J. Physiol. (1951) 112, 426–437

OBSERVATIONS ON A CENTRAL DILATOR ACTION OF ADRENALINE IN MAN

By H. J. C. SWAN

From the Sherrington School of Physiology, St Thomas's Hospital Medical School, London, S.E. 1

(*Received* 26 *May* 1950)

In the human subject the administration of adrenaline almost always causes pallor of the skin. If the adrenaline is given as a continuous intravenous infusion pallor occurs rapidly, but disappears a short time after the infusion has been discontinued. Koehler, Marsh & Hill (1937) reported a rise in skin temperature following infusions of adrenaline in normotensive and hypertensive human subjects. Barclay, Cooke & Kenny (1947) noted that the stage of pallor is frequently succeeded by facial flushing. This has also been commented on by Allen (1946) and Green, Johnson, Lobb & Cusick (1948). Green *et al.* found that continuous intravenous infusions of adrenaline at high dosage in normal and in hypertensive subjects were followed by a fall in blood pressure which occurred 3–5 min. after the infusion had been discontinued. They also noted that an 'intense flushing of the face' coincided with this hypotension. However, as a result of certain tests for autonomic function they concluded that vasomotor tone was not entirely abolished during this phase. Hyman & Mencher (1943) and Muntz, Ritchley & Gatch (1947) point out that the pallor during a paroxysm of hypertension due to a phaeochromocytoma is succeeded by flushing; the latter workers also report that a patient suffering from such a condition experienced a sensation of warmth after the paroxysm had passed off. Acute hypotension following removal of these tumours is a major problem in the surgical treatment of this condition.

Plethysmographic studies in man have shown that infusions of adrenaline cause a diminution in the flow of blood through the hand (Kunkle, Stead & Weiss, 1939; Allen, 1946). Swan (1950), in a brief communication, claimed that shortly after the end of intravenous infusions there is a transient increase in blood flow through the normal hand. This did not occur in a sympathectomized hand, nor, indeed, in a normal hand following intra-arterial infusion of adrenaline.

In view of the degree of spontaneous variation in the flow of blood through the human hand, care must be taken not to attribute normal fluctuations in vasomotor activity to changes induced by a preceding event. The present paper is an attempt to establish accurately the response of the hand blood flow after infusions of adrenaline, and to interpret as far as possible the results obtained.

METHODS

The subjects of the earlier work (Swan, 1950) were selected from a large group of people of differing ages and both sexes. Subjects who showed very labile resting blood flows, or in whom there was a high initial rate of flow, were considered unsuitable for that series. The normal subjects of the present series were selected from a group of forty-three members of a class of sixty medical students who had expressed their willingness to act as subjects for these and other experiments. The forty-three students were numbered and then selected by reference to a table of random numbers. Every person witnessed an experiment before he himself was called on to act as a subject, and was told of the symptoms which might be experienced. This was considered to minimize psychological influences when he was the subject.

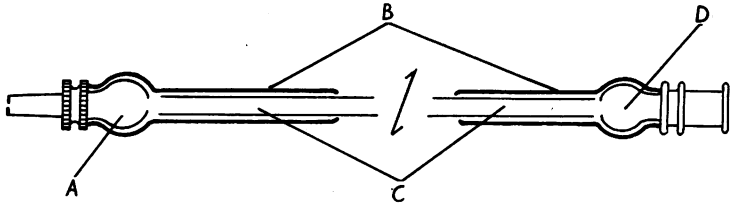

Fig. 1. The male and female metal adaptors, *A* and *D*, are connected by a 1 in. piece of 8 EA gauge Jaques catheter, *B*, to the polythene tubing, *C*. The rubber-metal and rubber-polythene connexions are sealed with rubber cement.

The experiments were performed between December and April in a laboratory thermostatically maintained between 20·5 and 21·5° C. The subject came to the laboratory usually after his class work, removed his jacket and lay comfortably on a couch. If it was proposed to give an intravenous infusion, a plethysmograph (Barcroft & Edholm, 1943) was fitted to the (*R*) hand and a sphygmomanometer cuff applied to the (*L*) arm. If an intra-arterial infusion was to be done plethysmographs were fitted to both hands. In every case the plethysmograph was filled with water at 33° C., after which the subject rested for 30 min.

Intravenous infusions in normal and in sympathectomized subjects. The procedure described by Barcroft & Konzett (1949) was followed, excepting that a modified form of connecting polythene tubing, suggested by Dr V. Rubio, was adopted. Fig. 1 shows the essential structure of these tubes. Where slight distensibility is of no consequence their use has the advantage of enabling selection of needles to be made just before use. Moreover, these connecting tubes can be easily handled. They may be sterilized by boiling and are then stored until required in a plastic tube containing formaline tablets.

