Papers and Originals

An Objective Study of Lumbar Sympathectomy I. Intermittent Claudication

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Brit. med. J., 1966, **1**, 879-883

The value of lumbar sympathectomy for intermittent claudication is disputed. Although many clinicians doubt that the operation ever results in relief, others have the impression that occasional cases gain considerable benefit. The incidence of improvement reported in clinical studies varies enormously, from approximately 13% (Gillespie, 1960) to 75% (Smithwick, 1957).

There are several reasons for being sceptical of the efficacy of the operation. First, the natural history of intermittent claudication is that spontaneous improvement occurs with the development of collateral vessels in 35-60% of patients (Singer and Rob, 1960; Bloor, 1961). Thus Taylor and Calo (1962) found that relief followed sympathectomy in 41% of patients, but that it also occurred in 39% of untreated cases. Secondly, clinical improvement is solely determined by the patients' subjective assessment of pain, which is unreliable. Even the use of a treadmill demands subjective determination of the end-point (Mackenzie and Loewenthal, 1962). The operation itself may produce a "placebo effect" or cause a beneficial reduction in the speed of walking. Thirdly, consideration of the sympathetic innervation of the muscle circulation lends little support to the rationale of denervation. The nervous control of the muscle vessels is much less pronounced than for the skin circulation. At rest muscle vasomotor tone is mainly determined by inherent myogenic tone in the arteriolar wall (Folkow, 1962), and under normal conditions the effect of the sympathetic vasoconstrictor innervation is minimal; stimulation of sympathetic vasodilator fibres may greatly increase muscle flow (Blair *et al.*, 1959), but these appear to be active only under situations of marked stress, and it is disputed whether this increased flow is through capillaries or through arteriovenous shunts (Uvnäs, 1960; Folkow *et al.*, 1961). At the onset of exercise there is a generalized reflex stimulation of muscle vasoconstrictor fibres (Blair *et al.*, 1961), but this is rapidly overwhelmed by the accumulation of local metabolites causing vasodilatation (Barcroft, 1963); the nature of these metabolites is unknown, but probably many factors are involved (Hilton, 1962), of which accumulation of potassium may be of particular importance (Kjellmer, 1965).

The pain resulting from the contraction of ischaemic muscle is due to accumulation of metabolites above a threshold level at which local sensory nerves are excited (Lewis *et al.*, 1931). The nature of the metabolites causing pain is also unknown, though lactic acid may be responsible (Elliot and Evans, 1936). It cannot be inferred that the metabolites causing pain and those producing hyperaemia are the same or are dealt with at similar rates.

In the presence of an arterial occlusion the hyperaemic response to exercise is both diminished and delayed, favouring accumulation of the "pain substance," and Fig. 1 diagrammatically represents this situation. An increased rate or level of development of the hyperaemic response would reduce the rate of accumulation of metabolites and increase the walking-distance at which claudication develops. There are at least four possible ways in which this might occur.

First, increase in the resting flow, resulting in a higher flow rate at the start of exercise, together with abolition of the initial reflex vasoconstriction of muscle vessels resulting from exercise, could result in an initial decrease of the rate of accumulation of metabolites, as is depicted in Fig. 2. The resting flow through muscle is usually determined by the arteriolar tone. In patients with arterial disease compensatory mechanisms are such that the resting flow is identical to that in normal subjects (Hillestad, 1963; Myers, 1964), though this is associated with a considerable reduction in sympathetic control (Lewis and Mellander, 1962). Sympathetic denervation of the normal muscle circulation causes an initial increase in flow (Barcroft and Edholm, 1946), but there remains a high degree of tone, and intra-arterial acetylcholine, exercise, or reactive hyperaemia further increases flow by five to seven times (Folkow, 1960). The increase of muscle flow after sympathectomy is short-lived, falling to about double basal levels within an hour (Barcroft and Edholm, 1946), and the final levels achieved are disputed, though Barcroft (1952) indicated a return to basal levels within one week.

