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EFFECT OF SYMPATHECTOMY ON THE RESPONSE TO ADRENALINE OF THE BLOOD VESSELS OF THE SKIN IN MAN

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The phenomenon of increased sensitivity of blood vessels to adrenaline and to other effective stimuli following interruption of the sympathetic nerve supply has been described in relation to the digits in man (Freeman, Smithwick & White, 1934) and monkey (Ascroft, 1937). It has been thought to occur only in completely sympathectomized vessels (Smithwick, Freeman & White, 1934), and to appear only after the interval required for degeneration of the interrupted nerves (Freeman *et al.* 1934).

Both Freeman *et al.* (1934) and Ascroft (1937) considered that removal of the related sympathetic ganglia produced a much greater increase in sensitivity than simple interruption of the preganglionic neurone, and such observations as this led Cannon, Rosenblueth & Garcia Ramos (1945) to formulate a general law of denervation, to the effect that 'the supersensitivity is greater for the links which immediately follow the cut neurone and decreases progressively for more distal elements'.

Inasmuch as the evidence concerning supersensitivity following sympathectomy in man is derived largely from measurements of temperature changes in the skin, it was thought desirable to make a quantitative study of the response of the blood flow in the hand to intra-arterial infusions of adrenaline, before and at varying intervals after surgical sympathectomy of the upper limb.

METHODS

The main investigation concerned three women and two men suffering from Raynaud's disease and one young woman with hyperhidrosis of the hands. Their ages ranged from 18 to 63 yr, and in only one instance had the Raynaud's disease caused evident impairment of the nutrition of the skin of the fingers.

The subject reclined on a couch, in a laboratory thermostatically maintained at a temperature of $22 \pm 1°$ C. A neatly fitting rubber glove sealed to a stout rubber diaphragm with an aperture to admit the wrist was fitted on to each hand. Thus gloved, the hand was placed inside a metal plethysmograph and the diaphragm maintained in position by screws so that the hand was supported comfortably inside the plethysmograph, which was then elevated a little above the level of the chest. The plethysmographs were now filled with water, and throughout the investigation the temperature of the water was kept within the range 32–34° C. The blood flow in both hands of each subject was measured simultaneously every half-minute throughout the test, and calculated in ml./100 ml. tissue/min.

Under local anaesthesia, consisting of an intracutaneous injection of $\frac{1}{4}$–$\frac{1}{2}$ ml. 2 % procaine solution, a needle, to the base of which 3 ft. of narrow-bore polythene connecting tube had been attached, was inserted into the brachial artery of the limb being tested (Duff & Swan, 1951), and a continuous infusion of saline started.

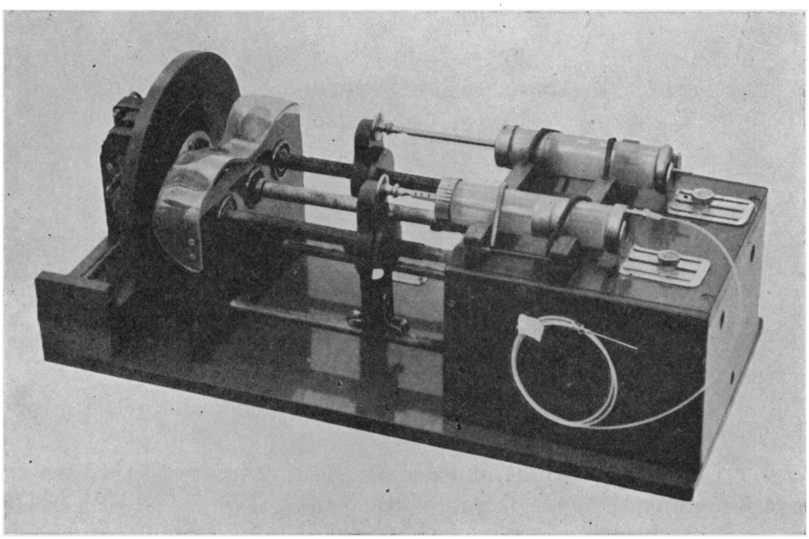

Fig. 1. The infusion apparatus, with needle and polythene connecting tube attached.

The infusion apparatus (Fig. 1) comprised an electric induction motor of which the transmission was geared down to drive the plungers of one or both 50 ml. syringes so that each delivered 4 ml. saline/min at a steady rate. By transferring the polythene tube from one to the other, the syringes could be alternately replenished, and continuity of flow maintained. After a control period of at least 8 min the required amount of synthetic L-adrenaline tartrate, B.P. (British Drug Houses Ltd.), was added to the saline and infused for 4 min, after which the saline infusion was resumed. At intervals of 12 min further test concentrations of adrenaline were infused in exactly the same way, each solution being freshly prepared less that 2 min prior to administration.

The blood flow in both hands of a given individual fluctuates synchronously, often within wide limits, as a result of sympathetic nervous activity in the normally innervated subject, and under the influence of variations in respiration, blood pressure and other factors in both normal and sympathectomized subjects. Changes in hand blood flow are usually approximately equal on both sides (Cooper, Cross, Greenfield, Hamilton & Scarborough, 1949). Changes in hand blood flow in the non-infused (control) limb were measured at every test, so that spontaneous fluctuations might not be ascribed, in the tested hand, to the adrenaline. To arrive at an estimate of the net effect of the adrenaline, the following procedure was adopted:

The average (A) of the six blood-flow measurements in the test hand during the 3 min period immediately prior to the arrival therein of the adrenaline was multiplied by the average (b) of the six measurements of the control hand blood flow during the first 3 min that the adrenaline was passing through the test hand; this product was divided by the average (a) of the six measurements of blood flow in the control hand corresponding in time with the pre-adrenaline average (A) for the test hand. The value obtained was an estimate (E) of what the blood flow in the test hand would have been during the experimental period *if the adrenaline had not been administered*. The difference between the actual average blood flow (B) in the test hand during the first 3 min of the adrenaline period and the estimated average (E) was taken to be the net effect of the adrenaline itself. Thus, if the average blood flow in the test hand fell from (A) 12 ml. before, to (B) 8 ml. during the adrenaline infusion, while the average blood flow in the control hand changed during the same time from (a) 10 ml. to (b) 9 ml., then, if the adrenaline had had no effect on the test hand, the expected blood flow (E) in the test hand during the adrenaline period would be given by the expression

$$A/E = a/b \quad \text{or} \quad E = Ab/a = 10{\cdot}8 \text{ ml.}$$

But since the actual average blood flow (B) in the test hand during the adrenaline infusion measured 8 ml., the reduction in flow below the estimated value ($E - B$) is attributable to the adrenaline, i.e. $10{\cdot}8 - 8{\cdot}0 = 2{\cdot}8$ ml./100 ml./min.

