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THE ROLE OF ACTIVE MUSCLE VASODILATATION IN THE ALERTING STAGE OF THE DEFENCE REACTION

BY V. C. ABRAHAMS,† S. M. HILTON AND A. W. ZBROŻYNA*
From the National Institute for Medical Research, Mill Hill, London, N.W.7

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Muscle vasodilatation, produced by cholinergic nerve fibres of the sympathetic system, appears to be an integral feature of the defence reaction which an animal displays as a reflex response to any sudden stimulus (Abrahams, Hilton & Zbrożyna, 1960*b*). This vasodilatation is itself only one component of a complex pattern of cardiovascular change in which a greatly increased cardiac output is directed chiefly through the skeletal musculature. As previously emphasized, the defence reaction is a graded response whose behavioural expression is manifested initially as alerting. With sufficiently intense stimulation it will culminate in flight or attack, and the complex cardiovascular reaction seems best regarded as a preparatory adjustment of the animal for the muscular exertion inseparable from these activities (Abrahams *et al.* 1960*b*; Abrahams, Hilton & Malcolm, 1962). Studies of the changes of muscle blood flow in the conscious cat have reinforced this view (Abrahams, Hilton & Zbrożyna, 1960*a*).

The experimental results which are described here show that atropine-sensitive muscle vasodilatation occurs when the earliest behavioural signs of alerting are seen, whether such alerting has been produced by direct electrical stimulation of the appropriate brain-stem regions, or by a sudden environmental stimulus such as a flash of light or the sound of a buzzer. Further, the vasodilatation is readily obtained as a conditioned-reflex response.

In all these experiments use has been made of temperature changes of the whole-limb venous effluent as an index of muscle blood flow in the conscious animal (Abrahams, 1959). The results of experiments on anaesthetized cats which demonstrate the validity of this technique are included in this paper.

METHODS

Anaesthetized cats. Cats were anaesthetized with chloralose, 70 mg/kg, injected intravenously after induction of anaesthesia with ethyl chloride and ether. One hind limb was

* Rockefeller Fellow. Present address: Medical Research Council, Clinical Research Wing, Institute of Orthopaedics, Stanmore, Middlesex.

† Present address: Physiology Department, Queen's University, Kingston, Ontario, Canada.

prepared for registration of changes of muscle blood flow, as previously described (Abrahams *et al.* 1960*b*) and the other for registration of changes of whole-limb flow by the same method, except that the skin was not separated from the underlying tissues. On each side the femoral venous outflow was passed via a polyethylene cannula through a photo-electric drop recorder and returned to the femoral vein more centrally. Localized stimulation in the region of the hypothalamus integrating the defence reaction was effected by the use of stereotactically placed steel micro-electrodes, also as previously described (Abrahams *et al.* 1960*b*).

Conscious cats. The cats were in a sound-proofed observation chamber with a double glass panel in the front wall. They were observed through a half-silvered mirror mounted outside and attached to the base of this wall at an angle of 45°. With good illumination in the chamber and a dim light outside, the animal could not see out of the chamber, neither could it see a reflexion of itself. A loudspeaker mounted on one inner wall and a 500 W projection lamp behind a protective wire-netting screen were used for delivering acoustic and visual stimuli respectively, and a microphone for monitoring sounds. Sockets in the wall were available for connexion to a multi-way lead which could be fixed to a connector on a thick polyethylene jacket worn by the animal. The lead was held by a light spring attached to the roof of the chamber, so that the animal could move freely.

Stimulation of brain-stem and skin. For these experiments electrodes were implanted stereotactically into the brain-stem in sterile operations under pentobarbitone anaesthesia, as previously described (Abrahams *et al.* 1960*b*). The leads from the electrodes were fixed to the connector on the polyethylene jacket. The skin of the footpads was stimulated by passing current through a metal grid on which the animal was standing. Square waves of 1·5 msec duration at 40/sec were applied, at whatever voltage was found necessary to produce behavioural alerting. In the conditioning experiments in which a more precise control of the stimulus was required, two sterile Michel clips, with leads attached, were fixed to the skin of the back about 2 in. (5 cm) apart. The intensity of the electrical stimulation was then 10 V, the other parameters being the same. The clips were protected by the polyethylene jacket, and the leads were fixed to a connector on it. These clips appeared to cause the animal no discomfort and could be left *in situ* for about a week without any untoward reaction.

