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VASODILATATION IN HUMAN SKELETAL MUSCLE DURING ADRENALINE INFUSIONS

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Allen, Barcroft & Edholm (1946) described the effects of adrenaline infusions on the blood flow through the muscles of the forearm and calf in normal human subjects. The response to 10 μg/min infused intravenously consisted of two distinct phases; an initial transient increase in the muscle blood flow of approximately four times the resting level, and a subsequent sustained dilatation of about twice the resting flow, which persisted throughout the remainder of the infusion, gradually returning to the resting value after the infusion was terminated. Allen *et al.* produced evidence to show that the initial transient vasodilatation was due to a direct local action of the adrenaline on the muscle vessels and that central vasomotor reflexes were not involved. They left open the question of the cause of the sustained dilatation.

Duff & Swan (1951) further investigated the sustained dilatation during adrenaline infusions and they showed that this phase of the response did not occur in chronically sympathectomized limbs, nor when the adrenaline was infused intra-arterially. They concluded that it was caused by a central release of vasomotor tone.

The present paper describes observations on the response of the muscle vessels to adrenaline after acute interruption of the sympathetic control (nerve block and section); the results suggest that release of sympathetic tone is not the cause of the sustained vasodilatation.

METHODS

The normal subjects were colleagues and medical students. The sympathectomized subjects were between 17 and 48 years of age and were operated on for mild Raynaud's disease or hyperhidrosis. The laboratory was temperature-controlled at 21–23° C.

Blood flow. Blood flow through the forearm was measured by venous occlusion plethysmography, according to the technique of Barcroft & Edholm (1943, 1945), a light rubber 'through-and-through' sleeve being fitted to the forearm. The water in the plethysmographs was maintained

at 33–35° C and records of flow were taken every half minute. The flow is expressed as ml. of blood per 100 ml. of tissue per minute.

The infusion. The intravascular infusions were maintained by means of a mechanically driven apparatus (Allen *et al.* 1946; Duff, 1952), with two interchangeable 50 ml. syringes which enabled rapid change-over from one infusion to another.

After the plethysmographs had been applied to the limbs an infusion of physiological saline containing ascorbic acid was commenced into the brachial artery or an antecubital vein as required.

The intra-arterial needle was connected by polythene or nylon tubing (dead space 0·5 ml.; 7·5 sec) to the mechanically driven syringe. In the case of the intravenous infusions a short length of transparent nylon tubing was inserted through a wide-bore, thin-walled needle into the median basilic or cephalic vein at the elbow. The cannula was passed up the vein for a distance of 10–15 cm and the needle withdrawn. This technique allowed a plethysmograph on the same forearm to be drawn up close to the elbow and, since the cannula extended proximally along the vein to a point above the upper edge of the collecting cuff, the infusion was not interrupted during the recording of flows.

During control periods saline containing ascorbic acid 0·001% was infused continuously at a rate of 4 ml./min. After 10–15 min this was replaced by a solution of L-adrenaline tartrate (B.D.H.) so that the minute flow was contained in 4 ml. of ascorbic acid saline. In the presence of 0·001% ascorbic acid in saline dilute adrenaline has been shown to remain stable for many hours (Gaddum, Peart & Vogt, 1949). The solutions were made up within 2–3 min of infusion.

Several subjects were given intravenous and intra-arterial infusions of adrenaline solvent which contained tartaric acid, sodium metabisulphate, sodium chloride and distilled water according to the British Pharmacopoeia formula. This solvent was supplied* by the manufacturers of the adrenaline 1:1000 solution used in these experiments, and the pH and the total acidity of the solvent were the same as in the adrenaline preparation. Infusion of an amount of the solvent equivalent to that carrying 10 μg/min of adrenaline when given intravenously, and 1–2 μg when given intra-arterially, did not produce any change in the forearm blood flow. It was therefore concluded that any changes in forearm flow during the infusion of solutions of adrenaline in the experiments to be described could be attributed solely to the adrenaline.

