Mechanisms in the Return of Vascular Tone Following Sympathectomy in Man


The greatly increased blood flow that follows surgical interruption of the sympathetic fibers supplying a limb rapidly subsides to the preoperative resting level over a period of approximately two weeks. The mechanism of this return of tone remains obscure, although several theories have been advanced to explain the phenomenon. Barcroft and Swan discuss in detail the current hypotheses which include the development of "intrinsic tone" and increased sensitivity to circulating catecholamines or some other hormone. In addition, following sympathectomy there may remain residual pathways which could contribute to return of tone. Regeneration of sympathetic fibers may account for the recurrence of signs and symptoms some months after operation but is unlikely to be the cause of the return of tone which is complete within two to three weeks.

The presence of a peripheral store of constrictor substance, which may influence vascular tone, has been suggested by the finding of "chromaffin cells" in human skin and by the observation that the local constrictor action of nicotine on the hand vessels is reduced by sympatholytics and ganglion-blocking agents. In addition, a local dilator action of reserpine has been described in the skin of man, and the findings indicate that this is due to the release of a tonic influence quite apart from the postganglionic fiber. This reserpine dilatation cannot be accounted for by an adrenergic blocking action and, since it is absent in the generally reserpinized individual, it is thought to be a consequence of interference with a local store of constrictor substance which normally exerts a tonic influence on the vessels. The observations are compatible with the hypothesis that the noradrenergic fiber and a peripheral store of norepinephrine with cholinergic innervation exist side by side.

Since the reserpine dilatation is unchanged in the chronically sympathectomized limb, the possibility has arisen that the local store of constrictor substance, upon which it is postulated reserpine acts, contributes to the return of tone following sympathectomy. This suggestion has been examined, and older theories have been re-evaluated by repeated observations of the responses of the hand blood vessels of a patient to various drugs before and at intervals after upper limb sympathectomy. Ephedrine was used to follow changes in the postganglionic fibers, reserpine for its probable effect on a peripheral store of constrictor substance, and norepinephrine to detect changes in sensitivity of the denervated vessels to circulating catecholamines.

Methods

The investigation was carried out on a female patient, aged 30 years, who had suffered from Raynaud's phenomenon of mild degree for the past two years. No secondary changes were present in skin, but operation was advised for symptomatic relief of pain and numbness. After the preoperative studies had been made, she was submitted to bilateral sympathectomy, the lower two-thirds of the stellate ganglion and the first, second, and third thoracic ganglia being removed from both sides. The studies were resumed 36 hours postoperatively and repeated at intervals during the succeeding three months.

The responses of the vessels of both hands were determined after infusion into the brachial artery of acetylcholine chloride (Roche), ephedrine hydro-
chloride (Eliots), and reserpine (Serpasil, Ciba), and of the right hand after the intravenous infusion of norepinephrine bitartrate (Levophed, Winthrop) into an antecubital vein of the opposite arm. As a preliminary test, in each experiment in which intra-arterial infusions were to be given, acetylcholine (30 µg./min. for two minutes) was injected and the dilator response used as a check that drugs given by this route were in fact reaching the hand vessels.

The patient was kept comfortably warm in an environmental temperature of 22 to 24°C and was at rest on a couch for half an hour prior to the commencement of each experiment. Hand blood flow was measured by venous occlusion plethysmography using water-filled, temperature-controlled plethysmographs at 32 to 33°C. A 23-gauge short-bevel needle was inserted into the brachial artery or an antecubital vein at the elbow and connected by polyethylene tubing to a constant infusion device. Arterial puncture was in approximately the same site on each occasion. In control periods saline was infused at a rate of 4 ml./min., and this was replaced as required by a solution of drug made up in normal saline, so that the dose per minute was contained in 4 ml. Ascorbic acid (1:50,000) was added to the stock solution of norepinephrine, and this was used within 15 minutes of preparation.

Results

The plan of the experiments and sequence of drug infusions are shown in figure 1, where the responses of one hand to the various drugs are illustrated before and on two occasions after sympathectomy. Comparable distribution of injected drugs in the hand on the different occasions is demonstrated by the similarity of the responses to acetylcholine.