Intra-arterial infusions in normal subjects. The (*R*) brachial artery was palpated as it lay medial to the biceps tendon, and its direction and depth estimated as accurately as possible. A small area of skin 1–2 in. distal to the point where the artery could be most easily palpated was anaesthetized with a little novocain. Next the subcutaneous tissue and arterial wall was infiltrated using 0·5 to 1·0 c.c. 4 % novocain. Then a sharp intramuscular needle was connected by the catheter described above to a 50 c.c. saline-filled syringe driven by a constant-speed infusion apparatus. The system was filled with saline and the needle pushed obliquely through the anaesthetized skin to penetrate the brachial artery at its most superficial point. As soon as the artery had been entered bright red blood was seen gushing into the polythene tubing and an infusion of saline was immediately started.

Of the ten subjects who underwent this procedure none complained of pain, and the majority were unaware that the vessel had been entered. No attempt at arterial puncture was unsuccessful in this series.

At this stage the subject was once more informed of the sort of symptoms he might expect to feel, and was told that should he experience excessive symptoms, the experiment would be discontinued if he desired it. This request was never made. Blood-flow measurements, and in subjects undergoing intravenous infusions blood-pressure readings, were then commenced. Flows were taken at about 2 min. intervals for the next 10 min., by which time any effects caused by insertion of the intravascular needle were considered to have passed off. Blood flows were measured at ½ or 1 min. intervals for the next 10 min. This second period was taken as the control or basal period. After a further minute an infusion of adrenaline in saline was given for exactly 3 min., after which the saline infusion was continued for a further 20 min. Blood-flow measurements continued to be made at ½ or 1 min. intervals during this period. The average level of flow during the control period was calculated and compared with the average of the flows obtained from the third to the thirteenth minute after the end of the infusion of adrenaline. The minute preceding the infusion was excluded from the control period, as subjective changes might have resulted from the changing of the syringes in the infusion apparatus. The 3 min. immediately succeeding the infusion were also excluded because some adrenaline might still be acting locally in the hand.

The plethysmograph temperatures were adjusted to 33° C. a few minutes before the control period. No further adjustment of temperature was made subsequently, and the plethysmograph temperature slowly fell to about 32° C. Since in the intravenous experiments a vasodilator effect has been demonstrated, any fall in temperature would tend to decrease rather than exaggerate this effect.

RESULTS

A. *Intravenous infusions in normal subjects*

A group of twelve normal subjects received an infusion of 20 μg. adrenaline for 3 min., as exemplified in Fig. 2. Following the infusion of adrenaline a transient increase in hand blood flow occurs; there was also a concomitant slight fall in the mean blood pressure. Spontaneous fluctuation of flow in the control is seen to return after the infusion. The increase in flow was accompanied by a flushing of the face. Fig. 3 shows the response of the whole group of twelve subjects.

Considering the group as a whole statistically, the difference between the average range of flow before and after the infusion is highly significant ($t = 5{\cdot}8$ for 11 degrees of freedom with $p < 0{\cdot}001$). Furthermore, it may be seen that the greatest recorded flow occurs shortly after the infusion in every subject.

Experiments have also been performed using lower and higher infusion rates. It was found that for adult males 'after-dilatation' was obtained only occasionally using doses of adrenaline under 10 μg./min. With 10 μg. and larger doses the after-dilatation could be observed with greater frequency, and it was also found to occur in one subject who received 35 μg./min. for 3 min. Green *et al.* (1948), using doses of up to 100 μg./min., noticed an intense flushing of the face 3–5 min. after the infusion of adrenaline was stopped. It is likely that had a higher dose of adrenaline been used in these experiments an increase in hand flow would also have been noted. The 'after-dilatation' may not be observed if the plethysmograph temperature falls below 30° C. or if the subject becomes cold.