The nerve blocks. In those experiments in which the nerves to the forearm and hand were blocked, 2–3 ml. of lignocaine (Xylocaine) to which was added adrenaline 1:60,000, was injected around the median nerve 1–1½ in. above the fold of the elbow; around the radial nerve in the musculo-spiral groove; and around the ulnar nerve in the groove between the medial epicondyle of the humerus and the olecranon process (Barcroft, Bonnar, Edholm & Effron, 1943). Block of these nerves produced paralysis of all the muscles of the forearm and hand (with the exception of the anconeus, a small muscle and one not included in the segment of the forearm under examination). A variable area of the skin of the forearm was often anaesthetized, as the blocking of some cutaneous branches was usually unavoidable, but the area so involved was generally less than ⅓ of the forearm skin, and it has been shown that blocking all the cutaneous nerves to the forearm only produces about a 20% increase in the total forearm blood flow (Bonnar, 1941).

The criteria of a successful block were: (*a*) complete paralysis of hand and wrist movements; (*b*) anaesthesia of the skin of the hand; and (*c*) doubling of the blood flow in the forearm of the blocked side. Three experiments in which all of these requirements were not satisfied were discarded.

RESULTS

Response of the nerve-blocked forearm to intravenous adrenaline

The effect of blocking the nerves to the forearm on the response of the muscle vessels to intravenous adrenaline was observed on six subjects. In each of these, after a 10–15 min control period during which ascorbic acid saline was

* Supplied by the courtesy of the British Drug Houses Ltd.

infused and blood flow observed, 10 μg of adrenaline per min were given for 10 min, and the blood flow in the blocked and the opposite control forearm recorded every $\frac{1}{2}$ min. When the flows had returned to a steady control level after the adrenaline infusion was stopped (usually 10–15 min) a second infusion of 10 μg of adrenaline was given in most cases. The response to this second infusion was always the same as to the first.

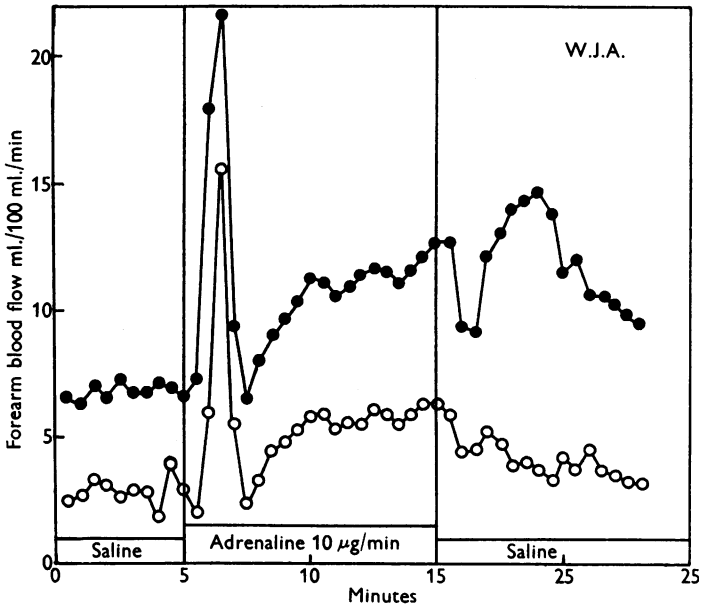

Fig. 1. A typical example of the response of the normal and the nerve-blocked forearms to intravenous adrenaline. Ordinate: blood flow in ml./100 ml./min; abscissa: time in minutes. The dots represent the flow through the nerve-blocked forearm and the circles that through the control normal forearm. During the period indicated by the vertical lines adrenaline at a rate of 10 μg/min was infused intravenously.

Fig. 1 shows a typical result on one of the subjects and Fig. 2 shows the averaged values of six such infusions, one on each of the six subjects. Flows were recorded at $\frac{1}{2}$ min intervals, but since the occluding cuff at the wrist was released for 30 sec every 5 min, of necessity there were some observations missing (82 out of a total of 576 in the six averaged runs). To a missing observation during the base-line period before the adrenaline was infused the average value of the other observations during that period was assigned, and to a missing observation during or after the infusion a value midway between that of adjacent observations was given.