Hand Blood Flow

The resting hand blood flow measured on three separate days before operation averaged 10.5, 8.9, and 11.9 ml./100 ml./min., respectively. The preoperative blood flow showed the usual variation, flows fluctuating from 3 to 20 ml./100 ml./min. Figure 2 (upper frame) illustrates the time course of the postoperative return of blood flow, which had reached a steady level 11 days after sympathectomy.

Prior to operation, the patient suffered continuously from cold hands and blueness of the finger tips, with white fingers a common occurrence. Following operation the hands were warm for one week; at three weeks slight blueness had returned, and at six weeks transient white spots appeared on the fingers. No further deterioration occurred during the period of observation.

External stimuli, such as a sudden loud noise or the application of ice to the forehead and neck, which before operation constricted the hand vessels, had no effect after operation. However, there were small simultaneous bi-
Figure 2
(Upper frame) Hand blood flow (ml./100 ml./min.) before and at intervals following operation. The vertical line at (S) denotes sympathectomy. (Middle frame) Change in hand blood flow (ml./100 ml./min.) from the resting level produced by intra-arterial ephedrine (100 and 500 \( \mu \)g./min. for one minute). The left and right hands were infused in successive experiments. At 36 hours the dose was raised from 100 to 500 \( \mu \)g. The larger dose was used thereafter. (Lower frame) Change in hand blood flow (ml./100 ml./min.) from the resting level produced by intra-arterial reserpine (50 \( \mu \)g./min. for 10 minutes). The left and right hands were infused in successive experiments.

lateral fluctuations in blood flow (fig. 3) at all times following operation, but these were unaffected by external stimuli. In calculating the effects of ephedrine or reserpine on hand blood flow, correction was made for these spontaneous fluctuations in flow by reference to the simultaneous measurements on the opposite control side.

Ephedrine Response
In normal subjects, injection of ephedrine into the brachial artery in a dose of 50 \( \mu \)g./min. for one minute causes a 50 per cent fall in hand blood flow lasting 5 to 10 minutes, and doses of 500 \( \mu \)g./min. cause a much greater reduction, recovery taking at least one hour. This response is absent in the chronically sympathectomized limb, in which doses as high as 1 mg./min. have no effect on the blood flow. In animal studies, the pressor effect of ephedrine has been shown to be due to release of norepinephrine from sympathetic nerve endings. In the present investigation, the response of the hand vessels to ephedrine was used as an index of the norepinephrine content of the postganglionic fibers and, hence, as a means of following the rate of postganglionic degeneration after sympathectomy.

The constrictor effect of local intra-arterial infusion of ephedrine hydrochloride (50, 100, or 500 \( \mu \)g./min. for one minute) on the blood vessels of both hands was determined before and at intervals following operation. Before operation, 50 and 100 \( \mu \)g. of ephedrine for one minute produced a constriction of normal degree, lasting approximately 5 and 20 minutes, respectively. After operation, infusions were given alternately in the left and right side in successive experiments to reduce the frequency of puncture of each brachial artery.

Thirty-six hours after operation, the response to 100 \( \mu \)g. of ephedrine had almost disappeared, but on increasing the dose to 500 \( \mu \)g. for one minute, a constriction similar in
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degree and duration to that produced by 100 µg. before operation was obtained (fig. 1). The response to 500 µg. of ephedrine gradually diminished over the subsequent six weeks, after which time it had disappeared completely (fig. 1). Figure 2 (middle frame) illustrates the combined data from both hands.

Reserpine Response

In the normal limb, injection of reserpine into the brachial artery causes a marked vasodilatation of the hand vessels which commences after a latent period of 10 to 30 minutes after the end of the infusion, reaches a maximum of two to three times the resting level of flow in about one hour, and gradually declines over the succeeding 24 hours.13 In the patient under investigation, the dilator response of the hand vessels of both sides to intra-arterial reserpine (500 µg. in 10 minutes) followed the above pattern prior to sympathectomy but, at 36 hours after operation, had disappeared (fig. 1). Subsequently the dilator response was slowly re-established and had almost regained preoperative levels after three months. Both hands responded in an identical manner, these combined data are illustrated in figure 2 (lower frame). The absence of a response at 36 hours cannot be a consequence of the elevated blood flow diluting the infused solution, because a normal dilatation has been demonstrated in subjects during complete release of sympathetic tone by indirect heating, with blood flows as high as 40 ml./100 ml./min.13 Furthermore, the reserpine dilatation at 72 hours is still greatly reduced, and yet resting blood flow is similar to the preoperative levels (fig. 2, upper frame).