Registration of venous-effluent temperature. In experiments lasting a single day changes of muscle blood flow were indicated by a venous-temperature method (Abrahams, 1959), in which a small chamber bearing a thermistor bead is inserted between the cut ends of the femoral vein. The operation was performed under ether anaesthesia, and heparin (1000 u./kg) was injected intravenously before the vein was opened. The leads were sutured to the fascia on the ventral aspect of the thigh at several points, then led under the skin and brought out between the scapulae at a site protected by the polyethylene jacket, to be fixed to a connector on the jacket. The actual experiment was carried out several hours after recovery from the anaesthetic and the animal was killed at the end of the day with an overdose of pentobarbitone, given intraperitoneally.

When the cat was to be observed over a period of days or weeks the method was modified as previously described (Abrahams *et al.* 1960*b*), the thermistor bead being mounted in a cuff placed round the unopened vessel.

RESULTS

Experiments on anaesthetized cats

In a previous investigation we showed that the atropine-sensitive vasodilatation in skeletal muscle, which appears to be a characteristic component of the defence reaction, can be obtained as a feature of the pseudaffective reflex response to stimulation of a peripheral nerve in the high-

decerebrate cat (Abrahams *et al.* 1960*b*). We also showed that this increase in muscle blood flow could be registered indirectly with a venous blood temperature recorder. Before we could extend the use of this simple recording technique to a study of the occurrence of similar vascular changes

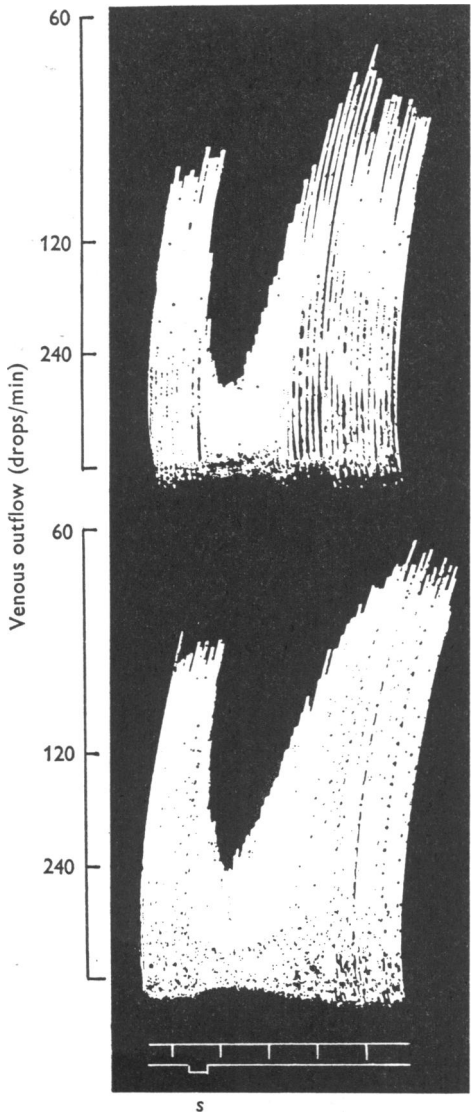

Fig. 1. Cat, chloralose. Records of venous outflow from skinned hind limb (upper record) and whole hind limb (lower record), showing similarity of increases in flow on stimulation (at *s*) in hypothalamic region for the defence reaction (cf. Abrahams *et al.* 1960*b*). Time marker, 30 sec.

in the normal, conscious animal without any operation to separate skin and muscle blood flow, it was necessary to carry out experiments on the changes in the flow of mixed venous blood through the femoral vein, and to see how these compared with the changes of muscle blood flow, recorded simultaneously. The experiments were performed on three cats, and it was found (Fig. 1) that localized stimulation, within the region of the hypothalamus