It can be seen that during the control period the blood flow in the nerve-blocked forearm was about double that of the normal side. The pattern of response to the infusion of adrenaline was the same on the two sides but

occurred at a higher level of flow on the blocked side. There was an initial transient large dilatation followed by a smaller sustained increase of flow persisting throughout the remainder of the infusion. The absolute sustained increase in flow during the infusion of adrenaline was approximately the same in the blocked as in the normal control limb (Figs. 1, 2 and 3) although the percentage increase was only about one-half as great an the blocked side. Thus the sustained dilator effect of adrenaline on the muscle flow is constant in degree and is not affected by the level of vasomotor tone.

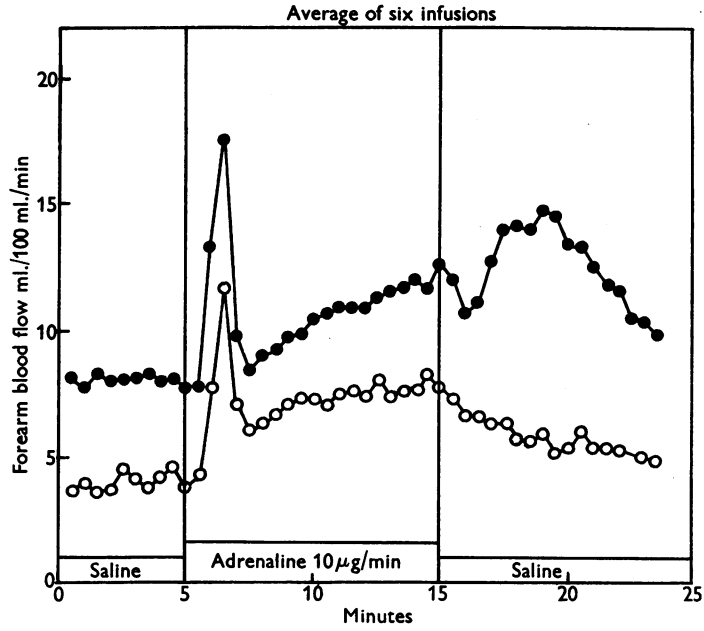

Fig. 2. Averaged results of six infusions (one on each of six subjects) on the normal and nerve-blocked forearms. The conventions are the same as in Fig. 1. Each point is the average of six observations.

The pattern after stopping the adrenaline and resuming the ascorbic acid saline showed a marked difference on the two sides. The flow in the control forearm fell gradually to base-line over a period which varied in individuals from 10 to 20 min. In the blocked forearms the flow showed a slight initial fall followed by a dilatation as high as, or higher than, that during the latter part of the adrenaline infusion, before returning slowly to base-line.

Fig. 3 shows the averaged results after the respective base-line levels of flow have been subtracted and this demonstrates clearly the remarkable similarity of the patterns on the two sides during the infusion, and the marked difference afterwards.

Response of the acutely sympathectomized forearm to intravenous adrenaline

The response of the forearm blood flow to intravenous adrenaline was examined in two cases of mild Raynaud's disease and one case of hyperhidrosis both before and after cervical sympathectomy. Fig. 4 shows the results on one of the patients suffering from Raynaud's disease. The lowest curve shows the response of the left forearm 2 days before the operation, and it follows the normal pattern. The topmost curve represents the response of the same forearm to the same dose of adrenaline 7 hr after the limb was surgically sympath-

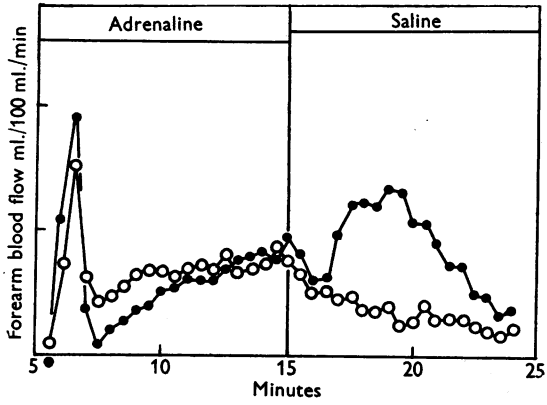

Fig. 3. The average flows in the control and nerve-blocked forearms during and after the six adrenaline infusions shown in Fig. 2 after subtraction from each of the respective averaged base-line levels.