Secondly, augmentation of the peak flow during the hyperaemic response would similarly increase the claudication distance. In the presence of an arterial block the peak flow during hyperaemia is usually determined by the adequacy of the collateral vessels. It has been suggested that sympathectomy might exert its effect through a reduction of collateral resistance. Exercise alone reduces collateral resistance by about 40%, compared with the maximum fall of 50-70% produced by acetylcholine infusion (Thulesius, 1963), probably due to a slow wave of relaxation mediated directly through the vessel wall (Hilton, 1959). Whether sympathectomy can further permanently reduce collateral tone is disputed. In the rabbit collateral development immediately following arterial ligation is initially increased after sympathectomy by about 60%, but this effect disappears within three months (Longland, 1953). In the cat sympathectomy initially reduces the collateral resistance following acute occlusion by about 30%, an effect which is also seen, but to a less extent, with a chronic occlusion (Thulesius, 1963). After acute occlusion of the common femoral artery in the normal human the collateral resistance during exercise can be reduced by indirect heating or ganglionic blockade by an average of about 50% and up to 75% (Shepherd, 1950b). Dornhorst and Sharpey-Schafer (1951) found that in seven patients with arterial blocks in the leg the collateral resistance was initially reduced after sympathectomy by an average of 30% and in one patient by 70%, but this effect was transient, disappearing within two weeks. Beaconsfield (1954) found a rise after sympathectomy in the peak flows during reactive hyperaemia in patients with a block in the

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superficial femoral or distal arteries, but not at other levels, and considered that this effect was most marked in the early stages of disease. In contradistinction, Eichna and Wilkins (1941), Shepherd (1950c), Barcroft (1952), and Bentley (1958) were unable to demonstrate a significant change in the peak flows with exercise or reactive hyperaemia. These findings are difficult to reconcile.

Thirdly, it is known that in the presence of an arterial occlusion development of the hyperaemic response is delayed (Myers, 1964), and reduction of this delay after sympathectomy would also reduce the accumulation of metabolites (Fig. 3). The reason for the delay in development of the peak flow is not clear. Shepherd (1950a) thought that it may result from a preferential shunting of the initial inflow to the proximal areas because of the lower resistance

and higher perfusion pressure of this segment; in this case the delay would be prolonged by either a high collateral or a high distal peripheral resistance. The effect of sympathectomy on the hyperaemia pattern is again disputed. Whereas Shepherd (1950c) could show no change in the pattern after sympathectomy, Beaconsfield (1954) thought that there was a significant reduction in the time for development of the peak and subsequent return to resting values.

Finally, the degree of impairment of arterial inflow during the phase of muscle contraction is dependent on the inflow pressure (Barcroft and Dornhorst, 1949; Walder, 1961), and following sympathectomy an increase in the pressure distal to the block might relieve claudication. Gilfillan (1958) thought that the distal pressure was frequently increased after sympathectomy.

This report is of a group of patients with intermittent claudication in whom blood flows have been measured before and after sympathectomy by a technique of strain-gauge plethysmography. Measurements were made of the resting flows, of the peak flows and the time of development of the peak during reactive hyperaemia, of the arterial pressure, and of the peripheral resistance during hyperaemia in the calf muscle. The findings have been analysed in relation to possible mechanisms of benefit, to the site and duration of disease, and to the symptomatic relief obtained.

Material

A total of 31 patients suffering from intermittent claudication were studied before and after lumbar sympathectomy. The operation was bilateral in nine patients, so that a total of 40 legs are considered. The numbers are relatively small owing to the preference in this unit for treatment by direct arterial surgery; such treatment was not chosen in this group, either because of a poor "run-off" distal to the popliteal artery or because of general disease. In 20 limbs the operation was performed for intermittent claudication alone; in the remaining 20 operations intermittent claudication was associated with rest pain.

Arteriography was performed in all patients. An occlusion involved both the aorto-iliac vessels and superficial femoral artery in nine legs, the superficial femoral artery alone in 27 legs, and the tibial vessels only in four legs.

Methods of Assessment

1. Clinical Assessment

Each patient was examined before and six to eight weeks after operation, without prior knowledge of the results of plethysmography. The patient's subjective opinion of his response to sympathectomy and the distance that he could walk on the flat were recorded.

2. Sweating Test

The adequacy of the sympathectomy was confirmed in each case by a sweating test. The policy of the operation was to attempt to remove the chain to above the level of the second lumbar ganglion, and in all patients sweating was subsequently abolished at least to the level of the knee. Removal of the sympathetic chain was confirmed by histological examination.

3. Plethysmography

Blood-flow studies were performed before and 10 to 14 days after sympathectomy by a technique of strain-gauge plethysmography.