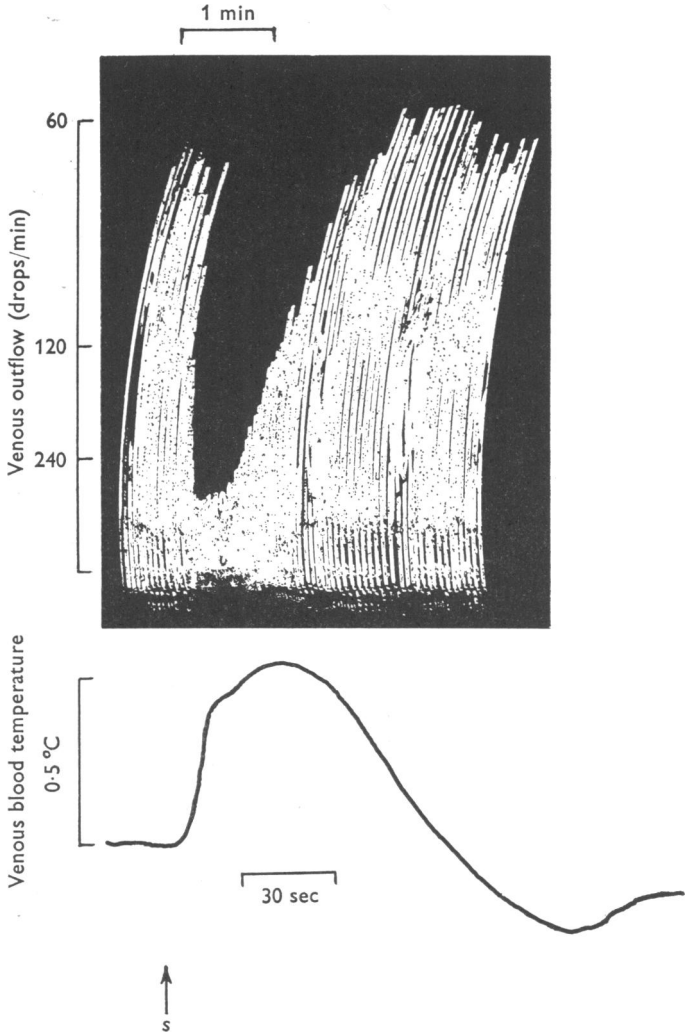

Fig. 2. Cat, chloralose. Upper record, venous outflow from whole hind limb. Lower record, venous effluent temperature, recorded simultaneously but with different time scale (upward deflexion = increase in temperature). At *s*, electrical stimulation for 10 sec in hypothalamic region for the defence reaction (cf. Abrahams *et al.* 1960*b*).

integrating the defence reaction, produces an increase in blood flow through the whole hind limb, which is practically as great as that recorded simultaneously in the muscles of the other hind limb. The contribution of the skin blood flow to the whole-limb flow appears to be so small that the skin vasoconstriction, which occurs as part of the complex circulatory response, is almost completely obscured by the increase in muscle blood flow. Thus, during this reaction the change in whole femoral venous flow is a reliable index of the increase in flow through the muscles of the hind limb. The femoral venous temperature changes associated with these increases in whole-limb flow were recorded in experiments on four cats. As is illustrated in Fig. 2, with an approximately fourfold increase in blood flow, which was the usual effect of hypothalamic stimulation, the venous blood temperature increased by 0·5° C or more. With greater increases in blood flow the venous effluent temperature could increase by as much as 1° C. When the increase in flow was only threefold, the temperature increase was about 0·3° C.