Norepinephrine Sensitivity

The response of the blood vessels of the right hand to intravenous infusions of norepinephrine bitartrate (5, 2.5, 1.25, and 0.625 µg./min. for five minutes) into a left ante-cubital vein was determined. Sensitivity was calculated by comparing the average blood flow for the three minutes prior to infusion of norepinephrine with the average blood flow in the last three minutes of the infusion period. In addition, the time was calculated for the blood flow to return to the preinfusion resting level on cessation of the infusion. Blood flow was not measured on the left hand since the norepinephrine infusion into the vein of that side might have influenced the measurements by interfering with venous drainage.

Figure 4 shows the responses of the vessels of the hand to intravenous epinephrine (5 µg./min. for five minutes, black rectangle) on hand blood flow before and at three and 12 weeks following sympathectomy.
Table 1
Sensitivity to Norepinephrine Before and After Sympathectomy

<table>
<thead>
<tr>
<th>Dose</th>
<th>Degree (ml./100 ml./min.)</th>
<th>Duration (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.625</td>
<td>Before: 1.5, 2.9, 3.3</td>
<td>0.625: 0.5, 1.0, 1.5</td>
</tr>
<tr>
<td></td>
<td>3 weeks: 0.8, 2.9, 3.5</td>
<td></td>
</tr>
<tr>
<td>1.25</td>
<td>2.9, 3.2</td>
<td>1.25: 2.0, 2.0, 3.0</td>
</tr>
<tr>
<td>2.5</td>
<td>3.1, 3.8</td>
<td>2.5: 2.0, 2.0, 3.0</td>
</tr>
<tr>
<td>5.0</td>
<td>3.5, 4.3</td>
<td>5.0: 2.0, 2.0, 3.0</td>
</tr>
</tbody>
</table>

*The degree and duration of the fall in right hand blood flow following intravenous infusions of norepinephrine in various doses. Doses in µg./min. Degree in ml./100 ml./min. below resting level. Duration in minutes from the end of the infusion until return to resting level.

Concentrations of norepinephrine are given in Table 1. The degree of constriction following operation was greater than the preoperative constrictor response, and the duration of the constriction was markedly prolonged. This increase in sensitivity was seen at all dose levels and was more marked at seven weeks postoperatively than at three weeks. The responses at 12 weeks were of similar duration to those at seven weeks and had not changed when recently examined at seven months after operation.

Observations on Other Patients

It has so far not been possible to carry out the whole range of investigations described above on other patients because of the rarity of the operation in an upper limb with normal vessels and the difficulty of securing the degree of cooperation necessary from the patient. However, the responses in the later stages after sympathectomy in this patient have been confirmed in two patients examined in the chronic stage after sympathectomy and in two patients suffering from idiopathic autonomic degeneration. In these patients, the constrictor response of the hand vessels to intra-arterial ephedrine in large doses was absent, and the response to intra-arterial reserpine followed the normal pattern. It was not possible to assess the change in sensitivity to norepinephrine in the absence of preoperative observations.

The immediate inhibitory effect of sympathectomy on the response to reserpine has been confirmed in one patient suffering from hyperhidrosis who was examined once preoperatively and 65 hours after operation. Before operation, reserpine (500 µg in 10 minutes) injected into the brachial artery increased the hand blood flow from 8 to 32 ml./100 ml./min. in one hour. After operation, the same dose caused a slight rise from 14 to 18 ml./100 ml./min. after two hours. The above observations served to substantiate the findings of the more complete investigation.

Discussion

This study illustrates the results in only one patient, but it is considered that conclusions can reasonably be drawn because serial observations were made, the changes were marked and consistent, both hands behaved in an identical manner, and the responses prior to operation were the same as those of normal subjects reported elsewhere. Furthermore, studies on a number of patients in the chronically sympathectomized phase only and on one other patient in whom serial observations were incomplete served to confirm the findings obtained in the patient studied more fully.

The patient was diagnosed as suffering from Raynaud's phenomenon, but it seemed probable that the hand blood vessels had suffered little organic change, since before operation they responded to drugs and to sympathetic activity by dilatation and constriction in a manner that was in no way different from normal. Furthermore, there were no secondary skin changes due to vascular insufficiency, and once the patient was comfortably warm, blood flow in the hands was normal.