ectomized. The resting blood flow was increased about sevenfold but the response during the adrenaline infusion was essentially the same as normal although it occurred at a higher level of flow; that is, the flow during the latter part of the infusion was approximately double that during the resting control period. This response is similar to that obtained following acute block of the nerves to the forearm. This pattern of response, however, was not maintained, and 24 hr after the operation, although the resting level of flow was still five times the pre-operative level, the response to adrenaline showed only a rise of one-half over the resting level. Four days after the operation the increase during the latter part of the infusion was still further reduced, although the resting flow was still considerably above the pre-operative level.

A similar sort of change in the response to adrenaline in the early days following sympathectomy is illustrated in Fig. 5 which shows the results on another patient who had a cervical sympathectomy performed for mild Raynaud's disease, and Fig. 6 shows the responses before and immediately after sympathectomy performed for hyperhidrosis, the vessels of the arm being normal.

These patients were subsequently tested for completeness of the sympathectomy by means of reflex heating. There was no increase of flow in the sympathectomized limb on immersion of the feet in a water bath at 45° C for 1 hr in any of the cases.

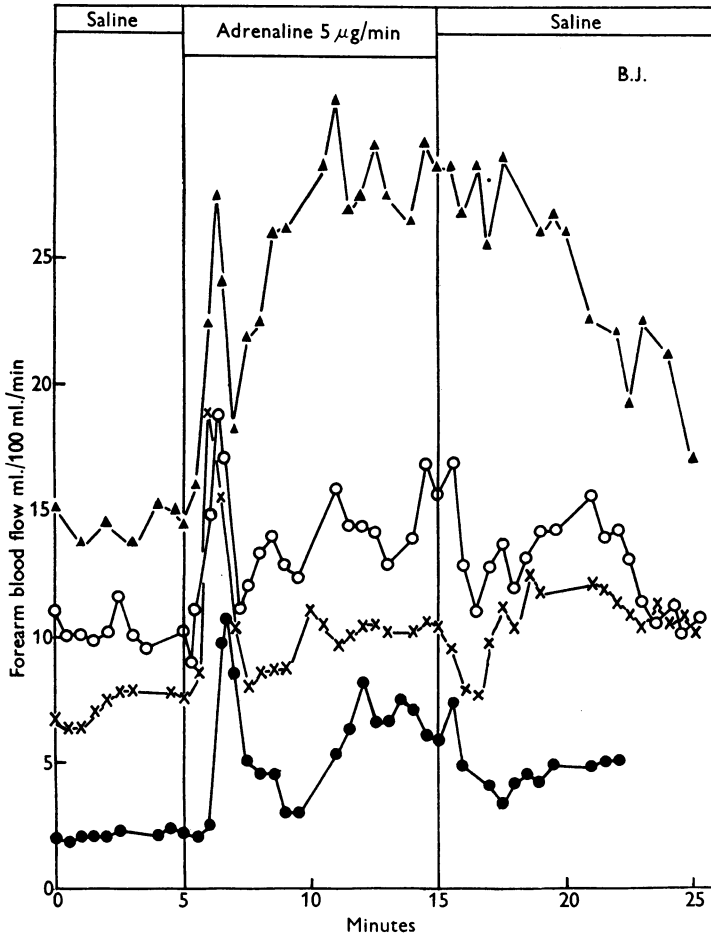

Fig. 4. The blood flow in the left forearm of B.J. in response to intravenous adrenaline before and after cervical sympathectomy. ●, 2 days before operation; ▲, 7 hr after operation; ○, 24 hr after operation; ×, 4 days after operation. The other conventions are as in Fig. 1.

It is of interest that the blood flow in the acutely sympathectomized forearm after the infusion of adrenaline was stopped (Figs. 4, 5 and 6) showed the same abnormal pattern of recovery as did that in the nerve-blocked forearms (Fig. 2). There was a transient fall followed by an increase in the flow before it fell to the resting level.

