S Y M P A T H E T I C C O N T R O L O F T H E

P E R I P H E R A L C I R C U L A T I O N

I N M A N

by

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P R E F A C E

Although many of the salient features of the sympathetic control of the peripheral circulation have been known for a number of years, the intimate nature of this control is not yet fully understood. This work is an endeavour to elucidate, in some measure, the manner in which the sympathetic nerves govern the peripheral blood flow in man. For such an enquiry two general methods are available: (1) to observe the effects of interruption of the sympathetic nerves, and (2) to observe the response of the circulation to sympathomimetic agents. Both approaches were used in the following investigations:

1. The circulatory changes in the skin and muscle following surgical sympathectomy of the upper limb were studied in a group of patients. The blood flow changes in the skin already described by Barcroft & Walker (1949) and by Lynn & Barcroft (1950) were confirmed. The circulatory changes in the skeletal muscle of the forearm were shown to follow a somewhat similar course to those in the skin. Previous information regarding the effects of sympathectomy on the circulation in muscle was both incomplete and contradictory.

2. The effects of sympathectomy on the purely local response of the blood vessels of the skin to adrenaline were determined in subjects with healthy blood vessels, operated on

for hyperhidrosis, and in patients with abnormal vessels, sympathectomized for Raynaud's disease. A technique was evolved whereby small circulatory changes might be evaluated. The sensitivity to adrenaline of the blood vessels in the hands of a group of patients was found to increase fourfold following sympathectomy. The range of response to adrenaline of groups of normally innervated subjects was ascertained in the same manner, and it was established that the reaction of the patients was within normal limits before sympathectomy. Previous work based on less direct methods had led to conflicting views on the effect of sympathectomy on the vascular response to adrenaline in man. The present study provides evidence incompatible with the general law of denervation of Cannon, Rosenblueth & Garcia Ramos (1945) that 'the supersensitivity is greater for the links which immediately follow the cut neurone, and decreases progressively for more distal elements.'

3. The systemic and local effects of adrenaline on the blood flow through skeletal muscle were contrasted in normally innervated and in sympathectomized limbs. Earlier work done in collaboration with Dr. H.J.C. Swan, in pursuance of a study initiated by Allen, Barcroft & Edholm (1946), had led to the suggestion that the difference in response to intravenous infusions of adrenaline as between normal and sympathectomized subjects might be related to a central action of the adrenaline

in the former group (Duff & Swan, 1951). The results of more recent studies have been incorporated, and the observed differences have been evaluated in terms of an altered local response of the sympathectomized blood vessels in skeletal muscle.

These three experimental studies have provided the basis for a hypothesis concerning the intimate relationship between sympathetic nervous activity and vascular reactivity.

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I N T R O D U C T I O N

CHANGES IN THE BLOOD FLOW THROUGH THE LIMBS FOLLOWING SYMPATHECTOMY

Surgical removal of the stellate ganglion in patients with Raynaud's disease was found by Lewis & Landis (1929) to produce a hot dry hand with increased pulsation of the digital arteries. Before the end of a week, however, the throbbing of these arteries was no longer palpable. Freeman, Smithwick & White (1934) measured the digital skin temperature by means of thermo-couples and found that the marked rise in temperature resulting from sympathectomy was not maintained, and they inferred that tone progressively returned to the denervated blood vessels in consequence of increasing sensitivity to circulating adrenaline.

Atlas (1938), Richards (1943) and Doupe (1943a) made similar observations in regard to changes in finger temperature following complete nerve section — the initial rise being replaced after two or three weeks by some degree of fall in temperature.

Barcroft & Walker (1949) made a plethysmographic study of blood flow changes in the hands following sympathectomy, and showed that the initial marked increase was of brief duration, blood flow having returned almost to the pre-operative resting level by the end of the first week. They observed further that the initial increase in flow was of equal duration after either pre-ganglionic section or ganglionectomy.

In the feet Hoobler, Avera, Little, Peet & Bassett (1949) noted a marked rise in blood flow shortly after lumbar sympathectomy, and Lynn & Barcroft (1950) made the further observation that the increase was much less after about the sixth post-operative day, even though the skin temperature remained elevated.

In the hand there is twice as much skin as muscle (Abramson & Ferris, 1940) and changes in total blood flow in the hand largely represent changes in skin blood flow, especially since only a small proportion of blood flows through the bones. The above observations concerning the effects of sympathectomy on the circulation in the digits (hands and feet), therefore, more specifically refer to the skin and are in agreement with the findings relative to the skin circulation in animals, such as the dog's foot (Burton-Opitz, 1903), and the ear of the rabbit and cat (LeCompte, 1941).

The effects of sympathectomy on the circulation through skeletal muscle have been less completely understood. In a variety of mammals, such as the dog and hare, the sympathetic innervation of vessels in skeletal muscle includes vasodilator as well as vasoconstrictor fibres (Bülbring & Burn, 1937). The early observation by Gaskell (1877) of an increased venous outflow from the quadriceps muscle in the dog immediately after cutting the nerve supply was no doubt attributable to interruption of sympathetic vasomotor fibres. Similarly, in the cat Hartman, Blatz & Kilborn (1919) found that

denervation was followed by swelling of the limb reaching a peak at some two to six hours, after which the volume returned to normal within 24 to 48 hours. It therefore seems likely that insofar as the vessels in skeletal muscle in a resting condition are under the influence of the sympathetic nervous system, that influence is vasoconstrictor, due to the activity of vasoconstrictor nerves (McDowell, 1950).

In man also the vasculature in skeletal muscle is now known to be supplied by sympathetic vasoconstrictor and vasodilator nerves (Barcroft & Edholm, 1945, 1946). In the forearm there is more than four times as much muscle as skin (Abramson & Ferris, 1940), and the proportion of muscle is no doubt even greater in the calf. Changes in blood flow through those two segments of the limbs are predominantly due to changes in the flow through the muscles (Grant & Pearson, 1937; Grant, 1938). In one patient, Grant & Holling (1938) found that the forearm blood flow rose suddenly after sympathectomy, but was no longer elevated one week later. In patients with occlusive vascular disease Stein, Harpuder & Byer (1948), however, found no significant increase in calf blood flow after lumbar sympathectomy, although they found, in contrast to Wilkins & Eichna (1941), that the blood flow in reactive hyperaemia was increased by this operation.

The contradiction of view regarding the role of the sympathetic nerves in the circulation through skeletal muscle

derives from incomplete evidence, and the main purpose of the first investigation was therefore to make a detailed plethysmographic study of the effect of sympathectomy on the blood flow through human skeletal muscle, in relation to the changes in skin circulation.

CHANGES IN THE RESPONSE TO ADRENALINE OF SKIN VESSELS FOLLOWING SYMPATHECTOMY

The earliest observation of a difference in the response to adrenaline of sympathectomized in contrast with normal blood vessels was made by Meltzer & Meltzer (1903). They found that the vasoconstriction in the rabbit's ear following intravenous adrenaline was slower and more prolonged in the denervated as compared with the normal ear. Vasodilatation followed the constriction on the normal but not on the sympathectomized side. These differences were attributed to a central vasodilator effect of the adrenaline acting through the sympathetic nerves, and therefore abolished by their interruption. Elliot (1905) made similar observations, but concluded that the difference in response to intravenous adrenaline was due to an increased sensitivity to the local action of the adrenaline on the part of the sympathectomized blood vessels. Dale & Richards (1918) confirmed this, and showed that the altered response was not confined to adrenaline, for

differences in the reaction to histamine and acetyl choline also were found to result from denervation.

Despite ample confirmation, in animals, of the occurrence of supersensitivity in blood vessels deprived of their sympathetic nerve supply, it was first demonstrated in man in 1934 by Freeman, Smithwick & White. In patients with Raynaud's disease they studied the effect of intravenous adrenaline infusions in reducing the digital skin temperature, measured by thermocouples. They found that adrenaline caused a greater fall in temperature in the fingers some 8 to 18 days after the limbs had been sympathectomized. Smithwick, Freeman & White (1934), using insulin hypoglycaemia as a stimulus to adrenaline liberation from the suprarenal medulla, obtained similar results and concluded that their tests demonstrated an increased sensitivity of sympathectomized blood vessels to adrenaline.

White, Okelberry & Whitelaw (1936) thought the increase in sensitivity to be much greater following ganglionectomy (post-ganglionic denervation) than after preganglionic section (decentralization). For these and other reasons they devised and advocated a preganglionic operation for the treatment of vasopastic disorders of the upper limb. Ascroft (1937) measured the temperature reduction with adrenaline before and after both types of sympathectomy in monkeys, and calculated that the preganglionic operation caused a threefold increase in sensitivity to adrenaline, while ganglionectomy

caused a tenfold increase.

In contrast to those results Fatheree, Adson & Allen (1940), using similar methods, found that the increase in sensitivity was of about equal degree after both operations, amounting only to a twofold increase. Phillips, Hinsey & Hardy (1939) obtained an identical decrease in digital temperature with slow infusions of adrenaline before and after sympathectomy, but the return to the initial temperature was greatly delayed in the sympathectomized extremity. Fatheree & Allen (1938), however, had earlier noted that following injections of adrenaline there was 'a marked variability in the response of the skin temperature of different digits of the same subject and in the response of the same digit of the same individual on different occasions.'

Doupe (1943 b) studied the effects of intravenous adrenaline on the digital circulation of patients with section of the median and ulnar nerves, and found a greater amd more prolonged fall in skin temperature in denervated as compared with normally innervated digits. He was unable to obtain consistent results using the digital plethysmograph, but believed that preganglionic sympathectomy as well as denervation resulted in a lowered threshold of the vessels to adrenaline.

Simeone & Felder (1951) used the Burch-Winsor plethysmograph to determine digital volume changes following repeated intravenous injections of adrenaline. In five cases there was a

greater and more prolonged decrease in volume after as compared with before sympathectomy. This intensification of the adrenaline vasoconstriction was noted for as long as 13 months after operation. Simmons & Sheehan (1939), employing the adrenaline test of Freeman et al. (1934), had earlier concluded that vascular supersensitivity was greatest at its first appearance 8 - 10 days after operation, thereafter steadily decreasing, to disappear after about three months.

The two main objections to using temperature changes as an index to vasoconstriction reside in the insusceptibility of such measurements to quantitative comparison (Fatheree & Allen, 1938), and in the very imperfect relationship between surface temperature and blood flow (Cooper, Cross, Greenfield, Hamilton & Scarborough, 1949). The second investigation was therefore designed (1) to make a quantitative plethysmographic determination of the direct vasoconstrictor effect of adrenaline on the blood vessels of the hand, in normal subjects and in patients before and after sympathectomy, and (2) to distinguish as far as possible between the effects of preganglionic section as compared with ganglionectomy.

CHANGES IN THE RESPONSE TO ADRENALINE OF THE VESSELS OF SKELETAL MUSCLE FOLLOWING SYMPATHECTOMY

That adrenaline is capable of causing vasodilatation in skeletal muscle has been fairly well established in a variety of warm-

blooded animals. In 1916, Hoskins, Gunning & Berry noted that the volume of the skinned limb regularly increased following intravenous injections of adrenaline. Gruber (1918) showed that adrenaline caused vasodilatation in the muscle of the hind leg of the cat, except during the phase of marked dilatation immediately following denervation. Hartman, Evans & Walker (1928) found that while small doses of adrenaline caused dilatation of all the vessels in muscle, larger doses might constrict the larger vessels leaving only the capillaries dilated. The latter workers observed that section of the nerve to the muscle abolished the dilator effect of adrenaline for a period of two to ten days, after which the dilator response returned. They further noted that the constrictor effect of large doses of adrenaline was increased after denervation.

Daniélopolu, Aslan & Marcou (1932) showed that the characteristic response in the limbs of dogs to intravenous adrenaline was vasodilatation followed by vasoconstriction, and that following sympathectomy both phases were exaggerated. The greater initial vasodilatation in the sympathectomized hind limbs was attributed to the prior enhancement of the vasoconstrictor phase in the earlier responding abdominal vessels. Clark (1934) noted that intra-arterial adrenaline caused a rise then a fall in the venous outflow from the muscle of the cat's leg, suggesting that the previous observations particularly concerned the vessels in skeletal muscle. Deterling & Essex (1949) thought that an increased sensitivity of muscle vessels

in the dog occurred within 30 minutes of lumbar sympethectomy.

In the human subject Grant & Pearson (1937) observed that small doses of adrenaline intravenously regularly caused an increase in limb volume and in blood flow in the forearm and calf, regions in which the vasculature is predominantly concerned with circulation through skeletal muscle. They noted that adrenaline had a greater dilator effect after sympathectomy. Allen, Barcroft & Edholm (1946) undertook a more detailed study of the blood flow changes in the forearm during infusions of a constant level of adrenaline. They found in normal subjects that the initial response to intravenous infusions was generally a four or fivefold increase in blood flow, after which the flow decreased to about twice the resting level, at which level it was maintained till the end of the infusion. The initial brief but marked vasodilatation was shown to be a direct local effect of adrenaline on the blood vessels, being present during intra-arterial infusions and also during intravenous infusions in sympathectomized subjects. Neither Grant & Pearson (1937) nor Allen et al. (1946) attempted to determine the effect of sympathectomy per se on the circulatory response to adrenaline in the muscles.

The third investigation was therefore directed to this end, in view of the suggestive evidence of an altered response following sympathectomy both in experimental animals and in man.

SUBJECTS

The information concerning blood flow changes resulting from sympathectomy of the upper limb, which comprised the first investigation, was obtained from 8 patients closely studied in the wards before and after operation. Three suffered from hyperhidrosis, two women and one man, aged between 17 and 21 years. The 6 upper limbs of these patients were studied, and as they had no evidence of circulatory or vascular disease their tests were considered to indicate the behaviour of healthy blood vessels. The remaining patients were 5 women with Raynaud's disease, whose ages ranged from 25 to 54 years. In each the vasopastic condition had been present for at least 3 years, but in only one instance was the condition severe enough to have caused evident impairment in the finger tips. Eight limbs of these patients were studied before and after sympathectomy.

Six patients were having both upper limbs sympathectomized on the same occasion or at an interval of a week, the remaining two having a unilateral operation. Where possible the operated was compared with the unoperated side, in addition to the comparison of each limb before and after operation, which was obtained on all the limbs. The postoperative observations relate mainly to the early weeks after sympathectomy, although in several cases measurements of blood flow were repeated up to 12 months later.

The direct responses of the vessels of the hand to intra-arterial infusions of adrenaline before and after sympathectomy, described at the beginning of the second investigation, were measured in 10 hands of 7 patients, 5 of whom suffered from Raynaud's disease, one from hyperhidrosis and one from traumatic avulsion of the brachial plexus. They were 3 men and 4 women aged 19 to 63 years. In both hands of one man there was some loss of tissue in the fingers, the other patients having only moderate disability. In nine instances serial tests of the same hand were made before and after sympathectomy, in the tenth the response of the sympathectomized hand was compared with that of the opposite normally innervated hand.

The later study of 6 previously sympathectomized hands included two of those whose blood flow changes after sympathectomy had been measured at the first investigation. In 5 the operation had been successfully performed for hyperhidrosis, in one for Raynaud's disease.

A group of 26 male and two female volunteers between the ages of 21 and 49 years provided the data concerning the normal responses in the hand to intra-arterial infusions of adrenaline obtained in the second investigation.

A further group of 28 healthy subjects, five of whom were women, between the ages of 19 and 39 years were studied in the third investigation, of the normal responses of the blood flow in the forearm and calf to intravenous and intra-arterial adrenaline infusions. The majority in this and the previous group of healthy subjects were medical students, the remainder being civil servants or professional colleagues. In most instances observations of the blood flow responses in a given part — hand, forearm or calf — were obtained on only one occasion from each individual, but the data include a few results from a repeated study of the same person. A few subjects provided data relative to both the forearm and calf, such information being obtained concurrently in the case of intravenous infusions, and on separate occasions in the case of intra-arterial infusions. During the latter the contralateral non-infused limb served as a control.

Finally the responses in sympathectomized forearms and calves to infusions of adrenaline were measured in 14 limbs of 12 patients who had had one or more limbs sympathectomized some weeks or months previously. The operations were performed variously for Raynaud's disease (7), hyperhidrosis (2) or causalgia (4); and one subject had traumatic sympathectomy of one upper limb. Measurements were not obtained before operation, except in one of the causalgia patients, but in all who had unilateral sympathectomy the

response of the limb was compared with that of the contralateral normally innervated limb. The ages of these subjects ranged from 19 to 44 years and none had any evidence of impaired circulation through the muscle of the extremity studied. In each the condition for which the patient had been operated had been completely or considerably alleviated.

GENERAL REMARKS

In respect of the lower limbs the operation producing sympathectomy was always the customary surgical procedure of removal of part of the lumbar chain above the level of synapse so as to cause preganglionic decentralization of the limb (White & Smithwick, 1941). To sympathectomize the upper limbs either preganglionic section or ganglionectomy was performed. In each case the type of operation was ascertained from the surgeon. A few patients in the second investigation had preganglionic section on one side and ganglionectomy on the opposite side, thereby affording valuable comparative information.

In all but two instances tests were performed to establish that the sympathectomized limbs referred to in all three investigations had had complete and effective interruption of the appropriate sympathetic pathway. The failure of these limbs to exhibit vasodilatation following indirect heating sufficient to

raise the body temperature by 1°C. was taken as good evidence of the absence of vasomotor nerves (Landis & Gibbon, 1933; Barcroft & Hamilton, 1948). Subjects in whom tests indicated incomplete sympathectomy were not included in any of the studies.

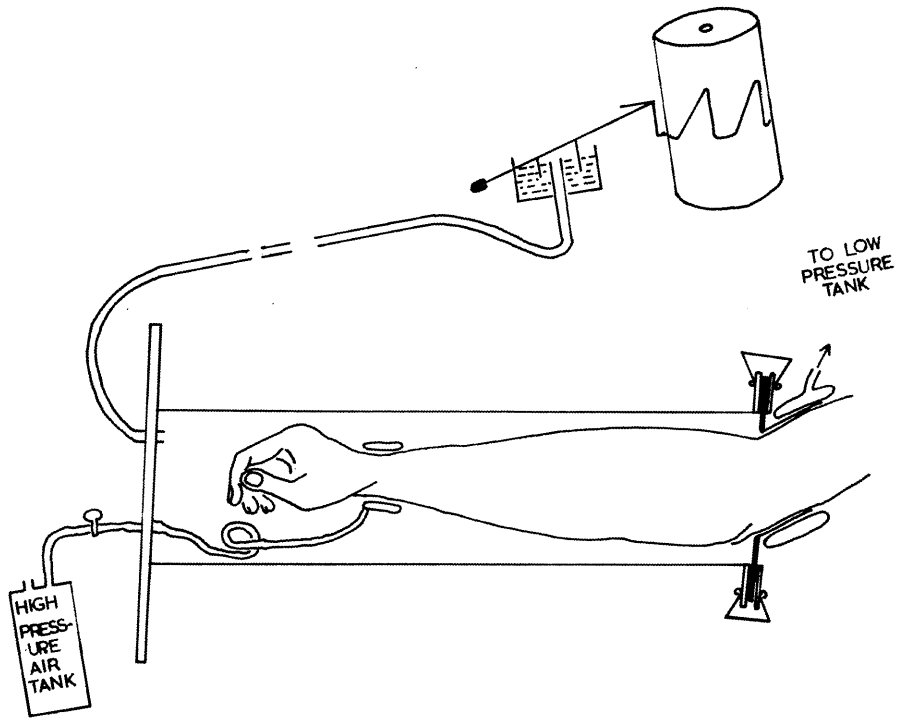


Fig. 1 Hand and forearm in lightweight air plethysmograph.

METHODS

(1) MEASUREMENT OF GROSS EFFECTS OF SYMPATHECTOMY ON BLOOD FLOW IN HAND AND FOREARM

The blood flow in the hands and forearms of two groups of subjects, with normal and vasopastic vessels, respectively, was measured on one, two or more days prior to operation and thereafter daily or on most days during the subsequent fortnight. The patients, each of whom was in bed in a hospital ward, were asked to avoid using the limbs for an hour before each test and to keep them under the bedclothes if they felt cold. On each occasion the ward temperature and oral temperature were noted and the blood pressure in the arm measured by the sphygmomanometer.

A simple lightweight plethysmograph (Fig. 1) was devised to enable the blood flow to be measured quickly and with the minimum of inconvenience to the patient. To a celluloid tube 17 inches long and 4 inches diameter a Perspex (plastic) base was cemented at one end and a Perspex ring at the other. The limb was inserted up to the elbow through a stout rubber diaphragm with a short rubber sheath of appropriate size for making an air seal. An inflatable rubber cuff was applied to the wrist and its tube led through a suitable airtight junction in the base of the plethysmograph to a pressure tank. The plethysmograph was drawn up to the elbow into

contact with the diaphragm, against which it was firmly held by spring clips. The apparatus with the contained limb now constituted an airtight plethysmograph, liquid paraffin being applied to ensure cohesion at the junctions. A second inflatable cuff was placed round the upper arm just above the elbow. The arm, with the attached apparatus, was elevated to just above the level of the heart and supported with pillows in a comfortable position. A tube from the interior of the plethysmograph was connected to a volume recorder whose ink-writing pen inscribed on the revolving drum of a portable kymograph.

The total blood flow in the forearm and hand was first measured by filling the proximal (arm) cuff with air from a tank for about 5 to 15 seconds at a pressure of 50 to 70 mm. Hg. This prevented venous blood from leaving the segment distal to the cuff but did not interfere with arterial inflow, the resultant swelling being a direct measure of the entry of arterial blood into the segment. The rate of change of volume of the hand and forearm within the plethysmograph was recorded on the revolving drum, whose speed was adjusted to obtain a gradient of about 45 degrees in the rise of the pen. In this manner the blood flow was measured 7 to 14 times at intervals of about 45 seconds.

Next, the circulation in the hand was arrested by inflating the wrist cuff (within the plethysmograph) at a maintained pressure

of 220 to 240 mm. Hg, after which 7 to 14 records of the forearm blood flow were obtained in the same way. This procedure was followed with every limb. The volume of each forearm and of each hand was obtained by water displacement, and it was then possible to calculate the hand blood flow from the mean values of the several measurements, as:

$$\begin{pmatrix}\text{total flow per min.}\\ \text{in forearm \& hand}\end{pmatrix} - \begin{pmatrix}\text{total flow per min.}\\ \text{in forearm alone}\end{pmatrix}$$

The value so obtained was divided by the volume of the hand in 100 ml. to give hand blood flow in ml./ 100 ml./ min.

The values for hand blood flow calculated by this method are remarkably similar to those obtained by direct plethysmography of the hand (Barcroft & Walker, 1949). Further comparisons with the individual values for hand blood flow and forearm blood flow obtained from time to time in these subjects in the course of other studies using the established but more time-consuming method of the water-containing plethysmograph (Grant & Pearson, 1937; Barcroft & Edholm, 1943, 1945) also have shown good agreement.

(2) MEASUREMENT OF BLOOD FLOW CHANGES IN THE HAND DURING INFUSIONS OF ADRENALINE

To assess small changes in blood flow in an individual hand it was necessary, for reasons described later, to obtain

simultaneous measurements from both hands of a given subject. Throughout each test the subject reclined comfortably on a couch in a laboratory thermostatically maintained at 22 ± 1° C. Since mental states may influence notably the activity of the sympathetic nerves and thereby affect the blood flow in normally innervated hands, precautions were adopted to allay the subject's apprehension. The purpose and technique of the tests were clearly explained and reassurance given as to the absence of pain and discomfort. Some of the patients and most of the healthy volunteers had been allowed previously to witness a test of another person. The subject was allowed to lie on the couch for at least half an hour before the study commenced. During the actual tests noise and movement in the laboratory were reduced to a minimum.

Water-filled plethysmographs were used to measure the blood flow in each hand, using a procedure based on that of Barcroft & Edholm (1943). 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, which was then elevated a little above the level of the chest. Inflatable rubber cuffs were placed round the wrists just proximal to the plethysmographs (Fig. 2), which were now filled with water at 33° C. This temperature — 3 degrees higher than that used by Freeman (1935) — was chosen to facilitate the demonstration of small decreases in blood flow. Lagging the plethysmographs with

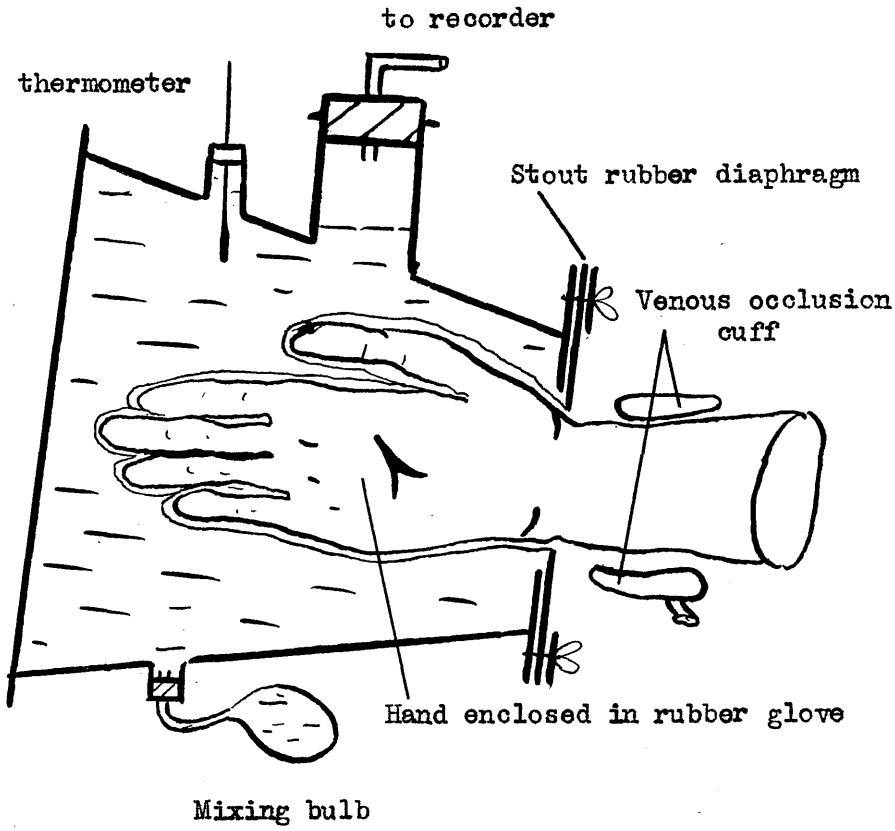


Fig. 2 Hand in water-filled plethysmograph.

cotton wool aided in minimizing loss of heat. When necessary a small electric heating pad was applied to the outside of a plethysmograph, and it was possible to maintain the temperature of the water within the range 32.5 - 33.5° C., the variation rarely being as much as 1° C. in any given experiment.

The blood flow in both hands of each subject was measured simultaneously every half-minute throughout the test by brief inflation of the cuffs at a pressure which occluded the venous return from the hand, the consequent swelling of the hand being measured by a volume recorder inscribing on smoked paper on a kymograph. The basic plethysmographic records thus consisted of regular half-minute tracings of the blood flow in each hand, for the whole duration of the period of observation, which usually was 1½ to 2 hours.

On the side of the hand whose responses were being studied a continuous intra-brachial arterial infusion of saline was started, as described later. After a further control period of 8 - 10 min. the requisite amount of adrenaline was added to the saline and infused for exactly 4 min., after which the saline infusion was continued. Every 12 min. further test concentrations of adrenaline were infused in exactly the same way, each solution being freshly prepared less than 2 min. prior to administration.

At the end of the experiment the infusion needle and

apparatus were removed and the volume of each hand determined by water displacement.