FIG. 1.—Hypothetical illustration of hyperaemic response and accumulation of metabolites during and after exercise in normal subject (left) and patient with arterial occlusion (right). In the latter the hyperaemic response is reduced and delayed, allowing accumulation of metabolites above the "pain threshold." FIG. 2.—Illustration of possible effect of increased resting flow on hyperaemic response during exercise in patient with arterial occlusion, allowing reduced accumulation of metabolites and increased walking-distance. FIG. 3.—Illustration of possible effect of increased rate of development of hyperaemic response during exercise in patient with arterial occlusion, allowing reduced accumulation of metabolites and increased walking-distance.

The strain-gauge plethysmograph was modified from that described by Whitney (1953). The gauge consisted of a length of highly extendible silicone rubber tubing applied around the calf at a known tension; the tubing was filled with mercury, which formed one arm of a balanced Wheatstone bridge; the bridge was A.C.-powered and chopper-amplified. Change in the circumference of the leg following venous occlusion by a cuff at the knee produced an equal change in the length of the mercury column and a proportional change in its resistance, so giving a current across the bridge, which was recorded. The slope of the tracing, the calibration of the gauge, and the circumference of the calf allowed calculation of the blood flow in ml./100 ml. of tissue/minute (Whitney, 1953). It was considered that the flow measured by the calf gauge at the environmental temperature used in the study of 22–24° C. is mainly through muscle (Abramson and Ferris, 1940; Clarke *et al.*, 1958a). Applications of the technique have been described previously (Myers, 1964).

The following measurements were made:

1. Resting flow in the calf under basal conditions with the patient comfortably warm and the leg exposed in a room temperature of 22–24° C.

2. Reactive hyperaemia flow in the calf following a five-minute period of arterial occlusion by a cuff at the knee. Flows were measured at 10-second intervals after release of the tourniquet, and the peak flow and the time at which it occurred were determined. The peak flows following exercise and following ischaemia of longer than two minutes are similar (Dornhorst, 1963) and close to maximal (Patterson and Whelan, 1955; Thulesius, 1963), and the mechanism of production of both is probably identical (Dornhorst, 1963). The reactive hyperaemia test thus provides a good index of flows to be expected during exercise and is considerably more simple to perform.

3. Blood-pressure at the level of the knee; gradual deflation of a cuff at the knee from above arterial pressure allowed determination of the systolic arterial and venous pressures and their difference, which is the perfusion pressure; the plethysmograph gauge detected the point of onset of swelling of the leg when the cuff pressure fell to the arterial level and subsequent deflation when the pressure reached the venous level. The pulse pressure below an arterial occlusion is small and the systolic arterial pressure closely corresponds to the mean arterial pressure. Pressures recorded in this manner correspond closely with direct intra-arterial recordings (Mason and Braunwald, 1962).

4. Peripheral resistance in the calf; the ratio of the perfusion pressure (mm. Hg) to the peak flow (ml./100 ml./min.) indicated the "minimum peripheral resistance" of the segment from the popliteal artery to the calf arteriolar bed, the ratio being expressed as arbitrary peripheral resistance units (P.R.U.). A fall in pressure at the time of peak flow during reactive hyperaemia could produce a high result.

Results

1. Symptomatic Response

Thirteen patients claimed that the claudication distance was increased to more than double the distance before operation; these are referred to as the "improved" group. Of these patients seven suffered from intermittent claudication alone and six from intermittent claudication and rest pain. The remaining 18 patients showed little convincing change or even claimed to be worse; these are referred to as the "unchanged" group. Of these patients five complained of intermittent claudication only and 13 of claudication and rest pain. In general the measured walking-distance corresponded closely

with the patient's assessment, and it was considered that difficulties in control of the rate of walking, length of stride, favouring of the leg, etc., rendered the patient's assessment no less reliable an index of response. There was a poor correlation between the walking-distance and the muscle flows. The clinical assessment was related to the flow studies, considering the predominantly affected leg in those patients who had a bilateral sympathectomy.