Experiments on conscious cats

Evidence for muscle vasodilatation as an early component of the defence reaction

Hypothalamic stimulation. The same parameters of stimulation of the same specific region of the hypothalamus elicit defence reactions in the conscious cat and atropine-sensitive muscle vasodilatation in the anaesthetized cat (Abrahams *et al.* 1960*b*). When the venous temperature recorder employed in the experiments described above is used in experiments on the whole femoral venous flow in conscious cats, and the specific hypothalamic region is stimulated by means of implanted electrodes, similar increases in venous blood temperature are recorded. This was established in experiments carried out on five cats. To elicit the vascular response seen in Fig. 3*a* stimulation was only at threshold intensity for alerting; the pupils were dilated, the head raised, the ears pricked and respiratory rate increased. That the vascular response itself is evidence for activation of the same cholinergic fibres to the muscle vessels is confirmed by its abolition after atropine 1 mg/kg (Fig. 3*b*). This was injected subcutaneously and the response was found to be abolished 25–30 min later. This dose of atropine, which represented a smaller effective dose than that used in our earlier investigation of the vasodilator innervation in anaesthetized cats, did not appear to be blocking the vascular response by an action on the central nervous system, since though the pupils were already dilated all the other signs of alerting were elicited as before; and increasing the stimulation intensity led, as usual, to the full reactions of flight or attack.

There was no evidence of habituation of the response elicited by hypothalamic stimulation, i.e. the response did not diminish when stimulation was repeated daily over a period of days or weeks. If anything, both the vascular response and the signs of alerting were elicited a little more readily with such repetition.

Auditory, visual and cutaneous stimulation evoked similar vascular responses. Indeed, the ease with which the response was elicited by

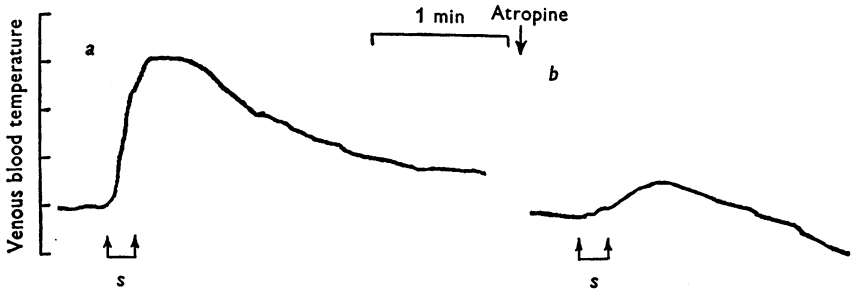

Fig. 3. Conscious cat. Records of femoral venous blood temperature (upward deflexion = increase in temperature, indicating increase in blood flow). Each scale division on temperature record indicates 0·1° C. Effect of electrical stimulation (at *s*) by means of an electrode implanted in hypothalamic region for the defence reaction, *a* before and *b* 30 min after subcutaneous injection of atropine (1 mg/kg).

natural stimuli made it essential that the animals should be familiar with the experimental surroundings before any of these tests were carried out. Otherwise, when introduced into the observation chamber the animal would show not only the behavioural signs of alerting, but also a prolonged and persistent muscle vasodilatation, as indicated by a steep rise of femoral venous temperature. No response could then be elicited by any of the stimuli, but the steady, high level of venous temperature was reduced by subcutaneous injection of atropine.

Figure 4 illustrates a response, in an animal familiar with its surroundings, to the 1000 c/s tone used as an auditory stimulus. In three out of five cats the responses to the auditory stimulus were smaller, while in the remaining cat the tone elicited no response (Fig. 5*a*). These responses were abolished by atropine, as is shown in the experiment illustrated in Fig. 4. Similar vasodilator responses were obtained to flashes of light, and to stimulation of the skin, and like those elicited by the auditory stimulus, these responses were accompanied by the same behavioural signs of alerting as are seen on threshold hypothalamic stimulation. This would be expected since these are well-known features of the reaction to a sudden stimulus.

When testing the effects of cutaneous stimuli, particular care had to be taken to produce alerting alone and to avoid movements of the limbs, for muscular contraction produces changes in limb blood flow independently of the vasodilator innervation. The skin stimulation used was therefore very mild, but nevertheless it was usually more effective than auditory