B. *Intra-arterial infusions*

This group of nine normal subjects received infusions of 1½ μg. adrenaline/min. into the (*R*) brachial artery for exactly 3 min. There is a striking decrease in the flow in the (*R*) hand during the infusion. After the infusions the rate of flow returns to its previous level but does not usually exceed it. The subjects frequently noticed a numb feeling in the (*R*) hand; less often a tingling sensation which was mildly unpleasant. In association with these symptoms a diminution in flow in the (*L*) hand was at times observed. Fig. 4 shows the response

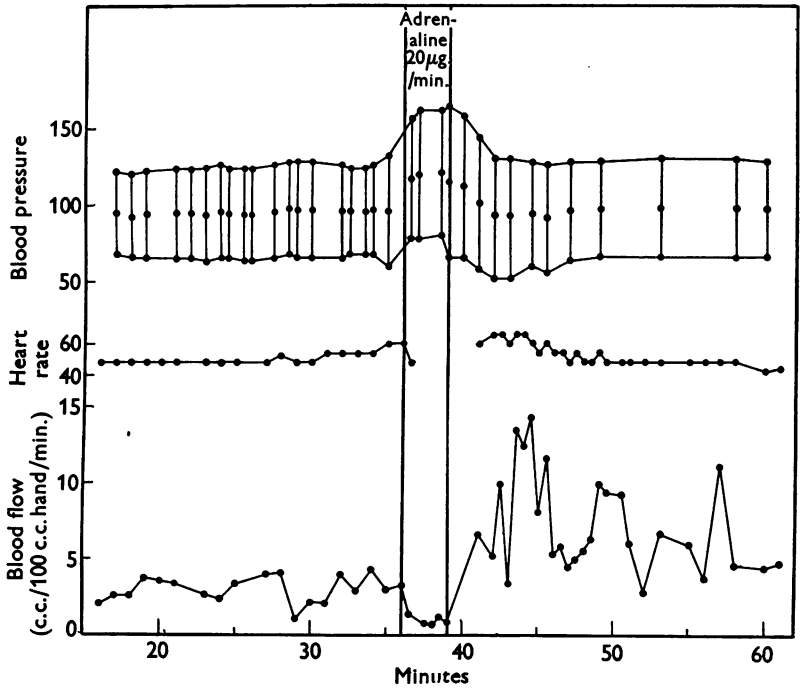

Fig. 2. The effect of an infusion of 20 μg. adrenaline/min. for 3 min. on the blood pressure, heart rate and hand flow of a normal subject.

of the group of nine subjects. It will be seen that the rate of flow returns to the general level of the control period but does not usually exceed it. In the two subjects in whom the blood flow in the (*R*) hand was greater after the infusion than before, the control (*L*) hand exhibited a similar increase—this excludes the possibility that the response in these two subjects is a local one in the (*R*) hand. Fig. 5 shows a good example of this sort of response in a further experiment. A comparison of the mean values before and after the infusion shows that in the group there was a slight fall in the rate of flow after the infusion. This change was not statistically significant ($t = 0{\cdot}48$).

Further experiments were performed using lesser and greater doses of adrenaline (range $\frac{1}{8}$–2 μg./min.) for 3 min. A response similar to that described