In every case the change in blood flow in each tested hand was measured in relation to an ascending series of concentrations of adrenaline, within the range $\frac{1}{64}$–$\frac{1}{8}$ μg/min, both before and on one or more occasions after sympathectomy. The majority of post-operative tests were performed within 3 months of operation, and none was done earlier than 6 days after operation. After operation, the patients were subjected to a vigorous heat test in which the mouth temperature was raised by at least 1° F by placing the feet in a water-bath at 45° C for 40–60 min. That the sympathetic pathway had been completely interrupted was established in each case by the failure of the hands to exhibit any significant increase in blood flow in these circumstances.

In order to determine the normal response under identical experimental conditions, the behaviour of the hands of a group of healthy subjects (mostly medical students) aged between 21 and 37 yr was studied, in relation to infusions of adrenaline at concentrations of $\frac{1}{32}$, $\frac{1}{16}$, $\frac{1}{8}$, $\frac{1}{4}$ and $\frac{1}{2}$ μg/min.

RESULTS

Behaviour of individual hands before and after sympathectomy. The method of comparing individual hands in their blood-flow response to the same range of concentrations of adrenaline was considered the most convenient approach to the problem. In Fig. 2 the blood flow in the hands of a woman with Raynaud's disease is shown. Before operation the intra-arterial infusion of $\frac{1}{32}$ μg adrenaline/min was coincident with vasoconstriction in both the tested left hand (heavy continuous line) and also the control right hand (faint interrupted line). Had the observations relating to the latter been omitted, this vasoconstriction might erroneously have been attributed to the adrenaline. The synchronous fluctuation in blood flow present throughout the test is seen to be of about equal degree in both hands, irrespective of whether adrenaline or saline is being infused; adrenaline has therefore had no independent effect in any of the three test infusions.

Tested in the same way 22 days after preganglionic section an entirely different response is seen (Fig. 2). All three dose levels of adrenaline were attended by marked vasoconstriction in the tested left hand, the right hand being unaffected.

A similar change is demonstrated in Fig. 3, the blood-flow response in the tested left hand of a man with Raynaud's disease. Before operation, a moderate amount of fluctuation occurred in the blood flow of both tested and control hands. None of the adrenaline infusions was associated with independent vasoconstriction of any notable degree in the tested hand. On retesting 22 days after preganglionic section, the same dose levels of adrenaline caused obvious vasoconstriction in the tested hand.

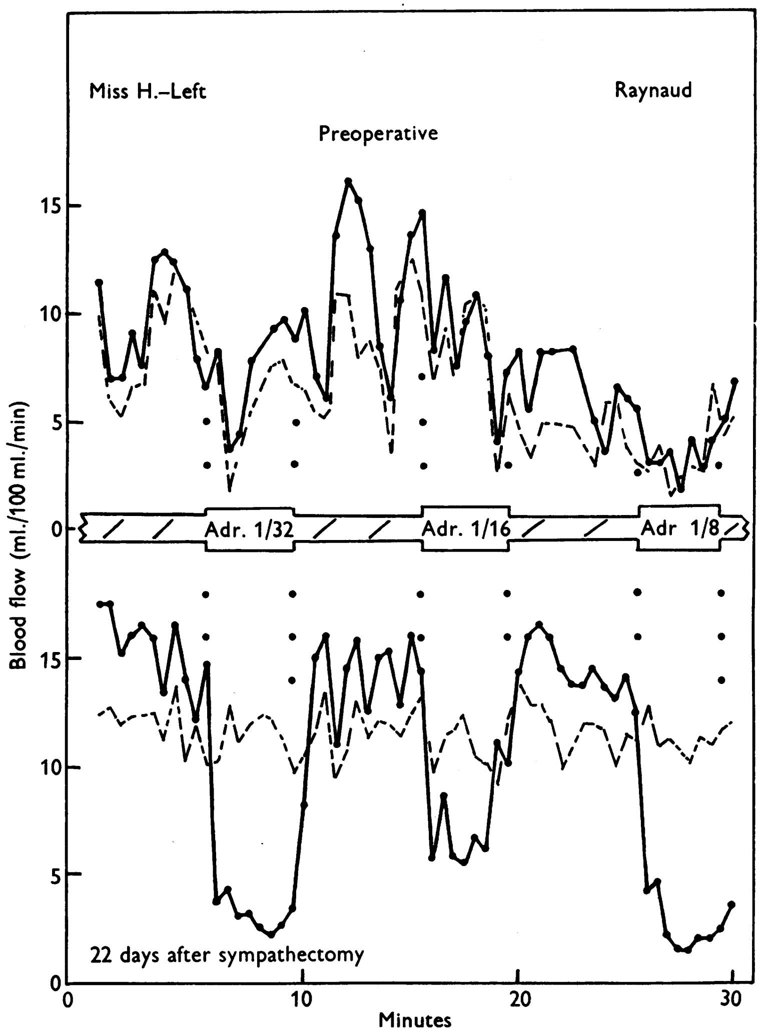

Fig. 2. Blood flow in tested left hand (heavy continuous line) and control right hand (faint interrupted line) of a patient with Raynaud's disease, during the course of infusions into the left brachial artery. The different responses to adrenaline before (upper half) and 22 days after sympathectomy (lower half) are shown.