2. Blood-flow Studies

Findings in Whole Group.—The means and standard errors of the results of the blood-flow studies are represented in Table I. There was no statistically significant change of the resting flow, of the peak flow during reactive hyperaemia, of the time of the peak flow, or of the arterial pressure following sympathectomy. Fig. 4 shows the range of the percentage change in these values after sympathectomy for the individual studies; in particular, in only six of the 40 limbs has there been more than a 25% increase of the peak flow, and the greatest increase was by 48%. Fig. 5 shows composite graphs of the hyperaemic patterns before and after operation, and again there has been no increase in the rate of development or disappearance of the response.

Findings According to Clinical Response.—The corresponding values in the predominantly affected legs of the patients claiming clinical improvement and of those who were clinically

TABLE I.—Results of Flow Studies in Relation to Symptoms and Clinical Outcome (Mean $\pm$ S.E.)

		Resting Flow	Peak Flow	Time of Peak (sec.)	Calf Pressure (mm. Hg)	Peripheral Resistance (units)
		ml./100 ml./min.	ml./100 ml./min.			
Total group (40 legs)	Pre-Post-	1.5 $\pm$ 0.1 1.6 $\pm$ 0.1	5.8 $\pm$ 0.7 5.2 $\pm$ 0.6	40 $\pm$ 5 40 $\pm$ 5	95 $\pm$ 5 90 $\pm$ 5	15.5 $\pm$ 1.5 16 $\pm$ 1.5
Clinical outcome:	Improved (13 legs)	1.6 $\pm$ 0.1	7.2 $\pm$ 1.5	40 $\pm$ 10	95 $\pm$ 10	11.5 $\pm$ 1
		1.8 $\pm$ 0.2	6.5 $\pm$ 1.2	40 $\pm$ 10	100 $\pm$ 10	13 $\pm$ 1
	Unchanged (18 legs)	1.3 $\pm$ 0.1	4.0 $\pm$ 0.5	50 $\pm$ 10	80 $\pm$ 10	19 $\pm$ 3
		1.3 $\pm$ 0.2	3.3 $\pm$ 0.3	55 $\pm$ 5	70 $\pm$ 10	19.5 $\pm$ 3.5
Nature of symptoms:	Claudication only (20 legs)	1.5 $\pm$ 0.1	7.0 $\pm$ 0.8	30 $\pm$ 5	105 $\pm$ 5	12.5 $\pm$ 1
		1.7 $\pm$ 0.1	6.3 $\pm$ 0.8	30 $\pm$ 5	100 $\pm$ 5	14 $\pm$ 1.5
	Claudication and rest pain (20 legs)	1.5 $\pm$ 0.2	4.8 $\pm$ 1.0	50 $\pm$ 10	85 $\pm$ 5	18 $\pm$ 2.5
		1.5 $\pm$ 0.2	4.1 $\pm$ 0.7	55 $\pm$ 5	80 $\pm$ 5	17.5 $\pm$ 2.5

Pre = Pre-sympathectomy. Post = Post-sympathectomy.

FIG. 4.—Nomograms showing changes of resting flows, peak flows, and distal arterial pressure after sympathectomy for whole group, for group claiming clinical improvement, and for group in which there has been no clinical improvement.

not improved are also shown in Table I and Fig. 4. Again there was no statistically significant change after sympathectomy of any of the parameters considered, in either the improved or unchanged groups. An increase of the peak flow of greater than 25% occurred in only three of the improved group and in three of the unchanged group. In the improved group the mean resting flow before sympathectomy was 1.6 ml./100 ml./min. and the mean peak flow was 7.2 ml./100 ml./min., while the peripheral resistance was 13 units; in the unchanged group the corresponding values were a resting flow of 1.3 ml./100 ml./min., a peak flow of 4.0 ml./100 ml./min., and a peripheral resistance of 19.5 units, suggesting the presence of more severe distal disease in the latter group.

FIG. 5.—Composite graph of pattern of hyperaemia before and after sympathectomy. For each test the flows, measured at 10-second intervals after release of the arterial tourniquet, were expressed as a percentage of the peak flow. A mean was then taken of the results at each 10-second interval.