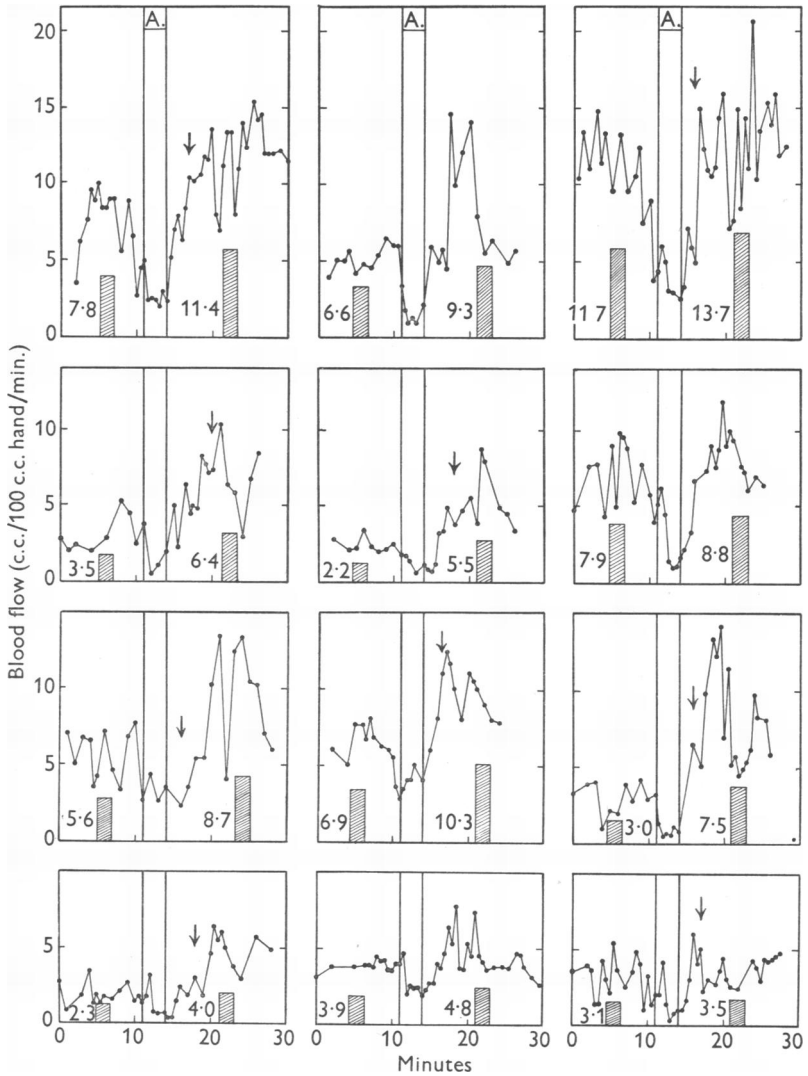

Fig. 3. In each of the twelve experiments 20 μg. adrenaline was given per min. for 3 min. The time is in minutes and the hand flow in c.c./100 c.c.hand/min. The infusions were all made from the 11th to 14th minute. The shaded blocks represent (half-scale) the average flows recorded in the periods 0–10 min. and 17–27 min. The arrow represents the commencement of flushing of the face.

above was observed. It was calculated that a dose rate of between $\frac{1}{4}$ and $\frac{1}{2}$ μg./min. given into the brachial artery would be equivalent to a dose of 20 μg. intravenously. As it appeared that the 'after-dilatation' on intravenous

infusion in the normal subject is more evident at the higher dose range, it was decided to use the large dose (i.e. $\frac{1}{2}\mu$g./min.) intra-arterially for the test series.

C. *Intravenous infusions in sympathectomized subjects*

This group of nine subjects were patients who had been sympathectomized for Raynaud's disease, hyperhidrosis or causalgia. It was soon found that in general these subjects show a greater rise in blood pressure to adrenaline than

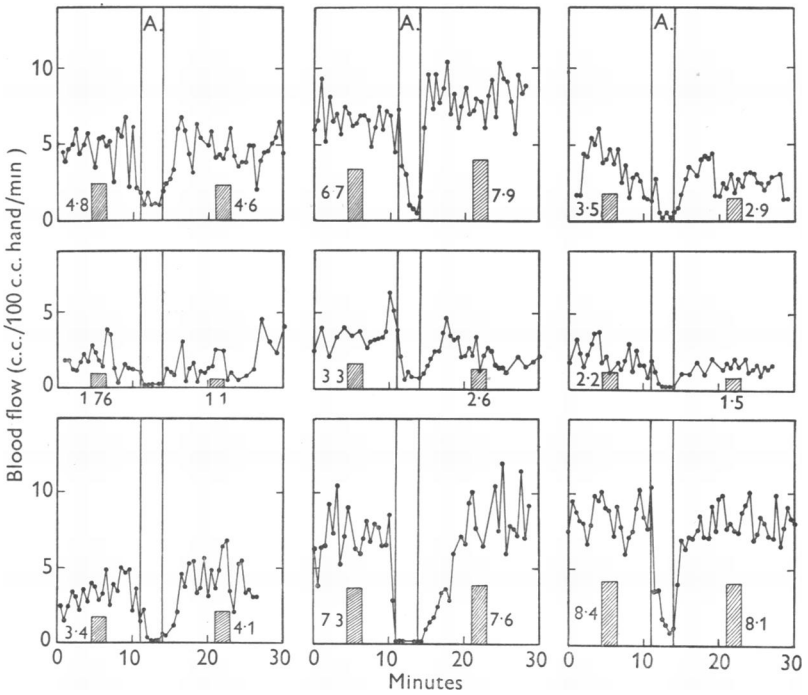

Fig. 4. The response in nine subjects each of whom received an infusion of $\frac{1}{2}\mu$g. adrenaline into the (*R*) brachial artery for 3 min. Other details as in Fig. 3.

do normals. Patients who had all four limbs sympathectomized appeared to be more reactive in this respect than others who had undergone a less extensive sympathectomy. For this reason 20μg. adrenaline was not given to all the sympathectomized subjects, and hence the results have not been statistically analysed. Fig. 6 shows a typical experiment in which 20μg. adrenaline was given for 3 min. to a woman 40 years of age who had undergone a four-limb sympathectomy. This subject showed a notable bradycardia with a brisk rise in blood pressure. Surprisingly, she experienced little in the way of symptomatic discomfort. Fig. 7 represents the hand-flow response of the group as a whole. The dose of adrenaline given is shown. It may be seen that there is no increase in flow after the infusion. In this respect the response is clearly different from that obtained in group A and similar to the effect in group B.

