives, the fall of blood pressure varied from that to be expected with placebos to large falls, occasionally to normal levels. In normotensives blood pressure falls were much smaller. The fall of blood pressure is accompanied by cutaneous vasodilatation. Cutaneous vasodilatation is also seen in animals; its abolition by severance of the cervical sympathetic chain shows that this effect is mediated via the sympathetic nervous system. Modification of reflex vasomotor responses occurs in both rabbits and cats. However in anesthetized rabbits a direct vasodilator effect on blood vessels is shown and evidence is put forward that reserpine may have a direct peripheral vasodilating effect in man.

**Acknowledgment**

We are grateful to Ciba Ltd., Basle, for supplies of reserpine (Serpasil) and the vehicle in which Serpasil is supplied.

**Summario in Interlingua**

Le effectos hypotensive de grande doses de reserpina esseva studiate in 33 patientes hypertensive e in 12 subjectos con pression sanguinee normal. In le hypertensivos le reduction del pression sanguinee producute per le administratzion de reserpina variava inter le non-significative grados que poterea esser expectate ab le administratzion de remedios fictive e abassamentos marcate que attingeva in alcun casos nivei noti. In normotensivos le reduction del pression sanguinee es accompaniate de vasodilatation cutanee. Un tal es etiam observate in animales. Le facto que illo pote esser supprimite per le section del sympathetic catena cervical demonstra que iste effecto es mediate via le sympathetic systeme nervose. Modificationes del responsas vasomotor reflexe occurre tanto in conilios como etiam in cattos. Nonobstante, in conilios anesthesiate un directe effecto vasodilatatari super le vasos sanguinee es demonstrabile. Nos presentata datos que pare indicare che reserpina ha un directe effecto vasodilatatori peripheric in homines.

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