This phenomenon of the recovery period has also been demonstrated in chronically sympathectomized patients (Duff & Swan, 1951), both in the forearm and in the calf, and was also seen in a completely denervated limb (Fig. 7).

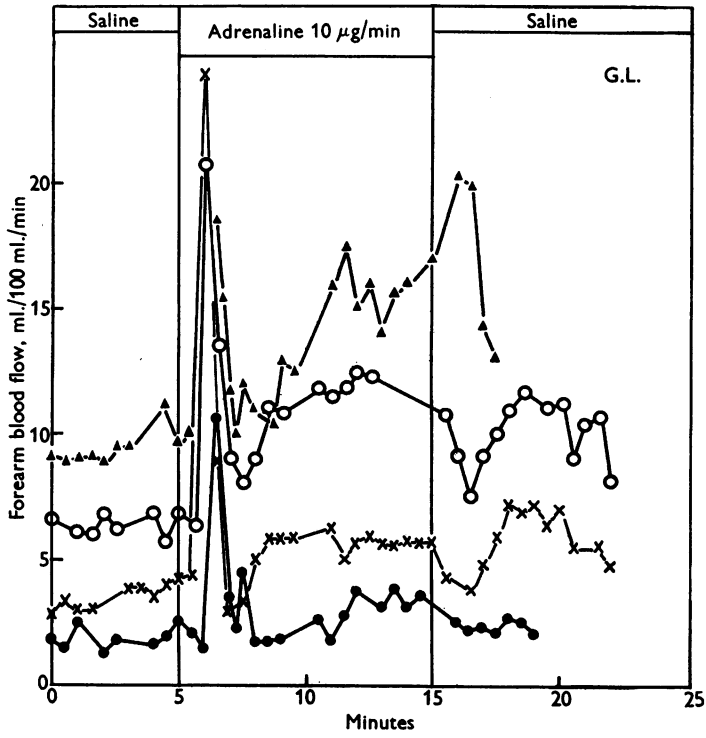

Fig. 5. The blood flow in the right forearm of G.L. in response to intravenous adrenaline before and after cervical sympathectomy. ●, 2 days before operation; ▲, 8 hr after operation; ○, 24 hr after operation; ×, 7 days after operation. The other conventions are as in Fig. 1.

Intra-arterial infusions

Twelve intra-arterial infusions of adrenaline were given to five normal subjects in doses ranging from 1/10–1/1000 μg/min for 10 min. In all of these an initial transient vasodilatation occurred in the forearm but the flow during the latter part of the infusion was either unchanged or only slightly increased. Fig. 8 shows three typical examples of the response to intra-arterial adrenaline and in Table 1 are shown the results of all the infusions, the average of the flows in the last 5 min of the control period being compared with the average of the flows during the last 5 min of the infusion. In a few of the experiments, after the intra-arterial infusion was stopped a definite 'after-dilatation' occurred, but in most it was absent or very doubtful. The pattern of response of the flow in the normal forearm during intra-arterial adrenaline is similar to