DISCUSSION

The above results clearly demonstrate that short intravenous infusions of adrenaline in moderate doses to normal subjects are followed by an increase in blood flow through the hand. Analysis of the difference between the means show the increased rate of flow after the infusion to be highly significant. It is

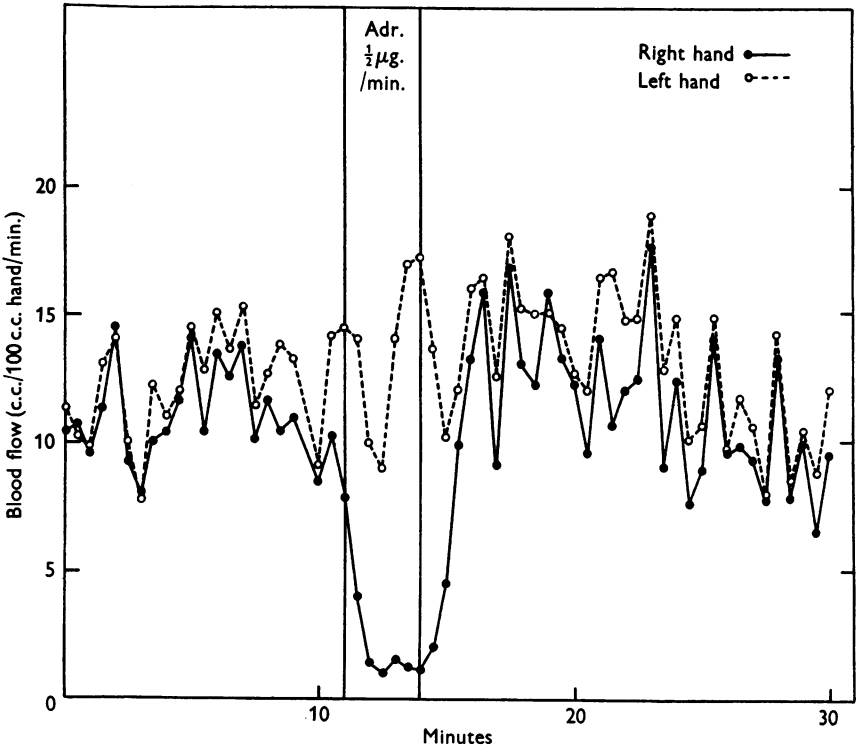

Fig. 5. The response of both hands in a subject who showed some degree of dilatation after ½ μg. adrenaline into the (*R*) brachial artery for 3 min. The solid line represents the (*R*) hand flows, the broken line the (*L*) hand flows.

reasonable to consider this increase to be related to the preceding infusion of adrenaline. In contrast to the results obtained on intravenous infusion, relative doses infused into the brachial artery do not produce a similar increase after the infusion. Indeed, the general tendency is for the flow to decrease slightly. Likewise, no increase in flow follows intravenous infusions in the sympathectomized subjects.

These results provide some information on the possible mechanism of the 'after-dilatation' which characterizes intravenous infusions of adrenaline. Fundamentally, any increase in flow may be due to an increase in the perfusion pressure, or to a decreased resistance, or to both. The effect described as the

'after-dilatation' is unlikely to be due to a simple increase in the perfusion pressure, because the mean blood pressure during this time was found to be equal to, or occasionally even below, the control value. Moreover, the sympathectomized subjects fail to show the 'after-dilatation'. Infusions of adrenaline