Ten hands were tested with infusions of adrenaline within the range $\frac{1}{64}$–$\frac{1}{8}$ μg/min and six were found, after sympathectomy, to be obviously constricted with concentrations of adrenaline that had had little or no effect before operation. All but one of these hands were sympathectomized by preganglionic section. In two of the remaining four hands in which no gross change in response to adrenaline was demonstrated, sympathectomy had been produced by removal of the cervico-dorsal ganglia.

The postoperative tests (Table 1) relate especially to the early weeks after operation, and the earliest was 6 days. In one case, however, of a young man

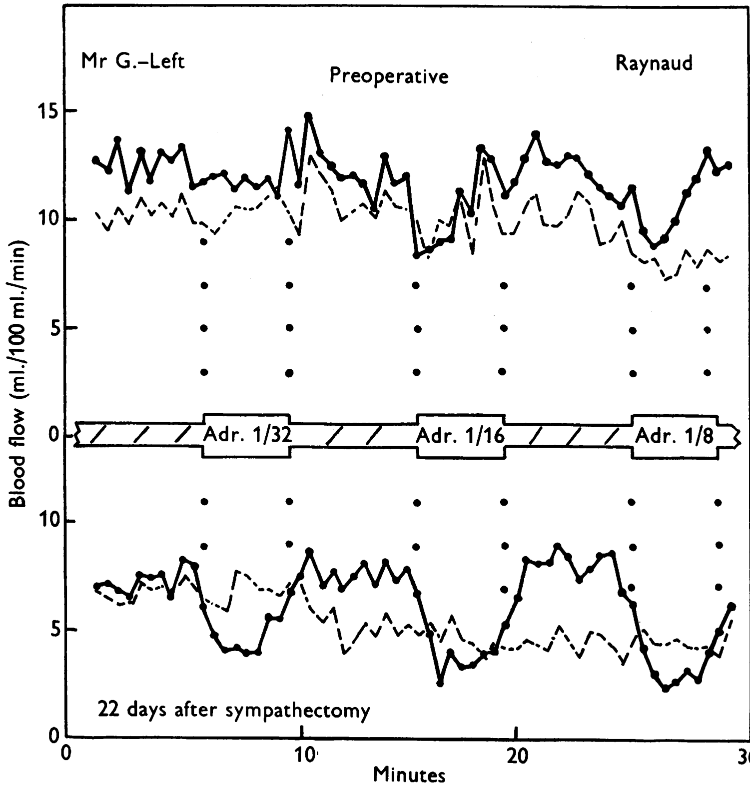

Fig. 3. Blood flow in tested left hand (heavy line) and control right hand (faint line) of a patient before (upper half) and after sympathectomy (lower half). On both occasions $\frac{1}{32}$, $\frac{1}{16}$ and $\frac{1}{8}$ μg adrenaline/min were infused into the left brachial artery. At the time of the postoperative test the level of flow in the hands was actually lower than in the preoperative test.

(Mr C.) who had sustained traumatic avulsion of the brachial plexus on the left side as a result of which the limb was completely sympathectomized, the test performed 1 year after his accident exhibited a definite vasoconstriction with $\frac{1}{64}$ μg adrenaline/min. In this sole instance the response of the sympathectomized hand has been compared with that of the healthy right hand, instead of the same hand before sympathectomy, as was the case in all other individuals. Normally innervated hands do not vasoconstrict with such a small concentration of adrenaline.

ABLE Comparison of adrenaline effect in thirty-three paired tests, pre- and postoperative. Difference in group means is highly significant ($t = 3{\cdot}25$, $P < 0{\cdot}001$)