(3) MEASUREMENT OF BLOOD FLOW CHANGES IN THE FOREARM AND CALF DURING INFUSIONS OF ADRENALINE

The same general procedure as that in the hand studies was adopted, the subject being rested in the laboratory prior to the start of the investigation. The limb to be tested was inserted into a thin rubber sheath of appropriate size, to either end of which had been sealed stout rubber diaphragms with holes neatly to admit the limb. The limb was adjusted so that the most muscular segment of forearm or calf was enclosed in the rubber sheath. The latter then was placed inside a Perspex plethysmograph with the diaphragms in close apposition to its apertures, to the rims of which they now were sealed by screws and gaskets. A segment of forearm or of calf thus lay within the plethysmograph, enclosed in a watertight thin rubber sheath. Inflatable rubber cuffs were applied to the limb proximal and distal to the plethysmograph (Fig. 3), following the general technique of Barcroft & Edholm (1943, 1945). The plethysmographs were filled with water and maintained at a temperature of 34 $\pm$ 1° C. (Barcroft & Edholm, 1946b), care being taken to ensure thorough mixing of the water to obtain a uniform temperature. Since the forearm and calf

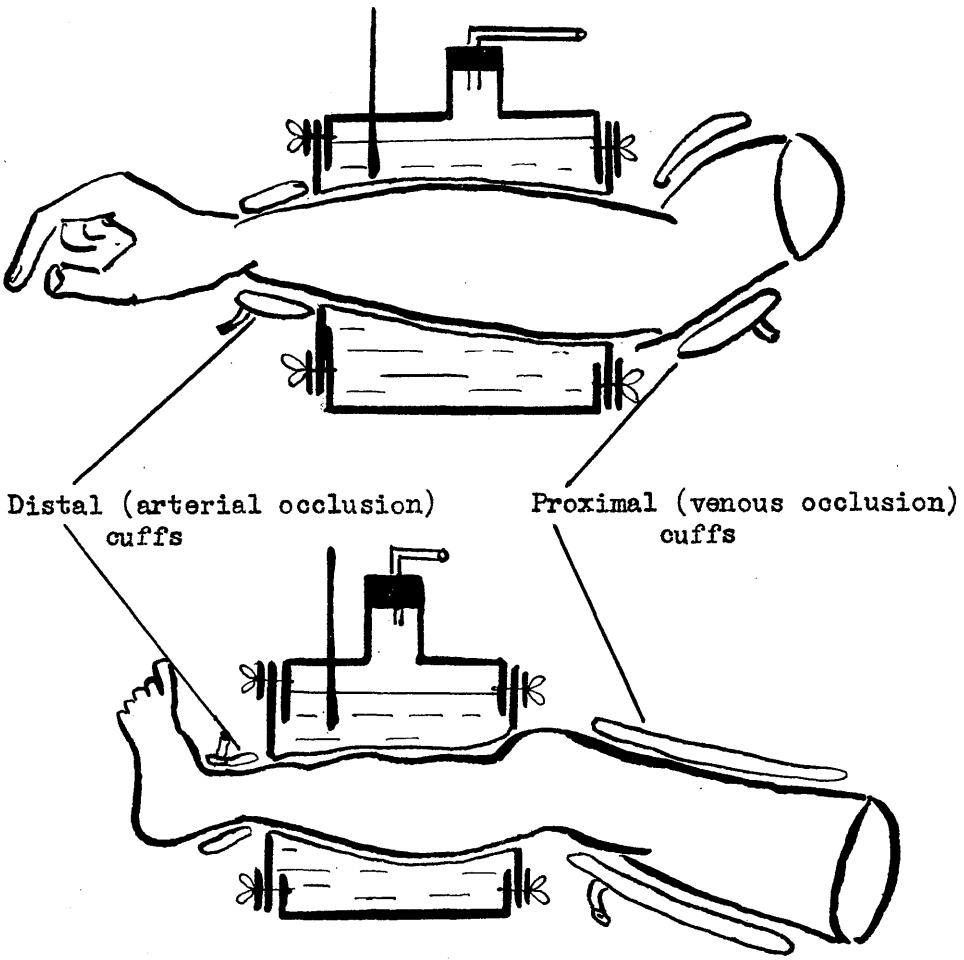


Fig. 3 Forearm and calf in water-filled plethysmographs.

plethysmographs were constructed of stout Perspex, little loss of heat occurred, but when required the water could be warmed from time to time by inserting a small immersion heater or by switching on the built-in heater and mixer in one of the calf plethysmographs (designed by Prof. H. Barcroft). In the earliest studies of forearm blood flow during intravenous infusions metal plethysmographs were used and stability of temperature ensured by submerging the whole limb, with the attached plethysmograph, in a water-bath of appropriate temperature. With the subsequent employment of Perspex apparatus the procedure already outlined was found to be sufficient.

To measure blood flow the distal cuff was first inflated and maintained at a pressure above the systolic arterial pressure, 200 mm. Hg being a suitable pressure for most subjects. After an interval of one minute the proximal cuff was inflated for 6 to 9 seconds at a pressure which prevented venous blood from escaping from the segment of limb in the plethysmograph, the consequent swelling of the tissue being recorded in the manner previously described for the hand. Allowing between measurements an interval of at least twice the duration of the venous occlusion, it was possible to obtain estimates of forearm or of calf blood flow regularly each half-min. for five min. after which the pressure in the distal cuff was released. One min. later the distal pressure was reapplied and a further series of half-min. readings of blood flow obtained during the next five min. This sequence was continued

throughout the experimental period, to provide a continuous record at half-min. intervals, whose regularity was briefly, but necessarily, interrupted every five min.

After fitting of the apparatus trial measurements of blood flow were made during a control period of 10 - 15 min., after which a saline infusion into the appropriate vessel —vein or artery— was started, as described later.

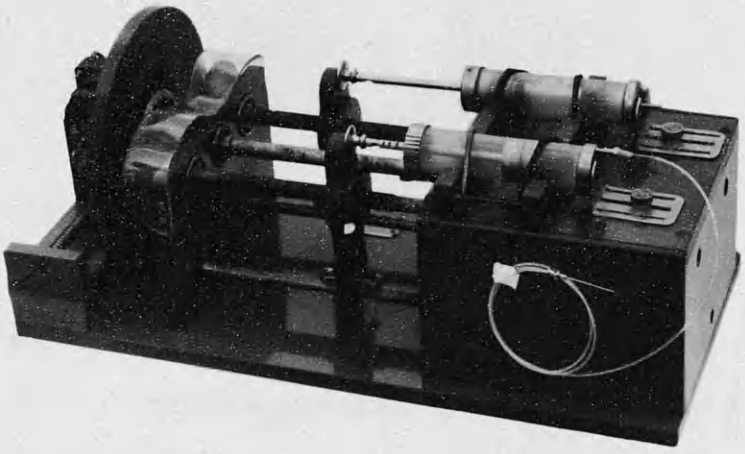
Blood pressure was measured in the arm by a clinical sphygmomanometer, usually immediately after each recording of blood flow. In the earlier forearm experiments, as one arm was generally required for the intravenous infusion and the other for the measurement of blood flow or blood pressure, two separate infusions of adrenaline were given; during the first, blood flow alone was recorded, and 25 to 30 min. later the second infusion was given while blood pressure was measured. To avoid this repetition, a technique was later evolved whereby, through a needle inserted into the antecubital or cephalic vein, a very fine polythene catheter was passed proximally in the vein for 6 inches or more. The needle was withdrawn and the catheter attached to the infusion syringe in the usual way. The infused arm then could be used to measure forearm blood flow, since the proximal (venous occlusion) cuff did not interrupt the intravenous infusion. Actually the earlier method also provided valid observations, for when two successive infusion of adrenaline are given to an individual at an interval of 20 min.

or more, the responses of the blood flow and blood pressure to the second infusion are not significantly different from those observed during the first infusion. This observation was made consistently in 8 subjects.

All the observations of blood flow and blood pressure were made during the course of the continuous saline infusion. After a saline control period of 20 min. the plain saline was replaced for a period of exactly 10 min. with saline containing adrenaline in the required concentration, after which the plain saline infusion was resumed for a further control period.

The concentration of adrenaline for every intravenous infusion was 10 µg./ min. In the intra-arterial infusions a proportionately smaller dose was given. Taking into account the relative bulk of the tissue supplied by the infused vessel and the average rate of blood flow in the extremity as compared with the total cardiac output, it was estimated that 1/8 µg. into the brachial artery at the elbow and 1 µg. into the femoral artery at the groin were approximately equivalent to the intravenous dose of 10 µg. A further series of intra-femoral arterial infusions of 2 µg. adrenaline/ min. was employed in the study of blood flow changes in the calf.

After each experiment the margins of the segment of forearm or calf within the plethysmograph were marked, and the volume of the part determined by water displacement.



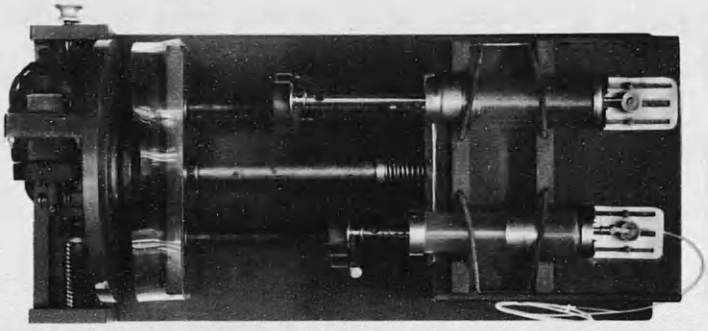


Fig. 4 Infusion apparatus.

(4) INFUSION TECHNIQUES

Perhaps the most important prerequisite of an investigation of a biological response to chemical substances is the recording of suitably controlled observations. In all the studies herein described this consideration was an integral part of the procedure.

In general, after fitting of the appropriate plethysmographs and cuffs, the limbs were placed in a comfortable position slightly elevated above the level of the heart. The skin over the vessel to be infused was cleaned with spirit, and $\frac{1}{4}$ to $\frac{1}{2}$ ml. of specially prepared adrenaline-free 2% procaine HCl solution was injected intradermally.

The infusion apparatus (Fig. 4) comprised an electric induction motor, of which the transmission was geared down to drive the plungers of two 50 ml. syringes so that each delivered 4.0 ml. saline/min. at a steady rate. The connecting tube was a 3 foot length of narrow bore polythene tubing of known capacity, to one end of which was attached a hypodermic needle and to the other end a "female" adaptor for attaching to the nipples of the 50 ml. (Record) syringes.

One of the syringes was filled with sterile 0.9% saline and the connecting tube attached and thoroughly flushed. With the tube filled with saline the needle was inserted through the

skin into the vessel, such puncture being accompanied by very little if any discomfort. That the vessel had been entered was immediately ascertained by permitting blood to flow into the polythene tube, where it could be seen. The infusion apparatus was promptly started, commencing the infusion of saline. The blood flow in the limb was now recorded regularly every half-min. and inspection of the kymograph tracings gave some indication when the blood flow became stable. In all experiments a further control period was observed (8 - 10 min. for the hand studies and 20 min. for the forearm and calf studies), during which half-minute recordings of blood flow were obtained continuously.

Each syringe being charged with 50 ml. saline was sufficient for about 12 min. infusion at the rate of 4 ml./min. Just before one syringe became empty the connecting tube base was suddenly transferred to the other (replenished) syringe to ensure continuity of flow. Two min. before the time for the adrenaline infusion the solution was rapidly prepared by serial dilution of the requisite amount of synthetic L-adrenaline tartrate, B.D.H., so as to incorporate the concentration required per min. in exactly 4 ml. saline. Generally the total amount of solution prepared was slightly in excess of that required for the length of the infusion and was placed in one of the 50 ml. syringes. At a given moment the connecting tube base was transferred rapidly to the adrenaline-charged syringe for the duration of the adrenaline

period, after which it was returned to the saline syringe. In no instance was the subject aware of the times of transference except insofar as the adrenaline produced symptoms during the intravenous infusions. The small quantities of adrenaline infused in the intra-arterial infusions were insufficient to cause any subjective sensations or, indeed, any alteration in heart rate, respiration or blood pressure.

Symptoms experienced during the intravenous infusions of 10 µg. adrenaline/min. varied in intensity in different subjects. The first sensation was a curious feeling of expectancy, amounting in some to real anxiety, immediately followed by an awareness of the need for greater respiratory effort and an increase in rate and depth of breathing. About the same time a sudden rise in heart rate was noticed, and shortly afterwards the subject experienced a sensation of fatigue in the back and lower limbs similar to that associated with strenuous exercise. A few subjects complained of slight frontal headache. The skin, especially of the face, remained pale throughout the infusion, after which a sudden flush associated with a subjective feeling of warmth was frequently observed. In about half the subjects some degree of coarse irregular tremor of the limbs was seen. The subjective symptoms diminished markedly after the first 2 - 4 min. despite maintenance of the adrenaline infusion at the same rate. Sympathectomized subjects usually had the same symptoms as normal subjects, but a few who had all 4 limbs

sympathectomized experienced more severe symptoms. In these adrenaline was found to cause a greater rise in arterial pressure than was usually seen in normal subjects. A similar observation was reported by Swan (1951).

The intrabrachial infusions were given into the brachial artery just above its bifurcation in the antecubital fossa, the needle being inserted into the vessel in a direction contrary to the flow of the blood stream. The intrafemoral infusions were given into the femoral artery just as it emerges from under the inguinal ligament, the needle being inserted almost at right angles to the axis of the vessel. Once placed securely in the lumen of the artery, the needle was retained in position with adhesive tape. Movement of the limb was discouraged during the actual recording of blood flow, but a little movement was permitted from time to time during intervening control periods. For about 2 hours the subjects generally remained quite comfortable and were actually in some instances able to go to sleep.

In the majority (90%) of cases puncture of the brachial or femoral artery was accomplished rapidly and with facility. In a few, however, one or two attempts were required to enter the vessel successfully. The study was forthwith abandoned in a small number of cases in which 2 unsuccessful attempts had been made and also those in which blood leaked around the needle to cause visible swelling

or in which some discomfort continued to be felt after the initial puncture.

In all but the earliest experiments new needles and newly prepared connecting tubes were used for each subject. These were sterilized by soaking overnight in 1/1000 Cetavlon (detergent) solution. Syringes were kept in ethyl alcohol when not in use, and other aseptic precautions adopted as required. A very small number of those subjected to the initial infusion studies complained of a feverish reaction some hours after the experiments, and for this reason all subsequent infusions were made with previously unused connecting tubes. No further untoward incidents occurred throughout the investigation.

(5) GENERAL PROCEDURE

The observations of the circulatory changes resulting from sympathectomy of the upper limb were, of necessity, obtained in the wards of the hospitals in which the various patients were operated on: St. Bartholomew's, Guy's and Middlesex Hospitals, London, and Southern General Hospital, Glasgow. While standardization of environmental temperature was not possible, on each occasion the actual conditions were recorded.

All the infusion studies were performed in the special laboratory at the Sherrington School of Physiology, St. Thomas's

Hospital, London. The laboratory was thermostatically maintained at a steady temperature* throughout each test, and was 22.5° C, and in a very few the temperature was 21.5° C. It was confirmed that between 21° and 24° C. the environment is comfortable and unlikely to induce much vasomotor activity (Ferris, Forster, Pillion & Christensen, 1947).

In general two operators were employed in each experiment. After fitting the plethysmographs and cuffs and connecting up the apparatus one operator (usually the technical assistant) assumed the responsibility of inflating the appropriate cuffs and obtaining regular recordings of blood flow in the studied extremity or extremities every half-minute. In addition he served as time keeper. The second operator performed the vascular puncture and set up the infusion, maintained a close watch on plethysmograph temperatures, and prepared and administered the adrenaline solutions. In the studies of vascular responses in muscle to intravenous adrenaline, in which concurrent observations of blood flow and arterial blood pressure were made, an additional operator was required to record the blood pressure every half-minute.

At the beginning of each study the position of the plethysmographs was adjusted so that the limb under investigation was elevated a little above the level of the heart, to avoid a local rise in venous pressure. In the case of the hands both were

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* For the great majority of tests temperature was between 22° & 23° C. In some of the initial studies of legs temperature was 21° - 22° C.

elevated to an equal degree and the upper limbs disposed symmetrically, except that the limb receiving the infusion was slightly more everted than its fellow. The laboratory couch consisted of a standard surgical operating table, admirably suited for placing the subject in the most appropriate position.

The water in the plethysmographs was kept within the desired range of temperature, being recorded periodically to 0.1°C., protocols falling outside the specified range being afterwards discarded.

The precautions taken to reduce psychic influences have been described; data from subjects who remained uncomfortable were not used. The majority, patients and others, were happy to volunteer for further similar tests.

In the studies of normal responses in the hand to intra-arterial adrenaline the blood flow often decreased for a few min. after the start of the initial saline infusion, as a result of sympathetic vasoconstrictor activity. As soon as the flow returned to what was adjudged from inspection of the kymograph tracings to be "normal", the true saline control period was deemed to commence, and 8 - 10 min. later the first adrenaline infusion was started. In fact data from only the last 3 min. of each saline control period was used in the analysis of results.

During the tests the subject, covered with a blanket and with exposed parts of limbs likewise covered, reclined on the table,

pressure points protected with an air-cushion and pillows. Silence was maintained as far as possible throughout and unnecessary movement on the part of the subject or others present discouraged.

At the end of each experiment the needle was withdrawn and pressure with a cotton swab applied to stop bleeding. The plethysmographs and cuffs were rapidly removed, and the volume of the segment of limb in each plethysmograph determined by water displacement. On each occasion also the speed of the kymograph and the sensitivity of the recorder were measured and included with the protocols for that particular experiment.

Since the plethysmograph is essentially an instrument which measures the rate of swelling of the tissue enclosed within it, under the condition of brief venous occlusion, the rate of swelling is equal to the rate of arterial inflow. The slope of the kymograph tracing is determined by two intrinsic factors: the capacity or "sensitivity" of the recorder (i.e., the rise in cm. per ml. increase in volume), and the speed of the revolving drum. With both factors known the rate of swelling of the tissue is measurable in ml. per min. This value is conveniently divided by the volume of the limb segment in 100 ml., to give blood flow in the standard units used throughout this work, ml./ 100 ml./ min.

Certain artefacts are liable to cause erroneous readings; these can mostly be eliminated with proper technique, but in any case are easily recognized by the experienced operator. All results

described in this thesis were derived from the means of multiple observations of individuals and of groups, and appropriate statistical treatment, shortly to be described, provided an estimate of the reliability of the methods. Needless to say, the plethysmograph is the only instrument which provides a direct measure of the volumetric blood flow in the extremities under physiological conditions.

(6) ANALYSIS OF RESULTS OF INFUSION STUDIES — ASSESSMENT OF VASOCONSTRICTOR EFFECT IN THE HAND OF INTRA-ARTERIAL INFUSIONS OF ADRENALINE

Since the hands have a rich vasomotor innervation, the blood flow through these extremities is subject to considerable fluctuation as a result of variations in sympathetic activity. Changes in blood flow are also to some extent influenced by the normal phasic variations in respiration and blood pressure which characterize even the resting state. These influences are essentially bilateral and synchronous, so that the blood flow changes are very similar in both hands. Fig. 5 exemplifies this, showing the blood flow in the right and left hands of a healthy young man over a 40 min. period. Blood flow was measured at half-min. intervals with separate plethysmographs and separate recorders in a similar manner to that adopted in the actual tests. The

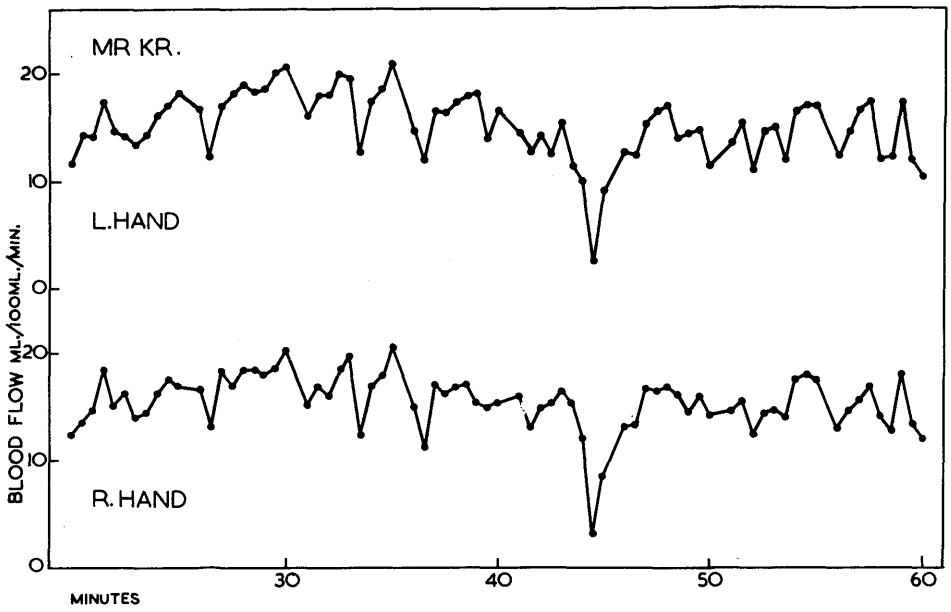


Fig. 5 Blood flow in both hands of a healthy subject at rest, recorded every half-minute.

subject was reclining comfortably in a pleasantly warm (22° C.) laboratory in which the temperature was constant; he was familiar with the procedure and had been allowed to rest for one hour before these observations were made.

It is noteworthy that rises and falls in blood flow in one hand were associated with changes in the same direction, though not always of equal degree, in the other hand. Despite the comparatively stable environment some change in blood flow occurred each half-minute. When the blood flow is recorded every quarter-minute the synchronous fluctuation is even more noticeable.

It might have been supposed that the pattern of changes is distinctive for a given individual, but this is not so. Fig. 6 shows the blood flow changes in the same individual under identical conditions, on the following day. The close similarity between the two hands is again noticeable, but the overall pattern is quite different from that obtained on the previous day.

Changes in hand blood flow are usually approximately equal on both sides (Cooper et al., 1949). It is therefore possible to predict with a determinable range of accuracy the blood flow in a given hand over a short period of time, provided the blood flow in that hand has been measured prior to this time and provided the blood flow in the other hand has been continuously measured. If A, B are the means of the 6 observations of flow in the right hand during two contiguous periods of 3 min. and a, b are the corresponding

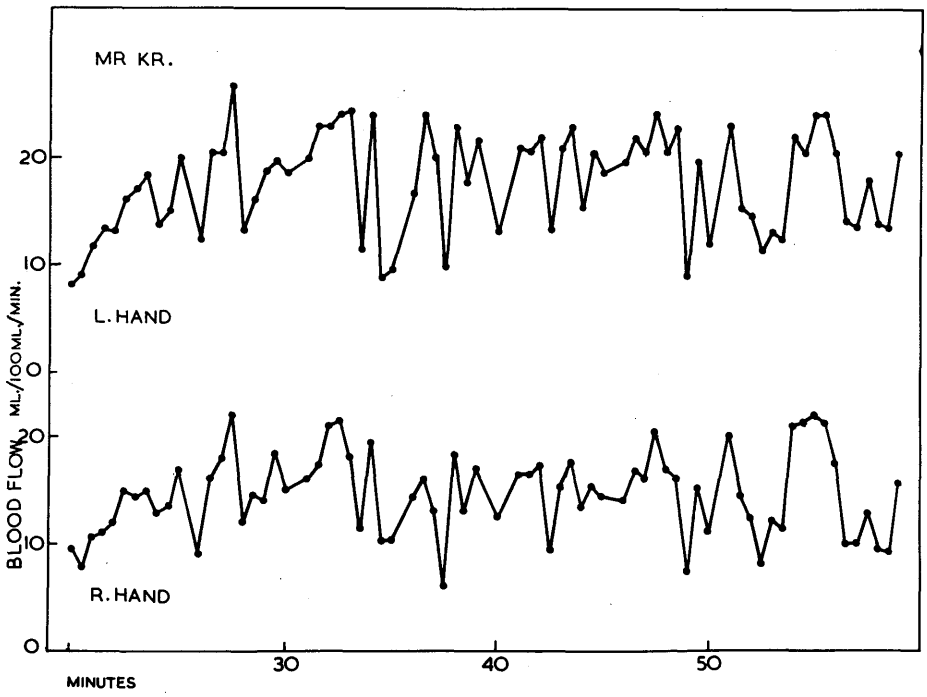


Fig. 6 Resting blood flow in the hands of the same subject on the following day.

means for the left hand, then A/B should approximate a/b. If the synchronous fluctuation in hand blood flow in a given subject were entirely equal on both sides then A/B would exactly equal a/b.

Likewise, in the adrenaline tests, if the average (A) of the 6 blood flow measurements in the test hand during the 3 min. period immediately prior to the arrival therein of the adrenaline be multiplied by the average (b) of the 6 measurements of blood flow in the control hand during the first 3 min. that the adrenaline was passing through the test hand; and if this product be divided by the average (a) of the 6 measurements of flow in the control hand corresponding in time with the pre-adrenaline average (A) for the test hand, then the value so obtained will be 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 infusion and the estimated average (E) may be taken to be the net volumetric effect of the adrenaline itself, independent of any bilateral changes in blood flow unrelated to the infusion.

For example, if as in Fig. 7 the average flow in the test hand fell from (A) 5.6 ml. before, to (B) 3.3 ml. during an adrenaline infusion, while the average blood flow in the control hand during the same period changed from (a) 9.0 ml. to (b) 7.3 ml.,

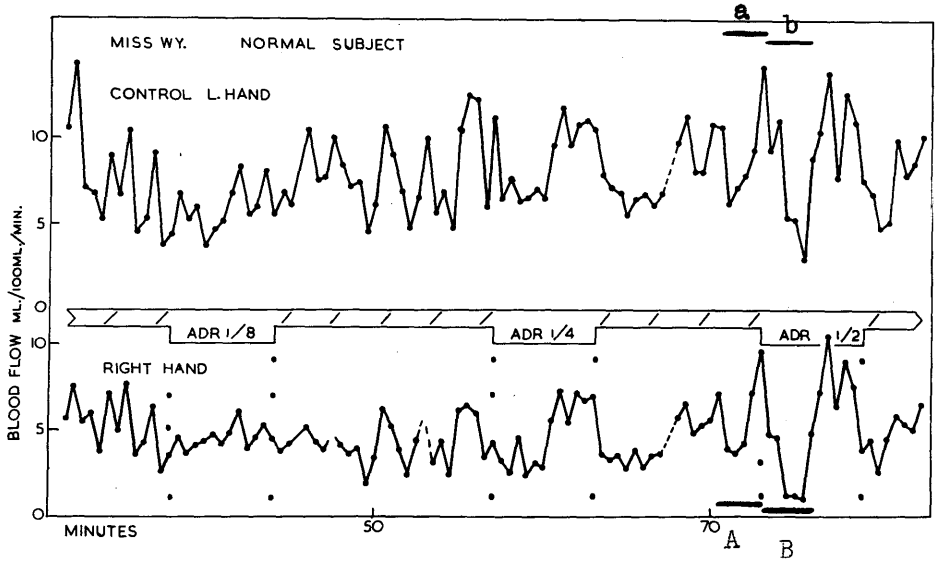


Fig. 7 Blood flow in both hands of a healthy woman during the course of a continuous intra-arterial infusion into the right brachial artery. During the 3 min. prior to the start of the infusion of adrenaline 1/2 µg./min. the mean blood flow (A) in the tested right hand was 5.6 ml. and in the control left hand (a) was 9.0 ml. During the first 3 min. of the adrenaline period the mean blood flow in the test hand (B) was 3.3 ml. and in the control hand 7.3 ml. If the adrenaline had been omitted the mean flow in the test hand (E) during the latter period would be estimated as

$$E = \frac{Ab}{a} = \frac{5.6 \times 7.3}{9.0} = 4.5 \text{ ml.}$$

The difference between the measured (B) and the estimated (E) means, (B - E) = -1.2 ml., represents the change in flow induced by the adrenaline.

then if the adrenaline had had no effect on the test hand the expected blood flow (E) in that hand during the adrenaline period would be given by the expression A/E = a/b = 4.5 ml. The reduction in flow below the estimated value, (E - B), is attributable to the adrenaline, i.e. 4.5 - 3.3 = 1.2 ml. This net change in flow expressed as a percentage, (B - E)/E % =-27%, may be taken to represent the percentage change in flow in the test hand resulting from the adrenaline. In Fig. 7 this constrictor effect of 1/2 µg. adrenaline is not at all obvious, but is evinced by these calculations. On analysis the two smaller doses had much less effect.

The expression (B - E)/E % should be nil if the adrenaline be ineffective, provided correlation in that pair of hands were perfect. However the correlation between the two hands is seldom perfect, so that estimates based on this expression have a certain error.