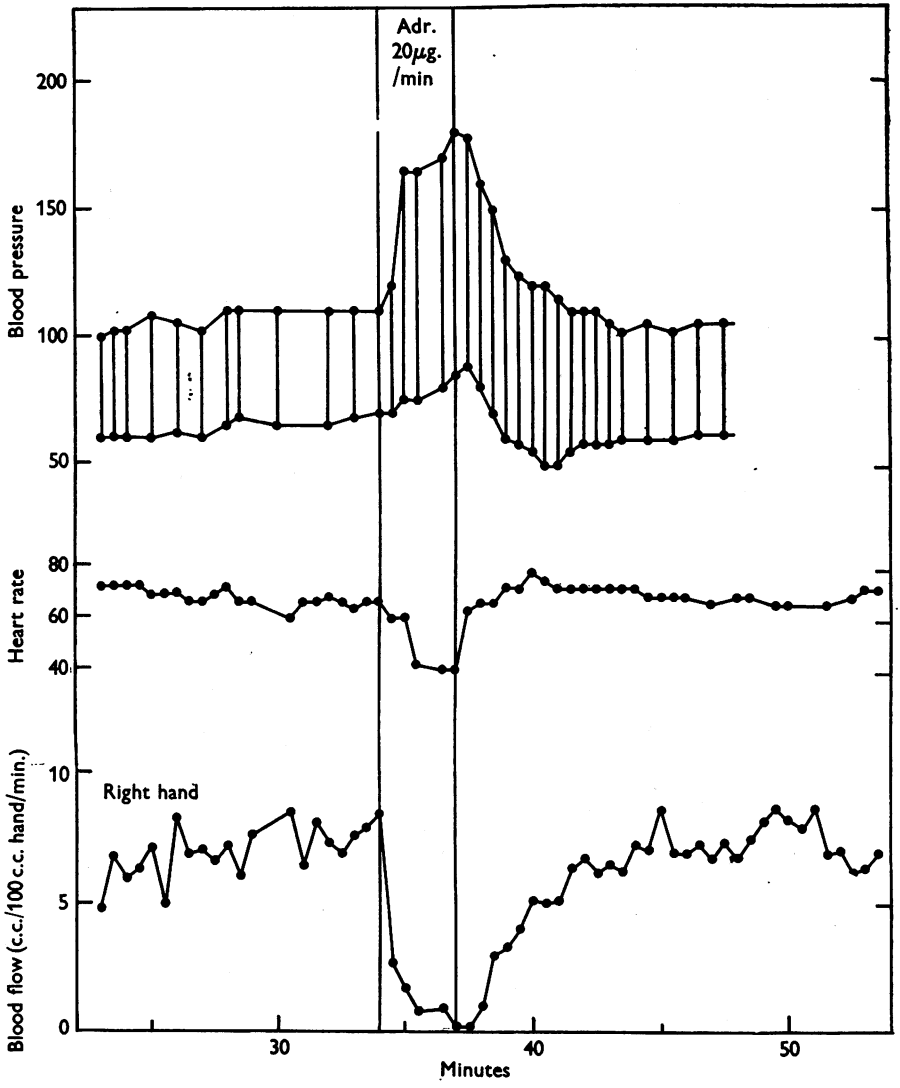

Fig. 6. An intravenous infusion of 20 μg. adrenaline/min. in a subject who had been sympathectomized in all four limbs for Raynaud's disease. Details as in Fig. 2.

in these subjects usually produce a greater rise in blood pressure than in the normal, and if the effect were simply a passive perfusion pressure response the sympathectomized subjects would certainly have shown it. A true vasodilata-

tion must be responsible for the increase in flow. This might be due to the local action of dilator substances or to a change in nervous activity. The results obtained on intra-arterial infusion exclude the action of locally produced dilator substances. The results on the sympathectomized subjects exclude the alternative possibility that it is due to dilator substances produced at another site acting locally on the vessels in the hand. The increase in flow must, by elimination,