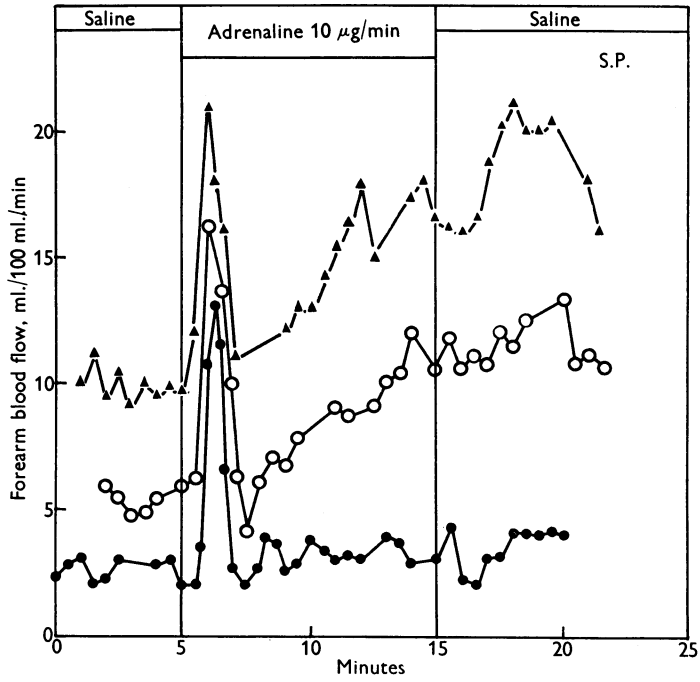

Fig. 6. The blood flow in the forearm of S.P. in response to intravenous adrenaline before and after cervical sympathectomy. ●, 1 day before operation; ▲, 4 hr after operation; ○, 20 hr after operation. The other conventions are as in Fig. 1.

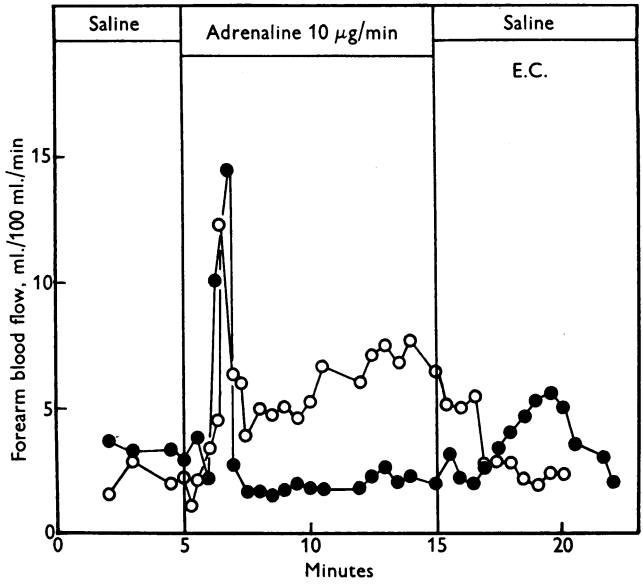

Fig. 7. The response to intravenous adrenaline of the forearm flows of E.C. ●, left forearm, completely denervated following brachial plexus avulsion 18 months previously. ○, right normal control forearm. The other conventions are as in Fig. 1.

that of the chronically sympathectomized forearm to intravenous adrenaline, and this finding agrees with the results of Duff & Swan (1951) with larger doses.

TABLE 1. Flow in normal forearms during intra-arterial adrenaline infusions. The average flow during the last 5 min of the control period is compared with the average during the last 5 min of the infusion. Blood flow in ml./100 ml./min.

Subject	Dose (μg/min)	Blood flow		% increase during infusion
		Control	Infusion	
W.R.	1/10	6·8	6·8	0
W.R.	1/20	4·8	6·5	+35
H.S.B.	1/20	2·2	2·6	+18
H.S.B.	1/40	3·2	3·2	0
W.R.	1/40	4·5	5·8	+29
W.R	1/50	5·2	4·9	− 6
A.T.	1/80	6·1	9·0	+50
A.T.	1/100	6·6	8·7	+32
T.M.W.	1/200	4·1	4·1	0
T.M.W.	1/400	4·1	4·6	+12
J.A.	1/500	7·1	9·1	+28
J.A.	1/1000	6·5	6·7	+ 3