It was therefore necessary at the beginning to define the limits of accuracy of this method of predicting the blood flow in a given member of a pair of hands. In 9 subjects the blood flow in both hands was measured every half min. during a 6 min. period, and the mean blood flow in each hand during both halves of this period determined. Taking account of 3 of the mean values so obtained, the fourth was calculated. Comparison of this value with the

corresponding mean derived from actual measurements of blood flow during this period revealed the accuracy of the prediction. If the amount of fluctuation in a pair of hands were equal, the calculated and the actual blood flow means would be equal, and the amounts of such departures from equality as in fact occurred provided a basis for calculating the reliability of the method. In 36 comparisons of estimated and actual blood flow means, the percentage departures from the theoretical difference of nil were found to have a standard deviation of 12%, with a standard error of 2%. Four of the subjects providing this data were bilaterally sympathectomized, one was sympathectomized on one side only, the remaining 4 being normally innervated. Until the accumulation of data provided a more accurate measure, 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 during an adrenaline infusion of less than 25% were not regarded as indicating a significant change in any individual. Moreover, the level of adrenaline at which 25% constriction occurred, could be regarded as the threshold of adrenaline concentration for that particular hand.

Albeit this method of analysis of the data was subject to this error, other methods were tried and found to provide more

erroneous estimates. In the absence of adrenaline, more accurate prediction of the blood flow in an individual hand could be obtained on the assumption that the ratio of flow/change in one hand, over successive 3 min. periods, was nearly equal to the ratio of change in the other hand of a pair during the same time. Less consistent and less satisfactory predictions, for example, were obtained when the assumption was made that the volumetric change in flow in one hand was nearly equal to the volumetric change in the other hand during the same period.

Corroboration of the efficiency of the "ratio" method was forthcoming when all the data for the individual adrenaline tests at various concentration levels was assembled. It was found that the "ratio" method provided a consistently smaller range of variation in response to a given adrenaline level than any other method of analysis. Moreover the results of repeating, on the same day, the same adrenaline concentrations in testing an individual hand were more consistent when evaluated by the "ratio" than by any other method.

With the accumulation of results in both healthy subjects and patients and especially after comparative repetitions of the same test concentrations of adrenaline in the same individual, it was soon confirmed that the adrenaline effect was better expressed as a percentage, $(B - E)/E\ \%$, than as a net volumetric effect $(B - E)$.

The volumetric reduction in flow (B - E) with a given adrenaline level was, in many tests, obviously greater when the estimated flow (E) was high, and per contra. This dependence could be measured by determining the linear regression of (B) on (E) in groups receiving the same levels of adrenaline. If the volume response were independent of the control level of flow, the regression of (B) on (E) would be unity. Analysis, however, showed that in normally innervated groups, with concentrations of 1/32, 1/16, 1/8, 1/4, and 1/2 µg. adrenaline/min., the respective regressions were .863, .960, .775, .949, and .794, indicating in each case that the higher the control level (E), the relatively less was the measured flow during the adrenaline period. Taking together the results of 120 tests, irrespective of adrenaline concentration, the mean regression of (B) on (E) was .865, which value is significantly different from both 1 and 0. By expressing adrenaline effects as a percentage, (B - E)/E %, this "bias" was removed, and comparison of individuals and of groups with differing control levels became more authentic. There was now no significant regression of (B - E)/E % on (E), indicating effective removal of the influence of the control level of flow.

Regression analyses also confirmed that a more efficient measure of the adrenaline effect in the hands was obtained when the volume difference (B-E) was expressed as a percentage, not of the

initial blood flow in the test hand itself (A), but of the estimate control (E). Thus the regression of (B - E)/E % on (A) was found to have twice as great a coefficient as that of (B - E)/E % on (E), both values, however, being insignificant. The explanation of the superiority of (E) over (A) no doubt lies in the fact of the former being a derivative of a greater number of observations, in addition to taking into account the blood flow in the contralateral (control) hand. Data relative to these regression analyses are summarized in Table I.

FOREARM AND CALF — ASSESSMENT OF BLOOD FLOW CHANGES DURING INFUSIONS OF ADRENALINE

As will be shown, during the infusion of a maintained level of adrenaline by either the intravenous or the intra-arterial route, phasic changes occurred in the blood flow through muscular segments of tissue. An initial rapid vasodilator effect was common to all groups of subjects studied, but the magnitude of this evanescent change, as measured by intermittent venous occlusion plethysmography, was not susceptible of comparative analysis except in one or two cases in which unilateral sympathectomy provided an ideal control. The greater part of the third investigation was concerned with the less rapid change in blood flow during the latter part of prolonged (10 minute) infusions, which proved

TABLE I.

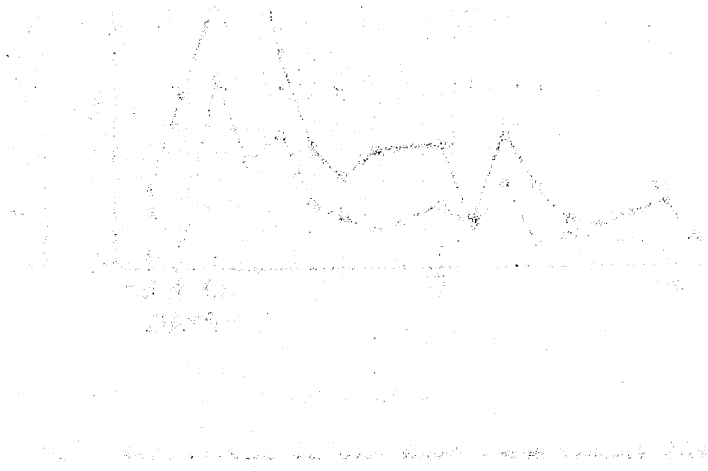
Analyses of Linear Regressions concerning the Responses of Normally Innervated Hands to Intra-arterial Infusions of Adrenaline.

Adrenaline conen. µg./min.	No. of cases.	Coefficient of B on E.	Coefficient of $\frac{E-B}{E}\%$ on A.	Coefficient of $\frac{E-B}{E}\%$ on E.
1/32	27	0.863	0.313	0.371
1/16	26	0.960	-1.025	-0.555
1/8	32	0.775	1.480	0.839
1/4	17	0.949	-0.975	-0.778
1/2	18	0.794	-5.900	-3.700
All groups	120	0.865	-0.322	-0.175
Standard deviation		0.041	0.378	0.386
Probability of not differing from unity		t 3.28 P < .01	t 1.79 P < .1	t 0.44 P < .6

A,B are mean blood flow in tested hand, during 3 min. prior to and during infusion of adrenaline, respectively; E is an estimate (E = Ab/a, where a,b are corresponding means for control hand) of what the blood flow in the tested hand would have been if the adrenaline had not been infused.

This table shows that the measured flow during an infusion of adrenaline (B) is relatively lower when the control blood flow (E) is raised, in other words that there is a greater volumetric reduction in flow with adrenaline in subjects with initially high hand blood flow. When the adrenaline effect is expressed as a percentage of the control level that effect ceases to be dependent upon the level of hand blood flow at the start of the infusion. The efficiency of the above coefficients is proportionate to their proximity to zero.

suitable for reliable comparison from group to group. For this purpose, in each subject the average of the 8 blood flow recordings during the last 4 min. of the adrenaline infusion (B) was compared with the average blood flow during the 4 min. immediately before the start of the infusion (A), and the difference (B-A) expressed as a percentage of the resting level (A) in that limb. The latter is a suitable control value because little fluctuation in flow occurs in these tissues at rest, and no advantage would result from further integration.



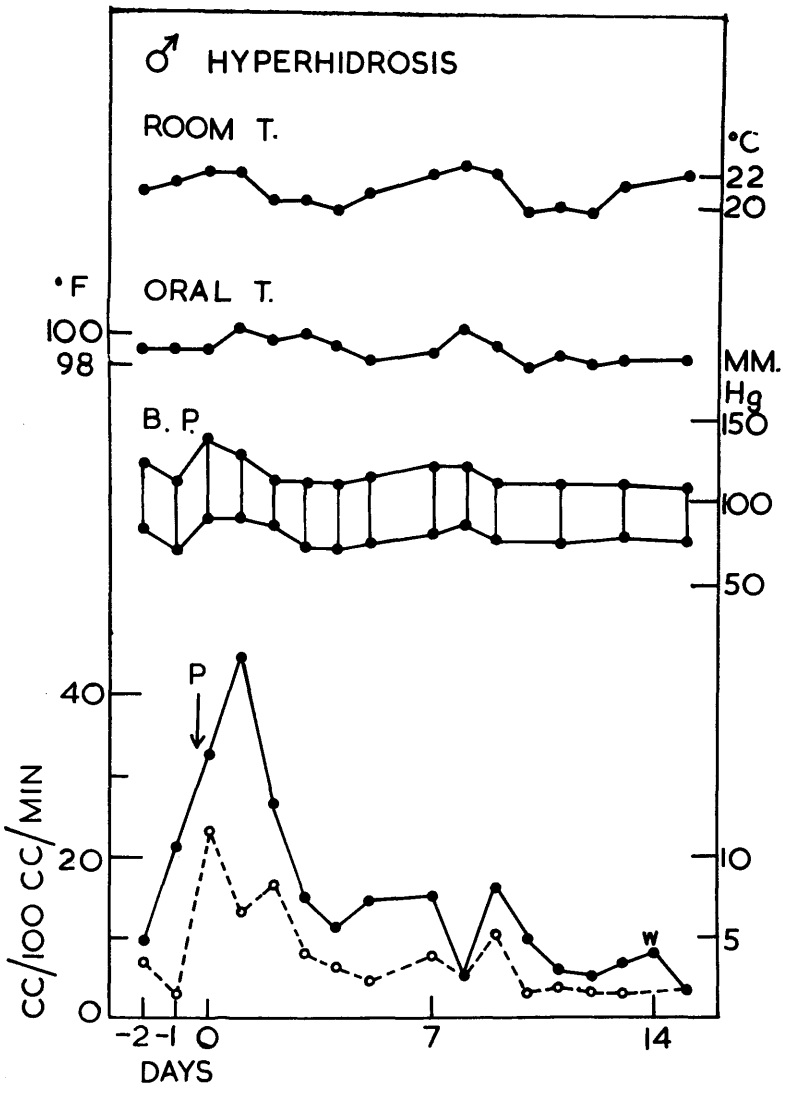


Fig. 8 Blood flow in the hand (continuous line) and forearm (interrupted line) of a young man before and after (P) preganglionic sympathectomy of one upper limb.

FIRST INVESTIGATION

EFFECT OF SYMPATHECTOMY ON HAND BLOOD FLOW OF PATIENTS WITH HEALTHY BLOOD VESSELS

Because of the infrequency with which non-circulatory disorders of the upper limb require treatment by sympathectomy, this study was confined to the 6 limbs of three patients suffering from hyperhidrosis of the hands and axillae. They were two women and one man, aged 17 - 22 years, and apart from the excessive sweating had no evidence of impaired health. They had no cardiovascular symptoms and were considered to have healthy blood vessels.

Under ward conditions, at rest in bed, the hand flow in different subjects fluctuated within moderate limits from day to day. The average preoperative flow in the 6 hands was 8.3 ml./ 100 ml./ min.

The first postoperative measurement was obtained as soon as the patients' condition permitted, in 4 cases less than 12 hours after operation, and in one at 17 hours. All observations during the 24-hour period following the end of the operation have been included in the first postoperative day (day "0") in the tables and figures.

On the first or second postoperative day the hand blood flow rose by between 8 and 66 ml., with an average rise for the

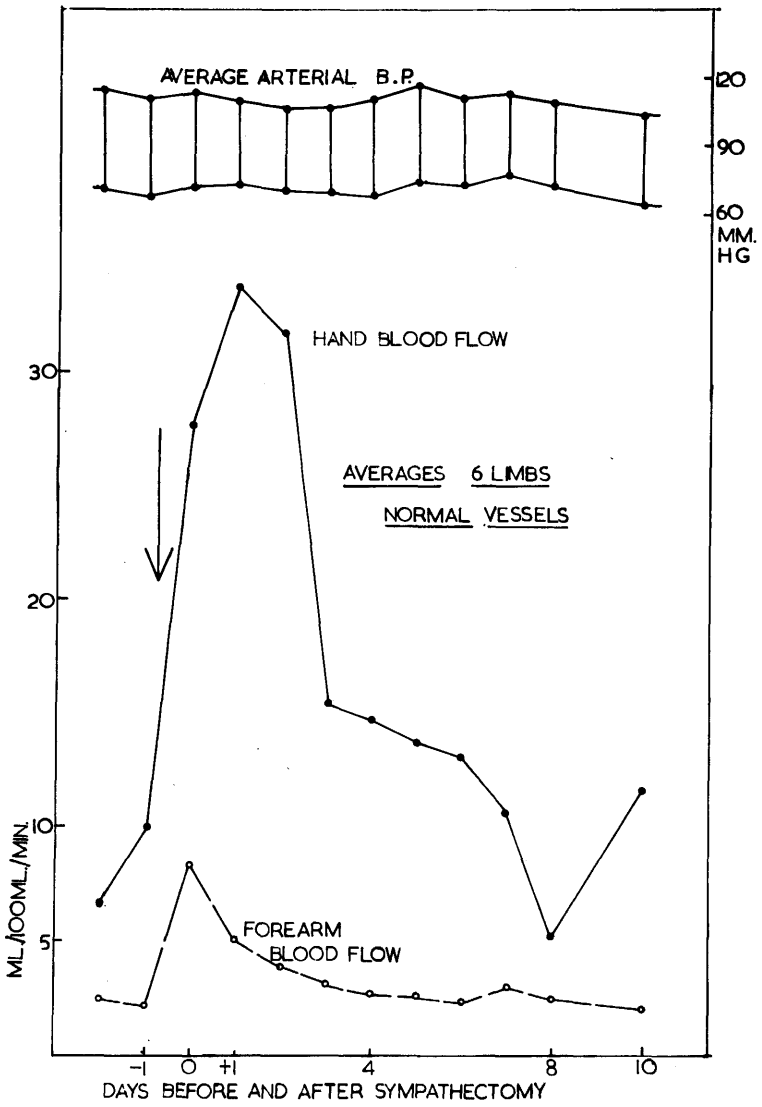


Fig. 9 Chart of averaged results in 6 limbs with hyperhidrosis sympathectomized at arrow mark. The values for the last two days are derived from fewer observations than those for earlier days, hence are less accurate.

6 hands of 19 ml. In four the peak dilatation occurred on the second day, in the other two on the first day (Table IIa).

The pattern of change in blood flow is shown in Fig. 9. The average duration of the vasodilatation in the hands was about 7 days, by which time the blood flow had generally returned to near the preoperative resting level.

CHANGES IN FOREARM BLOOD FLOW

Simultaneous study of the forearm blood flow in these 6 limbs was carried out as already described. The fluctuation in forearm blood flow, as expected, was much less than that in the hand. The average preoperative resting flow was 2.4 ml./ 100 ml./ min., with a range of 1.7 to 3.5 ml.

In 5 the blood flow rose during the first postoperative day by between 2 and 9 ml., a mean increase of about 300% (Table IIa), and the shorter the interval between the operation and the blood flow measurement, the greater the individual rise in flow found. In the 6th limb no observation was made on the first day.

During the next 24-hour period (day "1"), the forearm flow was still elevated in each limb, but generally at a lower level. Within the next 2 days the forearm blood flow was reduced in every case almost to the preoperative level (Table IIa) although small fluctuations in flow were subsequently recorded.

Table II

Blood Flow in ml./100 ml./min. in Hand (H) and Forearm (F) on Days Before and After Sympathectomy

Case No.	Sex	Age	Operation	Side	Day -2 H	Day -2 F	-1 H	-1 F	0 H	0 F	+1 H	+1 F	2 H	2 F
(A) Hyperhidrosis														
1	M	18	P	R	9.8	3.5	21.0	1.5	32.6	11.6	44.7	6.6	26.5	8.2
			G	L	13.6	2.5	21.5	2.3	14.1	7.5	25.7	9.8	9.0	2.1
2	F	21	P	R	4.0	1.9	2.0	1.7	68.6	11.0	60.0	3.9	63.2	4.1
			G	L	2.4	2.1	2.2	2.5	25.4	7.4	21.2	3.2	43.5	2.4
3	F	17	G	R	6.3	2.6	9.3	2.6	8.5	4.5	27.8	3.5	27.4	3.4
			G	L	3.3	2.3	3.7	2.4			23.1	3.4	21.2	3.2
			Averages		6.6	2.5	10.0	2.2	27.8	8.4	33.8	5.1	31.8	3.9
(B) Raynaud's disease														
4	F	25	P	R	4.0	2.5	5.1	2.6	4.3	7.6	5.6	3.7	24.5	1.8
			P	L	2.3	2.3	3.2	2.1	8.0	2.6	7.8	2.1	26.8	3.9
5	F	51	P	R	3.1	1.3	7.9	2.2	16.6	3.6	16.0	3.9	14.2	2.5
			P	L			9.5	2.0	41.0	4.7	25.0	2.9	11.7	2.2
6	F	52	P	L	2.5	1.9	1.3	1.9	7.8	5.1	9.0	3.0	9.2	1.4
7	F	54	G	R	3.8	3.5	14.6	3.1	11.8	17.9	29.0	12.0	16.9	5.4
			G	L	5.0	3.0	20.6	3.6	15.2	11.1	17.0	7.9	16.2	3.6
8	F	53	G	L			5.0	2.0	8.7	4.8	9.2	2.5	12.4	2.5
			Averages		3.5	2.4	8.4	2.4	14.2	7.2	14.8	4.8	16.5	2.9

Protocols of blood flow measurements in hands and forearms.
P = preganglionic section; G = ganglionectomy;
w = blood flow using water plethysmograph.

3		4		5		6		7		8		10	
H	F	H	F	H	F	H	F	H	F	H	F	H	F
14.9	4.0	11.0	3.2	14.6	2.3	14.0w		15.3	3.9	5.2	2.5	9.6	1.5
15.2	2.9	9.0	2.1	11.5	3.1	7.5w		5.3	2.6				
12.5	2.6	25.9	2.5	17.6	2.6	22.0w							
22.5	3.3	13.1	2.3	8.8	1.9	13.0w							
15.3	2.3	8.5	2.5	16.0	3.3	13.1	2.4	11.1	2.4			13.5	2.5
12.5	3.5	21.3	3.3			9.0w							
15.5	3.1	14.8	2.7	13.7	2.6	13.1	2.4	10.6	3.0	5.2	2.5	11.6	2.0
18.8	3.4	11.4	2.2			8.0	3.8	14.0	2.6				
20.2	2.7	22.6	3.5			16.0	3.6	13.7	3.3				
10.4	2.2	9.7	2.4	7.5	3.0			11.6	4.1	6.9	2.7	7.7	2.9
6.4	2.2	9.9	2.1			11.1	3.6			7.2	2.7		
6.3	2.1			5.9	1.7	5.0	2.3	7.1	1.7	4.6	1.3	6.4	1.9
				8.6	4.5	10.0	6.0	8.9	4.5			20.0	4.4
				10.7	4.3	10.4	4.6	9.1	4.0			17.0	4.3
7.5	2.5			6.6	2.7	5.5	1.9	6.7	2.0	5.3	1.1	8.9	3.2
11.6	2.5	13.4	2.6	7.9	3.2	9.4	3.7	10.2	3.2	6.0	2.0	12.0	3.3

It will be seen that certain average values (particularly on days 7, 8 and 10 in hyperhidrotic limbs and on days 4 and 8 in Raynaud's disease) are based on measurements in few of the cases only. These mean values are plotted in Figs. 9-11 but are less reliable and consistent than the other observations based on most or all of the cases.

On every occasion the mouth and ward temperatures and arterial blood pressure were recorded. Fig. 8 portrays the complete protocols for one individual. Although changes occurred in all these modalities, no clear relation between these and the blood flow changes was discernible in either the individual or the group records Figs. 8 & 9, Tables II, III, IV).

EFFECT OF SYMPATHECTOMY ON HAND BLOOD FLOW OF PATIENTS WITH RAYNAUD'S DISEASE

The patients in this study were 5 women aged between 25 and 55 years, having sympathectomy of 8 upper limbs for Raynaud's disease. None had any evidence of occlusive vascular disease, except when attacks of vasopasm caused discoloration of the fingers.

The average preoperative resting blood flow in the hands was 6.3 ml. On the first, second or third day following sympathectomy, the blood flow rose by between 4 and 31 ml., with an average rise of 15 ml. The peak rise in 2 of the hands occurred on the first day (day "0"), in 2 others on the second, and in the remainder on the third day following operation (Fig 10 & Table IIb).

As shown in Figs. 9 & 10, the main differences between this and the hyperhidrotic group were (1) the lower preoperative resting level of flow in the Raynaud hands, and (2) the smaller

Table III

Oral Temperature of the Patients, and Ward Temperatures on Days Before and After Sympathectomy

Case No.	Side	Days before and after sympathectomy: -2	-1	0	+1	2	3	4	5	6	7	8	10
						(A) Oral Temperature in °F.							
Hyperhidrosis													
1	R	99.0	99.0	99.0	100.3	99.6	100.0	99.3	98.4		98.9	100.3	98.1
	L	98.4	98.9	100.3	99.3	98.1	98.8	98.3	98.5		98.5		
2	R & L	98.7	98.7	99.5	99.0	98.9	98.4	98.3	98.5				
3	R	98.8	98.4	98.6	99.1	99.0	98.1	97.6	98.4	98.2		99.0	98.2
	L	98.4	98.2		99.0	97.9	98.2	99.0					
Ave.		98.7	98.6	99.4	99.3	98.7	98.7	98.5	98.5				
Raynaud's disease													
4	R & L	97.5	98.2	96.6	99.0	98.6	99.0	98.8		98.7	99.0		
5	R	98.0	98.2	99.2	99.4	99.4	98.4	98.6	98.7		99.6	99.2	99.4
	L		98.2	98.1	100.8	99.8	99.0	98.4		99.0		98.1	
6	L	98.0	98.0	99.3	98.4	100.0	99.0		99.2	98.2	98.8	99.1	98.4
7	R & L	99.2	99.0	99.0	100.7	100.0			99.6	99.7	99.0		
8	L	98.0		99.6	99.5	99.1	97.8		98.8	98.6	98.4	98.8	99.0
Ave.		98.1	98.3	98.6	99.6	99.5	98.6		99.1	98.8	99.0	98.8	99.0

(B) Ward Temperature in °C.

Hyperhidrosis													
1	R	20.8	21.4	22.0	22.0	20.3	20.3	19.7	20.8	22.0	22.0	22.5	19.7
	L	22.0	22.0	22.5	22.0	19.7	20.0	19.7	21.4	22.0	22.0		
2	R & L	17.0	17.0	19.7	17.8	18.1	18.6	18.6	17.0	23.0	22.0		
3	R	18.0	18.6	19.2	17.6	18.5	18.0	18.1	19.8	18.1		23.0	19.8
	L	19.8	18.1		23.0	18.1	19.8	16.4		23.0			
Ave.		19.5	19.4	20.9	20.5	18.9	19.3	18.5	19.8	21.6	22.0		
Raynaud's disease													
4	R & L	17.6	22.0	23.0	22.0		23.0	20.2		21.4	22.4		
5	R	17.0	18.0	21.0	21.4	18.6	24.0	18.0	17.6		19.7	18.0	17.9
	L		20.0	17.0	18.0	19.0	19.5	17.5		19.0		17.5	
6	L	16.0	17.0	17.5	14.0	17.0	16.0		17.0	15.0	18.0	16.5	17.0
7	R & L	20.8	21.4	18.6	23.0	20.0			20.9	20.6	20.9		19.2
8	L	17.5		17.5	14.0	16.5	16.0		17.0	15.0	17.0	16.0	17.0
Ave.		17.8	19.7	19.1	18.7	18.2	19.7		18.1	18.2	19.6	17.0	17.8

vasodilatation following sympathectomy. Both differences may well be the result of the vascular disorder in the Raynaud group.

CHANGES IN FOREARM BLOOD FLOW

The preoperative level of forearm blood flow in the 8 Raynaud limbs was about the same (2.4 ml.) as in the hyperhidrotic limbs. Six of the Raynaud limbs also had a maximal increase in forearm blood flow during the first 24 hours after operation, of from 2.7 to 14.4 ml. (Table IIb) averaging about 6. ml. In the 2 other limbs the maximal flow was recorded on one or other of the 2 subsequent days. Fig. 10 shows that in the Raynaud limbs also the forearm blood flow had returned nearly to the resting level by the third or fourth postoperative day. In these Raynaud limbs also the forearm blood flow fluctuated a little during the subsequent 10 days.

Figs. 9 & 10 show that the arterial blood pressure was practically unaltered in both groups during the peak vasodilatation following upper limb sympathectomy, even when the operation was performed simultaneously on both sides. All but one of the patients had normal blood pressures, and in these there appeared to be no consistent relationship between the actual levels of blood pressure and the hand or forearm blood flow. However, the greatest individual rise in forearm flow was recorded in a woman (Table II, case 7) with

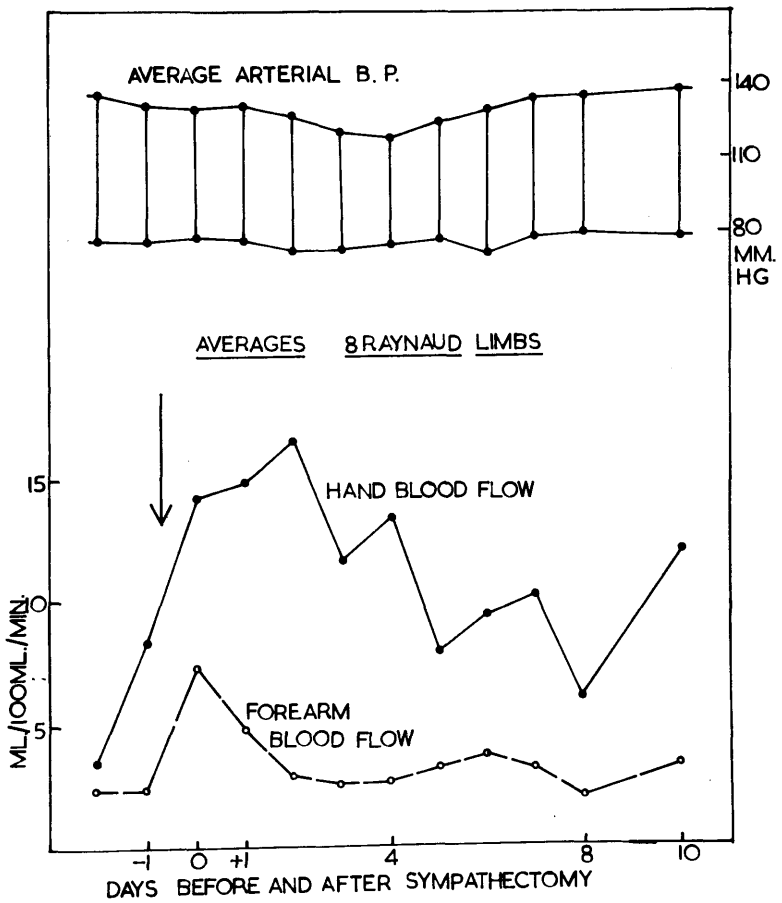


Fig. 10 **Chart of averaged results in 8 limbs sympathectomized at arrow mark for Raynaud's disease.**

a degree of systolic arterial hypertension who had bilateral cervicothoracic ganglionectomy for Raynaud's disease. The operation made little material difference to the level of blood pressure.

The ward temperatures were on the average slightly higher (17° to 23° C.) for the hyperhidrotic group, operated during the summer months, than for the Raynaud group (14° to 23° C.), who were mostly operated in autumn or winter (Table IIIb). In most individuals the environmental temperature bore little relation to changes in hand and forearm blood flow after operation, as found by Freeman (1935). In 2 Raynaud cases, however (Tables II & III, cases 6 & 8), the comparatively low figures for blood flow may have been partly due to the very low ward temperatures (14° to 18° C.) obtaining at that time.

In general, oral temperature (Table IIIa) was not shown to bear any precise relationship to the circulatory changes following sympathectomy. In every case the oral temperature was elevated for some days, presumably because of metabolic changes resulting from the operation.