Postganglionic Degeneration and the Response to Ephedrine

Burn and Rand and Stromblad have shown that the action of ephedrine and related sympathomimetic amines is diminished when...
norepinephrine is depleted from the particular tissue, either by denervation or reserpination. Parks et al.\(^\text{16}\) have reported the absence of any constrictor response of the hand vessels to at least 10 to 20 times the normal threshold dose of ephedrine and the amphetamines in patients with chronic sympathetic denervation of the upper limbs, either as a result of surgery or of idiopathic degeneration of the autonomic nerves. This suggests that these drugs have no direct action of their own and depend entirely on the presence of norepinephrine in the postganglionic mechanism for their effect. The fact that the constriction to small doses (50 to 100 \(\mu g./\text{min.}\)) of ephedrine was abolished immediately after operation and large doses (500 \(\mu g./\text{min.}\)) had to be given to elicit a response indicated an immediate reduction in the postganglionic content of norepinephrine. The gradual diminution of the response to the high dose is presumably a reflection of the progressive degeneration of postganglionic fibers, resulting in diminishing norepinephrine content. The absence of any constrictor response, even to high doses, six weeks following operation and thereafter demonstrated that there was complete interruption of all vasoconstrictor pathways and that residual constrictor fibers could not have played any part in the return of vascular tone.

Investigators who have reported residual pathways after sympathectomy in man\(^\text{3-5}\) have used sweating tests, which are indicative of cholinergic nerve activity only. The vascular response to ephedrine was used in the present investigation specifically to follow the activities of noradrenergic constrictor fibers, which alone could be involved in the return of tone to blood vessels.

Since large doses of ephedrine still produced a constriction of the hand vessels 17 days after operation, it can be concluded that the postganglionic fibers had not completely degenerated at this time. Histological evidence of the duration of survival of nerve terminals following removal of the ganglion at such a distance from the peripheral vessels is not available in man, but the fact that Wallerian degeneration pursues a centrifugal course\(^\text{20, 21}\) and that axon fragments have been seen as long as 26 days after section of the digital nerves in man\(^\text{22}\) support the suggestion that it takes three weeks or more after this type of operation for the nerve terminals to lose their property of holding norepinephrine.

The intra-arterial route of administration of ephedrine and reserpine was chosen, because it ensured a high local concentration of the drug in the hand and, at the same time, avoided the complication of possible central or reflex effects. This is particularly important in the case of reserpine, where central release of vasoconstrictor tone would obscure the local, direct, dilator action of the drug. This route also permitted the use of the opposite hand as a control. Uniform distribution of the drugs so injected was checked by the prior injection of acetylcholine, which caused a flush of the skin and increased hand blood flow to a comparable degree in successive experiments.

Small differences in response on different occasions to a drug given in this way might occur as a result of small differences in distribution in the vascular bed under study or of different concentrations of the drug arriving at the vessels if the blood flow varied between experiments. This was not of great consequence in the case of ephedrine and reserpine, where the changes in response after sympathectomy were very great, being permanent total abolition and temporary abolition, respectively.

In studying the changes in sensitivity of the hand vessels to norepinephrine, however, the intravenous route was used to ensure a comparable concentration of the drug arriving at the vessels, irrespective of blood flow on different occasions, and made the interpretations of changes from different initial levels of flow less difficult.

**Hypersensitivity to Norepinephrine**

An increase in sensitivity of the hand vessels to norepinephrine after operation was seen at all dose levels, increasing to a maximum at seven weeks, after which it remained constant. The increase in degree of constriction,
although definite, was less marked than the duration of the constriction after the infusion ceased. This was considerably prolonged, being as much as nine times the preoperative value for the larger doses. Hypersensitivity manifested by increased duration of response has been described in man and is frequently seen in animal experiments.

The observation that hypersensitivity to norepinephrine was less marked at three weeks than at seven weeks suggests that the phenomenon is related to the degeneration of the postganglionic fibers, since it was between these times that the response to ephedrine disappeared, indicating complete nerve degeneration. This finding of postganglionic degeneration and maximum hypersensitivity occurring at similar time is in agreement with the suggestion of Burn and Rand that hypersensitivity is associated with depletion of norepinephrine from the postganglionic mechanism.