				Before sympathectomy								After sympathectomy							
				Mean blood flow									Mean blood flow						
				Test hand		Control hand							Test hand		Control hand				
Subject	Hand	Condition	Age	A	B	a	b	E	$B-E$	$\frac{B-E}{E}\times 100$	Operation	Postop. test at	A	B	a	b	E	$B-E$	$\frac{B-E}{E}\times 100$
										Adrenaline $\frac{1}{64}$ µg/min									
Mr E.	R.	RD	63	4·5	4·9	6·9	8·2	5·3	−0·4	−07	P	7 days	6·5	6·3	6·4	6·5	6·6	−0·3	−05
	L.			3·4	4·9	6·1	8·2	4·5	0·4	09	P	8 weeks	6·7	5·4	6·2	5·8	6·3	−0·9	−14
Mr G.	R.	RD	50	9·1	9·5	4·8	5·1	9·7	−0·2	−02	P	10 days	5·9	4·1	5·9	6·1	6·1	−2·0	−33
	L.			9·4	9·6	11·0	9·5	8·1	1·5	19	P	22 days	5·9	5·5	6·8	6·7	5·8	−0·3	−05
Mrs C.	L.	RD	51	4·0	4·2	12·1	15·7	5·2	−1·0	−19	P	5 months	8·3	6·9	4·3	4·2	8·1	−1·2	−15
Mr C.		Acc.	25	13·8	13·1	2·9	3·4	16·2	−3·1	−19	Acc.	12 months	6·3	3·9	9·8	8·6	5·5	−1·6	−29
										Adrenaline $\frac{1}{32}$ µg/min									
Mr E.	R.			4·3	4·4	7·7	8·4	4·7	−0·3	−06	P	7 days	6·7	5·7	7·2	8·3	7·7	−2·0	−26
	L.			4·6	5·2	8·6	10·1	5·4	−0·2	−04	P	8 weeks	7·0	4·6	7·0	7·2	7·2	−2·6	−36
Mr G.	R.			10·7	11·4	4·8	5·4	12·0	−0·6	−05	P	10 days	9·4	5·8	6·4	6·3	9·3	−3·5	−38
	R.			9·7	9·8	6·3	6·7	10·3	−0·5	−05	P	10 days	8·1	5·5	6·5	6·2	7·7	−2·2	−29
	L.			12·4	11·9	10·3	10·4	12·5	−0·6	−05	P	22 days	7·6	4·5	4·8	4·8	7·6	−3·1	−41
	L.			10·7	10·3	8·2	8·3	10·8	−0·5	−05	P	22 days	7·3	4·5	7·0	6·8	7·1	−2·6	−37
Miss H.	R.	RD	25	5·0	5·1	10·0	9·6	4·8	0·3	06	P	14 days	10·3	10·0	10·1	10·1	10·3	−0·3	−03
	L.			10·5	6·4	10·7	5·7	5·6	0·8	14	P	22 days	14·7	4·0	11·8	11·5	14·4	−10·4	−72
Mrs W.	R.	RD	52	9·0	10·9	10·0	14·4	13·0	−2·1	−16	G	11 days	8·7	8·2	10·7	11·1	9·0	−0·8	−09
	R.			12·8	12·2	10·6	10·0	13·4	−1·2	−09	G	11 days	10·6	9·4	11·6	11·1	10·1	−0·7	−07
										Adrenaline $\frac{1}{16}$ µg/min									
Mr E.	R.			4·8	4·1	18·2	20·0	5·3	−1·2	−23	P	7 days	7·5	4·3	9·0	8·4	7·0	−2·7	−39
	R.			3·6	3·1	19·5	18·6	3·4	−0·3	−09	P	7 days	7·8	6·6	8·3	7·9	7·4	−1·8	−24
	L.			6·4	5·5	10·2	10·2	6·4	−0·9	−14	P	8 weeks	8·1	3·1	6·9	7·0	8·2	−5·1	−62
Mr G.	R.			10·6	9·1	5·8	5·7	10·4	−1·3	−13	P	10 days	9·0	3·3	6·7	6·2	8·3	−5·0	−60
	L.			11·3	10·5	10·7	10·2	10·7	−0·2	−02	P	22 days	7·6	3·6	5·2	4·8	7·0	−3·4	−49
Miss H.	R.			4·2	3·0	9·0	7·7	3·6	−0·6	−17	P	14 days	10·5	7·3	10·5	10·2	10·2	−2·9	−28
	L.			11·0	9·3	9·1	8·8	10·6	−1·3	−12	P	22 days	14·4	6·4	12·1	11·1	13·2	−6·8	−47
Mrs W.	R.			11·1	9·5	14·1	12·7	10·0	−0·5	−05	G	11 days	9·2	8·1	12·5	11·6	8·5	−0·4	−05
Miss B.	R.	H	19	4·6	4·3	5·9	6·3	4·9	−0·6	−12	G	14 days	6·7	5·8	9·4	9·4	6·7	−0·9	−13
										Adrenaline $\frac{1}{8}$ µg/min									
Mr E.	R.			2·8	3·6	14·7	15·1	2·9	0·7	24	P	7 days	6·6	2·5	6·8	6·7	6·5	−4·0	−62
	L.			7·8	4·0	12·1	11·5	7·4	−3·4	−46	P	8 weeks	9·2	1·8	7·0	6·9	9·1	−7·3	−80
Mr G.	R.			9·3	4·9	6·7	6·4	8·8	−3·9	−44	P	10 days	9·9	2·8	7·0	6·3	8·9	−6·1	−72
	L.			11·3	10·2	8·8	8·3	10·6	−0·4	−04	P	22 days	7·6	3·2	4·4	4·5	7·8	−4·6	−59
Miss H.	R.			3·7	5·5	6·4	8·7	5·0	0·5	10	P	4 months	8·1	5·9	9·9	9·4	7·6	−1·7	−22
	L.			5·3	3·0	4·3	2·7	3·3	−0·3	−09	P	22 days	13·7	2·7	11·4	11·2	13·5	−10·8	−80
Mrs W.	R.			13·0	7·4	16·9	13·7	10·5	−3·1	−30	G	14 days	7·8	4·9	11·1	11·2	7·9	−3·0	−39
Miss B.	R.			5·3	3·2	6·4	5·4	4·5	−1·3	−29	G	14 days	6·2	4·8	10·1	11·0	6·8	−2·0	−29
Mean				7·9						−09			8·5						−35

A, a = means of the six observations of blood flow during 3 min prior to start of adrenaline, in test and control hands, respectively; B, b = corresponding means during first 3 min of adrenaline period; $E = Ab/a$. P = preganglionic section; G = ganglionectomy. RD = Raynaud's disease; H = hyperhidrosis. Acc. = patient sympathectomized as a result of traumatic avulsion of the brachial plexus.

The contrast in the behaviour of a group of hands before and after operation, in response to any given level of adrenaline, may be portrayed by averaging the blood-flow measurements for each half-minute before and during the adrenaline infusions. Fig. 4 demonstrates the change in respect of $\frac{1}{8}$ μg/min. However, although graphs of hand blood flow, as in Figs. 2–4, clearly reveal the different response in the hands after sympathectomy, they do not permit precise evaluation of that difference.

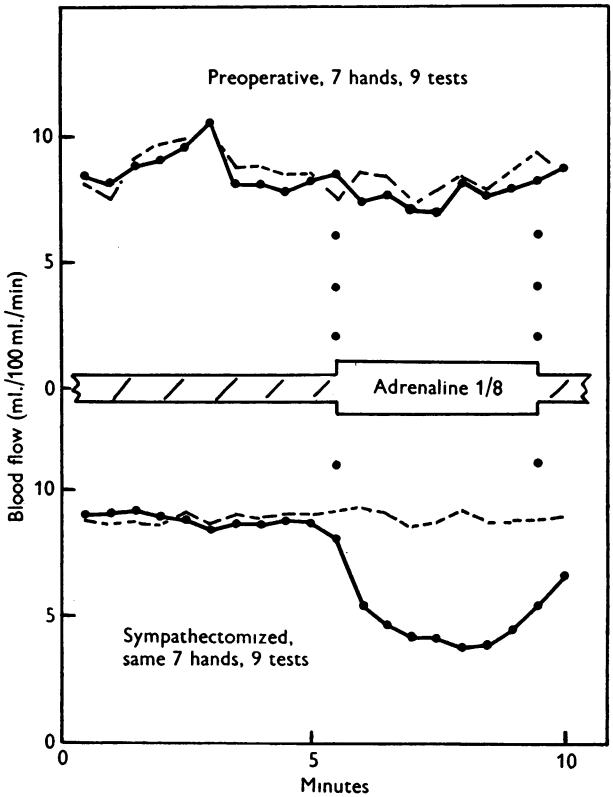

Fig. 4. Average blood flow in tested hands (heavy continuous line) and control hands (faint interrupted line) of a group of subjects in relation to infusions of $\frac{1}{8}$ μg adrenaline/min, before (above) and after (below) sympathectomy.