Table IV

Arterial Blood Pressure of Sympathectomized Patients

Case No.	Side	Days before and after sympathectomy											
		-2	-1	0	1	2	3	4	5	6	7	8	10
(a) Hyperhidrosis													
1	R	120/82	110/68	136/88	126/88	110/84	110/82	109/70	114/74		120/80	120/85	
	L	109/70	114/74	120/85	120/85		110/74		110/78		108/76		
2	R & L		110/65	104/60	100/66	108/74	112/72	118/78	122/78				
3	R	110/60	110/60	95/55	108/64	106/62	100/60	105/58	120/70	112/74		100/60	104/64
	L	120/70	112/74		100/60	104/64	106/62						
Averages		115/71	111/68	114/71	111/73	107/71	108/70	111/69	117/75				
(b) Raynaud's disease													
4	R & L	120/68	118/82	100/66	126/78	116/76	120/76	112/70		120/72	116/70		
5	R	124/78	124/78	128/72	128/76	120/60	124/74	122/76	126/70		126/70	116/66	130/82
5	L		134/80	126/82	116/76	116/78	116/70	122/82		116/72	137/90		
6	L	126/76		132/88	134/76	136/70	120/74		124/74	130/80	126/76	128/84	120/70
7	R & L	185/85	150/70	166/78	150/74	152/72				158/50	162/86	156/80	160/74
8	L	132/84		128/86	130/84	126/80	124/76		126/86	128/88	134/84	140/88	140/85
Averages		137/78	132/78	130/79	131/77	128/73	121/74	119/76	125/77	130/72	134/79	135/80	138/78

INTERPRETATION OF THE RESULTS OF THE FIRST INVESTIGATION

The results in both groups of subjects indicate that the blood flow in the forearm began to rise soon after sympathectomy and reached a peak usually within 24 hours of operation. During the succeeding two or three days the forearm blood flow returned fairly rapidly to normal resting levels (Figs. 8, 9 & 10). The maximal change in forearm flow varied in different individuals but there was on the average a threefold increase in both the hyperhidrotic and the Raynaud groups.

The hand blood flow, by contrast, generally took some 48 hours to reach a peak, and the increased flow in the hand remained evident for two or three days longer than that in the forearm (Figs. 9 & 10). The increase in flow was smaller in the Raynaud (Fig. 10) than in the hyperhidrotic group, but its duration was about the same.

With respect to the type of operation, Fig. 11 shows that while the overall increase in hand blood flow was somewhat greater following preganglionic section, the change in forearm flow was slightly, but not significantly, greater after ganglionectomy. It is noteworthy that in the mixed group of subjects having preganglionic section, the majority had Raynaud's disease, in contrast with the ganglionectomized group which included more subjects with healthy blood vessels. This indeed suggests that a slightly greater skin

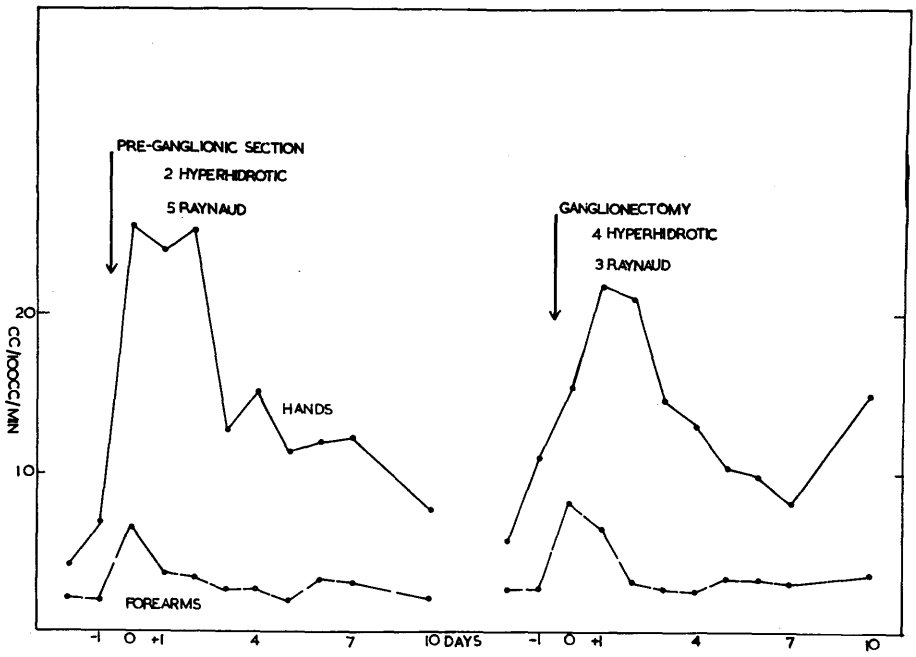


Fig. 11 Comparison of the effects of the two types of operation on blood flow in hand and forearm. Averaged results of all hyperhidrotic and Raynaud cases, contrasted only with respect to the operation.

vasodilatation, in the early days after operation, may result from preganglionic section. Confirmation of this must await further comparable studies of a larger number of cases.

In individual subjects (Table II) as well as in the group averages (Figs. 9 & 10) there was no precise positive correlation between changes in forearm and in hand blood flow. The blood flow in the forearm was often decreasing at a time when that in the hand was increasing, and vice versa. The forearm has more than four times as much muscle as skin, whereas the hand has twice as much skin as muscle. When the forearm skin was flushed by applying mustard paste Barcroft, Bonnar & Edholm (1947) found that the forearm blood flow increased by only 2 or 3 ml., but in recently sympathectomized limbs the forearm skin is not flushed but is puffy and pallid. Blocking the cutaneous nerves of the forearm caused only a slight rise in forearm blood flow (Barcroft, Bonnar, Edholm & Effron, 1943). In contrast, the reflex increase in forearm flow which, in the normally innervated upper limb, follows indirect heating of the body, amounts to about a threefold rise, and this has been shown to represent mainly an increase in the circulation through the skeletal muscle, due to release of vasoconstrictor tone (Barcroft & Edholm, 1945). An increase in skin blood flow doubtless occurs also, but cannot account for the change in forearm blood flow. The threefold rise in forearm blood flow after sympathectomy may

therefore be attributed largely to dilatation of the vessels in the muscle.

In the hands the increase in blood flow undoubtedly took place mainly through the vessels of the skin, hence the smaller than normal rise in those patients with disease of the cutaneous vessels.

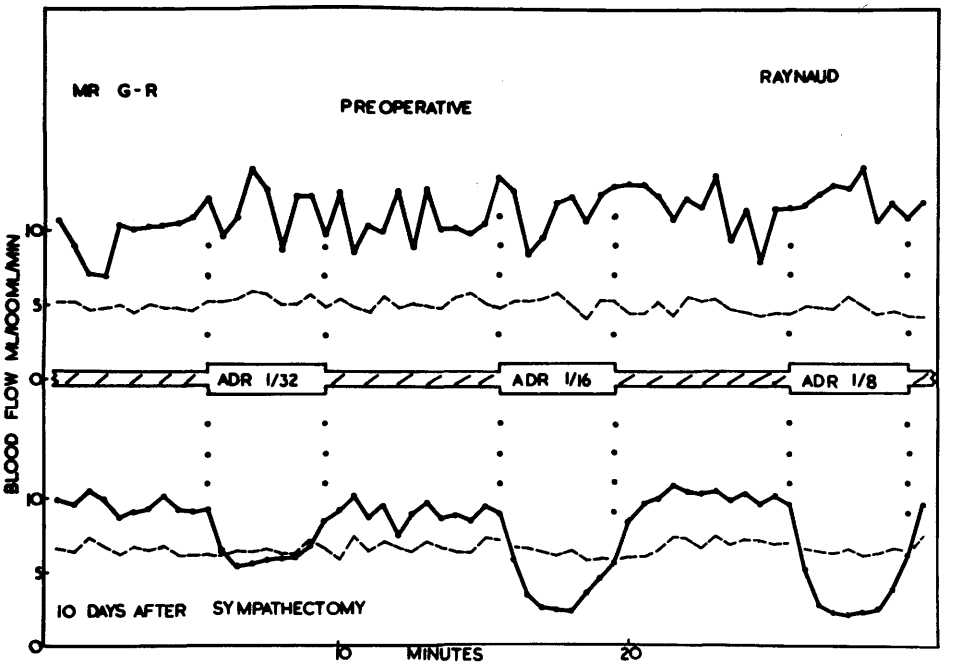


Fig. 12 Blood flow in the tested right hand (continuous heavy line) and in the control left hand (interrupted faint line) during the course of infusions into the right brachial artery. The upper half of the diagram indicates that virtually no change in flow resulted from the three adrenaline infusions before operation. After the right hand had been sympathectomized all three adrenaline concentrations caused obvious vasoconstriction (lower half).

SECOND INVESTIGATION

VASOCONSTRICTOR EFFECT IN THE HAND OF INTRA-ARTERIAL INFUSIONS OF ADRENALINE IN PATIENTS BEFORE AND AFTER SYMPATHECTOMY

The first requirement was to compare the responses of individual hands before and after sympathectomy to the same range of concentrations of adrenaline.

In Fig. 12 the blood flow in the hands of a man with Raynaud's disease is charted. The heavy continuous line in this and subsequent figures represents blood flow in the tested hand, the interrupted faint line being the blood flow in the opposite control hand. In this patient the control left hand had been sympathectomized before both the preoperative (upper) and post-operative (lower) tests of the right hand. Before operation infusions of 1/32, 1/16 and 1/8 µg. adrenaline/ min. had no obvious effect. Ten days after preganglionic section the same three infusions caused quite definite constriction in the tested right hand (Fig. 12).

A similar change is demonstrated in Fig. 13, the blood flow responses in the tested left hand of a young woman with Raynaud's disease. Before operation (upper half) the intra-arterial infusion of 1/32 µg. adrenaline/ min. was coincident with vasoconstriction in the tested left hand and also in the control right hand. Had the

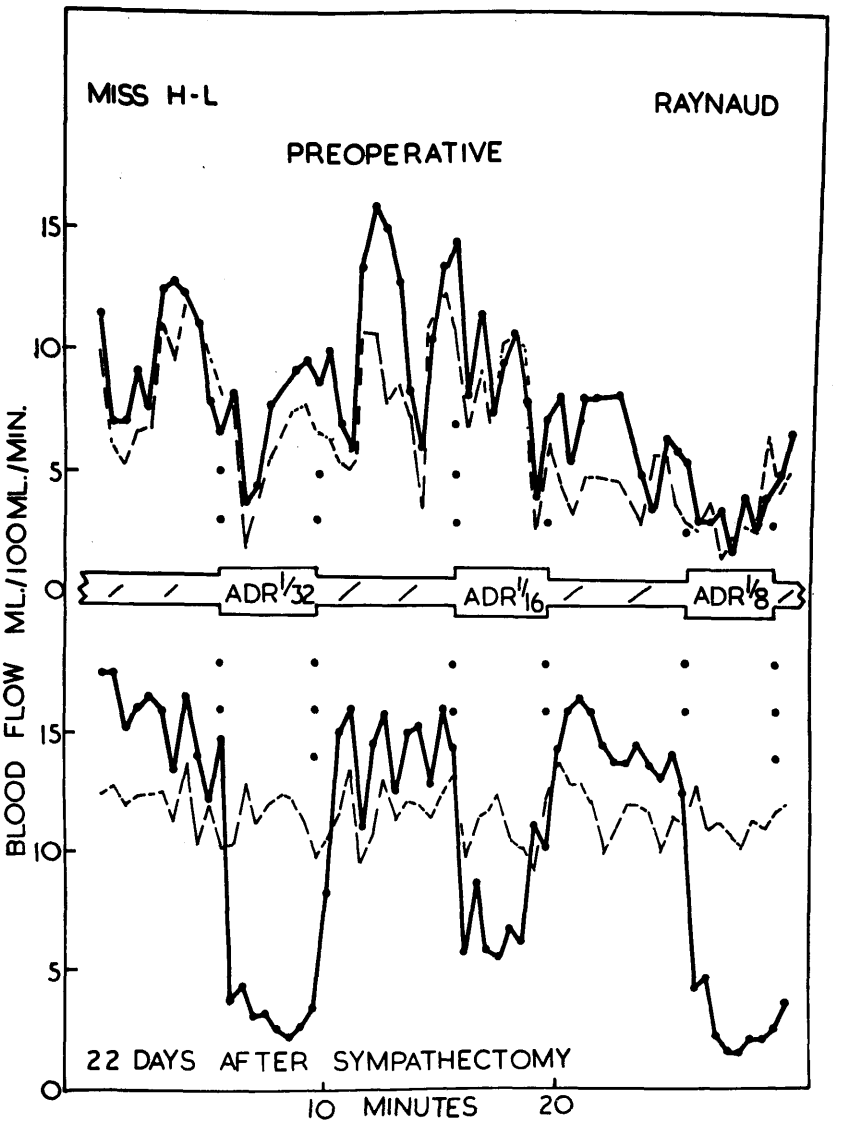


Fig. 13 Blood flow in the tested left hand (heavy line) and control right hand (faint line) of patient before (upper) and after (lower) sympathectomy of the left side. Adrenaline infusions into the left brachial artery had little independent effect on the left hand before operation, but produced marked reduction in flow after preganglionic section.

observations relating to the latter been omitted, this vaso-constriction might erroneously have been attributed to the adrenaline. The synchronous fluctuation in blood flow throughout the test is seen to be of about equal degree in both hands (both normally innervated), irrespective of whether adrenaline or saline was 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 was seen (Fig. 13 lower). All three dose levels of adrenaline were attended by marked vaso-constriction in the tested left hand, the right being unaffected.

A further example of the change resulting from sympathectomy is shown in Fig. 14. Before operation the infusion of adrenaline into the left brachial artery caused constriction in the left hand of this patient only when a concentration of 1/8 µg./min. was reached. Eight weeks after operation (preganglionic section), 1/32 and 1/16 µg. adrenaline caused definite constriction in the left hand, while the reduction in flow with 1/8 µg. was very much greater than had resulted from this adrenaline level before operation.

Ten hands (all but two of which had Raynaud's disease) were tested in this way with infusions of adrenaline within the range 1/64 to 1/8 µg./ min., and six were found, after sympathectomy, to be obviously constricted with concentrations that had had little or no

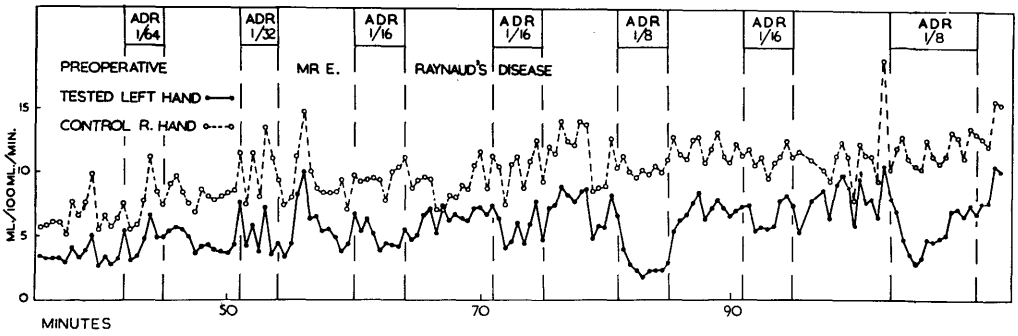
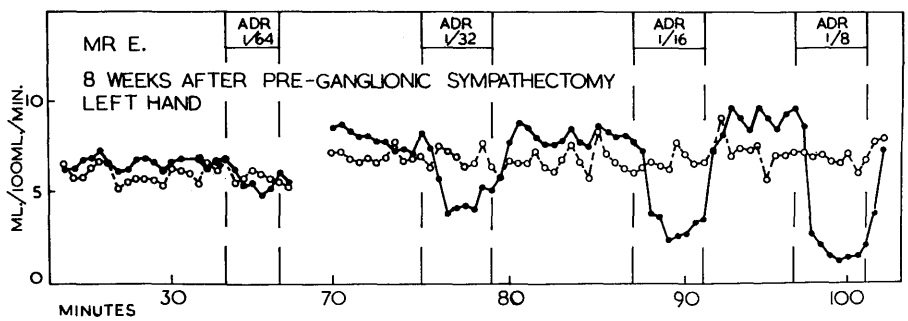


Fig. 14 Before operation adrenaline infusions into the left brachial artery had little effect on the blood flow in the left hand until a concentration of 1/8 µg./min. was reached.



After sympathectomy intrabrachial infusions of 1/32, 1/16 and 1/8 µg. adrenaline/min. caused notable vasoconstriction in the left hand.

effect before operation (Table V). 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 cervico-thoracic ganglia.

The postoperative tests (Table V) relate especially to the early weeks after operation, and the earliest was 6 days. In one case, however, of a young man, Mr. C., who had had traumatic avulsion of the brachial plexus on the left side as a result of which the limb was completely sympathectomized, tests performed one year after his accident revealed definite vasoconstriction with 1/64 µg. adrenaline/min. In this sole instance the response of the sympathectomized hand was 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 constrict with such a small concentration of adrenaline.

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-min. before and during the adrenaline infusions. Fig. 15 demonstrates the change in respect of 1/8 µg./min. Although the graphs of hand blood flow, as in Figs. 12, 13 & 15, clearly reveal the different response in the hands after sympathectomy, it was

Table V

Comparison of Adrenaline Effect in Thirty-Three Paired Tests, Pre- and Post-Operative

BEFORE SYMPATHECTOMY

Subject	Condition		Age	Mean blood flow: Test hand A	Test hand B	Control hand a	Control hand b	E	B - E	(B - E)/E %
Adrenaline 1/64 µg./min.										
Mr E.	R	RD	63	4.5	4.9	6.9	8.2	5.3	-0.4	- 7
	L	RD		3.4	4.9	6.1	8.2	4.5	0.4	9
Mr G.	R	RD	50	9.1	9.5	4.8	5.1	9.7	-0.2	- 2
	L	RD		9.4	9.6	11.0	9.5	8.1	1.5	19
Mrs C.	L	RD	51	4.0	4.2	12.1	15.7	5.2	-1.0	-19
Mr C.		T	25	13.8	13.1	2.9	3.4	16.2	-3.1	-19
Adrenaline 1/32 µg./min.										
Mr E.	R			4.3	4.4	7.7	8.4	4.7	-0.3	- 6
	L			4.6	5.2	8.6	10.1	5.4	-0.2	- 4
Mr G.	R			10.7	11.4	4.8	5.4	12.0	-0.6	- 5
	R			9.7	9.8	6.3	6.7	10.3	-0.5	- 5
	L			12.4	11.9	10.3	10.4	12.5	-0.6	- 5
	L			10.7	10.3	8.2	8.3	10.8	-0.5	- 5
Miss H.	R	RD	25	5.0	5.1	10.0	9.6	4.8	0.3	6
	L	RD		10.5	6.4	10.7	5.7	5.6	0.8	14
Mrs W.	R	RD	52	9.0	10.9	10.0	14.4	13.0	-2.1	-16
	R			12.8	12.2	10.6	10.0	13.4	-1.2	- 9
Adrenaline 1/16 µg./min.										
Mr E.	R			4.8	4.1	18.2	20.0	5.3	-1.2	-23
	R			3.6	3.1	19.5	18.6	3.4	-0.3	- 9
	L			6.4	5.5	10.2	10.2	6.4	-0.9	-14
Mr G.	R			10.6	9.1	5.8	5.7	10.4	-1.3	-13
	L			11.3	10.5	10.7	10.2	10.7	-0.2	- 2
Miss H.	R			4.2	3.0	9.0	7.7	3.6	-0.6	-17
	L			11.0	9.3	9.1	8.8	10.6	-1.3	-12
Mrs W.	R			11.1	9.5	14.1	12.7	10.0	-0.5	- 5
Miss B.	R	H	19	4.6	4.3	5.9	6.3	4.9	-0.6	-12
Adrenaline 1/8 µg./min.										
Mr E.	R			2.8	3.6	14.7	15.1	2.9	0.7	24
	L			7.8	4.0	12.1	11.5	7.4	-3.4	-46
Mr G.	R			9.3	4.9	6.7	6.4	8.8	-3.9	-44
	L			11.3	10.2	8.8	8.3	10.6	-0.4	- 4
Miss H.	R			3.7	5.5	6.4	8.7	5.0	0.5	10
	L			5.3	3.0	4.3	2.7	3.3	-0.3	- 9
Mr W.	R			13.0	7.4	16.9	13.7	10.5	-3.1	-30
Miss B.	R			5.3	3.2	6.4	5.4	4.5	-1.3	-29
Ave.				7.9						- 9

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;

AFTER SYMPATHECTOMY

Operation	Post-op test at:	Mean Blood Flow Test hand A	hand B	Control a	hand b	E	B - E	B - E/E %
P	7 days	6.5	6.3	6.4	6.5	6.6	- 0.3	- 5
P	8 weeks	6.7	5.4	6.2	5.8	6.3	- 0.9	-14
P	10 days	5.9	4.1	5.9	6.1	6.1	- 2.0	-33
P	22 days	5.9	5.5	6.8	6.7	5.8	- 0.3	- 5
P	5 months	8.3	6.9	4.3	4.2	8.1	- 1.2	-15
T	12 months	6.3	3.9	9.8	8.6	5.5	- 1.6	-29
P	7 days	6.7	5.7	7.2	8.3	7.7	- 2.0	-26
P	8 weeks	7.0	4.6	7.0	7.2	7.2	- 2.6	-36
P	10 days	9.4	5.8	6.4	6.3	9.3	- 3.5	-38
P	10 days	8.1	5.5	6.5	6.2	7.7	- 2.2	-29
P	22 days	7.6	4.5	4.8	4.8	7.6	- 3.1	-41
P	22 days	7.3	4.5	7.0	6.8	7.1	- 2.6	-37
P	14 days	10.3	10.0	10.1	10.1	10.3	- 0.3	- 3
P	22 days	14.7	4.0	11.8	11.5	14.4	-10.4	-72
G	11 days	8.7	8.2	10.7	11.1	9.0	- 0.8	- 9
G	11 days	10.6	9.4	11.6	11.1	10.1	- 0.7	- 7
P	7 days	7.5	4.3	9.0	8.4	7.0	- 2.7	-39
P	7 days	7.8	6.6	8.3	7.9	7.4	- 1.8	-24
P	8 weeks	8.1	3.1	6.9	7.0	8.2	- 5.1	-62
P	10 days	9.0	3.3	6.7	6.2	8.3	- 5.0	-60
P	22 days	7.6	3.6	5.2	4.8	7.0	- 3.4	-49
P	14 days	10.5	7.3	10.5	10.2	10.2	- 2.9	-28
P	22 days	14.4	6.4	12.1	11.1	13.2	- 6.8	-47
G	11 days	9.2	8.1	12.5	11.6	8.5	- 0.4	- 5
G	14 days	6.7	5.8	9.4	9.4	6.7	- 0.9	-13
P	7 days	6.6	2.5	6.8	6.7	6.5	- 4.0	-62
P	8 weeks	9.2	1.8	7.0	6.9	9.1	- 7.3	-80
P	10 days	9.9	2.8	7.0	6.3	8.9	- 6.1	-72
P	22 days	7.6	3.2	4.4	4.5	7.8	- 4.6	-59
P	4 months	8.1	5.9	9.9	9.4	7.6	- 1.7	-22
P	22 days	13.7	2.7	11.4	11.2	13.5	-10.8	-80
G	11 days	7.8	4.9	11.1	11.2	7.9	- 3.0	-39
G	14 days	6.2	4.8	10.1	11.0	6.8	- 2.0	-29
		8.5						-35

E = Ab/a; P = preganglionic; G = ganglionectomy; RD = Raynaud's disease; H = hyperhidrosis; T = patient sympathectomized as result of traumatic avulsion of brachial plexus.

necessary to adopt the scheme of analysis described in Methods, section (6) to obtain a numerical expression of that difference in response.

In a precise comparison of thirty-three tests of the ten hands before and after sympathectomy, exactly paired with respect to the levels of adrenaline (Table V), only 4 preoperative tests (all at infusion rates of 1/8 µg./min.) resulted in significant vasoconstriction, whereas after operation twenty-two of the thirty-three tests revealed significant (i.e., more than 25%) 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 ($t = 3.25$, $P < 0.001$).

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.

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 in the next project.

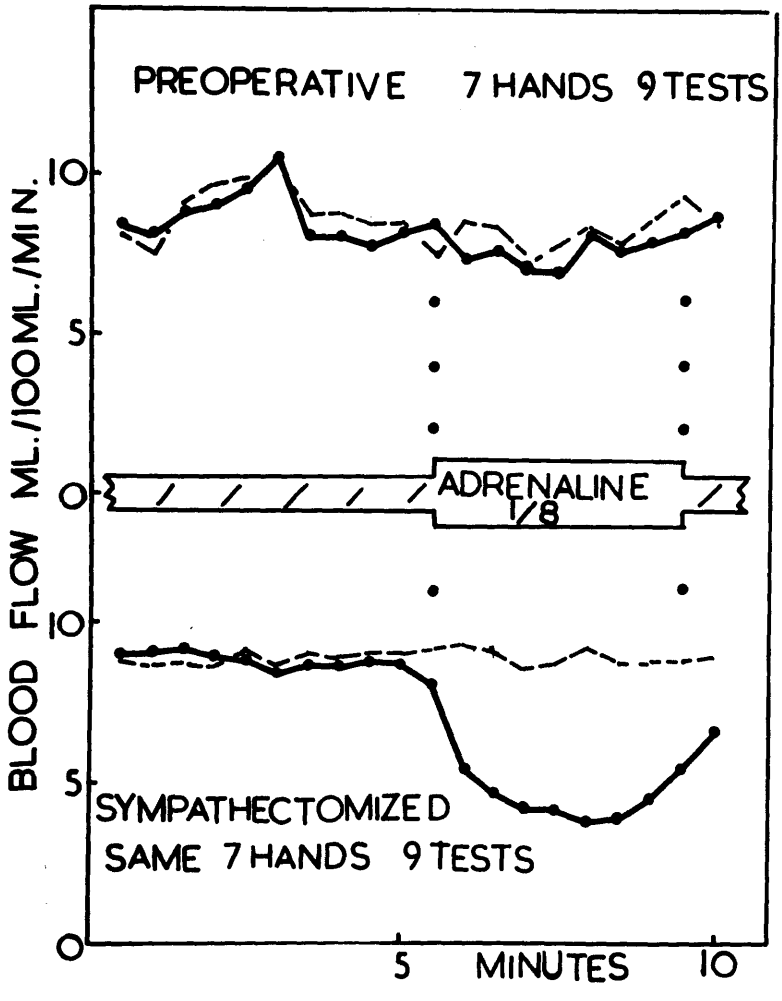


Fig. 15 Average blood flow changes each half minute before and during intrabrachial infusions of adrenaline 1/8 µg./min. in 7 hands before and after sympathectomy. The heavy line represents the average blood flow in the tested hands and the faint line the average for the respective control hands.

VASOCONSTRICTOR EFFECT IN THE HANDS OF HEALTHY SUBJECTS OF INTRA-ARTERIAL INFUSIONS OF ADRENALINE

To establish the normal range of response of the blood vessels of the hand to graded doses of adrenaline, similar studies of 28 healthy subjects were made. The procedure already outlined enabled the response of the blood flow in the tested hand of each individual to be measured during successive intra-arterial infusions of adrenaline. The control observations of "spontaneous" changes in the circulation in the hand on the opposite non-infused side provided a basis for analyzing the independent local effect of the adrenaline in the tested hand. In each experiment, lasting about two hours, the response to betweeen 4 and 8 separate infusions of adrenaline could be measured. The usual procedure was to commence with a level (1/64 µg./min.) which would have no effect, and, after the regular control period of 8 min. (in earlier experiments 10 or 12 min., unnecessarily long periods) to give 1/32 µg./min., and so on, with successive doubling of concentration levels. In most cases one or more test-levels of adrenaline were repeated at some point in the experiment. To test the full range of concentrations of 1/64 to 1/2 µg./min. intermediate levels were omitted in some subjects.

Since the level of 1/64 µg. was found to have no effect in the healthy subjects, protocols relating to this are not presented.