Lecompte showed that hypersensitivity in the rabbit ear artery was fully established seven days after sympathetic denervation, while Freeman et al. found hypersensitivity of the hands at eight days and Duff at four days after sympathectomy in man. The present evidence carries these observations further and demonstrates that the hypersensitivity, as indicated by the duration of the constrictor response, only reaches a maximum after a longer time. This time agrees more closely with the course of hypersensitivity described by White et al. who state that maximum sensitivity in man is only attained at the end of the second week.

Barrer and Swan have drawn attention to the similarity between the time of onset of hypersensitivity, as described by Lecompte in the rabbit, and the return of blood flow following sympathectomy in man and discuss the possibility that increased sensitivity to circulating catecholamine is responsible for the return of vascular tone. The plasma level of total catecholamines in man is approximately 0.5 ng/ml with an increase in the upright position. This low concentration is, nevertheless, of the order that will constrict even normally innervated vessels. Thus, in this patient, an infusion of 0.625 µg./min. for five minutes preoperatively caused a clear constriction of hand blood vessels. In a plasma volume of 3 L., this would produce, at the most, a concentration of 1 ng./ml. arriving in the arterial supply to the arm, assuming no destruction en route. The circulating level of catecholamines is, therefore, theoretically large enough to contribute to the return of tone. However, the present findings suggest that the two phenomena are unrelated, since blood flow remained relatively fixed after 11 days, whereas sensitivity continued to increase until sometime between three and seven weeks.

Reserpine Response

The dilator effect of reserpine on the blood vessels of the hand, when it is infused into the brachial artery in doses which are insufficient to have any general systemic effects and which do not produce effects on the opposite limb, demonstrates that this drug has a local action on peripheral vessels which is independent of any central depression of vasomotor activity. The dilatation is fully developed within an hour and persists for at least 24 hours. It appears to be due to depletion of peripheral stores of vasoconstrictor substance in skin since it is absent in generally reserpinized subjects. During the dilatation, there is no interference with sympathetic nerve activity nor with the action of ephedrine and other drugs which depend on the release of norepinephrine from the nerve endings for their action. This lack of dependence of the dilator effect of reserpine on the integrity of the sympathetic nerves is further shown by the presence of the response in the hands of chronically sympathectomized subjects and in patients with autonomic degeneration. The present finding of an absent reserpine response soon after sympathectomy suggests that the peripheral store of constrictor substance is normally under nervous control, and following denervation, it is temporarily depleted but is replenished slowly over a period of more than three months, even in the absence of regeneration of vasoconstrictor fibers.
Goodall\textsuperscript{33} and Euler and Purkhold\textsuperscript{34} have demonstrated the gradual return of catecholamine content of heart, spleen, kidney, liver, and salivary gland over two to four months after sympathectomy. Although they attribute the return to reinervation, there is no direct evidence of this return, and the findings are also compatible with the restoration of the amine content in an independent store.

The extent to which these suggested changes in catecholamine content of the peripheral store play a part in the return of tone is not clear. Certainly, the reserpine response is returning during the period of increasing tone, and it is possible that the combined effect of a rising local accumulation of catecholamine, plus heightened sensitivity both to this store and to circulating amines, may together play a part in the lowering of blood flow from the immediate, high postoperative level. However, the fact that the increases in sensitivity and the restoration of the response to reserpine continue for several weeks after the flow has reached a steady level suggests that additional factors must be involved in this earlier return of tone.

Slight variations in blood flow are present after operation (fig. 3). These cannot be accounted for by residual sympathetic pathways, since they were unaffected by external stimuli and since the disappearance of a constrictor response to ephedrine demonstrated complete postganglionic degeneration. Attention has not been drawn to these small fluctuations previously, although they are apparent in the data given by Duff\textsuperscript{29,35}

The recurrence of ischemic spots on the fingers six weeks after operation coincided with the height of increased sensitivity, together with the probable reaccumulation of constrictor substance, as evidenced by the return of the response to reserpine. While it has been demonstrated that the recurrence of ischemic areas is usually associated with functional reinervation,\textsuperscript{7,23} the absent ephedrine response in the present experiments excludes the possibility of either residual or regenerating pathways mediating these intermittent ischemic episodes and suggests that a peripher-
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Veronica J. Parks, Sandford L. Skinner and Robert F. Whelan

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