Comparison of the group of ten hands before and after sympathectomy. Recourse to statistical analysis was found desirable in view of inequalities in the amount of constriction in individual hands produced by the same concentrations of adrenaline. To obtain a quantitative estimate of the amount of vasoconstriction in an individual test, the procedure described in Methods was adopted. The net change in flow, $B-E$, was expressed as a percentage, $(B-E)\times 100/E$, and taken to represent the percentage change in flow. If the synchronous fluctuation in hand blood flow in a given subject were entirely equal on both sides, this value would be the exact percentage change in flow as between the two contiguous periods *A* and *B*. However, the correlation between the two hands is seldom perfect, especially in normally innervated hands; hence it was first necessary to determine the limits of accuracy of this method of analysis.

In nine subjects the blood flow in both hands was measured every half-minute during a 6 min period in order to determine the mean blood flow in each hand during both halves of this period. Taking account of three of the mean values so obtained, the fourth can be calculated. Comparison of this value with the corresponding mean derived from actual measurement of the blood flow during this period reveals the accuracy of the prediction. If the amount of fluctuation in a pair of hands were equal, the predicted and the actual blood-flow means would be equal, and the amounts of such departures from equality as occur are a basis for calculating the reliability of the method. In thirty-six comparisons of actual and estimated blood-flow means, the percentage departures from the expected value of nil were found to have a standard deviation of 12 %, with a standard error of 2 %. Four of the subjects providing the data were bilaterally sympathectomized, one was sympathectomized on one side only, the remainder being normally innervated. The standard deviation of 12 % was therefore taken to be a valid expression of the standard deviation of percentage changes in blood flow with which to determine the significance of changes in blood flow in the adrenaline tests of individual hands before and after sympathectomy. Thus changes in blood flow during an adrenaline infusion of less than 25 % were not regarded as significant. It was also convenient to regard the level of adrenaline concentration at which 25 % reduction in blood flow occurred as the threshold of the tested hand to adrenaline.

In a precise comparison of thirty-three tests on ten hands before and after sympathectomy, exactly paired in respect of the test concentration of adrenaline (Table 1), only 4 preoperative tests (all at infusion rates of $\frac{1}{8}\,\mu$g/min) resulted in significant vasoconstriction, whereas after operation twenty-two out of the thirty-three tests revealed significant reduction in blood flow due to lowering of the adrenaline threshold in six hands. The mean change in the whole group before sympathectomy was 9 % vasoconstriction; after sympathectomy 35 % vasoconstriction, a fourfold increase in response. The difference between the means is highly significant ($t=3{\cdot}25$, $P<0{\cdot}001$).

It seemed therefore to be established that the sensitivity of this group of ten hands, to the vasoconstrictor action of intra-arterial infusions of adrenaline, had been increased about fourfold by sympathectomy.

Determination of the response of groups of normal hands. In order to ascertain whether the hands of these patients, most of whom suffered from Raynaud's disease, were more or less sensitive than normal, before operation, the behaviour of the hands of healthy persons was studied under identical conditions. Considerable variation in response to the same levels of adrenaline was encountered also in the normal hands. Table 2 gives the results obtained with infusions of $\frac{1}{32}$ μg adrenaline/min while the results with $\frac{1}{16}$ and $\frac{1}{8}$ μg/min are summarized

TABLE 2. Effect of intrabrachial infusions of adrenaline $\frac{1}{32}$ μg/min on blood flow in normal hands

		Mean blood flow						
		Test hand		Control hand				
Hand	Sex	A	B	a	b	E	$B-E$	$\frac{B-E}{E}\times 100$
R.	M.	7·0	6·0	6·8	5·7	5·9	0·1	2
R.	M.	7·8	7·9	4·9	5·1	8·1	−0·2	−3
R.	M.	6·8	6·8	10·1	9·5	6·4	0·4	6
L.	M.	11·2	10·8	11·8	11·1	10·5	0·3	3
L.	M.	17·3	17·0	12·1	13·0	18·6	−1·6	−9
R.	M.	12·8	12·1	14·6	16·1	14·1	−2·0	−14
R.	M.	12·5	7·3	9·8	8·8	11·2	−3·9	−35
R.	M.	18·8	20·7	15·8	18·2	21·7	−1·0	−5
R.	M.	6·0	5·4	5·5	7·1	7·7	−2·3	−30
R.	M.	19·3	21·7	19·2	23·7	23·8	−2·1	−9
R.	M.	14·5	17·9	13·3	16·4	17·9	0·0	0
L.	M.	17·7	21·0	15·4	22·1	25·4	−4·4	−17
L.	M.	21·9	19·4	20·2	21·1	22·9	−3·5	−15
R.	M.	23·0	19·3	19·3	18·4	21·9	−2·6	−12
L.	M.	22·4	19·6	19·2	20·5	23·9	−4·3	−18
L.	M.	25·9	22·2	23·3	21·8	24·2	−2·0	−8
R.	M.	28·2	31·9	21·4	24·7	32·5	−0·6	−2
	Mean	16·1	—	—	—	—	—	−10

A, a = means of the six observations of blood flow during 3 min immediately prior to start of adrenaline, in test and control hands, respectively; B, b = corresponding means during first 3 min of adrenaline period; $E = Ab/a$.

in Table 3. With $\frac{1}{32}$ μg/min the mean blood-flow change in seventeen tests was a reduction of 10%, standard error 2·6%. In the group of patients' hands before operation (Table 1) the mean change was a reduction in flow of 4%, standard error 2·5%.