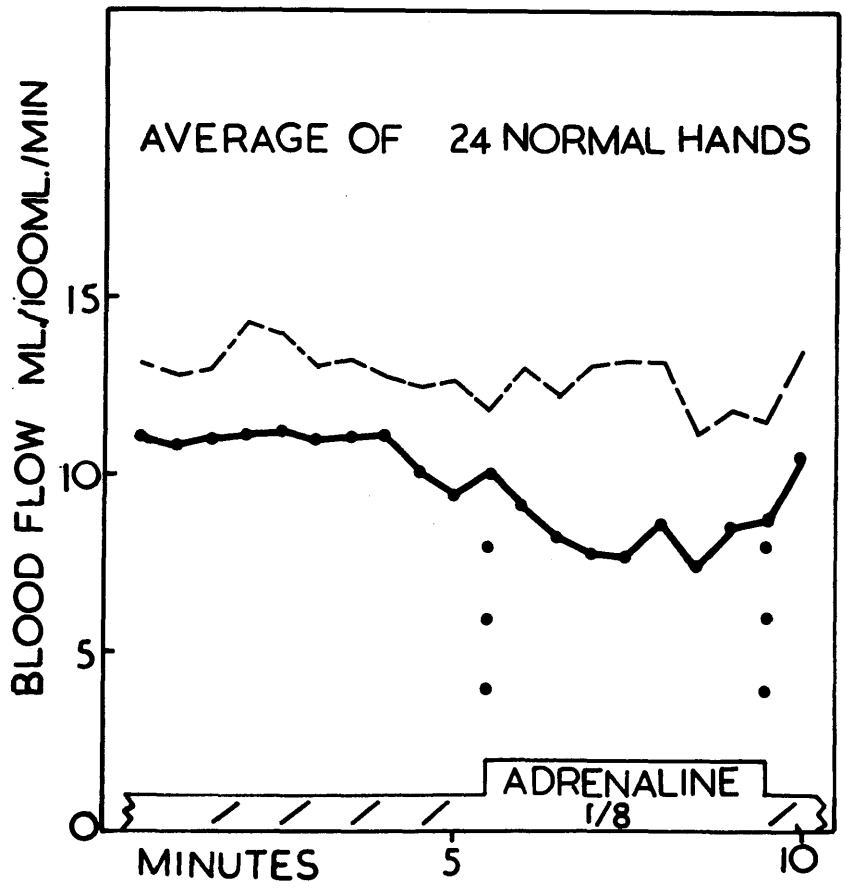


Fig. 16 Average blood flow changes each half minute before and during intrabrachial infusions of adrenaline 1/8 µg./min. in the hands of 24 healthy subjects. The heavy line represents the average blood flow in the tested hands and the faint line the average for the respective control hands.

A small number of subjects exhibited vasoconstriction in the hand with infusions of 1/32 µg. adrenaline. In 17 tests (Table VI) only two had more than 25% reduction in blood flow. The mean change of the group was a reduction of 10%.

With 1/16 µg. adrenaline/min. the mean blood flow change in 17 tests was a reduction of 7%, three members having significant reduction (Table VII). Both these levels of adrenaline are therefore without effect in the majority of subjects, under the conditions of the tests.

In 24 tests with the concentration 1/8 µg./min. the mean change was 19% reduction, 9 individuals having significant changes (Table VIII). The average blood flow change each half-min. in the hands of this large group is plotted in Fig. 16, which may be compared with the upper half of Fig. 15, the preoperative response of the patients to this level of adrenaline.

In 17 tests with 1/4 µg. and 18 tests with 1/2 µg. adrenaline/min., mean changes of 27% and 53% reduction, respectively, were found (Table IX).

With this information on the response of the hands of healthy subjects to the various levels of adrenaline it was possible to determine whether the results of the patients' preoperative tests did or did not fall within the normal range. Taking account of the standard deviations of the observations there was seen (Table X) to

Table VI

Effect of Intra-brachial Infusions of Adrenaline 1/32 µg./min. on Blood Flow in Normal Hands

Hand	Sex	Mean Blood Flow: Test hand A	Test hand B	Control hand a	Control hand b	E	E - B	$\frac{E - B}{E}$%
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
Ave.		16.1						-10

A,a = means of the 6 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.

Table VII

Effect of Intra-brachial Infusions of Adrenaline 1/16 µg./min. on Blood Flow in Normal Hands

Hand	Age	Sex	Mean Blood Flow Test hand A	Test hand B	Control hand a	Control hand b	E	B - E	$\frac{B-E}{E}$ %
R	42	M	6.3	5.3	7.8	6.9	5.6	-0.3	- 5
R	23	M	2.7	2.8	3.5	4.1	3.2	-0.4	-13
R	29	M	3.6	3.4	3.4	3.5	3.7	-0.3	- 8
R	21	M	19.4	20.5	26.8	24.9	18.0	2.5	14
R	35	M	11.0	13.0	9.7	10.4	11.8	1.2	10
R	26	M	4.4	3.7	2.3	2.6	5.0	-1.3	-26
R	24	M	13.3	10.1	9.8	9.8	13.3	-3.2	-24
R	26	M	8.5	9.2	4.2	4.8	9.7	-0.5	- 5
R	26	M	4.3	2.7	4.6	5.2	4.9	-2.2	-45
R	24	M	13.8	10.5	17.4	22.0	17.4	-6.9	-40
R	25	M	19.5	22.8	18.5	23.8	25.1	-2.3	- 9
R	24	M	6.0	5.7	7.0	6.1	5.2	0.5	10
R	25	M	4.7	4.4	6.5	6.0	4.3	0.1	2
R	27	M	14.8	16.1	37.3	41.2	16.3	-0.2	- 1
R	27	M	15.1	15.3	37.1	31.8	12.9	2.4	19
R	27	M	16.6	15.6	34.0	33.0	16.1	-0.5	- 3
R	27	M	18.2	16.6	27.2	23.4	15.7	0.9	6
Ave.			10.7						- 7

A,a = means of the 6 observations of blood flow during 3 min. immediately prior to start of adrenaline, in test and control hands, respectively;
B, = corresponding means during first 3 min. of adrenaline period;
E = Ab/a.

Table VIII

Effect of Intra-brachial Infusions of Adrenaline 1/8 µg./min. on Blood Flow in Normal Hands

	Age	Sex	Mean Blood Flow: Test hand A	Test hand B	Control hand a	Control hand b	E	B - E	$\frac{B-E}{E}$ %
R	24	M	17.4	8.2	13.8	11.3	14.2	- 6.0	-42
R	25	M	19.8	13.0	20.6	22.4	21.5	- 8.5	-40
R	28	M	22.2	1.7	20.1	12.4	13.7	-12.0	-88
R	26	M	13.2	5.8	7.3	7.1	12.8	- 7.0	-55
R	24	M	14.1	13.8	20.8	23.7	16.1	- 2.3	-14
R	21	M	21.3	22.2	31.9	32.9	22.0	0.2	1
R	27	M	18.0	15.9	35.4	34.9	17.7	- 1.8	-10
R	27	M	15.1	16.6	32.7	32.1	14.8	1.8	12
R	42	M	2.0	2.4	3.4	3.5	2.1	0.3	14
R	42	M	3.4	2.9	3.9	2.9	2.5	0.4	16
R	30	F	3.0	3.6	3.6	4.0	3.3	0.3	9
R	35	M	3.0	2.9	3.0	3.0	3.0	- 0.1	- 3
R	26	M	10.2	13.9	9.5	12.8	13.7	0.2	2
R	26	M	13.7	11.7	18.6	14.1	10.4	0.7	7
R	29	M	10.1	11.5	10.8	12.7	11.9	- 0.4	- 3
R	25	F	4.2	4.3	5.7	5.3	3.9	0.4	10
R	25	M	5.3	5.9	6.4	7.6	6.3	- 0.4	- 6
R	25	M	8.3	4.5	7.4	9.2	10.3	- 5.8	-56
L	49	M	12.2	9.2	12.9	11.1	10.4	- 1.2	-12
L	49	M	14.3	10.4	11.6	12.3	15.1	- 4.7	-31
R	26	M	4.7	2.7	5.7	5.7	4.7	- 2.0	-43
R	27	M	5.3	2.9	8.6	7.3	4.5	- 1.6	-36
R	25	M	3.8	0.4	5.0	3.6	2.7	- 2.3	-85
R	24	M	7.9	10.4	7.7	9.8	10.1	0.3	3
Ave.			10.5						-19

A, a means of the 6 observations of blood flow during 3 min. immediately prior to start of adrenaline, in test and control hands, respectively;

B, b means corresponding to first 3 min. of adrenaline period;

E Ab/a.

Table IX

Effect of Intra-brachial Adrenaline Infusions on Blood Flow in Normal Hands

Age	Sex	Mean blood flow: Test hand A	Test hand B	Control hand a	Control hand b	E	B - E	(B - E)/E %
(a) Adrenaline 1/4 µg./min.								
21	M	9.1	11.8	8.3	12.4	13.6	-1.8	-13
21	M	9.7	9.6	8.3	9.4	11.0	-1.4	-13
23	M	25.2	22.0	33.8	32.4	24.2	-2.2	- 9
30	F	4.3	3.4	5.3	4.6	3.7	-0.3	- 8
21	M	2.8	3.3	2.6	2.8	3.0	0.3	10
35	M	11.3	9.7	9.8	8.5	9.8	-0.1	- 1
26	M	14.7	13.9	15.9	15.3	14.1	-0.2	- 1
26	M	20.4	15.4	19.7	13.6	14.1	1.3	9
29	F	5.1	3.5	9.9	7.2	3.7	-0.2	- 5
49	F	12.8	8.1	11.3	11.9	13.5	-5.4	-40
29	F	12.6	7.8	12.3	12.7	13.0	-5.2	-40
27	F	11.7	3.1	11.1	10.5	11.1	-8.0	-72
26	F	12.5	4.3	5.6	3.7	8.3	-4.0	-48
27	F	7.7	1.3	10.3	8.3	6.2	-4.9	-79
26	F	5.6	0.5	6.5	8.4	7.2	-6.7	-93
24	F	5.4	6.2	6.3	6.6	5.7	0.5	9
25	F	5.0	1.8	5.4	5.9	5.5	-3.7	-67
Ave.		10.3						-27%
(b) Adrenaline 1/2 µg./min.								
22	M	9.5	1.7	12.9	13.5	9.9	-8.2	-83
19	M	2.1	0.8	3.6	5.5	3.2	-2.4	-75
21	M	11.4	13.6	9.1	12.6	15.7	-2.1	-13
21	M	18.3	16.8	25.8	15.1	10.7	6.1	57
21	M	9.2	11.2	8.7	12.5	13.2	-2.0	-15
35	M	9.5	6.3	4.8	8.2	16.2	-9.9	-61
26	M	14.0	10.5	14.2	13.3	13.1	-2.6	-20
26	M	13.1	7.5	12.4	10.5	11.1	-3.6	-32
29	F	5.6	3.3	9.0	7.3	4.5	-1.2	-27
24	M	6.5	0.0	6.2	3.9	4.1	-4.1	-100
30	M	4.0	0.7	4.9	3.1	2.5	-1.8	-72
23	M	4.2	1.5	3.0	3.2	4.5	-3.0	-67
24	M	10.9	2.2	17.5	15.5	9.7	-7.5	-77
25	M	6.6	1.8	5.7	6.3	7.3	-5.5	-75
25	M	4.1	1.3	5.7	3.9	2.8	-1.5	-54
29	M	8.9	2.0	3.4	3.7	9.7	-7.7	-79
25	M	1.6	0.3	1.0	1.4	2.2	-1.9	-86
24	M	9.5	1.7	12.9	13.5	9.9	-8.2	-83
Ave.		8.3						-53%

A, B, a, b, E as in previous tables.

be no significant difference between the two groups at dose levels of 1/32, 1/16 and 1/8 µg./min.

Thus Raynaud's disease per se was not found to be associated with any increase or decrease in sensitivity of the blood vessels to adrenaline. It was therefore permissible to take together data from the tests of healthy subjects and of patients before operation, to provide a more precise evaluation of the response of "normally innervated" hands to 1/32, 1/16 and 1/8 µg./ min adrenaline. It is seen, Table X, that the differences in mean effect between "normally innervated" and sympathectomized hands are significant in respect of these three adrenaline concentrations.

In Fig. 17 the responses of the same 10 hands before and after operation and of the large group of "normally innervated" hands have been plotted together in relation to dose of adrenaline. The greater response of the hands after sympathectomy is clearly shown. Whereas 1/8 µg. was sufficient to cause 55% vasoconstriction in the group of sympathectomized hands, normal hands required 1/2 µg. or four times the concentration, to sustain an equal degree of vasoconstriction (53%) thus confirming the conclusion drawn from the results of the previous project.

The opportunities of determining the effect of sympathectomy by comparable studies before and after operation were necessarily restricted to the small number of suitable patients available in

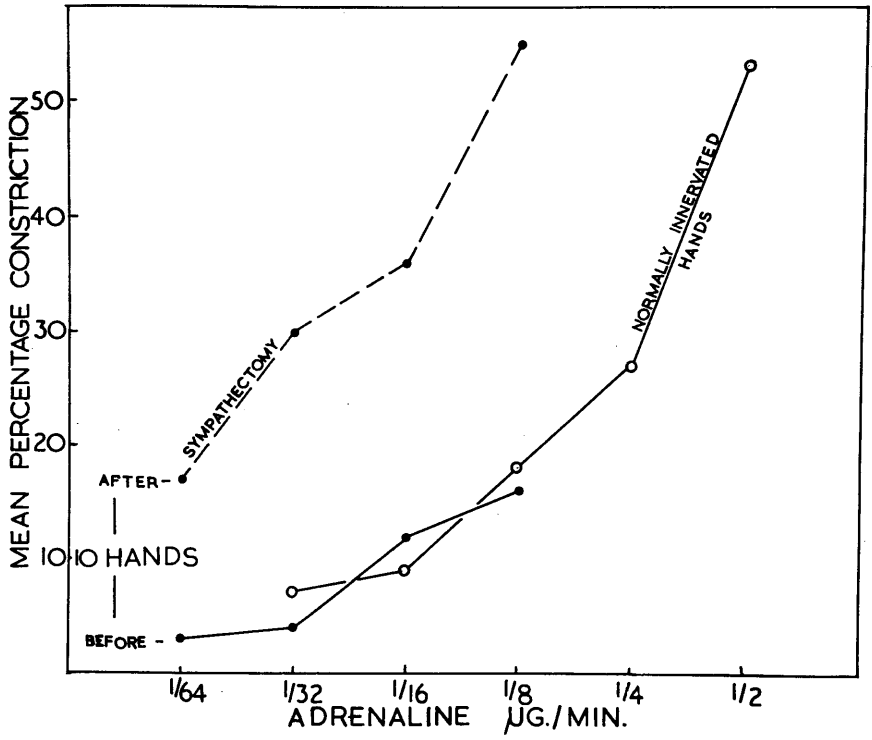


Fig. 17 Dose-response curves of a group of hands before and after sympathectomy and of a larger group of normally innervated hands. The increased constrictor effect of adrenaline after sympathectomy is obvious.

hospitals within a convenient distance from the laboratory. The aggregate data concerning the effect of adrenaline of the blood flow in "normally innervated" hands now provided a statistically defined background against which the response of any individual could be measured.

It was, therefore, now possible to survey an additional number of patients in whom the upper limb or limbs had been sympathectomized on some former occasion, and to assess the degree of sensitivity in each, in comparison with what it was likely to have been before operation.

VASOCONSTRICTOR EFFECT IN THE HAND OF INTRA-ARTERIAL INFUSIONS OF ADRENALINE IN PREVIOUSLY SYMPATHECTOMIZED SUBJECTS

The blood flow responses to adrenaline were studied in six hands of four patients who had had cervico-dorsal sympathectomy some time previously; none had had preoperative tests of adrenaline sensitivity. In the first 5 instances the operation was for hyperhidrosis, the sixth for Raynaud's disease. Repeated heat tests had demonstrated that interruption of the vasomotor pathway remained complete at the times of those tests performed at a considerable interval after operation.

A young woman, Mrs K., had a preganglionic section on the right side and ganglionectomy on the left. Tested on the 6th post-

operative day, the right hand exhibited 23%, 33%, and 79% reduction in flow with adrenaline concentrations of 1/16, 1/8 and 1/4 µg./min., respectively. Those three values are greater than the average responses in the "normally innervated" groups, but in fact do not differ significantly, the probability of such differences occurring by chance being more than one in ten.

When her hand was tested 7 days after ganglionectomy, infusions of 1/8 and 1/4 µg. adrenaline/min. caused 41% and 88% vasoconstriction, respectively; an increase over the average for corresponding groups of "normally innervated" subjects,which in neither instance however is significant.

A second patient, Roy T., troubled with hyperhidrosis, also was subjected to the preganglionic operation on the right side and ganglionectomy on the left. On the 6th day after operation 85% and 71% vasoconstriction of the right hand resulted from 1/16 and 1/8 µg./adrenaline/min., both figures representing significant increases ($t = 5.1$ and 2.3, $P < .001$ and $< .05$).

On testing his left hand on the 7th postoperative day, adrenaline infusions of 1/16 µg./min. caused 9% and on repetition 29% vasoconstriction, neither figure being significant. With 1/8 µg./min., however, 74% vasoconstriction occurred, a significant change ($t = 2.43$, $P < .05$). That a real increase in sensitivity was present at this time must therefore be considered likely in the case of the right hand and equivocal in the case of the left.

Three months after operation significantly increased vasoconstriction in the left hand (36% and 65%) resulted from 1/32 and 1/16 µg. adrenaline. In terms of the rigorous statistical criteria, the evidence suggests some degree of supersensitivity in this hand in the first three months.

In the right hand, two out of three tests at the 8th postoperative month revealed significantly increased vasoconstriction. The tests in this subject, conducted under identical circumstances, appear to have shown a considerable and lasting increase in sensitivity following preganglionic section, and a smaller increase after ganglionectomy.

The remaining two subjects had had ganglionectomy two years previously, one hand of each being tested. Mr GN. was given replicated infusions of adrenaline 1/64, 1/32, and 1/16 µg./min., which caused 4% and 6%, 9% and 10%, and 15% and 20% constriction, respectively. One infusion of 1/8 µg. caused 50% vasoconstriction. None of these results indicated a significant departure from normal. Miss S., a young woman with Raynaud's disease, had 75% reduction in flow with 1/8 µg. adrenaline, a significant increase over normal ($t = 2.5$, $P < .05$).

The results of all these tests are summarized in Table XI, and show that two hands had definite increases in sensitivity, one had some increase, the remaining three having no significant increase.

TABLE X.

Percentage Constrictor Effect, in Groups of Hands, of Adrenaline, 1/64 - 1/2 µg./min.

Adrenaline µg./min.		Healthy subjects	Pre-operative	Normally innervated	Sympathectomized.
	No.	--	6	--	6
1/64	Mean	--	3	--	17
	S.D.	--	15	--	20
	S.E.	--	6.0	--	7.8
	No.	17	10	27	10
1/32	Mean	10	4	8	30
	S.D.	11	8	9	22
	S.E.	2.6	2.5	1.8	6.8
	No.	17	9	26	9
1/16	Mean	7	12	9	36
	S.D.	18	6	15	20
	S.E.	4.3	2.1	2.9	6.7
	No.	24	8	32	8
1/8	Mean	19	16	18	55
	S.D.	22	25	23	23
	S.E.	4.5	8.9	4.0	8.1
	No.	17			
1/4	Mean	27			
	S.D.	33			
	S.E.	7.9			
	No.	18			
1/2	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. Percentage constriction :: $\frac{E-B}{E}\%$.

Of the two having consistent increases, one was sympathectomized by preganglionic section. Thus the present study provides evidence in support of the results of the initial investigation of 10 hands, of which only a proportion had an increase in sensitivity, the preganglionic operation no less than the postganglionic being responsible.

Table XI

Changes in Hand Blood Flow of Previously Sympathectomized Subjects with Intra-arterial Infusions of Adrenaline

Subject	Age	Hand	Operation	Tested at	Mean Blood Flow: Test hand A	Test hand B	Control hand a	Control hand b	E	$\frac{B-E}{E}$ %	Significant Change
Adrenaline 1/64 µg./min.											
1	Roy T 18	R	P	8 months	13.0	12.9	14.7	15.7	13.9	- 7	No
2		L	G	8 months	11.0	10.0	8.0	6.6	9.1	10	No
3	Mr GN 42	R	G	2 years	26.2	26.5	21.2	22.3	27.6	- 4	No
4		R		2 years	22.7	21.6	22.3	22.5	22.9	- 6	No
Adrenaline 1/32 µg./min.											
1	Roy T	R		8 months	12.8	9.6	15.6	15.9	13.0	-26	No
2		R		8 months	13.7	10.1	17.3	16.8	13.3	-24	No
3		L		3 months	16.0	10.6	16.5	17.0	16.5	-36	Yes $P < .01$
4		L			14.1	11.0	7.9	7.2	12.8	-14	No
5		L		8 months	14.9	12.0	7.5	6.6	13.1	- 8	No
6		L			14.6	12.0	6.3	5.6	13.0	- 8	No
7	Mr GN	R		2 years	27.6	26.9	21.4	22.9	29.5	- 9	No
8	-	R		2 years	23.1	21.5	22.7	23.5	23.9	-10	No

Adrenaline 1/16 µg./min.												
1	Mrs K 21	R	P	6 days	33.5	26.5	14.4	14.8	34.4	-23	No	
2	Roy T	R		6 days	16.6	2.5	7.3	7.3	16.6	-85	Yes	P <.001
3		R		8 months	12.9	6.1	16.2	17.6	14.0	-56	Yes	P <.01
4		L		7 days	10.1	9.1	8.7	8.6	10.0	- 9	No	
5		L		7 days	10.3	7.3	8.0	8.0	10.3	-29	No	
6		L		3 months	14.9	4.4	19.7	16.6	12.6	-65	Yes	P <.01
7	Mr G	R		2 years	24.8	20.3	20.8	20.0	23.8	-15	No	
8		R		2 years	20.8	17.5	21.2	22.3	21.9	-20	No	
Adrenaline 1/8 µg./min.												
1	Mrs K	R	P	6 days	28.0	18.6	16.0	15.9	27.8	-33	No	
2		L	G	7 days	20.5	12.7	19.9	21.0	21.6	-41	No	
3	Roy T	R	P	6 days	13.7	3.3	10.8	9.1	11.5	-71	Yes	P <.05
4		L	G	7 days	10.7	2.4	8.4	7.2	9.1	-74	Yes	P <.05
5	Mr GN	R	G	2 years	19.9	9.8	21.2	20.8	19.5	-50	No	
6	Miss S 23	R	G	2 years	8.6	1.7	2.6	2.1	6.9	-75	Yes	P <.05
Adrenaline 1/4 µg./min.												
1	Mrs K	R		6 days	28.4	6.3	14.3	15.3	30.3	-79	No	
2		L		7 days	22.9	2.4	22.7	20.0	20.2	-88	No	

A, a = Means of the 6 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.

INTERPRETATION OF THE RESULTS OF THE SECOND INVESTIGATION

The study of the responses in a group of ten hands before and after sympathectomy showed clearly that six of the hands exhibited a postoperative lowering of the threshold to the vaso-constrictor action of intra-arterial adrenaline infusions. Five of these hands had been sympathectomized by preganglionic section, and two of the remaining four hands in which no significant change was revealed were sympathectomized by ganglionectomy.

Since the majority of these subjects suffered from Raynaud's disease it was next necessary to determine whether their sensitivity to adrenaline was within normal limits before operative interference. The circulatory changes in the hands of a large number of healthy subjects were studied under identical circumstances and the patients' hands were found on comparison to have similar responses before operation to those of the healthy subjects. Taking together the results of the patients' preoperative tests with those of the healthy subjects, the range of response of a widely representative group of "normally innervated" hands was established. It was then possible to compare with this the responses of a further six hands of patients previously sympathectomized for hyperhidrosis or Raynaud's disease. Two or perhaps three of these were found to have significantly increased responses to adrenaline, following preganglionic section and

ganglionectomy, respectively. Altogether an increased sensitivity to adrenaline seemed to have occurred in 8 or 9 out of 16 hands, following sympathectomy. The incidence and degree of supersensitivity appeared to be essentially independent of the type of operation and of the nature and severity of the clinical condition for which the operation was performed.

Supersensitivity was found as early as the 6th day and as late as two years after operation, but the data are insufficient to determine adequately the influence of time upon the phenomenon.

Preliminary analysis of the protocols had revealed the important fact that the net volumetric reduction in flow with adrenaline was proportional to the control level of blood flow. Although for comparative purposes the adrenaline effect in each instance was expressed in terms of percentage departure from the control level, yet marked and significant changes in the post-sympathectomy tests were still present. The mean control blood flow of the first group of hands in the postoperative tests was in fact very little greater than that before operation.

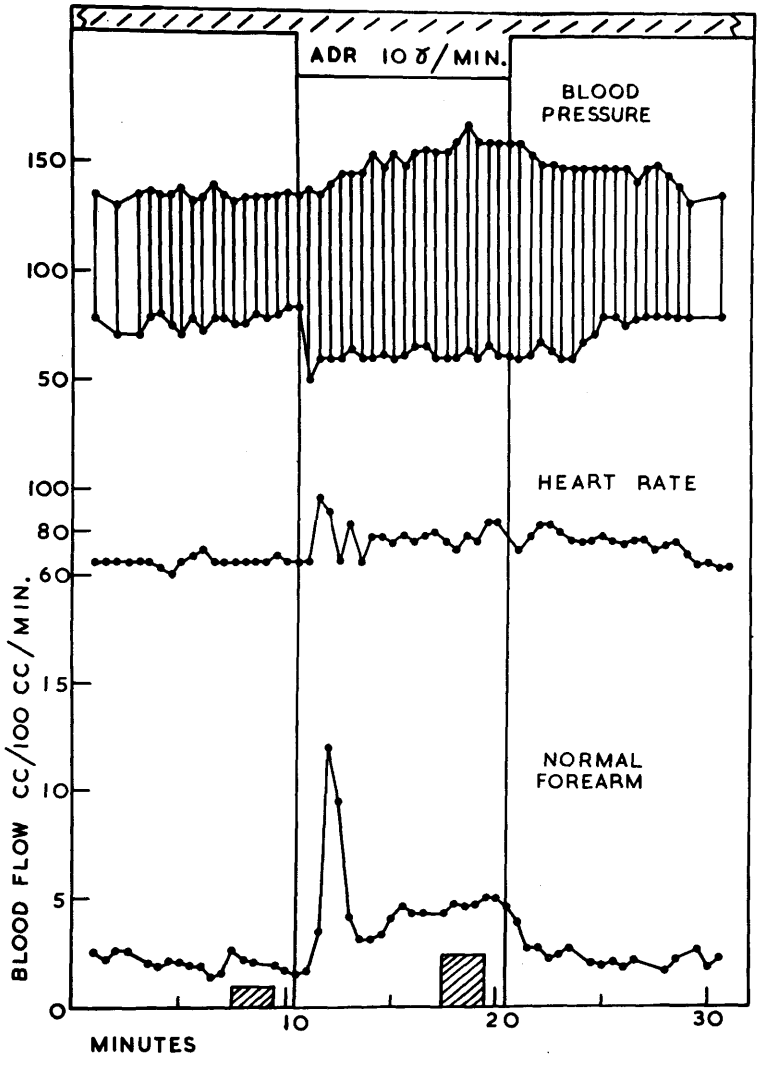


Fig. 18 Intravenous infusion of adrenaline in a healthy subject. Arterial blood pressure, heart rate and forearm blood flow. The hatched blocks represent the mean blood flow (half scale) during the last 4 min. of the control and adrenaline periods.

THIRD INVESTIGATION

EFFECT OF ADRENALINE ON BLOOD FLOW IN FOREARMS OF HEALTHY SUBJECTS USING INTRAVENOUS INFUSIONS

In the third investigation the blood flow in muscular segments of the upper and lower limbs was measured every half minute before and during 10 min. infusions of adrenaline. The intravenous adrenaline level was always 10 µg./min.