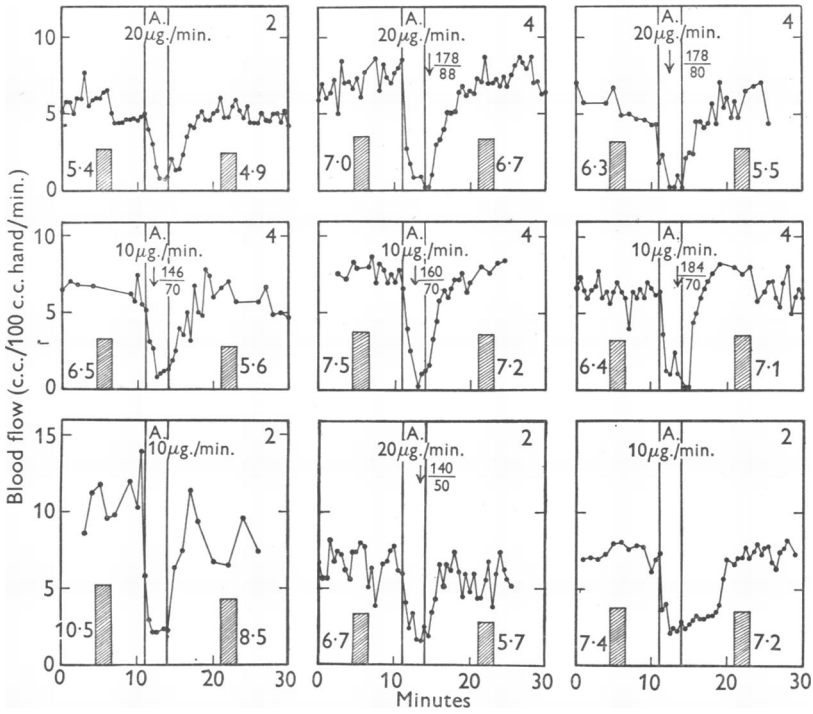

Fig. 7. The responses of nine subjects who had been sympathectomized. The dose of adrenaline given is indicated. The maximal recorded blood pressure is noted, and its occurrence in time indicated by the arrow. The numeral in the top right-hand corner indicates the number of limbs sympathectomized, including the test limb.

be due to vasomotor changes. Arnot & Macfie (1948) have failed to find any evidence for dilator nerves in the skin of the finger in man. Hence it is concluded on these grounds that the 'after-dilatation' in man following intravenous infusions of adrenaline must be due to inhibition of sympathetic vasoconstrictor tone. However, this inhibition is only partial, for spontaneous fluctuations still occur. This is in accord with the observations of Green *et al.* (1948). It must be postulated that this central action of adrenaline, if present from the beginning of the infusion, is obscured during the infusion by the intense local constrictor action of adrenaline.

The present study is confined to the hand, but the effect has also been observed in the feet. Moreover, the fall in blood pressure frequently observed after the infusion suggests a more general effect.

It appears to be relevant to the present work to refer to the effects observed on animals, for although the amount of adrenaline per unit weight given to the human subject is much less than that given to the animals, man is thought to be more sensitive to adrenaline (Goldenberg, Pines, Baldwin, Green & Roh, 1948).

Two general actions appear possible. Adrenaline may cause an inhibition of vasomotor tone either directly or by an indirect effect on autonomic transmission. Concerning the direct effect of adrenaline on central vasomotor control, it is of interest to note that Dale & Richards (1927) described an 'abnormal' depressor effect of adrenaline in the dog. After rendering the animal hypertensive by restricting the blood supply to the brain-stem they showed that an injection of adrenaline into the remaining untied vertebral artery caused a fall in blood pressure. They did not analyse the effect in detail. Von Euler (1938) found that in the rabbit intracarotid injections of adrenaline also cause a fall in blood pressure. He suggested that this effect was due to anoxia of the vasomotor centres.

Adrenaline is known to influence autonomic transmission outside the central nervous system. Marrazzi (1939*a*, *b*) claimed that adrenaline inhibits ganglionic transmission in the rabbit and in the cat. Recording impulses in the post-ganglionic fibres from the superior cervical ganglion resulting from repetitive submaximal stimulation of the proximal part of the cervical sympathetic, he found that the number of impulses was reduced during splanchnic stimulation, and also after an injection of adrenaline. This effect was not due to anoxia because there was no reduction of impulses for several minutes after cardiac arrest.

Bülbring & Burn (1942) investigated the problem in the dog using a preparation with a double circulation in which the hind limb could be perfused independently of the upper part of the body; the sympathetic ganglia were supplied by one circuit, while their post-ganglionic fibres terminated in relation to blood vessels supplied by an independent circulation. These observers found that small doses of adrenaline augmented ganglionic transmission while larger doses depressed it. Using a different technique in the cat a similar response was observed. While Marrazzi considered that the ganglion depressing action was beneficial to the extent that it restricted excessive sympathetic activity, Bülbring & Burn thought that this depressant action might play some part in the production of shock. It is apparent, therefore, that adrenaline may influence autonomic activity by an effect on ganglionic transmission.

Schweitzer & Wright (1937) have shown that adrenaline also inhibits the knee jerk in the cat, and they conclude that this is due to a direct depression of somatic nervous transmission.

In addition to their general conclusions Bülbring & Burn (1942) make further observations which apply to the present study. In their paper they noted that depression of ganglionic transmission occurred after the infusion of adrenaline had ceased. The 'after-dilatation' described in this paper occurs with a comparable relationship to time. They also show that an effect on ganglionic transmission is present for some time after the general effect on the blood pressure has passed off. It is considered that in this paper a vasomotor inhibition in man has been demonstrated after the major changes in blood pressure have subsided.