With $\frac{1}{16}$ μg adrenaline/min, the mean change in seventeen tests of healthy hands was a reduction of 7%, standard error 4·3%, as compared with 12 and 2·1% for the group of preoperative hands.

Likewise, with infusions of $\frac{1}{8}$ μg adrenaline/min the mean constriction in twenty-four healthy hands was 19%, standard error 4·5%, and in the preoperative hands 16 and 8·9% respectively.

With infusions of $\frac{1}{32}$, $\frac{1}{16}$ and $\frac{1}{8}$ μg adrenaline/min there is thus no significant difference in the behaviour of the blood flow in healthy and preoperative hands. It was therefore concluded that before operation the patients' hands were neither more nor less sensitive then normal.

In Table 3, data from tests of healthy subjects and of patients before operation are taken together, to provide a more precise evaluation of the response of 'normally innervated' hands to test concentrations of $\frac{1}{32}$, $\frac{1}{16}$ and

$\frac{1}{8}\mu g$ adrenaline/min. It is seen, from Table 3, that the difference in mean effect between 'normally innervated' and sympathectomized hands is significant in respect of these three adrenaline concentrations.

Normal response to higher concentrations of adrenaline. In thirty-five tests of healthy subjects the hand blood-flow responses to $\frac{1}{4}$ and $\frac{1}{2}\mu g$ were determined (Table 3). The mean constriction with $\frac{1}{4}\mu g$/min was 27%, with $\frac{1}{2}\mu g$/min 53%. The mean values in all the groups of tests are summarized in Table 3, in which it is seen that whereas $\frac{1}{8}\mu g$ adrenaline/min is sufficient to

TABLE 3. Percentage constrictive effect, in groups of hands, of adrenaline, $\frac{1}{64}$–$\frac{1}{2}\mu g$/min

Adrenaline (μg/min)		Normal subjects	Preoperative	Normally innervated	Sympathectomized
$\frac{1}{64}$	No.	—	6	—	6
	Mean	—	3	—	17
	S.D.	—	15	—	20
	S.E.	—	6·0	—	7·8
$\frac{1}{32}$	No.	17	10	27	10
	Mean	10	4	8	30
	S.D.	11	8	9	22
	S.E.	2·6	2·5	1·8	6·8
$\frac{1}{16}$	No.	17	9	26	9
	Mean	7	12	9	36
	S.D.	18	6	15	20
	S.E.	4·3	2·1	2·9	6·7
$\frac{1}{8}$	No.	24	8	32	8
	Mean	19	16	18	55
	S.D.	22	25	23	23
	S.E.	4·5	8·9	4·0	8·1
$\frac{1}{4}$	No.	17			
	Mean	27			
	S.D.	33			
	S.E.	7·9			
$\frac{1}{2}$	No.	18			
	Mean	53			
	S.D.	34			
	S.E.	7·9			

No. = number of tests; S.D. = standard deviation of group; S.E. = standard error of mean.

$$\text{Percentage effect} = \frac{E-B}{E} \times 100.$$

cause 55% vasoconstriction in the group of sympathectomized hands, normal hands require $\frac{1}{2}\mu g$, or four times the concentration, in order to sustain an equal degree of vasoconstriction (53%).

In Fig. 5 the responses of the same hands before and after operation and of 'normally innervated' hands have been plotted together, in relation to dose of adrenaline. The greater response of hands after sympathectomy is clearly shown.

DISCUSSION

The results indicate (Table 3) that while there is a certain amount of variation in the response to a given dose of adrenaline of the hand circulation in healthy subjects as well as patients, there is no evidence that the latter are more sensitive before operation. After operation six out of ten of the hands were found to be definitely more sensitive than before.

If the concentration of adrenaline at which 25% constriction occurs be taken as the threshold level for an individual hand, supersensitivity may conveniently be expressed as a lowering of this threshold. A reduction of flow of 25%, or more, occurred in about 10% of normally innervated hands with $\frac{1}{32}$–$\frac{1}{16}$ μg, of about 40% with $\frac{1}{16}$–$\frac{1}{8}$ μg, and of about 80% with $\frac{1}{8}$–$\frac{1}{2}$ μg/min.

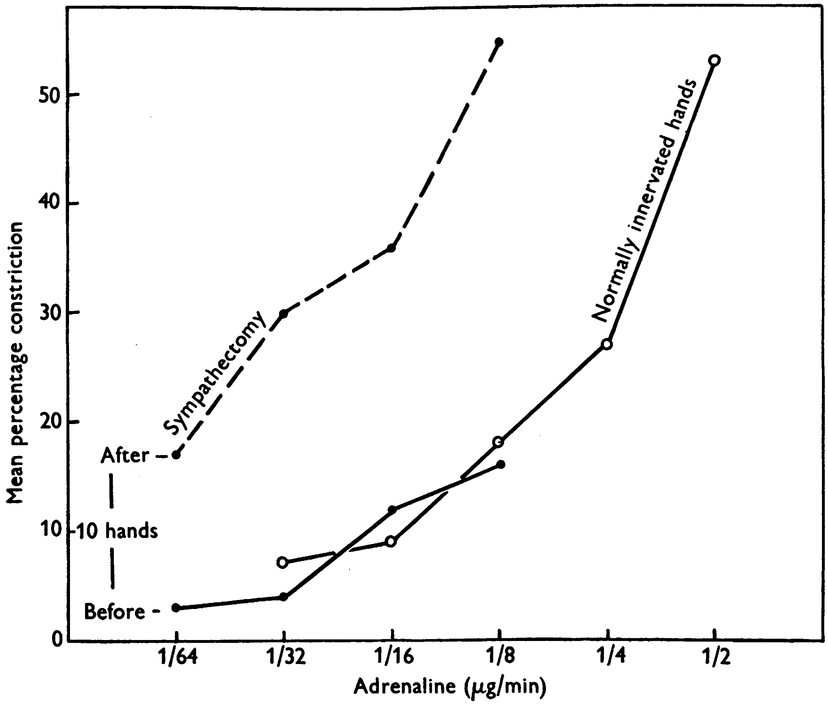

Fig. 5. Mean percentage reduction in blood flow in groups of hands tested before and after sympathectomy, and of normally innervated hands, in relation to different concentrations of adrenaline in intra-arterial infusions.