First, intravenous infusions were given to 12 healthy subjects while blood flow in the forearm was measured. Fig. 18 illustrates a typical experiment in a man of 32. After a latent period during which the adrenaline solution passed through the infusion tube into the circulation, the diastolic arterial pressure fell slightly, after which the systolic pressure rose by 10 - 20 mm. Hg. The heart rate increased a little but remained less elevated toward the end of the infusion. The symptoms generally experienced during the intravenous infusions have already been described (page 26).

The first change in forearm blood flow was a sudden marked increase to between four and five times the resting level. This increase was of brief duration, and within a minute the flow returned to about twice the resting level. From this point to the

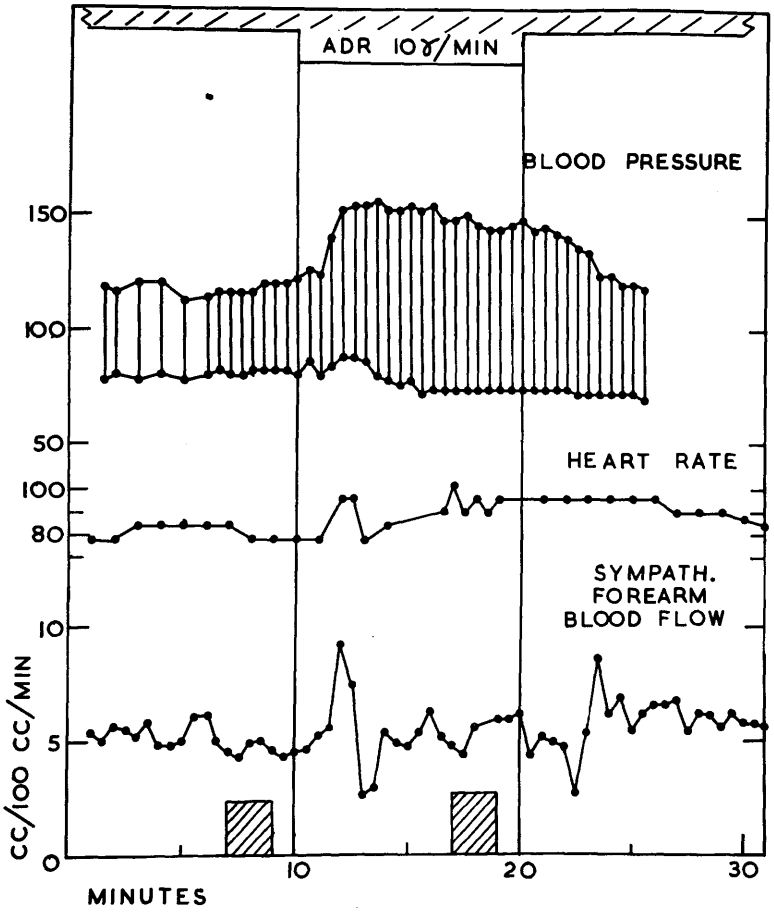


Fig. 19 Intravenous infusion of adrenaline, sympathectomized subject. Arterial blood pressure, heart rate and forearm blood flow. The hatched blocks represent the mean blood flow during the last 4 min. of the control and adrenaline periods.

end of the infusion the flow remained about this level, gradually rising a little during the last few minutes. After the end of the infusion, the blood flow soon returned to near the resting level. For the whole group of 12 subjects the mean resting level was 2.4 ml./100 ml./min., and the blood flow during the last 4 min. of the adrenaline period was 5.1 ml., the average increase being 122%. The difference between the means is highly significant ($t = 9.9$, $P < .0001$). Results are detailed in Table XIIa.

INTRAVENOUS INFUSIONS, SYMPATHECTOMIZED SUBJECTS

Observations on the effect of intravenous infusions with respect to eleven sympathectomized forearms were obtained. The results in a typical experiment are illustrated in Fig. 19. This subject was a man who had had bilateral cervico-dorsal sympathectomy one year previously for hyperhidrosis. In this instance blood pressure and heart rate changes were similar to those found in healthy subjects.

The forearm blood flow had an initial brief rise to a peak from which it rapidly returned to below the resting level. During the rest of the infusion, however, the flow remained, with some fluctuation, near the resting level, there being no substantial increase as in the normal forearm. The resting blood flow in this subject was 4.6 ml., and the corresponding value during the last 4

Table XII

Changes in Forearm Blood Flow in (a) Normal and (b) Sympathectomized Limbs During Intravenous Infusions of 10 µg. Adrenaline/Min.

Age	Sex	Condition	Tested at (Months)	Mean Blood Flow A	B	B-A	$\frac{B-A}{A}$ %	Mean Blood Pressure A	B
(a) Normal									
18	M	-	-	3.4	5.6	2.2	65	128/80	160/65
19	M	-	-	3.4	6.4	3.0	88	116/85	140/80
18	M	-	-	3.4	7.7	4.3	127	135/80	165/65
19	M	-	-	2.0	4.6	2.6	130	135/80	155/70
19	M	-	-	2.4	3.2	0.8	33	135/80	150/75
19	M	-	-	1.7	3.9	2.2	130		
19	M	-	-	3.5	5.4	1.9	54	134/80	160/62
33	M	-	-	1.9	4.7	2.8	147		
33	M	-	-	1.8	4.2	2.4	133		
25	M	-	-	1.9	4.8	2.9	153	130/75	145/75
24	M	-	-	2.1	5.7	3.6	171		
24	M	-	-	1.6	5.4	3.8	237	135/75	145/70
Ave.				2.4	5.1	2.7	122		
(b) Sympathectomized									
22	M	H	6	3.1	3.9	0.8	26	122/76	140/76
43	M	C	7	4.0	3.5	-0.5	- 13	130/74	156/60
32	M	H	12	4.6	5.5	0.9	19		
32	F	R	24	2.6	4.4	1.8	69	118/92	148/74
29	M	C	4	5.9	5.2	-0.7	- 12	110/66	140/64
29	M	C	4	6.7	5.9	-0.8	- 12		
22	F	R	18	2.5	4.4	1.9	76	112/70	140/68
	F	R		1.7	3.7	2.0	117		
25	M	T	13	1.8	1.4	-0.4	- 22		
24	M	T	7	4.2	3.2	-1.0	- 24	135/75	145/70
24	M	T	7	8.0	4.8	-3.2	- 40		
Ave.				4.1	4.2	0.1	17		

A = mean during the 4 min. prior to the start of adrenaline; B = mean during last 4 min. of infusion; C = causalgia; H = hyperhidrosis; R = Raynaud's disease; T = traumatic sympathectomy.

min. of the adrenaline period was 5.5 ml., an insignificant change. The results in the whole series of 11 sympathectomized forearms are summarized in Table XIIb. There was no significant difference between the means of the blood flow before, and during the last 4 min. of, the adrenaline infusion ($t = 2.1$, $P = .8$).

It will be noted that the mean control blood flow was greater in the sympathectomized than in the normal group. This difference is largely attributable to chance variations of small numbers of observations, but its occurrence made desirable an analysis of the influence of the control rate of blood flow on the response to adrenaline (Table XV). When the blood flow means were adjusted by regression analysis for inequality of the resting values, there remained a statistically significant difference between normal and sympathectomized forearms during intravenous adrenaline infusions.

INTRAVENOUS INFUSIONS, NORMAL CALVES

Since the blood flow through the calf represents, even more completely than the forearm, the circulation through skeletal muscle, analogous experiments with respect to the calf were carried out. These had the further advantage that during every infusion the blood pressure in the arm could be measured more easily, and simultaneously with the calf blood flow.

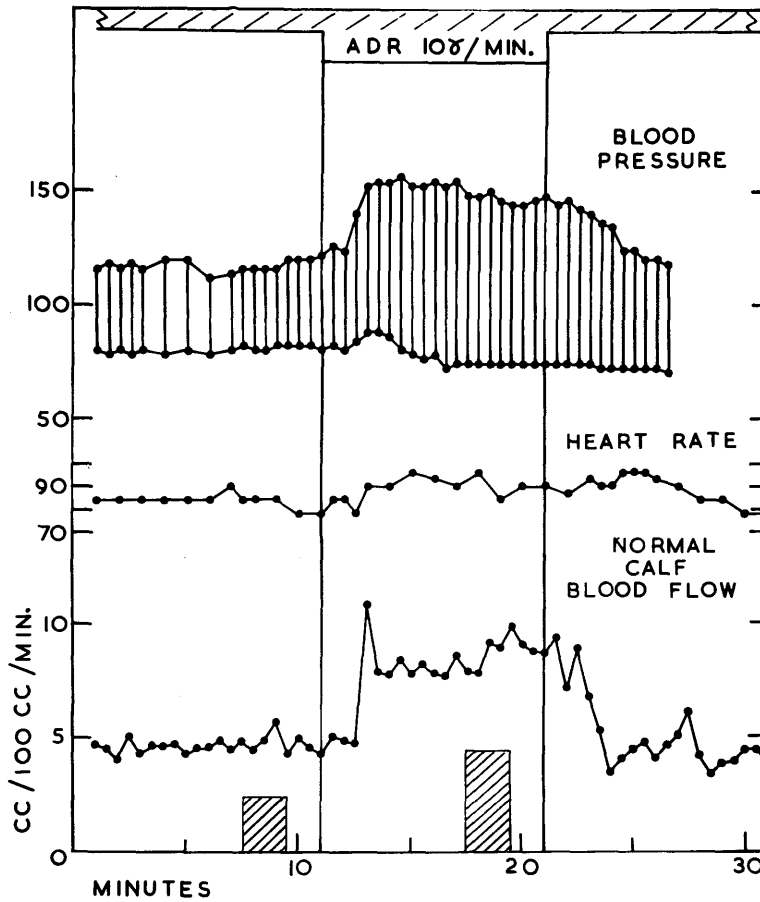


Fig. 20 Intravenous infusion of adrenaline, healthy subject. Arterial blood pressure, heart rate and calf blood flow. The hatched blocks represent (in half scale) blood flow during control and response periods.

Fifteen healthy individuals were studied. Fig. 20 illustrates one experiment in a man 38 years of age. After a short latent period the systolic arterial pressure rose sharply by 30 mm. Hg, remaining elevated until after the end of the infusion. The diastolic pressure rose a little and then fell below the resting level for the remainder of the infusion. In many subjects the diastolic pressure fell initially, and in every case the mean diastolic pressure during the adrenaline period was less than the resting level.

The blood flow in the calf increased suddenly to a peak from which it declined less rapidly to a level above the resting rate of 4.7 ml. Thereafter the flow rose gradually, to average 8.7 ml. during the last 4 min. of the infusion. In the group of 15 subjects the average resting level was 3.5 ml. and the flow during the last 4 min. of the adrenaline was 5.7 ml. (Table XIIIa). These figures indicate a significantly raised flow ($t = 5.08$, $P < .001$). The blood flow during the latter adrenaline period was increased on the average by 73% over the resting level.

INTRAVENOUS INFUSIONS, SYMPATHECTOMIZED CALVES

Seven sympathectomized limbs were studied in the same way. The response in a typical experiment is illustrated in

Table XIII

Changes in Calf Blood Flow in (a) Normal and in (b) Sympathectomized Limbs during Intravenous Infusions of 10 µg. Adrenaline/Min.

Age	Sex	Condition	Tested at (months)	Mean Blood Flow A	B	B-A	B-A% A	Mean Blood Pressure A	B
(a) Normal									
21	F	-	-	1.7	4.7	3.0	176	124/80	140/60
19	F	-	-	4.6	5.4	0.8	18	116/55	148/48
19	F	-	-	3.3	4.9	1.6	48	121/70	149/52
22	F	-	-	4.2	8.2	4.0	95		
22	F	-	-	4.3	9.8	5.5	128	112/70	139/71
23	M	-	-	4.5	5.4	0.9	20	142/78	152/58
20	M	-	-	5.7	5.5	-0.2	- 3	118/76	144/66
28	M	-	-	1.9	4.3	2.4	126	119/70	150/70
38	M	-	-	4.7	8.7	4.0	85	116/81	148/74
32	F	-	-	2.9	6.9	4.0	165		
32	F	-	-	3.2	6.1	2.9	69	110/68	140/65
19	F	-	-	4.6	5.4	0.8	17		
39	M	-	-	2.2	3.1	0.9	41		
39	M	-	-	2.3	2.5	0.2	9		
22	M	-	-	2.1	4.3	2.2	105	118/76	144/66
Ave.				3.5	5.7	2.2	73		
(b) Sympathectomized									
19	F	C	1	2.7	2.3	-0.4	- 15	121/70	140/60
20	F	R	6	2.9	2.6	-0.3	- 10	132/72	180/66
25	F	R	13	5.6	4.4	-1.2	- 21	116/65	150/60
44	F	R	5	3.2	3.0	-0.2	- 6	103/60	140/70
31	F	R	6	2.4	2.7	0.3	12	118/78	118/76
31	F	R	6	2.8	2.5	-0.3	- 10	118/78	118/76
19	F	C	8	4.9	3.2	-1.7	- 35		
Ave.				3.5	3.0	-0.5	- 12		

A = mean during the 4 min. prior to start of adrenalin; B = mean during last 4 min. of adrenaline infusion; C = causalgia; R = Raynaud's disease.

Table XIII

Changes in Calf Blood Flow in (a) Normal and in (b) Sympathectomized Limbs during Intravenous Infusions of 10 µg. Adrenaline/Min.

Age	Sex	Condition	Tested at (months)	Mean Blood Flow A	B	B-A	B-A% A	Mean Blood Pressure A	B
(a) Normal									
21	F	-	-	1.7	4.7	3.0	176	124/80	140/60
19	F	-	-	4.6	5.4	0.8	18	116/55	148/48
19	F	-	-	3.3	4.9	1.6	48	121/70	149/52
22	F	-	-	4.2	8.2	4.0	95		
22	F	-	-	4.3	9.8	5.5	128	112/70	139/71
23	M	-	-	4.5	5.4	0.9	20	142/78	152/58
20	M	-	-	5.7	5.5	-0.2	- 3	118/76	144/66
28	M	-	-	1.9	4.3	2.4	126	119/70	150/70
38	M	-	-	4.7	8.7	4.0	85	116/81	148/74
32	F	-	-	2.9	6.9	4.0	165		
32	F	-	-	3.2	6.1	2.9	69	110/68	140/65
19	F	-	-	4.6	5.4	0.8	17		
39	M	-	-	2.2	3.1	0.9	41		
39	M	-	-	2.3	2.5	0.2	9		
22	M	-	-	2.1	4.3	2.2	105	118/76	144/66
Ave.				3.5	5.7	2.2	73		
(b) Sympathectomized									
19	F	C	1	2.7	2.3	-0.4	- 15	121/70	140/60
20	F	R	6	2.9	2.6	-0.3	- 10	132/72	180/66
25	F	R	13	5.6	4.4	-1.2	- 21	116/65	150/60
44	F	R	5	3.2	3.0	-0.2	- 6	103/60	140/70
31	F	R	6	2.4	2.7	0.3	12	118/78	118/76
31	F	R	6	2.8	2.5	-0.3	- 10	118/78	118/76
19	F	C	8	4.9	3.2	-1.7	- 35		
Ave.				3.5	3.0	-0.5	- 12		

A = mean during the 4 min. prior to start of adrenalin; B = mean during last 4 min. of adrenaline infusion; C = causalgia; R = Raynaud's disease.

Fig. 21. The subject was a young woman who had had all four limbs sympathectomized for Raynaud's disease, with complete clinical cure. The systolic blood pressure, in this case, rose from the resting level of 132 mm. Hg to reach the high level of 190 after the beginning of the infusion; it later settled at 180 mm. till after the infusion, when it soon returned to the previous level. The diastolic pressure showed an average fall of about 10 mm. Hg during the infusion. The heart rate rose from 60 to 102/min., thereafter varying between 70 and 84 until after the infusion. The calf flow exhibited an initial rise and rapid fall to a low level from which it gradually rose a little; the average level during the last 4 min. of the infusion was 2.6 ml. compared with a resting level of 2.9 ml.

In 6 of the 7 subjects, after the initial brief rise the blood flow was reduced below the resting level. The results in the series are summarized in Table XIIIb. There was a significant reduction in blood flow during the last 4 min. of the adrenaline infusions ($t = 2.45$, $P < .05$).

These experiments show that in the sympathectomized calf the second phase of the adrenaline effect is a reduction in blood flow below the resting level, in contrast with the elevation above the resting level in normal limbs.

The forearm experiments indicated that after the initial

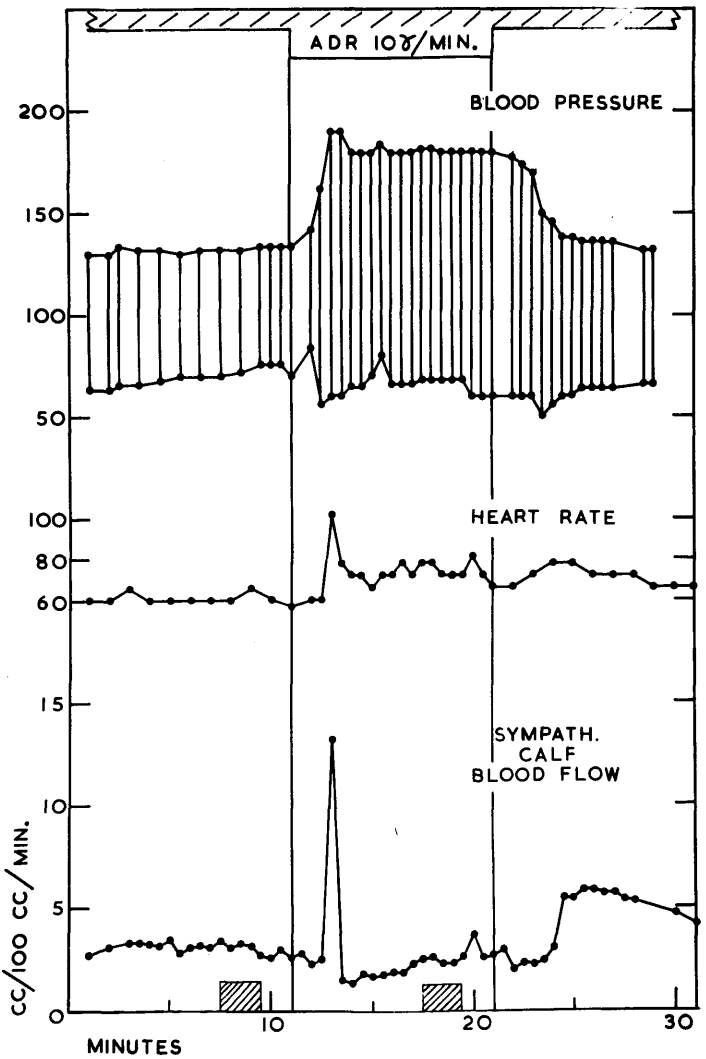


Fig. 21 Intravenous infusion of adrenaline, sympathectomized subject. Arterial blood pressure, heart rate and calf blood flow.

vasodilatation sympathectomized blood vessels are relatively more constricted with adrenaline. In the lower limb, not only was the normal second phase of vasodilatation shown to be absent, but the occurrence of an absolute reduction in flow below the resting level was revealed. Although the findings in the sympathectomized forearms might have been due to the absence of an indirect vasodilator effect normally mediated by the sympathetic nerves, the results of the calf experiments could not be so explained. Indeed the evidence suggested that adrenaline might be capable by direct action of constricting the blood vessels in skeletal muscle. To test this, intra-arterial infusions of lower concentrations of adrenaline were given to normal subjects and the blood flow changes measured in the same way.

INTRA-ARTERIAL INFUSIONS, NORMAL FOREARMS

Intra-brachial arterial infusions of a proportionately reduced amount of adrenaline (1/8 µg./ min.) were given to six subjects. The result in a typical experiment on a young man is represented in Fig. 22. No alteration in blood pressure was observed.

The characteristic initial increase in blood flow was followed by a rapid decline to below the resting level of 3 ml. The blood flow then rose slightly, but remained at about the

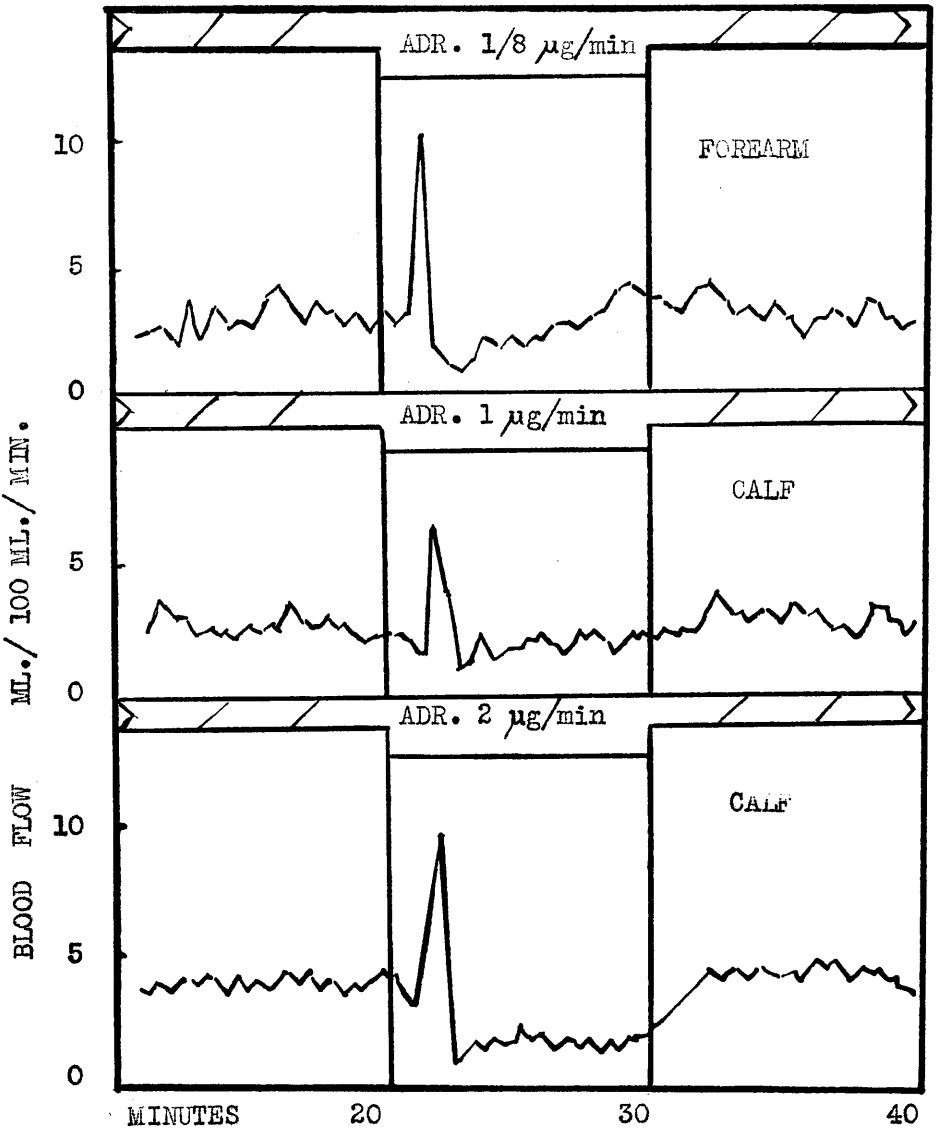


Fig. 22 Intra-arterial infusions of adrenaline, healthy subjects. Forearm blood flow, 1/8 µg. adrenaline/min.; calf blood flow, 1 µg. and 2 µg./min.

resting level throughout the remainder of the infusion. During the last 4 min. the average flow was 3.1 mm., an increase of only 3% over the resting level.

In none of the six experiments in this group was there a sustained increase in flow. The observations are summarized in Table XIVa. The average change was a decrease of 5%. The difference in blood flow during the later adrenaline period by comparison with the resting period, is not significant ($t = 0.5$, $P = 0.6$).

These experiments would seem to show that the second phase of dilatation in the vessels of skeletal muscle with intravenous infusions of adrenaline is normally due to an indirect effect presumably initiated by some systemic action of the adrenaline, for it is absent when adrenaline is introduced directly into the artery in amounts insufficient to cause systemic effects on recirculation.

INTRA-ARTERIAL INFUSIONS, NORMAL CALVES

In pursuance of the analogy between the forearm and the calf, similar experiments were carried out on the lower limb. Intra-arterial infusions of 1 µg. adrenaline/min. into the femoral artery were given to seven healthy subjects. During these experiments neither heart rate nor arterial blood pressure was influenced by the infusions. In these experiments also, since the dose of adrenaline

TABLE XIV.

Changes in Blood Flow in Forearms and in Calves of Healthy Subjects during Intra-arterial Infusions of Adrenaline.

Age	Sex	Mean Blood Flow A	B	B - A	$\frac{B - A}{A}$ %
(a) Intra-brachial adrenaline 1/8 µg./min.					
21	M	3.0	3.1	0.1	3
29	M	8.7	3.8	-4.9	-56
21	M	1.9	1.7	-0.2	-10
21	M	6.0	6.3	0.3	5
20	M	6.0	7.0	1.0	17
20	M	5.3	6.0	0.7	13
Ave		5.2	4.7	-0.5	- 5 %
(b) Intra-femoral adrenaline 1 µg./min.					
27	M	1.8	2.7	0.9	50
23	M	3.2	3.6	0.4	13
21	M	2.5	2.1	-0.4	-16
25	M	3.5	2.9	-0.6	-17
22	M	3.8	2.8	-1.0	-26
26	M	3.3	4.0	0.7	21
30	M	2.8	1.9	-0.9	-32
Ave		3.0	2.9	-0.1	- 1 %
(c) Intra-femoral adrenaline 2 µg./min.					
23	M	3.6	3.6	0.0	0
21	M	2.3	1.6	-0.7	-30
25	M	5.0	2.4	-2.6	-52
22	M	3.8	1.9	-1.9	-50
25	M	4.8	1.5	-3.3	-68
23	M	7.8	7.4	-0.4	- 5
25	M	3.2	1.8	-1.4	-44
Ave		4.4	2.9	-1.5	-36 %

A is mean during 4 min. prior to start of adrenaline;
B is mean during last 4 min. of adrenaline infusion.

was small and no systemic effects were observed, the blood flow changes may be presumed to represent essentially the local effect of the adrenaline on muscle blood vessels.

The response observed in a healthy young man is shown in Fig. 22. There was an initial increase in blood flow and then a fall; for the remainder of the infusion the level of flow was below the resting rate. During the last 4 min. it averaged 2.1 ml. as compared with the resting value of 2.5 ml., a decrease of 16%. Only one of the series of 7 normal calves showed an appreciable increase in blood flow during the last 4 min. of the infusion. The average change in flow for the group was a decrease of 1%, an insignificant change.

This study confirmed the previous study in the forearm in showing that the second phase of vasodilatation found with intravenous infusions in normal subjects was absent when the adrenaline was given by a direct route in proportionately reduced amounts. It remained to determine if adrenaline was actually capable of constricting the vessels in skeletal muscle by a local action.

The blood flow changes in seven normal calves were measured in relation to intra-arterial infusions of 2 µg. adrenaline/min. In all there was the initial brief vasodilatation which is common to every group, and in 6 out of 7 the blood flow

was subsequently reduced below the resting control level, as shown in Fig. 22. The average resting flow for the group was 4.4 ml., and during the last 4 min. of the adrenaline the flow averaged 2.9 ml., indicating a significant reduction in blood flow ($t = 3.29$, $P < .02$). Results are summarized in Table XIV.

These studies seemed to establish that the direct action of adrenaline on vessels in skeletal muscle is normally a biphasic effect consisting of a transient but marked dilatation followed by a sustained but less marked constriction. That the second phase of this response was not manifest during intravenous adrenaline infusions was no doubt attributable to a superadded vasodilator effect consequent upon some systemic action of the adrenaline. Were the latter entirely mediated by the sympathetic nerves, absence of the second phase of vasodilatation in sympathectomized subjects during intravenous infusions would be expected. But the fact that in the sympathectomized calves there was an actual reduction in blood flow below the control resting level during this period (Table XIIIb) indicated a true enhancement of the direct constrictor action of the adrenaline.