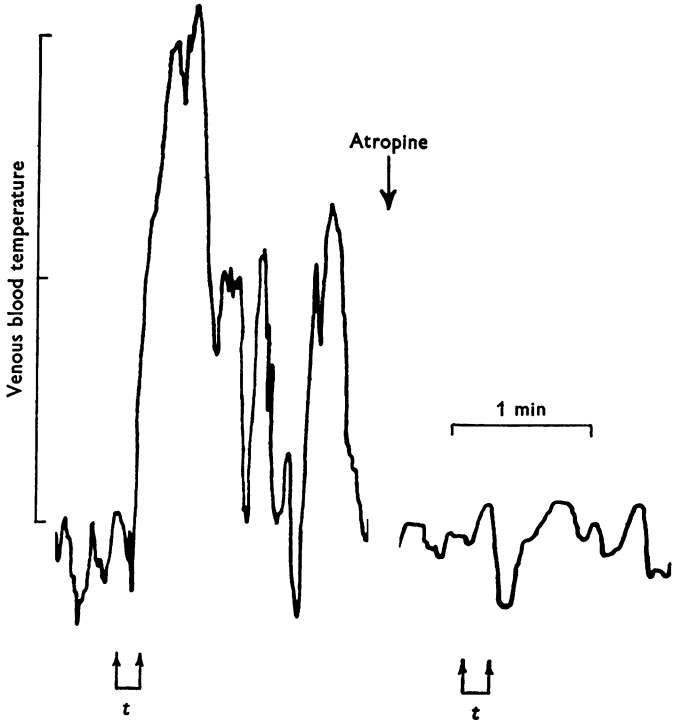

Fig. 4. Conscious cat. Records of femoral venous blood temperature (upward deflexion = increase in temperature, indicating increase in blood flow). Each scale division on temperature record indicates 0·5° C. Effect of 1000 c/s tone (at *t*) before and 30 min after subcutaneous injection of atropine (1 mg/kg).

or visual stimuli in eliciting a vasodilator response. Such responses were obtained in all five cats and one is illustrated in Fig. 5*b*.

In the cats giving vasodilator responses at the initial trial, repetition of the auditory, visual or cutaneous stimuli led to gradual diminution of the response. This habituation proceeded at different rates in the different animals, and habituation to cutaneous stimulation was the least marked.

Evidence for muscle vasodilatation as a conditioned reflex reaction

It is known that conditioned defence reactions are readily established and that once established they are relatively stable, in that they can be

obtained after long intervals of no reinforcement. It was therefore to be expected that the vascular response could be obtained as a conditioned reflex.

The experiments were performed on three of the five cats whose responses to natural stimuli had been tested. In the cat whose responses are illustrated in Fig. 5, the tone itself did not elicit vasodilatation. Conditioning experiments were carried out in the following way: the tone was

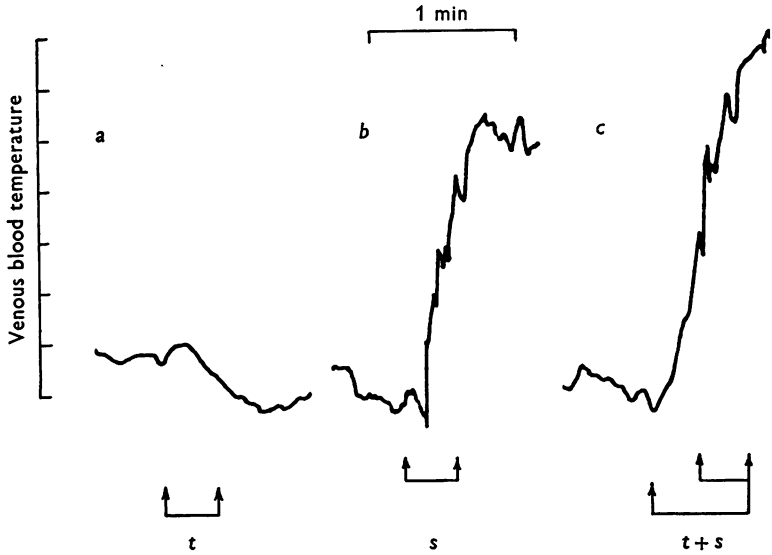

Fig. 5. Conscious cat. Records of femoral venous blood temperature (upward deflexion = increase in temperature, indicating increase in blood flow). Each scale division on temperature record indicates 0·1° C. Effects of *a* 1000 c/s tone, at signal *t*; *b* stimulation of foot pads, at signal *s*; *c* 1000 c/s tone, initially alone, then combined with stimulation of foot pads (4th trial of combination) at signals *t*+*s*.