Findings According to Nature of Symptoms (Table I).—The means of the peak flows and pressures were lower and the delay in the peak flows longer in the group with intermittent claudication and rest pain than in the group with claudication alone, though the mean resting flows were identical, suggesting more severe involvement of collaterals in the former group. However, there was no apparent difference in the changes after sympathectomy of these measurements in the two groups. The mean of the peak flows was considerably lower in the group with a short history, perhaps suggesting inadequate time for complete development of collateral vessels. However, the fall in the peak flows appeared to be independent of the length of the history, being from 2.8 ± 0.7 to 2.3 ± 0.5 ml./100 ml./min. in five patients with a history of less than three months, 6.9 ± 1.5 to 5.9 ± 1.3 ml./100 ml./min. in 12 patients with symptoms of 3 to 12 months' duration, and 5.0 ± 0.8 to 4.4 ± 0.6 ml./100 ml./min. in 14 patients in whom symptoms had been present for longer than 12 months.

Findings in Relation to Arteriography (Table II).—There was no evidence of a significant improvement after sympathectomy of any of the measurements after analysis of the group according to the predominant site of disease. Nor did the

arteriographic grading of the "run-off" distal to the popliteal artery seem to affect the results. However, the peripheral resistance showed a poor correlation with the arteriographic grading, and it appeared that the radiological assessment of the run-off was so difficult that it was quite unreliable.

Discussion

No convincing evidence could be demonstrated in this study of a haemodynamic basis for relief of intermittent claudication by sympathectomy. At 10 to 14 days after the operation the resting flows were unchanged, the peak flows during hyperaemia were usually slightly reduced, the pattern of development of the hyperaemic response was not altered, and the arterial pressure distal to the occlusion was also unaffected. Moreover, this lack of change of any of these parameters occurred independent of whether the patient claimed to be improved or not, and was not influenced by the duration or severity of the symptoms, or the arteriographic localization of disease, or assessment of the peripheral run-off. The results suggested that clinical improvement was more likely to occur in those with less severe disease of both collateral and distal vessels, but beyond this no prediction could be made of the likely outcome of sympathectomy for intermittent claudication in individual patients.

It is thus necessary to consider other possible mechanisms of benefit. Improvement of blood flows after sympathectomy might become apparent under different conditions of testing. First, sympathectomy might significantly modify the effect on muscle flow of local cooling; direct cooling of the muscle down to 25° C. results in a marked rise in resting peripheral resistance (Yonce *et al.*, 1962) and a fall of resting flow (Burton and Edholm, 1955); cooling causes a fall in post-exercise and reactive hyperaemia flows (Clarke *et al.*, 1958b; Coles and Cooper, 1959); and both direct and indirect heating results in a rise in reactive hyperaemia flows (Patterson and Whelan, 1955). Many patients claim that claudication is worse in cold weather. The effect of sympathectomy on the response at low temperatures is uncertain, though Tice *et al.* (1963) could show no difference in the change of resting flows. Secondly, it is possible that the effect of posture is of importance; standing results in reflex constriction of muscle vessels due to stimulation of intrathoracic pressure receptors (Brigden *et al.*, 1950; Roddie and Shepherd, 1956), and this is abolished by sympathectomy allowing a possible increase in resting flows.

A possible alternative mechanism for relief of muscle pain after sympathectomy is by division of afferent pathways. This mechanism might be suggested by the fact that occasional patients in this study claimed that although the claudication distance was unchanged the severity of the pain was diminished. Whether primary or internuncial fibres pass from the dorsal root ganglia to the sympathetic trunk is not certain. Kuntz (1951) demonstrated large numbers of myelinated fibres in the grey rami and considered these to be afferent; Hirsch (1925) claimed to have shown afferent cells in sympathetic ganglia and ascending and descending sensory fibres in the trunk, though Woollard (1926) noted that peripheral afferent fibres do not degenerate after sympathectomy. Freeman *et al.* (1950) claimed that the vasomotor effect of intravascular irritant agents in the experimental animal was abolished by sympathectomy; but other authors, including Van Harreveld and Lindsley (1952), have denied this. Harris (1936), Echlin (1949), and Kuntz (1951) claimed that sympathetic stimulation under local anaesthesia in the human caused pain in the leg, although Simeone (1950) and White (1954) denied this.

The rationale for the use of sympathectomy for intermittent claudication is thus obscure. Subjective improvement might result from spontaneous development of collateral pathways or simply from the fact that an operation has been performed. Nevertheless, occasional cases are seen in which there has been immediate, striking improvement which must be ascribed to

TABLE II.—Results of Flow Studies in Relation to Site Disease (Mean $\pm$ S.E.)