It might have been thought that in the normal subject the difference between the effects of intravenous and intra-arterial infusions could be a simple consequence of the greater total dose of adrenaline given in the former experiments. The results of the

two series of intra-arterial infusions in the calf indicated on the average that the 2 µg. level caused a greater departure from the normal intravenous response than the smaller 1 µg. level. Had the effect previously observed with the intravenous infusions been due merely to the accumulation of adrenaline in the blood stream, the response to the higher dose of intra-arterial adrenaline should have reduced, rather than increased, the disparity evinced by the different routes of administration.

TABLE XV.

Analyses of Linear Regression of Blood Flow in Groups of Forearms and Calves during Adrenaline infusions (B), on Resting Blood Flow (A).

Forearms	Adrenaline µg./min.		(B) estimated to equal:	Significance of coefficient:
Normal	IV	10	2.8 + .967A	P <.05 Sig.
Sympathectomized	IV	10	2.6 + .389A	P <.05 Sig.
Normal	IA	1/8	2.3 + .462A	P <.02 Sig.
Calves				
Normal	IV	10	2.6 + .891A	P <.05 Sig.
Sympathectomized	IV	10	1.2 + .510A	P <.01 Sig.
Normal	IA	1	1.5 + .444A	P= .4 Not sig.
Normal	IA	2	-1.4 + .979A	P <.05 Sig.

	If A is 3.0 B will be:	Estimated $\frac{B-A}{A}$%
Forearms		
Normal	5.7	90%
Sympathectomized	3.8	27%
Normal	3.7	23%
Calves		
Normal	5.3	77%
Sympathectomized	2.7	-10%
Normal	2.8	- 7%
Normal	1.5	-50%

A is mean blood flow during 4 min. prior to start of adrenaline;
B is mean blood flow during last 4 min. of adrenaline infusions.

This table shows the behaviour of the various groups after adjustment for inequalities of resting blood flow.

INTERPRETATION OF THE RESULTS OF THE THIRD INVESTIGATION

The results confirm that in normal subjects the vessels in skeletal muscle exhibit two phases of dilatation when an intravenous infusion of adrenaline is given. The initial large increase in flow is due to a direct local action of adrenaline on the blood vessels in the muscle, as suggested by Allen et al. (1946), for it occurs in sympathectomized limbs and with intra-arterial infusions; and its onset in response to the latter is too rapid to be the result of any non-local effect.

It was next shown that there is a significant difference between normal and sympathectomized limbs in the response to intravenous adrenaline infusions, in that there is subsequently moderate dilatation of normal vessels, but no increase or an actual decrease in calibre of sympathectomized vessels. Fig. 23 illustrates this difference with respect to the calf. In this figure the graphs of the average blood flow results in 3 groups of calves have been superimposed, small differences in timing being eliminated by aligning each series in relation to the peak of the initial vasodilatation common to all groups. Usually, of course, with intra-arterial infusions the blood flow changes earlier because the adrenaline passes directly into the limb.

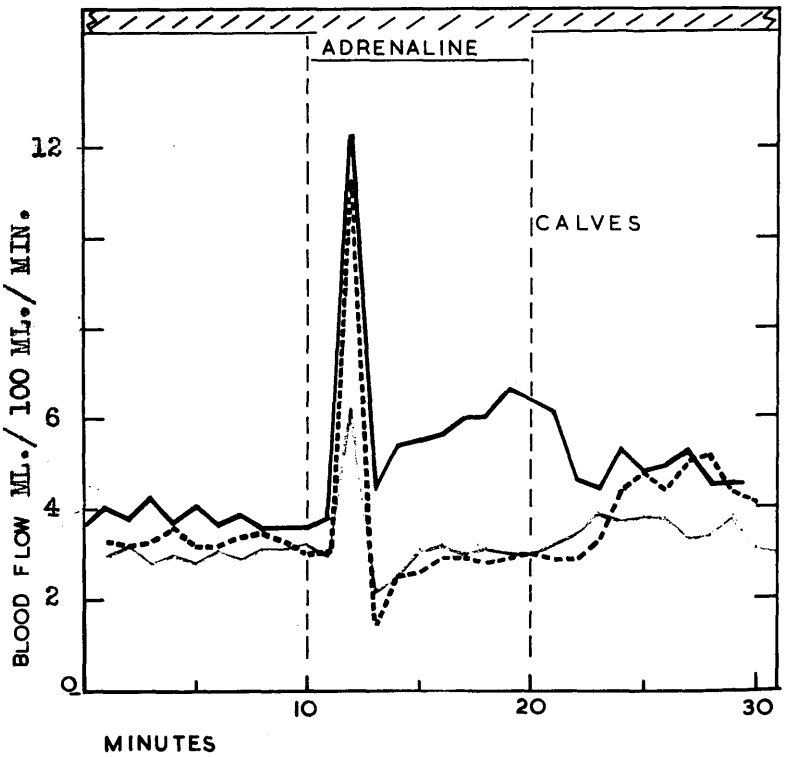


Fig. 23 Mean calf blood flow in three groups of subjects receiving infusions of adrenaline: heavy line, 12 normals, intravenous infusions; pecked line, 6 sympathectomized, intravenous infusions; faint line, 6 normals, intra-arterial infusions. The close similarity of the two latter is shown.

During the latter part of the intravenous infusions, whereas the normal forearms had 122% vasodilatation, a small but insignificant increase occurred in sympathectomized forearms. In the calf, likewise, there was normally a significantly raised blood flow during this period, while in sympathectomized subjects the calf blood flow was significantly reduced below the resting level. To facilitate comparison, in view of inequalities in the resting blood flow levels in different groups, the regression of the blood flow during the last 4 min. of the adrenaline period on the resting blood flow was calculated for each group (Table XV). For an adjusted mean resting level of 3 ml. the mean forearm and calf values for the aforementioned adrenaline period were estimated to be, respectively, 5.7 and 5.3 ml. for the normal; and 3.8 and 2.7 ml. for the sympathectomized limbs. Thus the sympathectomized groups exhibited a relative reduction in flow during this time amounting to 1.9 and 2.6 ml. in forearm and calf respectively. When both are sympathectomized, therefore, the calf has more vasoconstriction than the forearm during this period.

The intra-arterial experiments showed that the second phase of the direct local action of adrenaline is a constrictor effect on the blood vessels in muscle. Determination of the estimated means in the calves for an adjusted resting level of 3 ml. shows that with infusions of 1 µg./min. the blood flow will

be 2.8 ml., and with 2 µg. 1.5 ml., during the period in question. Doubling of the concentration almost halves the flow.

It may be concluded that the blood flow response to intravenous adrenaline infusions in sympathectomized muscle (forearm and calf) resembles that resulting from intra-arterial adrenaline infusions, in that the second phase of moderate vasodilatation characteristic of healthy subjects is usually replaced by a relative or absolute vasoconstriction.

D I S C U S S I O N

EFFECT OF SYMPATHECTOMY ON THE CIRCULATION IN THE LIMBS

The results of the bedside studies of blood flow in the upper limb indicate that relaxation of vascular smooth muscle in both skin and skeletal muscle results from sympathectomy in man, as in a variety of animals. That the postoperative increase in muscle blood flow was less than that in the skin, in subjects with healthy vessels, may be related to the fact that the vasculature of skeletal muscle is normally under less complete autonomic nervous control than that of the skin (Grant & Pearson, 1937). Nevertheless, since the forearm has normally a lower resting rate of flow than the hand (Table II), an equal percentage or absolute increase in the calibre of both groups of vessels would be expected on physical principles alone to cause a smaller percentage or absolute rise in forearm than in hand blood flow.

Not unexpectedly, the vasodilatation in the hands of patients sympathectomized for Raynaud's disease was less than that in patients with normal vessels who were sympathectomized for hyperhidrosis. The elevation in blood flow, however, lasts about the same time in both (Figs. 9 & 10). Before the end of a week the blood flow has returned practically to the preoperative resting level. This "return of vascular tone" has been the subject of much speculation.

The most widely held view attributes the phenomenon to the development of supersensitivity of the denervated blood vessels to circulating adrenaline. The present work provides a basis for critical appraisal of this hypothesis. Evidence has been presented of an increased sensitivity to the constrictor effect of adrenaline in sympathectomized vessels in the hand, forearm and calf.

Despite the small number of cases, it is clear that the pattern of blood flow restoration following preganglionic section is very similar to that following ganglionectomy (Fig. 11). According to the law of denervation of Cannon et al. (1945) the vessels in limbs sympathectomized by ganglionectomy should have constricted earlier or more intensely than those sympathectomized by preganglionic section. This objection to the theory becomes invalid, however, in the light of the investigation showing that marked supersensitivity follows preganglionic section no less than ganglionectomy.

The reduction in blood flow starts within two or three days of operation, and "tone" has almost completely returned before the end of a week. Supersensitivity has been thought to develop however only after complete degeneration of the cut neurones, a process which must occupy at least several days (Lewis & Landis, 1929). Tone therefore commences to return to the vessels before degeneration of the nerves is complete. The earliest study of

adrenaline sensitivity in the hand — on the 6th postoperative day — certainly revealed an increase, and attention will be drawn to other studies revealing the possibility of a more rapid postoperative appearance of supersensitivity. If, therefore, some supersensitivity may develop before complete degeneration of the sympathetic nerves — as seems probable — then this objection to the theory cannot be sustained.

It has been shown that the flow through the sympathectomized vessels in the muscle of the forearm rises and falls at a slightly shorter postoperative interval than in the case of the hand. In most cases (Table II) the blood flow in the hand was still elevated after the forearm flow had returned to normal. The adrenaline sensitivity theory of "return of tone" must therefore attribute to the vessels in skeletal muscle an earlier or greater development of supersensitivity than in the skin vessels. Regarding the degree of sensitivity to adrenaline in muscle as compared with skin vessels, there is indeed some evidence that the former have normally a lower threshold to adrenaline. In 5 healthy, normally innervated subjects intra-arterial infusions of such a small concentration of adrenaline as 1/100 µg./min. caused significant changes in forearm blood flow. Under similar circumstances the threshold of the vessels of the hand was shown (Fig. 17, Table X) to be normally between 1/32 and 1/8 µg. or more, no normal hands responding to concentrations below 1/32 µg./min.

It is therefore likely that normally the vessels in muscle can respond to concentrations of adrenaline below the level effective for the skin vessels. But the response of the vessels in muscle is complex (Figs. 18, 19 & 23) inasmuch as there is initially marked vasodilatation, followed, during continued intravenous infusions, by a relatively smaller or greater vasoconstriction, depending on whether the vessels are or are not innervated. There is evidence, reviewed later, that the initial brief vasodilator action of adrenaline also is enhanced by sympathectomy; but if the sympathectomized vessels in the forearm develop an equal degree of supersensitivity to the more prolonged vasoconstrictor phase of the adrenaline response, then vasoconstriction in muscle might well be manifest with a level of adrenaline below the threshold for the skin vessels.

It must, however, be remembered that the studies of sympathectomized individuals herein reported have revealed several in whom an increased sensitivity was not demonstrated; although the majority had some increase, it was significant in only 8 or 9 out of 16 hands. But the blood flow in the hand or forearm did not remain chronically elevated after sympathectomy in any of the 14 limbs studied, even in those in whom subsequent tests did not reveal adrenaline supersensitivity. It has been reported (Lynn & Martin, 1950) that the blood flow through an extremity may remain

greatly increased for a considerable time after sympathectomy, but this is a rare occurrence; such individuals might be expected to have developed no increase in adrenaline sensitivity. In every other instance supersensitivity following sympathectomy may perhaps be susceptible of demonstration by more refined methods.

While the present evidence admits of a relationship between the "return of vascular tone" or restoration of blood flow, after sympathectomy, and the development of adrenaline supersensitivity, the transience of the increased blood flow cannot be directly attributed to vascular supersensitivity.

It would be well to review certain other known consequences of sympathectomy before further considering the theoretical aspects of the "return of tone".

Kvale, Smith & Allen (1940) demonstrated that the velocity of the blood stream in the arteries and veins of an extremity is increased by sympathectomy, even after the immediate postoperative period. This probably accounts for the slightly earlier response to intravenous infusions of adrenaline in the sympathectomized forearm (Fig. 25) and calf (Fig. 24) as compared with the opposite normal limb.

There is evidence that the blood flow in the skin (Burton, 1939) and muscle (Wilkins & Eichna, 1941) tends more closely to follow the arterial blood pressure after sympathectomy. In accord

with this was the observation (Table II,case 7) of a very great postoperative vasodilatation in the forearm of a hypertensive woman sympathectomized for Raynaud's disease.

There have been consistent reports (Hoobler et al., 1949; Walker, Lynn & Barcroft, 1950) that despite the early restoration of the blood flow in the sympathectomized extremity to a level at or slightly above the resting level, the surface temperature, measured especially in the digits, often remains considerably elevated. No doubt part of the warmth of the skin is due to the absence of sweating as a result of interruption of the sympathetic sudomotor nerves. But the discrepancy between temperature and blood flow is often so great as to demand further explanation.

Goetz (1950) thought that the blood was enabled to remain longer in relaxed veins of the skin, thereby losing more heat to the surface. Following sympathectomy there may be a redistribution of blood within the skin so that a greater proportion of blood passes through the arterio-venous anastomoses which have been shown to be so abundant in the skin, especially of the digits. These arterio-venous anastomoses have a rich sympathetic nerve supply and are notably concerned in the normal response of the skin to changes in temperature (Grant & Bland, 1931; Clark, 1938; Mendlowitz, 1951). Mufson (1951) and Mendlowitz (1951) found that sympathetic nerve block caused marked relaxation of the arterio-

venous anastomoses of the skin.

There is good circumstantial evidence that redistribution of blood within the skin may occur independently of any marked change in the total volume of blood flowing through the skin. Belding, Mead & Bader (1949) showed that on entering a warm atmosphere the skin temperature may rise suddenly — implying an increased surface flow — before the total skin flow has increased much. Presumably relaxation of the arterio-venous anastomoses is responsible for bringing blood nearer the surface, in order to remove heat, perhaps at the expense of the deeper layers of the dermis. One of the notable benefits of sympathectomy of the upper limb for Raynaud's disease is the increased warmth of the extremity, which renders it less subject to vasopasm on exposure to cold. Plethysmography usually fails to demonstrate a permanent volumetric increase in blood flow in such hands, even when clinical improvement is marked. Chambers (1948) envisaged a differential activity of specialized "preferential channels" in the peripheral bed as causing periodic redistribution of the blood within a given tissue.

If there be an increase in the number of patent circulatory channels after sympathectomy, then a feasible hypothesis may be constructed to encompass the changes in total blood flow after sympathectomy.

The volume of blood flowing through an individual vessel

is governed by the pressure gradient and resistance in that vessel. A small increase in the mean calibre or in the number of patent vessels with a low internal resistance, leading to a moderate rise in total vascular capacity, would cause a proportionately increased blood flow. The subsequent opening up of additional but more peripheral and smaller vessels with an appreciable internal resistance would lead to a reduction in total blood flow. It was early observed (Lewis & Landis, 1929) that the throbbing of the digital arteries following sympathectomy ceased after three or four days, at a time when subsequent studies, including the present, have shown the blood flow in the hands to decrease markedly. It is not inconceivable that by the third or fourth day the progressive opening up of small vessels such as the arterio-venous anastomoses in the skin reaches such a degree as to cause an increase in total peripheral resistance. Dornhorst & Sharpey-Schafer (1951) have shown that the resistance of collateral by-pass vessels in a limb is first reduced then increased, after sympathectomy.

When the blood flow rises after sympathectomy some swelling and oedema of the tissues of the limb is often detected, suggesting a rise in capillary pressure such as would result from more proximal vasodilatation. Eichna (1943) made direct measurements of digital capillary pressure in acutely sympathectomized

subjects and found it to be raised at the arteriolar end of the capillary. It would be of interest to know whether, as would be expected, the capillary pressure falls when the total flow returns to normal.

The restoration of blood flow in a sympathectomized limb and the cessation of throbbing of the digital arteries may be due, as it were, to depletion of the larger vessels to provide more blood for an increased number of smaller vessels, the process being associated with a rise in the total resistance to the circulation in the limb. The finding, herein reported, of earlier changes in forearm than in hand blood flow and the observation (Barcroft & Walker, 1949) of a 48-hour delay in the peak vasodilatation in the feet after sympathectomy may be some indication that the vasodilatation progresses distally in an extremity.

It is therefore possible to account for the circulatory changes after sympathectomy on a broad physical basis whereby the mysterious phenomenon of "return of tone" in arteries becomes a comprehensible and necessary consequence of the opening up of a more peripheral vascular bed.

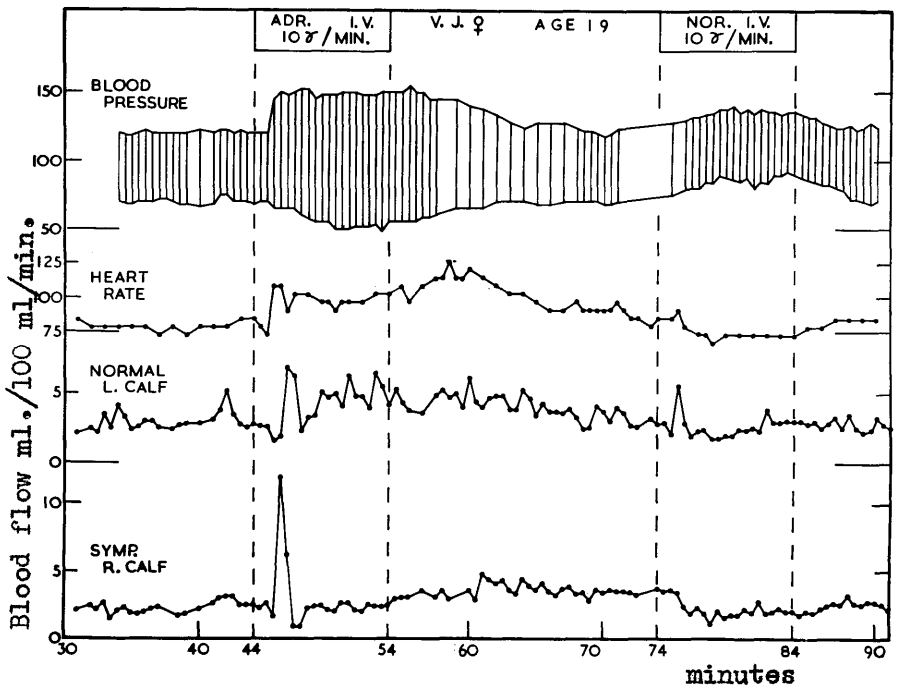


Fig. 24 Arterial blood pressure, heart rate and blood flow in both calves of a patient whose right lower extremity was sympathectomized one month previously. Between the 44th and 54th minutes an infusion of 10 μg. adrenaline/min. was given intravenously. The earlier onset and higher peak of the initial vasodilatation on the sympathectomized side is shown.

EFFECT OF SYMPATHECTOMY ON THE VASCULAR RESPONSE TO ADRENALINE IN THE SKIN

The development of supersensitivity of the blood vessels of the hand to the direct action of adrenaline was clearly demonstrated in the comparative study of a group of ten hands before and after sympathectomy. With the same doses the vasoconstrictor response of the group after operation (35%) averaged four times as much as before operation (9%). It was next revealed by the tests of large numbers of healthy persons that to produce an average vasoconstriction of 53% required adrenaline concentrations of 1/2 µg./min., whereas in the sympathectomized hands an equal amount of vasoconstriction (55%) was caused by one quarter of the concentration (1/8 µg./min.). Both studies therefore corroborated the conclusion that sympathectomy causes, on the average, a fourfold increase in the sensitivity of the blood vessels of the skin of the hands to the constrictor action of intra-arterial adrenaline.

It was also shown that before sympathectomy none of the hands, whether affected by Raynaud's disease or hyperhidrosis, had greater or less sensitivity than normal. The natural occurrence in man of supersensitivity to adrenaline is not unknown (Holling, 1951).

In the initial group of hands the majority were sympathectomized by preganglionic section. Analysis of the results in this and in the second group, of previously sympathectomized hands, affords evidence that preganglionic section is at least as liable as ganglionectomy to produce supersensitivity, but that following either operation a significant increase in sensitivity may not develop in some individuals.

Cognizance must be taken of the fact that removal of the lower cervical and upper thoracic ganglia may additionally cause preganglionic interruption of a small number of sympathetic neurones to the upper limb (Muller, 1909; Lewis & Landis, 1929). The converse — that section of the sympathetic chain in the customary site between the third and fourth ganglia (Telford, 1935; Smithwick, 1940) may also result in postganglionic interruption of some fibres — has less anatomical support (Ranson & Billingsley, 1918). Despite these considerations and the possibility of anomalous sympathetic pathways (Kirgis & Kuntz, 1942; Alexander, 1949; Boyd & Munro, 1949) the belief that the operations achieve predominantly either preganglionic or postganglionic sympathectomy remains valid.

The only other reports on the degree of adrenaline supersensitivity resulting from sympathectomy in man are derived from measurements of temperature changes in the digits. Generally

the ratio of differences in temperature reduction with intravenous adrenaline has been used uncritically as a measure of the enhanced sensitivity. White et al. (1936) concluded from such observations that ganglionectomy produced a very much greater increase in sensitivity than preganglionic section, with which opinion Simmons & Sheehan (1939) concurred. From similar findings in the monkey Ascroft (1937) assessed the supersensitivity following preganglionic section as a threefold increase over normal, and that following gnaglionectomy as a tenfold increase. Fatheree et al. (1940) employing similar methods of whose inefficacy they were aware (Fatheree & Allen, 1938) concluded that both operations caused about the same increase in sensitivity, namely twofold. These conflicting views are largely attributable to the inadequacy of temperature measurements as a guage of blood flow, and there has been no direct and valid evidence in man to support or contradict the present thesis.

Concerning the time of onset of supersensitivity Freeman et al. (1934) found an increased fall in digital temperature with intravenous adrenaline coming on some 8 to 18 days after sympathectomy, at which time they concluded supersensitivity of the blood vessels had appeared. Likewise Smithwick et al. (1934) thought that sensitization was not present during the first postoperative week. In the present investigation the earliest tests, on the 6th postoperative day, have shown unequivocal

increases in sensitivity. In the limbs of dogs Deterling & Essex (1949) noted the appearance of supersensitivity to adrenaline immediately after sympathectomy. Doubt has therefore been cast on the theory that degeneration of the vasomotor nerves is a necessary pre-requisite to sensitization of the blood vessels in man. In further conflict with this theory is the finding that preganglionic section no less than postganglionic denervation may also result in marked supersensitivity. Deterling & Essex (1949) also found an increase in sensitivity to result from both operations in the dog.

It is uncertain how long supersensitivity may persist after sympathectomy. The present finding that supersensitivity may be demonstrated as long as two years after operation conflicts with the view of Simmons & Sheehan (1939) that it is maximal at onset, decreasing steadily till no longer present after 3 months. Simeone & Felder (1951) reported that the intensification of adrenaline vasoconstriction in the digits persists for at least 13 months after sympathectomy. Unfortunately none of the aforementioned papers concerning the onset, degree or duration of supersensitivity presented adequate statistical analyses or data susceptible of such analysis.

The mechanism of supersensitivity of the vessels following sympathectomy has remained obscure. 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 in the tests. The bulk of the blood entering a limb passes through skin and skeletal muscle. It was first confirmed that the considerable rise in blood flow through the skin of the hand after sympathectomy lasts for only a week (Barcroft & Walker, 1949). The first investigation next showed that the threefold rise in forearm blood flow (mainly muscle) is of even shorter duration. 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 vascular change present. The blood flow in muscular segments of chronically sympathectomized limbs is generally within normal limits (Duff & Swan, 1951). In the present postoperative series, however, the actual distribution of circulating blood as between the hand and forearm was measured plethysmographically in a number of cases, and it was confirmed that increased sensitivity might be present when the blood flow in the hand and forearm were the same as before operation. The increased sensitivity of sympathectomized hands cannot therefore be attributed in general to an altered partition of the blood flow to different segments of the limbs.

The postoperative tests of a few individuals did take place at a time when the control blood flow in the hand was

elevated (Table V). If a given reduction in calibre restricts the blood flow in a degree proportional to the initial calibre of the vessel — in obedience to the mathematical relationship between the radius and capacity of tubes — then it might be thought that adrenaline would have a greater effect by virtue of such dilatation as was present in these individuals. However the results herein presented have all been expressed as a function of the control values, so that any increase in adrenaline effect is over and above this influence. Furthermore, Table V shows that although the average increase in sensitivity was fourfold, the mean control blood flow (A) for the whole group had increased by only 0.6 ml. after sympathectomy.

The speed of a stimulus may well determine what response is evoked. Kvale, Allen & Adson (1939) demonstrated that the velocity of the blood stream in the arteries of sympathectomized limbs is increased, especially immediately after operation. In the present investigation infusions of a steady concentration of adrenaline were used, 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 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, when volumetric and linear blood flow are greatly increased. The shortening of vascular length in the peripheral bed might well alter the orientation of those responsive elements in the walls of vessels whose function it is to initiate constriction. But this theory does not, without modification, explain the persistence of supersensitivity beyond the initial period of increased blood flow.

During the actual adrenaline tests of normally innervated subjects an impression was gained that those individuals with a relatively stable blood flow in the hands tended to have greater vasoconstriction than others with more marked fluctuation in blood flow. To test this the coefficient of variation in the blood flow during the period (A) prior to the adrenaline was calculated for each of normally innervated hands in the groups receiving 1/8 and 1/4 µg. adrenaline/min. It was confirmed that, in general, the

lower the coefficient of variation the greater the vasoconstriction resulting from a given amount of adrenaline. The mathematical relationship between fluctuation and vasoconstriction was evaluated by linear regression (Table XVI). Those individuals with minimal fluctuation in hand blood flow may perhaps be regarded as having less sympathetic vasomotor activity in the hands in contrast with those in whom large and frequent changes in flow occur.

This finding was of great interest in view of the fact that a distinctive feature of sympathectomized hands is marked reduction of fluctuation in blood flow (as shown in Figs. 12 & 14). In the hands of the initial group of patients, for example, the coefficient of variation (i.e., of blood flow fluctuation) averaged .219 before and .079 after sympathectomy, fluctuation having decreased to one third of the preoperative level.

The tendency of normally innervated subjects with minimal sympathetic activity in the hands to have a greater vasoconstriction with adrenaline may be analogous to the tendency of sympathectomized subjects, in whom there is no sympathetic activity, to exhibit supersensitivity. This, then, provides a clue as to the nature of the phenomenon of supersensitivity.

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 blood vessels of the skin in man, it seems likely that the concentration of the

TABLE XVI.

(a) Relationship between Fluctuation of the Blood Flow in Tested Hands and their Responses to Adrenaline Infusions.

Normally innervated hands, 1/8 µg. adrenaline/min.

No.	34
Ave. percentage constriction	19
Ave. coefficient of fluctuation	0.224
Coefficient of regression of constriction on fluctuation	-53.9

Normally innervated hands, 1/4 µg. adrenaline/min.

No.	17
Ave. percentage constriction	27
Ave. coefficient of fluctuation	0.252
Coefficient of regression of constriction on fluctuation	-15.5

Both groups
Coefficient of regression of constriction on fluctuation -41.8

Estimated reduction in flow with adrenaline ::
(32 - 41.8 times coefficient of fluctuation)%.

(b) Comparison of Ten Hands in Thirty Three Paired Tests Before and After Sympathectomy, in respect of Blood Flow Fluctuation aand of Constrictor Response to Adrenaline.

	Pre-operative tests	Post-operative tests
Ave. Coefficient of fluctuation	0.219	0.079
Ave. Constriction with adrenaline	9%	35%

After sympathectomy blood flow fluctuation is notably reduced, while response to adrenaline is greatly increased.

effective substance in a given tissue is related to the amount of nervous stimulation to which that tissue has been subjected (von Euler, 1951, 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 similar vasoconstricting agents. Conversely, the concentration of the effector agent in relation to vessels with rapid or marked changes in calibre (resulting from either sympathetic nervous activity or more direct local influences), would be expected to be greater thereby imparting to these vessels a reduced sensitivity to infused adrenaline. Certainly in many tissues a relationship between the state of tonus of smooth muscle in its response to adrenaline has already been noted (McSwiney & Brown, 1926; Gruber, 1929; Roome, 1938; Goetz, 1939; Allen, 1948) but speculation concerning its nature has been scanty and unfruitful.