sounded for 7 sec, skin stimulation commenced 2 sec after the tone had been turned on, and both stimuli were turned off together. After this combination of stimuli had been applied three times, the response illustrated in Fig. 5*c* was obtained. Even at this early stage of the experiment the response was developing during the tone alone. Such early conditioning was observed in each cat during the first training session. The action of atropine on these responses was not tested, because the procedure of injection would itself have a disturbing effect. However, there seems little reason to doubt that the conditioned and unconditioned vascular responses were the same.

In one of the cats training was continued over a period of several weeks. This cat initially gave a small response to the tone, as shown in Fig. 6*a*. It was brought into the experimental chamber several times a week and the buzzer sounded five or six times at each session. At the end of a month, habituation was firmly established and the cat was giving no response at all to the tone. Conditioning experiments were started a week later. As before, the tone was sounded for 7 sec, and combined with skin stimulation for the last 5 sec. On the first day the conditioning combination was applied three times, and on the second day five times. On the third day the tone was tested at the beginning of the experiment, and was

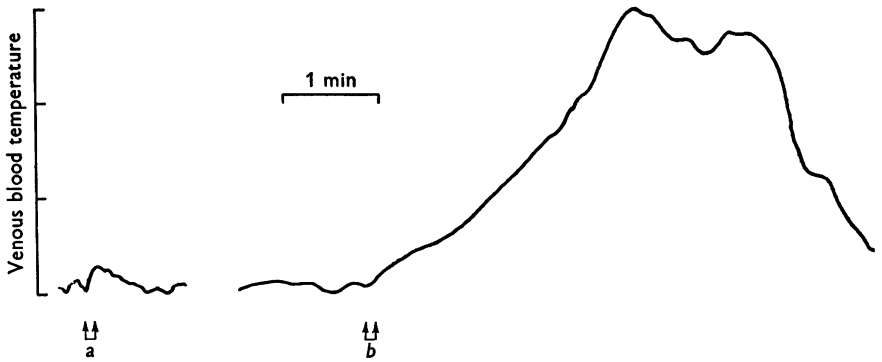

Fig. 6. Conscious cat. Records of femoral venous blood temperature (upward deflexion = increase in temperature, indicating increase in blood flow). Each scale division on temperature record indicates 0·5° C. Effects of 1000 c/s tone before habituation, at signal *a*. Response to same tone at signal *b* after prolonged habituation, followed by combination with electrical stimulation of the skin of the back on 4 days, and 5 subsequent days without experiment.

found to cause some ear movements and turning of the head. The reinforcing combination was then applied three times. At the beginning of the experiment on the fourth day, the tone alone caused behavioural alerting, together with vasodilatation in the hind limb: the reinforcing combination was applied once. No experiments were carried out during the following 5 days. On the next day, the tone alone produced the full reaction, including the large vascular response shown in Fig. 6*b*. Reinforcement was applied once. Two days later the tone produced a strong behavioural reaction in which the cat appeared to be trying to escape from the cage. No reliability could therefore be placed on the venous-temperature record. Skin stimulation was not attempted. Two days later the tone produced a strong alerting reaction and vasodilatation. At this stage the cat was beginning to give a reaction to being placed in the experimental chamber and experiments were discontinued.

DISCUSSION

The initial behavioural responses to any sudden stimulus have in the past been variously termed. They include alerting and arousal, the Pavlovian orientation reflex and the startle reaction. Although there are small differences in these reactions, there is no reason to doubt that they are basically one response arising from near-threshold activation of specific regions in the hypothalamus and mid-brain. When the same brain-stem regions are activated more intensely, the fully-fledged defence reactions of flight or attack are elicited. It is not surprising, therefore, that autonomic changes characteristic of the defence reaction occur during the orientation reflex (Birjukov, Korneva, Šljafer & Jakovleva, 1962).