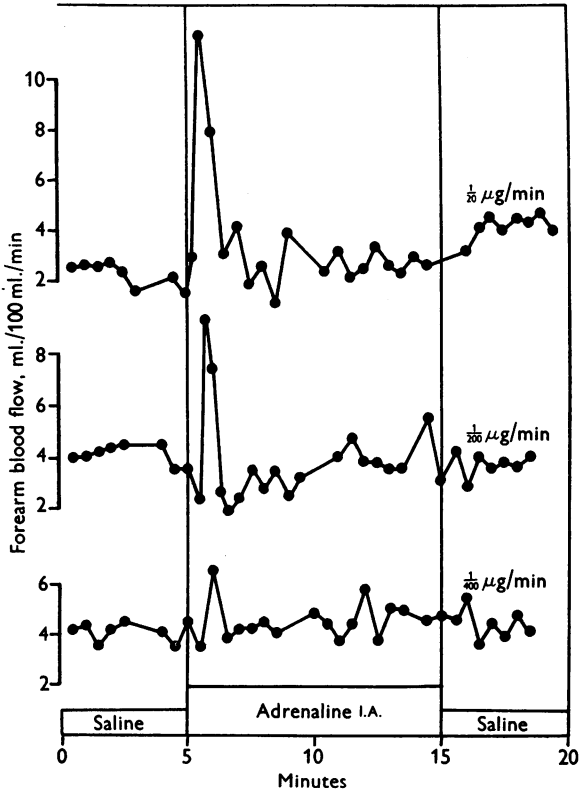

Fig. 8. The response of the forearm blood flow to intra-arterial adrenaline. Three typical examples with different doses. The flow scale is given to the left of each curve and the dose is given to the right. The abscissa is the time in minutes.

DISCUSSION

The initial transient vasodilatation. This phase of the response of the muscle blood-flow to adrenaline is seen in the normal, the nerve-blocked and the acutely and the chronically sympathectomized forearms. It is present whether the drug is infused intravenously or intra-arterially and it occurs in response to a very wide range of doses. The conclusion is therefore reached that the initial transient vasodilatation is a consequence of the direct action of the adrenaline on the muscle vessels and this view is in agreement with that of Allen *et al.* (1946) and with the results of Duff & Swan (1951).

The sustained vasodilatation. The finding in the present series of experiments that intravenous adrenaline causes a sustained increase in flow in the acutely sympathectomized and nerve-blocked forearms as well as in the normal forearm indicates that the dilatation is not a nervous effect mediated by the sympathetic nerves. This conclusion is in direct contrast to that of Duff & Swan (1951). They found that no sustained dilatation occurred on intravenous infusion in the chronically sympathectomized forearm, and concluded that the dilatation depended on a central effect of adrenaline resulting in a release of vasomotor tone and required the presence of intact sympathetic nerves. Since, however, the dilatation has been shown to occur immediately after sympathectomy whether by surgical interference or by nerve block, this view would appear to be no longer tenable. The differences in the responses of the normal and the chronically sympathectomized limbs must be explained in some other way.

The stage in which there is failure to show a sustained dilatation develops rapidly after sympathectomy is performed (Figs. 4, 5 and 6) and may be related to the rapid return of intrinsic tone which occurs in the first few days after operation (Barcroft & Walker, 1949; Duff, 1951). It may also be associated with the development of an increase in sensitivity of the muscle vessels to the constrictor action of adrenaline. Duff (1952) has shown that the vessels of the hand are more sensitive to adrenaline following sympathectomy than they are before operation. None of his cases was tested earlier than 6 days after operation, and it is not known when this sensitivity first develops. The sensitivity of the vessels of the nerve-blocked hand was examined in two subjects of the present series and it was found that it did not differ from the normal, which suggests that the increased sensitivity of the chronically sympathectomized vessels is not a direct consequence of the release of sympathetic control, but appears with the development of the chronic state.

That the sustained dilatation is not a nervous effect has just been shown. That it is not the effect of the direct action of adrenaline on the vessels was demonstrated by Duff & Swan (1951) who showed that doses of $\frac{1}{8}$ μg/min given intra-arterially in the forearm did not result in any sustained increase in flow.

It was considered possible that the doses used by these workers might have been somewhat greater than the amount arriving in the forearm during the infusion of 10 μg/min intravenously. It was calculated that with a resting blood flow of 5 ml./100 ml./min, a forearm volume of 1000 ml., and a cardiac output of 5000 ml./min, an intra-arterial dose of 0·1 μg/min was equivalent to 10 μg/min intravenously, and this is assuming that none of the intravenous adrenaline is destroyed before reaching the forearm. The effects of intra-arterial infusions of small doses were therefore examined and it was found that doses between 0·1 and 0·01 μg/min produced an initial transient vasodilatation in the forearm approximately equal to that of 10 μg/min intravenously, but even doses as small as 0·001 μg/min (1 mμg/min) produced distinct, though small, transient dilatations. None of these doses, however, produced a sustained vasodilatation in any way comparable to that of an intravenous infusion, the flow during the latter part of the intra-arterial infusion being little different from the control level (Table 1).