In contrast, 90% of sympathectomized hands were constricted by $\frac{1}{8}$ μg, 60% by $\frac{1}{32}$–$\frac{1}{16}$ μg/min, while with the concentration of $\frac{1}{64}$ μg/min, at which level normal hands are generally unaffected, 20% of sympathectomized hands were constricted. Six out of ten hands revealed a lowering of the threshold at which vasoconstriction with adrenaline occurred, in tests at one or more concentration levels.

Comparison of the degree of reduction in blood flow of individual hands in identical tests at the same dose levels shows a consistent trend towards greater constriction (Table 1), amounting, on the average, to a fourfold increase. All six of the hands, in which an increase in sensitivity was found, had been sympathectomized by preganglionic section. The operation in respect of the remaining four, in which a change was not demonstrated, was ganglionectomy in two, preganglionic section in two. One of the latter was the right hand of a patient, Miss H., whose left hand exhibited a notable increase in sensitivity. The preganglionic operation has therefore not been shown, in this small series, to cause any less supersensitivity than ganglionectomy.

Freeman *et al.* (1934) measured the finger temperature during intravenous infusions of fairly large amounts of adrenaline in patients from whom the cervico-dorsal ganglia were removed for Raynaud's disease. They found that an increased fall in temperature occurred some time between the 8th and 18th days after operation, which they attributed to the appearance at that time of supersensitivity to adrenaline. White, Okelberry & Whitelaw (1936) concluded that ganglionectomy caused a greater increase in adrenaline sensitivity than preganglionic section. In the same way Ascroft (1937) found that ganglionectomy produced about three times as much supersensitivity in monkeys as preganglionic section. In contrast, Fatheree, Adson & Allen (1940), using similar methods, found that both operations caused about the same amount of adrenaline supersensitivity. In the present study a fourfold increase in sensitivity has been demonstrated in a small group of hands, the majority of which were sympathectomized by preganglionic section.

The hypoglycaemia induced by a large subcutaneous injection of insulin was found by Smithwick *et al.* (1934) to cause a fall in temperature in the sympathectomized hand (presumably in consequence of the endogenous liberation of adrenaline) but not in the opposite unoperated side. They stated that a positive test (reduction in digital temperature following the injection of insulin) occurred only in completely sympathectomized limbs. The present study is confined to normal subjects and to cases having completely sympathectomized hands, and offers no information regarding incompletely sympathectomized extremities.

Concerning the onset of supersensitivity following sympathectomy, Simmons & Sheehan (1939) and Freeman *et al.* (1934) found that supersensitivity appeared first after an interval of 8 or more days. In the present investigation one hand was supersensitive when first tested 6 days after preganglionic section, and another, when tested on the 7th day. No tests were performed at a shorter interval after operation.

Simmons & Sheehan (1939) stated that supersensitivity was maximal at its onset, thereafter decreasing steadily till it was no longer present after 3 months. In the present series, hands tested at 2, 4, 5 and 12 months were found to have remained more sensitive than before sympathectomy. While this is scanty evidence of the perpetuation of adrenaline supersensitivity, it may be noted that the authors already cited have based conclusions on skin temperature changes as indicating changes in blood flow. Apart from the general insusceptibility of such measurements to quantitative comparison, the relationship between temperature and blood flow is imprecise by virtue of such factors as ambient temperature and circulatory changes in underlying muscles. It has been shown (Freeman, 1935) that the blood flow in recently sympathectomized hands remains steady despite considerable changes in surface temperature. Moreover, Belding, Mead & Bader (1949) have found that after vasoconstriction the fall in temperature of the fingers is gradual, whereas the converse obtains when the finger temperature rises in a warm atmosphere. Simeone & Felder (1951) measured the plethysmographic digital volume during repeated intravenous injections of about 4 μg adrenaline. They found a greater and more prolonged reduction in digital volume in sympathectomized patients, even up to 1 year after operation. These observations support the findings in the present study.

The mechanism of supersensitivity of the vessels following sympathectomy has remained obscure. Liberation of the vessels of the hands from the tonic influence of the sympathetic nerves results in an augmentation of blood flow which largely subsides towards the end of the first postoperative week (Barcroft & Walker, 1949). The blood flow under resting conditions may subsequently be a little higher than before operation. If the same reduction in calibre restricts the blood flow in a degree proportional to the initial calibre of the vessel, it might be thought that adrenaline would have a greater effect by virtue of such vasodilatation as might result from the operation. Table 1 shows, however, that the average resting blood flow (A) was very little greater in many of the hands when tested after operation, and in thirty-three tests the mean for the group had risen by only 0·6 ml./100ml./min after sympathectomy. Supersensitivity to adrenaline is not clearly related to the height of the resting blood flow. It may, however, be relevant to note that the actual concentration of adrenaline in a given vascular circuit will, for a constant rate of infusion into the related artery, be inversely proportional to the mean blood flow. It may, therefore, still be conceivable that the proportional response to a unit amount of adrenaline, of a given segment of vessel, is greater when that vessel is dilated. In view of such considerations, it is fortunate that, in the present investigation, the resting blood flow of many of the hands was about the same before and after operation, so that the tests are fairly comparable.