However attractive this theory, it only partially explains the observed results. The expression relating blood flow fluctuation and adrenaline constriction (Table XVI) may be used to show that the selection of normally innervated subjects with no fluctuation in hand blood flow would not provide a group with increased sensitivity of the degree found in the group of sympathectomized patients. Also,

it might have been expected that those sympathectomized hands in which supersensitivity was not demonstrated would have a greater degree of fluctuation in flow than those in which an obvious increase in sensitivity was found. However, there was no significant difference, in respect of the coefficient of fluctuation, between sensitive (.078) and non-sensitive (.081) groupsof hands. While reduction in fluctuation is clearly associated, however indirectly, with some increase in response to adrenaline, sympathectomy must be responsible for some further vascular or circulatory change to cause the additional increase in sensitivity.

Consideration of the circulatory changes following sympathectomy led to the hypothesis that an initial dilatation of the larger vessels associated with marked increase in blood flow was followed by an extensive opening up of a more peripheral vascular bed, attended by such an increase in vascular surface resistance as to reduce the total volume of blood flowing through the limb to the preoperative level. This conception may now be extended to account, in some measure, for the changes in vascular responses in the skin.

Normally, constriction of a given small vessel may be due to the general contraction of its circular smooth muscle in continuation of a process initiated focally by specially responsive, discrete elements with the double property (1) of being able to

initiate contraction, and (2) of being specially sensitive to chemical, nervous and physical stimuli. It may be postulated that the density of these "effector elements" is proportional to the intensity of sympathetic innervation, being especially abundant in relation to the arterio-venous anastomoses near the surface of the skin, and less numerous in other vessels of the dermis.

Under the conditions of the experiments the behaviour of these surface vessels in a given healthy individual may be largely governed by two more or less opposing influences (1) the local warmth of the water in the plethysmograph, tending to relax the vessels or maintain their calibre, and (2) the activity of the sympathetic nerves, with a smaller or greater tendency to close the vessels, according as the subject's general metabolic state is relatively high or low and the general atmosphere above or below the temperature at which the subject is in specific caloric equilibrium. Depending on individual circumstances a steady or variable amount of blood passes through the superficial vessels, greater fluctuation implying greater opposition between local and systemic influences, and therefore greater total activity of both. The finding that in normally innervated subjects the greater the fluctuation the less the adrenaline vasoconstriction is, on this hypothesis, an indication that with increased activity the smooth muscle of the surface vessels, or more specifically the "effector

cells" in these vessels, are relatively refractory to chemical stimuli.

Sympathectomy may be envisaged as causing, after the initial transient changes in blood flow, a more or less permanent opening up of many if not all of the surface vessels of the skin, so that a much higher proportion of total skin circulation flows through these widely dilated and specially responsive channels.

Let it be supposed that the reactivity of the special vessels is so much greater than that of the other vessels that all the reduction in blood flow through the hand with an effective dose of adrenaline may be attributed to closure of the former. Then, if the total blood flow in a given hand, before operation, be 10 ml./ 100 ml./ min., of which one ml. passes through the superficial vessels; and if, after sympathectomy, with the same total flow of 10 ml., four ml. now passes regularly through the surface vessels, than an adrenaline infusion which previously caused one ml. reduction would cause four ml. reduction in flow after sympathectomy. Thus the theory is applicable to the various findings of the present investigation. It postulates (1) that normally certain skin vessels are more specifically dominated by the sympathetic nerves and (2) have a greater sensitivity to chemical constricting agents, and also (3) carry a greater proportion of the total skin circulation after sympathectomy. Actually all three postulates may be deduced

from the single assumption of a differential innervation of the blood vessels in skin.

Finally one further physical consideration must be taken into account. Recent papers (Freis, Stanton & Emerson, 1949) have stressed the possibility of laminar streams in the circulating blood in certain vessels. In particular, radio-opaque and dye-containing solutions introduced by slow infusion through a needle into a relatively large artery have been shown under some circumstances to flow with a restricted distribution in the vascular bed supplied by the artery. It might have been argued with respect to the present investigation that the difference in the response to infusions of adrenaline in different subjects was dependent upon the degree of mixing of the adrenaline with the blood in the periphery and upon the proportion actually reaching the skin of the hand. But such and similar possibilities of technical invalidity are satisfactorily eliminated by the statistical analyses of the data, which adequately substantiate the conclusion that significant differences are present after sympathectomy in a proportion of hands. That such results could have been produced by chance variations in the disposition of the infusion needle within the vessel is certainly possible, but of inconceivably small likelihood. The method of obtaining the measurements, by intermittent venous occlusion, no doubt aided the mixing of the blood in the veno-capillary bed; but

irrespective of whether minimal or complete mixing occurred, the validity of the results is entirely based upon their statistical characteristics.

EFFECT OF SYMPATHECTOMY ON VASCULAR RESPONSES TO ADRENALINE IN MUSCLE

With intravenous and intra-arterial infusions of adrenaline the blood flow through muscular segments of both healthy and sympathectomized limbs was found invariably to rise markedly at the beginning of the infusion. This great increase in blood flow rapidly subsided with continuance of the infusions, to be succeeded by a second phase, consisting of an increase in flow in only one group of experiments — those in which healthy subjects received intravenous adrenaline.

The suggestion (Grant & Pearson, 1937) that the initial vasodilatation is greater after sympathectomy had not led to any detailed study of the change. Comparison of the magnitude of this initial vasodilatation in the muscle of healthy and sympathectomized limbs is most reliable when drawn from the changes in a pair of limbs of a subject with unilateral sympathectomy. A young woman with right lumbar sympathectomy for causalgia was given an intravenous infusion of 10 µg. adrenaline/min. while blood flow in both

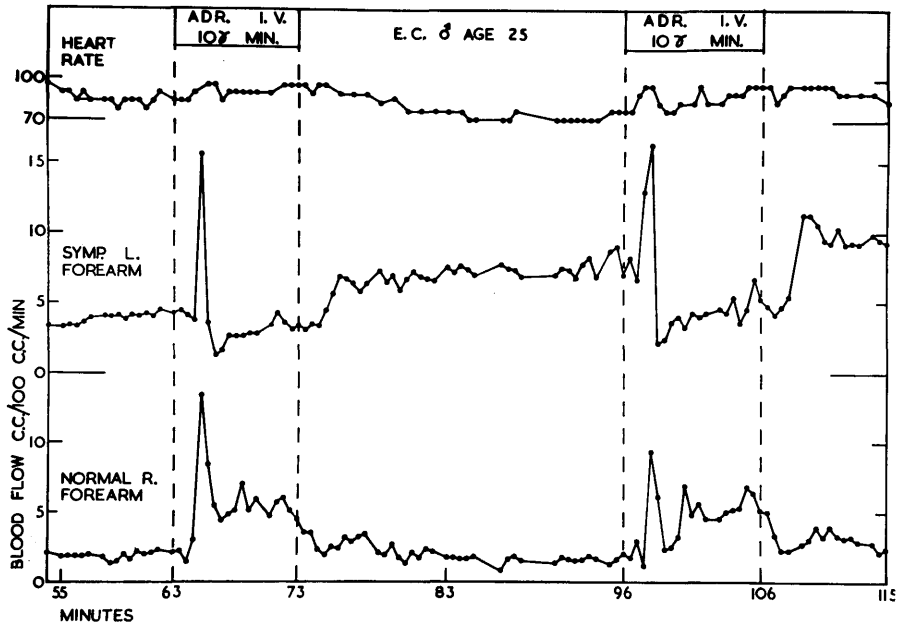


Fig. 25 Blood flow in both forearms of a patient with a sympathectomized left upper limb. This shows the greater initial vasodilatation and subsequent vasoconstriction on the sympathectomized side during intravenous infusions of 10 μg. adrenaline per min.

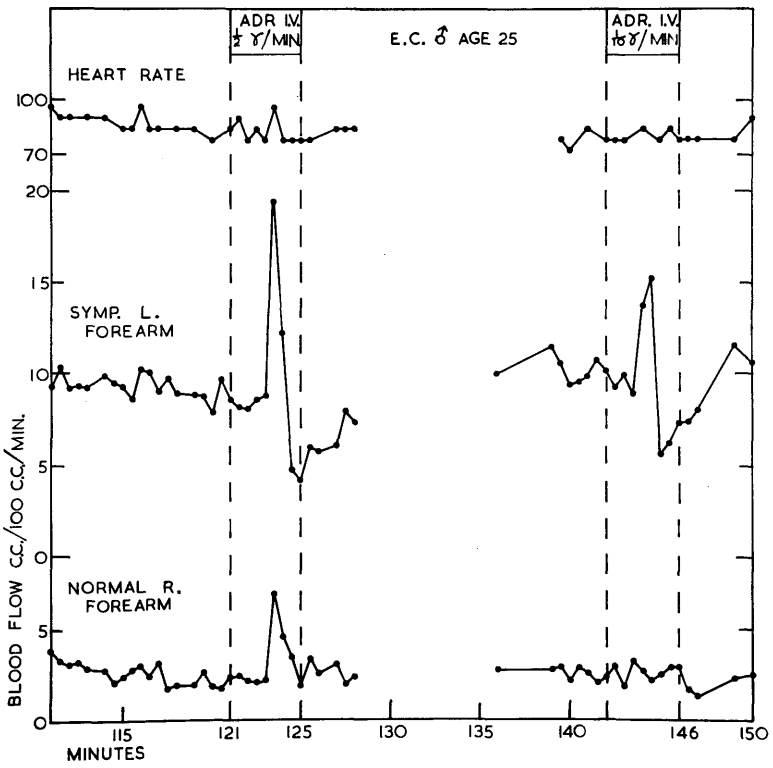


Fig. 26 Blood flow in the forearms of the same patient during intravenous infusions of 1/2 µg. and 1/10 µg. adrenaline/min. The contrast between the normal and the sympathectomized limbs is even more marked.

calves was measured. As shown in Fig. 24 the blood flow at the beginning of the infusion rose to a much higher peak on the sympathectomized than on the normal side. This difference is better revealed by using minimal concentrations of adrenaline, since the level of 10 µg./min. is well above the threshold of this response. Figs. 25 & 26 portray the blood flow in both forearms of the young man whose left upper limb was sympathectomized as a result of traumatic avulsion of the brachial plexus (and who was shown in the previous investigation to have developed super-sensitivity of the hand). With the lowering of the concentration of adrenaline in successive intravenous infusions the difference between the two sides in respect to the initial dilator phase became more marked. Finally an infusion of 1/10 µg./min. evoked a distinct vasodilatation on the sympathectomized side without any significant change in blood flow in the opposite normal forearm. While there is insufficient data of this sort for precise appraisal of the change in this response resulting from sympathectomy, the operation is clearly capable of causing a definite augmentation of the initial direct dilator response of the vessels in skeletal muscle, together with a lowering of the threshold at which adrenaline specifically evokes the response.

The blood flow responses in the forearms and calves of healthy as compared with sympathectomized limbs with 10 min.

intravenous infusions of adrenaline were found to differ significantly also during the latter half of the infusions. The blood flow in both the forearm and calf of healthy subjects during this period was generally raised above the resting level by some 70 to 120%. In sympathectomized forearms and calves during the same period, however, this elevation in blood flow was usually absent and there was an actual reduction of blood flow in the lower limb experiments. These observations indicate a relatively greater constrictor response during the second phase, in the sympathectomized vessels of skeletal muscle, with intravenous adrenaline.

In healthy subjects the intra-arterial infusion of proportionately reduced concentrations of adrenaline was found to be associated with a similar initial rise in muscle blood flow but no sustained increase during the remainder of the infusion. Indeed, it was found that increasing the adrenaline concentration in the intra-arterial infusions caused the blood flow during the latter half of infusion to be actually reduced below the resting level, indicating that the direct local action of the adrenaline on vessels in skeletal muscle is an initial powerful but evanescent relaxation followed by a weak but sustained constriction. The resemblance of this latter to the response of sympathectomized limbs during intravenous infusions is portrayed in Fig. 23.

Before enquiring into the significance of these

observations it is well to consider first the nature of the blood flow increase in the normal limb during the latter half of an intravenous adrenaline infusion.

The sustained increase in flow occurs at a time when arterial blood pressure is elevated, so it might be considered a passive consequence of the increased "perfusion pressure". But the increase in systolic pressure averaged about 30 mm. Hg, while the diastolic pressure was reduced by about 10 mm. Hg. If conditions are such that the blood flow is directly proportional to the head of perfusion pressure, the mean increase in arterial pressure alone could account at most for an increase in blood flow of about 10% (Wiggers & Werle, 1942), which is much less than the observed increase of 70 to 120%. Further, the blood pressure rises rapidly after the start of the infusion to a fairly steady level during the remainder of the infusion, while the secondary rise in blood flow often takes 1 - 3 minutes to appear. Indeed, it is usual for the blood flow to continue to increase slowly during the remainder of the infusion, while further elevation in blood pressure usually does not occur. Moreover, when fluctuations in blood pressure and in blood flow occur, these are seldom coincident; nor is there any general association between the degree of blood pressure rise in different subjects during this period, and the actual level of blood flow (Tables XII & XIII).

The secondary rise in blood flow in normal muscle during the intravenous infusion of adrenaline might be due to the arrival at the periphery of some vasodilating substance directly or indirectly released into the circulation in response to the adrenaline. Indeed, recent observations (Staub, 1946) suggest that following intravenous infusions of adrenaline in man there may be a considerable rise in the blood histamine level. The absence of the secondary vasodilatation during intra-arterial infusions might then be due to the dose of adrenaline administered by that route being insufficient to provoke a rise in blood histamine. Nevertheless, the evidence of the two series of calf experiments using different adrenaline levels in intra-arterial infusions strongly suggests that adrenaline itself is capable of causing a local constrictor effect. Possibly the intra-arterial infusion of adrenaline leads to the predominance of the local constrictor effect, whereas the intravenous infusion is normally associated with additional vasodilator effects, originating elsewhere, which are sufficient to mask the local adrenaline effect on the muscle vessels.

If this be the case, then it might be expected that the intravenous infusions would lead to a similar action in both sympathectomized and normal limbs. But the previous investigation demonstrated the occurrence of supersensitivity to the constrictor action of adrenaline in the blood vessels of the hand. It would be

reasonable, therefore, to suppose that a similar supersensitivity had developed in the vessels of skeletal muscle causing them to constrict more powerfully even despite these other vasodilator influences.

The vasodilatation in the course of an intravenous adrenaline infusion may have a further basis in normally innervated limbs. Adrenaline has been found to depress transmission in sympathetic ganglia (Darrow & Gellhorn, 1939; Marrazzi, 1939) thereby inhibiting vasoconstrictor tone. Swan (1951) found that intravenous infusions of 20 µg. adrenaline/min. were followed by a rise in the blood flow in the hands of normal but not of sympathectomized subjects. This 'after-dilatation' he attributed to the inhibition of vasoconstrictor tone, and its failure to appear regularly in the sympathectomized hands was thought to be due to the absence of the vasomotor pathway to the vessels. Early animal studies had suggested that adrenaline may normally be responsible, by means of a central inhibitory effect mediated by the sympathetic system, for a relaxation of vascular tone at the periphery (Meltzer & Meltzer, 1903; Hartman, Kilborn & Fraser, 1918). However, in sympathectomized subjects supersensitivity of the blood vessels of the hands might well have intensified and prolonged the constriction of these vessels, directly preventing the 'after-dilatation'. One of the earliest studies of the enhanced effect of adrenaline on denervated smooth muscle (Elliott, 1905)

pointed out that the adrenaline effect was prolonged as well as intensified and this has subsequently been confirmed (Essex, Herrick, Baldes & Mann, 1943). There is, moreover, some recent evidence that the second phase of vasodilatation in the forearm during intravenous infusions of adrenaline is not dependent upon a vasomotor effect (Whelan, 1952) for it still occurred in forearms in which all the vasomotor nerves had been effectively blocked by injections of procaine.

The behaviour of the blood vessels during the latter half of infusions of adrenaline seems therefore to be governed by a variety of influences. The direct action — as seen especially with intra-arterial infusions — appears to be constrictor, in a degree proportional to the local concentration of the adrenaline. With intravenous infusions, in normal subjects, this local effect is counteracted by vasodilator factors — especially the arrival in the blood stream of histamine or histamine-like substances. In sympathectomized limbs, however, supersensitivity of the vessels to the direct constrictor actionof the adrenaline is apparently sufficient to cause predominantly a reduction in blood flow.

If so, then certain interesting conclusions may be drawn from the comparison of sympathectomized forearms and calves. As previously mentioned, the operation to produce sympathectomy of the lower limb consisted, exclusively, in interrupting the preganglionic

neurones (Telford, 1935; White et al., 1936) whereas the upper limbs were sympathectomized either by preganglionic section or by ganglionectomy. In the present study the reduction in blood flow during the latter half of intravenous infusions — presumably the result of vascular supersensitivity — was greater in the calves than in the forearms (Table XV). This strikingly supports the conclusion derived from the investigation of supersensitivity in the blood vessels of the hand — that preganglionic section causes no less supersensitivity, or perhaps even more, than ganglionectomy.

It had hitherto been assumed (Simmons & Sheehan, 1939) that the consistently better clinical results with lower than with upper limb sympathectomy were largely due to the reduced liability to supersensitivity following lumbar sympathectomy because the operation produces decentralization rather than denervation of the vessels of the lower limb. There is little doubt that sympathectomy is more often beneficial in the case of the lower than the upper limb, but this advantage has not, in the opinion of many practising surgeons, been removed by the adoption of a preganglionic operation for the upper limb (Haxton, 1947; Learmonth, 1950).

The present study provides evidence that both phases — the initial dilator and the subsequent constrictor — of the direct action of adrenaline in the muscle vessels are intensified by sympathectomy.

This finding is of profound interest in view of the fact that the vasculature of skeletal muscle in man is normally supplied with both constrictor and dilator sympathetic nerves (Barcroft & Edholm, 1946). Presumably in the innervated vessels there are two types of effector elements, responsible for constriction and dilatation, respectively, (Ahlquist, 1948). If the not unreasonable assumption is made that there is a focal distribution of sympathetic nerve endings in the vasculature, then those vessels in more intimate juxtaposition to the nerve endings may be expected to be preferentially equipped with effector elements. The direct vasodilator and vasoconstrictor effect of adrenaline is probably determined largely by the behaviour of these vessels (Ahlquist, 1948). The latter would also be specially influenced by sympathectomy so as to receive a higher proportion of the blood entering the muscles at the expense of the rest of the vessels. Augmentation of the biphasic response to adrenaline after sympathectomy would necessarily follow.

Thus the theory evolved to elucidate the phenomenon of vascular supersensitivity in the skin may be extended to include the changed responses of the vessels in muscle after sympathectomy.

RELATIONSHIP BETWEEN SYMPATHETIC NERVOUS ACTIVITY AND VASCULAR REACTIVITY

The first investigation indicated that although major changes in the circulation through the skin and muscle result from sympathectomy, after a week the total volume of blood flowing through these tissues has returned to a level little different from the preoperative resting level. The circulatory changes were not found to be affected by the particular type of operation, provided complete interruption of the vasomotor pathway was achieved. Despite the absence of a maintained rise in blood flow the available evidence was considered to show that sympathectomy causes some permanent change in the circulatory pattern within both tissues.

In the second investigation supersensitivity of the vessels in the skin of the hand to adrenaline was demonstrated to result from sympathectomy. Analyzing the degree of supersensitivity a wide variation in the response of different subjects was found. It was concluded that the site of interruption of the sympathetic neurone — whether pre- or postganglionic — had little material influence on the development of supersensitivity. The amount of vasomotor activity in the hands of normally innervated subjects — as shown by fluctuation in blood flow — was found to bear a measureable relationship to the response to adrenaline. The theory

was proposed that a certain group of minute vessels in the skin — normally under more complete vasomotor control than other vessels — are specially responsive to adrenaline and other constricting agents, and that their reaction to infused adrenaline is conditioned by their state of activity prior to the infusion. The marked reduction in fluctuation resulting from sympathectomy was described and an analogy was drawn between supersensitivity in sympathectomized hands and the increased, though normal, response of those healthy subjects with quiescent blood vessels.

The possibility that the same change might be responsible both for the maintained warmth of the skin and for the increased sensitivity of the vessels to adrenaline after sympathectomy was reviewed. Since the total blood flow through the hand does not remain elevated, a rise in the proportion of blood flowing through specially responsive vascular channels located at a convenient depth for disseminating heat was thought to be an important and lasting consequence of sympathectomy.

The third investigation was concerned with the direct and indirect responses to adrenaline of the vessels in skeletal muscle. The occurrence after sympathectomy of an augmentation of the initial direct vasodilator response to adrenaline was briefly described. Systematic analysis of the subsequent phase, during prolonged infusions of adrenaline, provided evidence that normally during

this phase, with intravenous infusions, the direct weakly constrictor action of adrenaline is masked by systemic vasodilator influences. In sympathectomized limbs however relative or absolute vasoconstriction is manifest during this phase, and this was taken to indicate increased sensitivity to adrenaline of the vessels in skeletal muscle. The possibility that in chronically sympathectomized limbs there is a shift in the circulation within the muscles so that a larger proportion of blood is distributed to specially responsive channels without an increase in total blood flow was discussed.

The results of the three investigations provide a basis for the following conception of the relationship between sympathetic nervous activity and vascular reactivity. In a given portion of skin or muscle the minute contractile vessels — whose aggregate calibre and resistance determine the total volume of blood entering the tissue — may be regarded as of two functional types (1) those which carry sufficient blood for the ordinary basic metabolic activities of the tissue, and (2) those vessels specially adapted for sudden or marked changes in the circulatory requirements of the tissue or of the body as a whole. Control of the latter is the classical prerogative of the sympathetic system, so it seems reasonable to postulate that there may normally be an economic provision of more intense vasomotor innervation to those "emergency"

vessels. No matter how complex the physico-chemical process underlying the transmutation of vasomotor nervous impulses into alterations of vascular calibre, it is reasonable to assume that this process involves, in the first instance, the activity of specially adapted cellular or subcellular effector elements. The latter are likely therefore to be focally distributed in numerical proportion to, and with spacial orientation toward, the vasomotor nerve-endings. The density of these effector organs in a given vasculature will be related to the functional activity of the vessels. Gollwitzer-Meier (1932) and Franklin (1951) have suggested that different vessels normally have a varying sensitivity to adrenaline. If any such specific chemo-active equipment does exist it may be deduced that effective chemical agents introduced into the circulation must exert their actions primarily through these effector elements. To them also may be attributed the property of responding not solely to the products of nervous activity and to similar chemical agents but also — within limits — to all other effective stimuli such as alterations in temperature or in the constitution of circulating blood or extravascular fluid. The reactivity of these elements is no doubt determined by the intensity or rapidity of the effective stimuli, and since they are finite biological entities they must be subject to the principle of accommodation — liable to become refractory for a brief period after activity and rendered unresponsive by unchanging stimuli.

In a normally innervated subject the reduction of blood flow through the hand with adrenaline is presumably due mainly to constriction of vessels of the type well supplied with effector elements. The phasic changes in the circulation through skeletal muscle with adrenaline may also be attributed to the predominant activity of analogous vessels in that tissue.

Sympathectomy may be conceived as permanently removing these more active vessels from the regular constricting influence of vasomotor tone. The consequent opening up of these vessels — at a rate dependent upon the exhaustion of the supply of chemical transmitter still remaining at the nerve endings — must occupy some time. Immediately after sympathectomy, when only a moderate number of these vascular channels have become patent, it is possible to envisage a circulatory state in which the aggregate calibre of the peripheral vascular bed is sufficiently increased to permit a volumetric increase in the total amount of blood flowing through the tissue. With the progressive opening up of more and more channels, however, despite a greater total vascular capacity, a rise in the resistance to flow must soon result from the increasing frictional area of vascular surface. Beyond a critical point the opening up of further vessels would be associated with such an increase in circulatory resistance as to reduce the total volume of blood flowing through the tissue. In these terms the subsidence

of the initial increase in total flow in the upper limb after sympathectomy becomes comprehensible.

The shift of a higher proportion of the available blood to the more responsive vessels is liable to be more or less permanent until the regrowth of vasomotor connexions takes place. The effect of infused adrenaline is likely to be proportional to its distribution to these more responsive vessels. Sympathectomized subjects with vessels relatively poorly equipped with effector elements, or in whom normally a relatively smaller number of vessels were supplied by vasomotor nerve-endings, or in whom other anatomical circumstances were such as to preserve a relatively high blood flow through more inert vessels, would exhibit a smaller increase in adrenaline sensitivity.

On this theory the onset, degree and duration of adrenaline supersensitivity are determined essentially by the change in the proportion of blood flowing through the specially sensitive vessels. Supersensitivity would be expected to appear very soon after operation, increasing rapidly to become maximal shortly after the disappearance of the initial vasodilatation, to remain thus so long as interruption of the vasomotor pathway remained complete.

It is submitted that the diverse evidence reviewed throughout this thesis, and especially that presented in the three experimental investigations affords more adequate support for this, than for any other single hypothesis.

SUMMARY

I 1. Using a specially constructed plethysmograph the blood flow in the hands and forearms of patients was studied before and after sympathectomy.

2. After sympathectomy there was an immediate threefold increase in forearm blood flow lasting for three or four days in six hyperhidrotic and eight Raynaud limbs.

3. In the hands the blood flow took 24 to 48 hours longer to reach a peak, but the increase was greater, especially in the hyperhidrotic hands, and lasted longer.

4. Preganglionic section was found to cause as much increase in blood flow as ganglionectomy.

II 1. The effects of intra-arterial infusions of graded levels of adrenaline on blood flow in the hands of patients before and after sympathectomy, and in the hands of healthy subjects, were measured by plethysmography.

2. An analytical technique was evolved to assess small changes in sensitivity to adrenaline and the range of response of the hands to a series of concentrations of adrenaline was determined.

3. The sensitivity 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 with 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. Five of the six hands which exhibited a distinct increase in sensitivity had been sympathectomized by preganglionic section. Two of the four hands in which no increase was demonstrated were sympathectomized by ganglionectomy.

7. A further six hands of patients previously sympathectomized for hyperhidrosis or Raynaud's disease were studied at various intervals after operation. Two had significant increases in sensitivity after ganglionectomy and one after preganglionic section. No significant increase was demonstrated in two hands after ganglionectomy nor in one after preganglionic section.

8. Altogether, by the criteria adopted, supersensitivity was present in nine hands, following preganglionic section (6), ganglionectomy (2) and traumatic sympathectomy (1); and absent in seven hands, following ganglionectomy (4) and preganglionic section (3).

9. The evidence was considered to indicate that preganglionic section is no less liable than ganglionectomy to cause supersensitivity of the skin vessels to adrenaline.

10. Supersensitivity was found in tests as early as the sixth day and as late as the 24th month after sympathectomy.

III 1. The normal blood flow response in the forearm and calf to 10 minute intravenous infusions of 10 ug. adrenaline per minute was found to consist of an initial marked (four or fivefold) but brief increase followed by a moderate (twofold) but sustained elevation in blood flow.

2. Some evidence that the initial phase is increased after sympathectomy was presented.

3. In sympathectomized forearms the second phase of increased blood flow was shown to be absent and in sympathectomized calves there was found to be, instead, an actual reduction of flow.

4. Intra-arterial infusions of proportionately reduced amounts of adrenaline given to normal subjects produced only a brief initial increase in blood flow in the forearm and calf; during the remainder of the infusions the blood flow was either at the resting level or lower. These effects were considered to be due to the local direct action of adrenaline on vessels in skeletal muscle.

5. The findings thus showed that sympathectomy causes an augmentation of both the initial dilator and the subsequent constrictor phases of the direct action of adrenaline on the muscle vessels.

IV 1. All three experimental approaches give consistent evidence that the degree of supersensitivity of the vessels in skin and skeletal muscle resulting from preganglionic section is no less than that following ganglionectomy, in direct contradiction of 'the general law of denervation' of Cannon et al. (1945).

2. The literature concerning the changes following sympathectomy and the circulatory effects of adrenaline is briefly surveyed and certain current views critically reviewed.

3. A hypothesis is put forward to account for the salient changes after sympathectomy in terms of a circulatory redistribution within sympathectomized tissues causing a higher proportion of blood to flow through specially responsive channels.

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