The conclusion that muscle vasodilatation, produced by cholinergic fibres of the sympathetic outflow, is an integral part of the defence reaction has so far been based on the following evidence: (1) When the hypothalamus, central grey matter or mid-brain tegmentum are stimulated with micro-electrodes, the regions from which active muscle vasodilatation is elicited under anaesthesia are identical with those from which alerting, flight and attack are obtained in the same animals when conscious. (2) Active muscle vasodilatation is obtained as part of the pseudaffective reflex response in the high-decerebrate cat (Abrahams *et al.* 1960*b*).

The opportunity to obtain information about changes in muscle blood flow in the conscious cat has now enabled us to show that atropine-sensitive vasodilatation occurs at the initial stage of the defence reaction, no matter whether elicited by threshold electrical stimulation of the brain stem or by an environmental stimulus. At this stage of the reaction the only outward signs are pricking of the ears, pupillary dilatation and an increase in the rate of respiration. The muscle vasodilatation therefore occurs at a sufficiently early stage of the graded reaction for it to fulfil the role of a preparatory response.

When the muscle vasodilatation is elicited by electrical stimulation of the brain stem of anaesthetized animals, it appears as part of a complex pattern of cardiovascular change. Uvnäs and his colleagues (Uvnäs, 1954) noted concomitant vasoconstriction in skin and intestine, and tachycardia, which we could readily confirm (Abrahams *et al.* 1960*b*). There is also evidence of increased contractile force of the heart and increased cardiac output (Rosén, 1961), while simultaneous venoconstriction has been suggested by Folkow, Mellander & Öberg (1961) and Hilton (1963). When all these changes are taken together it appears that the cardiovascular system is being adjusted in such a way that it is fully prepared for the demands of sudden widespread muscular activity, characteristic of flight or attack. Since in all these experiments the atropine-sensitive vasodilatation has

appeared together with the other cardiovascular changes, it may be assumed that the vasodilatation observed in the present experiments is part of this same pattern of cardiovascular response.

Cutaneous, visual and auditory pathways converge on the brain-stem regions integrating the defence reaction; and the active muscle vasodilatation is a component of the pseudaffective reflex elicited in the high-decerebrate cat when these regions of the brain stem have been spared (Abrahams *et al.* 1960*b*; Abrahams *et al.* 1962). We therefore regard the integrative centre for the defence reaction as a reflex centre in the classical sense, and hence we would class this pattern of cardiovascular response as a preparatory reflex reaction. The well-known cardiovascular reflexes are usually categorized as homoeostatic, in that they appear to function in a way that will maintain or restore the *status quo*. The new state of equilibrium produced by a preparatory reflex is appropriate in relation to long-term homoeostasis; but in the short term it may lead to a radical departure from the *status quo*. It was the finding of Uvnäs (1960), that O_2-uptake in skeletal muscle is reduced during activation of the vasodilator nerve fibres, that led him to disclaim any belief that these nerve fibres could be activated as part of a response in preparation for muscular exertion. Since, however, our present findings show that they are so activated, the pattern of cardiovascular adjustment appears to be of over-riding importance. Contracting skeletal muscles can no doubt provide for their own metabolic requirements, through the widespread capillary dilatation that so rapidly develops within them, so long as the circulation is adjusted to provide the necessary blood flow. This still leaves open the question whether such an over-all pattern of circulatory adjustment is maintained by the same regulatory mechanism *during* muscular exertion (Barcroft, 1960).

It is possible to incorporate, within the framework of this concept, other findings of similar cardiovascular changes produced by sudden or intense stimuli in conscious animals and men. For instance, when conscious dogs were subjected to a sudden shower of water, cardiac output was almost doubled, with an increase in both stroke volume and heart rate, and mean arterial blood pressure increased while total peripheral resistance was unchanged or fell (Charlier, Guz, Keatinge & Wilcken, 1962). This seems to be evidence for the same preparatory reflex in the conscious dog, particularly when it is recalled that the whole pattern of cardiovascular response, including the active muscle vasodilatation, has been found in anaesthetized dogs on stimulation of the same brain-stem regions from which the response is elicited in the cat (Eliasson, Lindgren & Uvnäs, 1952; Lindgren & Uvnäs, 1953; Lindgren, 1955). The cardiac responses characteristic of muscular exertion have been obtained on electrical stimulation at some points in the posterior hypothalamus of conscious

dogs (Smith, Jabbur, Rushmer & Lasher, 1960). Moreover, the same changes of heart rate and left ventricular performance were obtained in dogs exercising on a treadmill and in well-trained dogs when the experimenter held the treadmill switch (Rushmer, Smith & Lasher, 1960). The latter observation demonstrates once again the preparatory or anticipatory nature of the circulatory response, and also how readily it can be produced as a conditioned reflex.