However, it may be that adrenaline affects vasomotor tone in an indirect manner, by initiating a chain of physical, biochemical or hormonal changes leading to a degree of vasomotor inhibition. Thus Pickering (1932) claimed that the generalized vasodilatation occurring when the skin is warmed is due to 'the action of the central mechanism excited by a rise in blood temperature'. Adrenaline infusions in the human subject cause an increase in oxygen consumption which, together with a vasoconstriction, may result in an increased heat production and decreased heat elimination. It is possible that a rise in blood temperature may occur. Recently also, Ström (1950) has shown that warming the blood supplying the hypothalamus causes a vasodilatation in the pad of the cat. The results described in this paper do not exclude the possibility that a rise in blood temperature is responsible for the 'after-dilatation'.

Staub (1946) has reported that infusions of 0·2 mg. adrenaline in the human subject over 10 min. cause a rise in plasma histamine. The 'after-dilatation' in the present series is not due to circulating histamine acting locally on the vessels. The increase in the blood histamine level might, however, cause a central inhibition of vasomotor tone.

Goldenberg *et al.* (1948) measured the cardiac output and arterial blood pressure in human subjects undergoing infusions of adrenaline. They found that the total peripheral resistance was reduced during the infusion. They conclude that adrenaline is predominantly a dilator substance in man, but, having examined the data of Allen, Barcroft & Edholm (1946) they consider that the over-all dilatation is not only confined to skeletal muscle. The present results suggest that a central depression of vasoconstrictor tone might be a factor in the production of this vasodilatation.

SUMMARY

1. The response of the human hand to short infusions of adrenaline has been studied using the venous occlusion plethysmograph.

2. If a moderate dose of adrenaline is given as an intravenous infusion a dilatation occurs in the hand a few minutes after the end of the infusion.

3. This 'after-dilatation' is not seen in the sympathectomized limb, nor does it occur if comparable doses are infused directly into the brachial artery.

4. The 'after-dilatation' is due to a central inhibition of vasomotor tone.

5. The 'after-dilatation' is discussed in relation to theories of adrenaline as a dilator substance.

The author wishes to express his thanks to the medical students and others who acted as subjects; to Drs R. S. Duff and V. Rubio for valuable assistance, to Dr J. M. Tanner, and to Mrs M. Lyddon, Miss M. Gould and Mr G. Hales.

Certain expenses were defrayed by a grant from the Medical Research Council.

REFERENCES

Allen, W. J. (1946). University of Belfast M.D. Thesis.
Allen, W. J., Barcroft, H. & Edholm, O. G. (1946). *J. Physiol.* **105**, 255.
Arnot, W. M. & Macfie, J. M. (1948). *J. Physiol.* **107**, 233.
Barclay, J. A., Cooke, W. T. & Kenny, R. A. (1947). *Amer. J. Physiol.* **151**, 621.
Barcroft, H. & Edholm, O. G. (1943). *J. Physiol.* **102**, 5.
Barcroft, H. & Konzett, H. (1949). *J. Physiol.* **110**, 194.
Bülbring, E. & Burn, J. H. (1942). *J. Physiol.* **101**, 289.
Dale, H. H. & Richards, A. N. (1927). *J. Physiol.* **63**, 201.
von Euler, U. S. (1938). *J. Physiol.* **92**, 111.
Goldenberg, M., Pines, K. L., Baldwin, E. de F., Green, D. G. & Roh, C. E. (1948). *Amer. J. Med.* **5**, 792.
Green, D. M., Johnson, A. D., Lobb, A. & Cusick, G. (1948). *J. Lab. clin. Med.* **33**, 332.
Hyman, A. & Mencher, W. H. (1943). *J. Urol.* **49**, 755.
Koehler, A. E., Marsh, N. & Hill, E. (1937). *J. biol. Chem.* **119**, lix.
Kunkle, P., Stead, E. A. & Weiss, S. J. (1939). *J. clin. Invest.* **18**, 225.
Marrazzi, A. S. (1939*a*). *J. Pharmacol.* **65**, 395.
Marrazzi, A. S. (1939*b*). *Science*, **90**, 251.
Muntz, H. H., Ritchley, J. O. & Gatch, W. D. (1947). *Ann. intern. Med.* **26**, 133.
Pickering, G. W. (1932). *Heart*, **16**, 115.
Schweitzer, A. & Wright, S. (1937). *J. Physiol.* **88**, 476.
Staub, H. (1946). *Schweiz. med. Wschr.* **36**, 818.
Ström, G. (1950). *Acta physiol. Scand.* **20**, Suppl. 70, 47.
Swan, H. J. C. (1950). *J. Physiol.* **111**, 5*P*.