Site of Disease		Resting Flow	Peak Flow	Time of Peak (sec.)	Calf Pressure (mm. Hg)	Peripheral Resistance (units)
		ml./100ml./min.				
Aorto-iliac and femoro-popliteal occlusion (9 legs)	Pre-	1.2 ± 0.1	4.7 ± 0.9	55 ± 10	65 ± 5	18 ± 3.5
	Post-	1.6 ± 0.3	3.8 ± 0.6	60 ± 10	75 ± 5	20.5 ± 5
Femoro-popliteal occlusion (27 legs)	Pre-	1.5 ± 0.1	4.8 ± 0.4	45 ± 5	90 ± 10	16 ± 1.5
	Post-	1.6 ± 0.1	4.4 ± 0.4	40 ± 5	85 ± 5	15 ± 3.5
Diffuse disease (4 legs)	Pre-	1.8 ± 0.5	15.2 ± 3.1	0	150 ± 10	9.5 ± 3
	Post-	1.5 ± 0.2	13.7 ± 2.6	0	145 ± 15	10 ± 3

Pre- = Pre-sympathectomy. Post- = Post-sympathectomy.

the operation. It is believed that these cases are few in number and that the explanation for the response has yet to be provided.

Summary

The value of lumbar sympathectomy for intermittent claudication is disputed. Improvement would imply persistent release of collateral or vasomotor tone. It is doubtful whether afferent fibres are carried in the sympathetic trunk in sufficient number to be of significance. Thirty-one patients having 40 lumbar sympathectomies for intermittent claudication were studied before and 10 to 14 days after operation by strain-gauge plethysmography. Measurements were made of the resting flow, of the peak flow and time of its development during reactive hyperaemia, and of the distal arterial pressure in the calf muscle. No statistically significant increase could be demonstrated after sympathectomy in any of these parameters in the group as a whole. Nor could significant change be shown according to the clinical response to the operation, to the severity or duration of the symptoms, or to the site of the occlusion or extent of the disease. The flows both before and after sympathectomy were higher in the group showing clinical improvement, suggesting that spontaneous remission is more likely to occur when the disease is less severe. It is considered that there is no objective evidence of consistent haemodynamic benefit from lumbar sympathectomy for intermittent claudication.

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(Part II (Skin Ischaemia) will be printed next week.)

Vascular Responses in Diabetic Peripheral Neuropathy*

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Brit. med. J., 1966, **1**, 883–888

Degenerative lesions of the peripheral nerves in the extremities of diabetic patients were first described in 1887 by Pryce, who later noted that “these patients are occasionally liable to vasomotor and trophic signs” (Pryce, 1893). The vasomotor signs which he observed were not objectively measured until nearly 50 years later (Shumacker, 1942). Soon thereafter the high frequency of vasomotor disturbances in patients with diabetic neuropathy began to be emphasized by a number of authors (Rundles, 1945; Berner, 1952; Handelsman *et al.*, 1952; Martin, 1953; Odel *et al.*, 1955).

Studies of the nature and pathogenesis of the disturbance of peripheral vascular responsiveness in diabetic neuropathy have been controversial and confusing. The abnormalities have been attributed by some (Mendlowitz *et al.*, 1953; Megibow *et al.*, 1953) purely to impedance of blood-flow by occlusive vascular disease. Though there is now more general agreement that they can be due entirely to disordered vasomotor control resulting from damage to peripheral autonomic nerve fibres

(Rundles, 1945; Doupe and Cherniack, 1950; Martin, 1953; Odel *et al.*, 1955; Bárány, 1955; Keen, 1959), there has been no agreement about the nervous mechanisms involved. Doupe and Cherniack (1950), noting that peripheral nerve injuries greatly increase the sensitivity of blood-vessels to adrenaline (Meltzer and Meltzer, 1903; Freeman *et al.*, 1934) and to cold (Ascroft, 1937; Doupe, 1943; Richards, 1946), suggested that the persistent coldness of the feet often seen in neuropathic subjects might be due to denervation hypersensitivity. This suggestion was supported by later authors (Bárány, 1955; Bárány and Cooper, 1957; Stone *et al.*, 1961), but has recently

* Presented in part at the Fifth Congress of the International Diabetes Federation, Toronto, Ontario, Canada, July 1964. Supported by grants from the Medical Research Council of Canada.

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