A considerable amount of work has been carried out on dogs by Gantt and his colleagues (Gantt, 1960) showing that the tachycardia and hypertension which are produced by a painful stimulus can be readily conditioned and that the conditioned reflex thus obtained is remarkably persistent, surviving up to 13 months without reinforcement, even when the motor components of the reaction have long been extinguished. In our experiments, the muscle vasodilatation was also readily conditioned. As in the corresponding experiments of Gantt (1960) and his colleagues, we found that the conditioned vasodilator response was easily developed, and once established was remarkably stable.

A similar cardiovascular response occurs in man, when in situations causing 'anxiety'. In addition to the well-known rise of arterial blood pressure and heart rate, the cardiac output is usually increased, and the total peripheral resistance reduced (Stead, Warren, Merrill & Brannon, 1945; Hickam, Cargill & Golden, 1948). The muscle blood flow increases (Wilkins & Eichna, 1941; Golenhofen & Hildebrandt, 1957). Brod, Fencl, Hejl & Jirka (1959) measured arterial blood pressure, cardiac output, forearm blood flow and renal plasma flow simultaneously in subjects given a severe test in mental arithmetic, and thereby revealed a general pattern of response which is the same as that found in anaesthetized and conscious animals. It is of particular interest that the increase in muscle blood flow was shown to result mainly from a decrease of flow resistance, since activation of the vasodilator nerve fibres to skeletal muscle is characteristic of the defence reaction in experimental animals (Abrahams *et al.* 1960*b*). Atropine-sensitive vasodilator nerve fibres of the sympathetic outflow have since been shown to be involved in the response to a frightening situation in man (Blair, Glover, Greenfield & Roddie, 1959), although in some subjects circulating adrenaline may make a significant contribution to the muscle vasodilatation (Barcroft, Brod, Hejl, Hirsjärvi & Kitchin, 1960).

There is every reason to believe that the pattern of cardiovascular response underlying defence reactions in man, as in animals, will result from stimuli of different modalities, and if this response is as readily conditioned in man as it is in animals it might be expected to play an important part in pathological as well as physiological reactions. Indeed,

muscle blood flow has been found to be significantly higher in hypertensive than in normotensive human subjects (Brod, Fencl, Hejl, Jirka & Ulrych, 1962). The increase in blood flow is too great to be explained by the increase in perfusion pressure. Apparently the resistance vessels in skeletal muscle do not usually participate in the general increase in vascular tone observed in hypertension, and they may even be dilated. Brod *et al.* (1962) therefore suggest that the pattern of cardiovascular response characteristic of the defence reaction may participate in the pathogenesis of essential hypertension in man.

SUMMARY

1. In cats anaesthetized with chloralose, active vasodilatation in the muscles of the hind limb, elicited by electrical stimulation of the hypothalamus, leads to an increase in temperature of the femoral venous effluent.

2. This change of temperature has been used in experiments on conscious cats as an index of the onset and course of the atropine-sensitive muscle vasodilatation occurring during defence reactions.

3. Atropine-sensitive vasodilatation in the muscles is invariably found to accompany the early, alerting stage of the defence reaction produced by near-threshold electrical stimulation of the hypothalamus or by environmental stimuli.

4. It is proposed that the pattern of circulatory change, of which this vasodilatation is a characteristic component, should be regarded as a preparatory cardiovascular reflex.

5. The muscle vasodilatation is readily obtained as a conditioned-reflex response which appears to be stable, whereas the unconditioned response to environmental stimuli shows rapid habituation.

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