Since the sustained effect of adrenaline on the muscle blood flow is neither a direct one nor a central one mediated by the sympathetic nerves it would appear reasonable to seek for some humoral explanation of its action. It is possible that when adrenaline is administered intravenously it may become modified in some way during its circulation through the body, or that it may release some other dilator substance from an internal organ or endocrine gland. Such a change or release would not occur when it is infused intra-arterially, and could result in a difference in effect between the two methods of infusion. Staub (1946) found an increase in the level of plasma histamine during intravenous infusions of 20 μg/min of adrenaline and suggested that the circulating histamine might account for some of the effects of adrenaline. If this histamine were released from some organ other than the tissues of the forearm, and were responsible for muscle dilatation, then its release might account for the difference between the responses to intravenous and intra-arterial adrenaline. Mongar & Whelan (1952, unpublished), however, were unable to confirm the observations of Staub and could not detect any increase in the level of the plasma histamine with infusions of adrenaline whether intravenous or intra-arterial.

Adrenaline has been shown to stimulate the release of adrenocorticotrophic hormone and of thyrotropin from the anterior pituitary (Long, 1947; McDermott, Fry, Brobeck & Long, 1950) and may well have a direct action on the thyroid gland. Further work is necessary to determine whether such endocrine secretions can be held responsible for changes in muscle flow and metabolism.

It was thought possible that some, if not all, of the muscle dilatation might be accounted for by a change in the blood chemistry produced by the hyperpnoea which is present during adrenaline infusions by the intravenous route

and that this effect was obscured in the chronic sympathectomy by hypersensitivity. However, it has been found (Dornhorst & Whelan, 1952, unpublished) that the increase in flow produced by the adrenaline hyperpnoea contributes little, if anything, to the sustained dilatation.

The 'after-vasodilatation'. The phase of dilatation which occurs in the nerve-blocked forearm after an adrenaline infusion is stopped is also seen in the sympathectomized limb whether acute or chronic. It is not seen in the normal, and it appears to be a consequence of the removal of sympathetic control, and is not dependent upon the development of the chronic state. It corresponds in time with the flushing of the face and with the similar 'after-dilatation' in the normal hand described by Swan (1951), which, however, did not occur in the sympathectomized subject, and the mechanisms of the two phenomena must be quite different. Since the absence of the after-dilatation depends on the intact sympathetic nerves it would appear that the sympathetic normally controls the return of the forearm flow to base-line level by a constrictor action which is abolished when the nerves are cut or blocked. The transient acceleration of the heart which usually occurs at the same time may also be a result of this sympathetic activity on cessation of the adrenaline infusion. Only infrequently was any after-vasodilatation seen with intra-arterial adrenaline.

It is apparent from a consideration of the three phases of the response which have been described that the reaction of the muscle blood flow to circulating adrenaline is a complex one and appears to have several components, the pattern of the response being built up from a combination of direct action on the muscle vessels, reflex sympathetic activity and possibly a secondary hormone release from one or more of the endocrine glands.

SUMMARY

1. Intravenous infusions of adrenaline cause an initial forearm vasodilatation followed by a sustained increase of flow.

2. This response is found in nerve-blocked and acutely sympathectomized as well as in normal forearms. It is not seen in the chronically sympathectomized or chronically denervated forearm.

3. Intra-arterial infusions of adrenaline over a wide range of doses produce an initial vasodilatation but no sustained increase in flow.

4. The sustained increase in flow with intravenous infusions is not a direct action of the adrenaline on the muscle vessels nor is it a nervous reflex effect. This conclusion is contrary to that of other workers and possible explanations for the difference are discussed.

5. An 'after-dilatation' occurs in nerve-blocked, sympathectomized and denervated forearms after the adrenaline infusion ceases. The cause of this phenomenon is not known.

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