A distinctive feature of sympathectomized hands—marked reduction of fluctuation in blood flow—is partly indicated in the postoperative tests (Table 1) by the smaller differences between the blood flow during two concurrent periods (a) and (b) in the control hands (which also were usually sympathectomized at the time of the postoperative tests). It is noteworthy that when very little change in flow had occurred between (a) and (b), the response to adrenaline of the tested hands was often greater. Closer examination reveals, further, that in the groups of healthy subjects (Table 2) and of patients before operation, many individuals who have a relatively steady blood flow in the control hand (small differences between (*a*) and (*b*)) are indeed more sensitive to the constrictor effect of adrenaline. Those individuals with minimal fluctuation in hand blood flow may perhaps be regarded as having less sympathetic nervous activity in the hands, in contrast with others in whom large and frequent changes in blood flow are seen.

Although it has not been decided whether adrenaline or noradrenaline (if either) is the hormonal agent liberated by sympathetic nervous activity in relation to the skin blood vessels in man, it seems likely that the concentration of the effective substance in a given tissue is related to the amount of nervous stimulation to which that tissue has been subjected (von Euler, 1950, 1951). It is easy, therefore, to conceive that vessels in the resting state (whether temporarily, by virtue of a normal central relaxation of sympathetic tone, or permanently in consequence of surgical interruption of the nervous pathway) would be more likely than otherwise to constrict in response to adrenaline and other vasoconstrictor agents. Certainly, in other tissues, a relationship between the state of tonus of smooth muscle and its response to adrenaline has already been noted (McSwiney & Brown, 1926), but speculation concerning its nature has been scanty.

Certain other circulatory consequences of sympathectomy have to be considered in relation to adrenaline supersensitivity. If the proportion of blood flowing into the skin of the hand were greatly increased by the operation, then that tissue would receive a greater total amount of adrenaline. The bulk of the blood entering a limb passes through skin and skeletal muscle. The considerable rise in blood flow through the skin of the hand in Raynaud cases after sympathectomy lasts for only a week (Barcroft & Walker, 1949; Duff, 1951). The threefold rise in forearm blood flow (mainly muscle) is of even shorter duration (Duff, 1951). Subsequent examination of sympathectomized limbs reveals that the hand blood flow under resting conditions is either unchanged or very slightly greater than before operation, depending partly on the amount of organic vascular change produced by the Raynaud's disease. The blood flow in muscular segments of chronically sympathectomized limbs is generally within normal limits (Duff & Swan, 1951). The actual distribution of the circulating blood as between hand and forearm was measured plethysmographically in a number of cases in the present series, and it was confirmed that increased sensitivity might be present when the blood flow in the hand and in the forearm was the same as before operation. The increased sensitivity of sympathectomized hands cannot therefore be attributed to altered partition of the blood flow in the limbs.

The work of Kvale, Allen & Adson (1939) provides evidence that the velocity of the blood stream in the artery of sympathectomized limbs is increased. In the present investigation infusions of a steady concentration of adrenaline were employed, and the average change over a period of 3 min determined. The effect is therefore less likely to have been influenced by the slightly greater speed at which the adrenaline may have initially arrived in the hand. However, if the continued effect of a hormonal stimulus is normally conditioned by the rate at which such a stimulus builds up to an effective level in a given blood vessel, this would afford some measure of explanation for the increased response of sympathectomized hands.

Exact knowledge of such dimensional changes as occur in blood vessels for given changes in blood flow would doubtless help to clarify the problem. When a segment of vessel dilates, if the total as distinct from the cross-sectional area of the wall remains unchanged, then the length of the segment must decrease (Shipley & Gregg, 1944). This may well happen in the early days after sympathectomy (before tone has returned to the vessels), when volumetric and linear blood flow are greatly increased. The shortening of vascular length in the peripheral bed might well be sufficient to prevent minimal concentrations of rapidly circulating adrenaline from making effective contact with those responsive elements in the walls of vessels whose function it is to initiate vasoconstriction. With the return of vascular tone between the 6th and 12th day after operation, the reduction in calibre would be accompanied by vascular lengthening such as might permit the adrenaline to act. Future investigations of adrenaline sensitivity in the period immediately following sympathectomy may, however, render such speculative *apologia* unnecessary.

The evidence in the present study would seem to lead to the conclusion that whatever intimate biochemical and cytological changes are brought about by sympathectomy, the supersensitivity of blood vessels in the hand may be partly attributable to direct physical consequences of the removal of sympathetic activity, perhaps analogous to the altered temperature response of smooth muscle in a variety of animal tissues after denervation, described by Perkins, Li, Nicholas, Lassen & Gertler (1950). It is of interest that Nordmann (1931), reviewing the special variety of induced sensitization known as Arthus's phenomenon, arrived at the complementary conclusion that sensitization decreases the reactivity of nerves on blood vessels.

SUMMARY

1. The effect of intra-arterial infusions of standard amounts of adrenaline on the rate of blood flow in the hands (plethysmographic method) has been studied in normal subjects, in patients with Raynaud's disease and in a patient with hyperhidrosis.

2. The range of response to the same concentrations of adrenaline, of normally innervated hands, has been determined, and attention drawn to the importance of comparing individual hands under identical conditions.

3. The sensitivity to adrenaline of the hands of patients with Raynaud's disease before sympathectomy was found to be within normal limits.

4. In a group of ten hands tested before and after sympathectomy, the mean vasoconstriction in response to adrenaline was found to increase fourfold after operation, as a result of lowering of the threshold to adrenaline in six of the hands.

5. The concentration of adrenaline required to produce an equal amount of vasoconstriction was four times as much in normal as in sympathectomized hands.

6. All six of the hands which exhibited a distinct increase in sensitivity to adrenaline had been sympathectomized by preganglionic section. Two of the four hands in which no increase in sensitivity was demonstrated were sympathectomized by ganglionectomy.

7. Supersensitivity has been found in tests as early as the 6th day and as late as 12 months after sympathectomy.

8. Some evidence concerning the mechanism of the supersensitivity to adrenaline has been presented, and the nature of the phenomenon discussed.

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