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VASOMOTOR CONTROL OF THE CUTANEOUS BLOOD VESSELS IN THE HUMAN FOREARM

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Considerable evidence has recently accumulated to show that the increased blood flow in the forearm elicited by body heating is confined to the skin vessels (Barcroft, Bock, Hensel & Kitchin, 1955; Edholm, Fox & Macpherson, 1956; Roddie, Shepherd & Whelan, 1956), so that the usual methods of venous-occlusion plethysmography can be used to study the changes which occur in the blood flow of the skin of the forearm when the body is heated. In this paper results are presented of experiments using these methods which indicate that the blood flow in the forearm skin is controlled by a vasodilator mechanism, in contrast to the vasoconstrictor release mechanism found in the skin of the fingers and hand. They provide, by the use of a direct method for measuring blood flow, confirmation of the conclusions arrived at by Grant & Holling (1938) based on measurements of skin temperature.

METHODS

Subjects. Twelve adult male subjects were used, but the majority of the experiments were performed on three subjects whose ages ranged from 33 to 47 years.

Blood-flow measurements. The method used followed closely that described by Edholm *et al.* (1956). The blood flow in both forearms, supported at the level of the right atrium, was measured simultaneously by means of two water-filled venous-occlusion plethysmographs. The subject reclined comfortably in a bath. The bath water could be controlled at any desired temperature. Except where otherwise stated, the temperature of the plethysmograph was maintained at 34° C and that of the room at 26°–27° C. Ten in-flow traces, each of 5 sec duration with 10 sec intervals, were automatically recorded in 150 sec, and the subject then rested for 150 sec; the recording was only interrupted for manipulative procedures. Each value shown in the graphs is the mean of the last eight of each ten in-flow traces.

Nerve block. The cutaneous nerve supply to the forearm was blocked by injecting approximately 10 ml. of a 2% solution of lignocaine (containing 1:67,000 adrenaline hydrochloride) in a continuous subcutaneous ring about 3–4 cm distal to the tip of the olecranon. If anaesthesia of the forearm was then found to be incomplete, the unanaesthetized nerves were located by faradic stimulation and separately injected. Anaesthesia was considered to be complete when the

sensation of light touch was absent from the area enclosed within the plethysmograph. Once achieved, complete anaesthesia would persist for at least 2 hr. In control experiments the lignocaine was replaced by normal saline, with or without adrenaline, and injected in the same way.

Procedure. The following four types of experiments were performed.

The first was intended to demonstrate the effect of cutaneous nerve block on skin blood flow under 'normal' or neutral temperature conditions—that is, when the bath and the plethysmograph were maintained at 34° C. The skin of one forearm was anaesthetized as described and then the blood flows in the two arms were measured and compared. A variant of this type of experiment was performed in which the blood flow in both forearms was measured for a period of at least 20 min, and then the skin of one forearm was anaesthetized and the measurements of blood flow were repeated in both forearms. Control experiments were performed in which saline and adrenaline were used instead of lignocaine and adrenaline.

The second type was intended to demonstrate the effect of cutaneous nerve block on the vasodilatation in the skin which accompanies body heating. In these experiments the skin of one arm was anaesthetized as before and the blood flow in both arms measured while the bath temperature was maintained at 34° C. The temperature of the bath was then raised so as to produce an oral temperature of 38° C and thereafter adjusted so as to maintain the oral temperature constant at this value. Blood-flow measurements were made on both arms throughout the period of heating. The experiments were concluded by observing the effect of cooling the bath. Control experiments were performed as before.

The third type of experiment was intended to show the effect of anaesthetizing the cutaneous nerves during the phase of increased blood flow that accompanies body heating. Resting blood flows were measured in both forearms, the body temperature was then raised as described above and, when the blood flow had become stable at the new raised level, the skin of one forearm was anaesthetized and the measurements of blood flow continued. Control experiments were performed in which saline, both with and without adrenaline, was used instead of lignocaine and adrenaline.

A fourth group of experiments was also performed which were intended to show whether, by varying local or general temperature conditions, a vasoconstrictor release mechanism could be demonstrated. These experiments were similar to the first type, differing only in that various plethysmograph, bath or room temperatures, or a combination of these, were employed.

RESULTS

Cutaneous nerve block at neutral temperatures

There were nineteen experiments on eleven subjects in which cutaneous nerve block was performed on one arm before measuring the blood flow. The mean blood flow in the blocked arm was $3{\cdot}7 \pm 0{\cdot}19$ ml./100 ml. tissue/min, and in the control arm it was $3{\cdot}4 \pm 0{\cdot}25$ ml./100 ml. tissue/min (if the results of three experiments on subject 3 were excluded the values were $3{\cdot}6 \pm 0{\cdot}20$ and $3{\cdot}6 \pm 0{\cdot}27$ ml./100 ml. tissue/min respectively), so that, on the average, blocking the cutaneous nerves was without significant effect on the forearm blood flow in the resting condition.

Three experiments were performed in which saline and adrenaline replaced the lignocaine and adrenaline. The mean blood flow in the control arms was 2·7 ml./100 ml. tissue/min, and in the treated forearm 3·0 ml./100 ml. tissue/min.

In general, the small differences that existed between the anaesthetized and control arms varied in a random fashion, the flow sometimes being greater in the treated arm, sometimes in the control arm, but it was observed that one

subject (subject 3) consistently had a higher level of blood flow in the anaesthetized arm. For this reason a further eight experiments were performed and, in order to provide a more stringent control, the procedure was varied in that the blood flow was measured in both arms before blocking the cutaneous nerves in one.

The results of these experiments are set out in Table 1. They confirm the findings in the previous experiments. On the average, there is no significant difference between the blood flows before and after the cutaneous nerve block, either in the treated arm ($t = 1{\cdot}65$) or in the control arm ($t = 2{\cdot}22$), but subject 3, as before, showed an increased blood flow in the treated forearm after the cutaneous nerve block.

TABLE 1. Comparison of the blood flows before and after nerve block under neutral temperature conditions (bath and plethysmograph at 34° C) in treated and control forearms. Each value is the mean of 32 in-flow traces.

		Blood flow (ml./100 ml. tissue/min)			
		Control arm		Blocked arm	
Subject no.	Arm blocked	Before nerve block	After nerve block	Before nerve block	After nerve block
1	Left	2·3	3·2	2·8	4·4
	Right	1·6	1·9	1·7	1·8
	Left	3·3	3·4	3·8	3·0
2	Left	3·0	4·9	2·4	4·4
	Left	2·4	3·7	3·9	4·3
3	Left	1·7	2·3	1·8	4·4
4	Right	1·9	1·4	1·7	1·4
5	Left	2·2	2·3	2·6	2·8
Mean		2·3	2·9	2·6	3·3
't'		2·22*		1·65*	

* Not significant.

Cutaneous nerve block followed by body heating

Nine experiments were performed in which, after the cutaneous nerves in one arm had been blocked and the blood flow in both arms measured, the bath temperature was raised and the blood flow measurements continued. The results of one such experiment are shown in detail in Fig. 1. The mean resting blood flow was similar in the control and the treated arm (5·3 and 4·2 ml./100 ml. tissue/min respectively), as would be expected from the results of the experiments already described. Heating the body produced a rapid and large response in the control arm in which the blood flow increased to a maximum value of 14·0 ml./100 ml. tissue/min. In the treated arm the response to body heating was very small. On cooling the bath the blood flow fell rapidly in the control arm and at the conclusion of the experiment the blood flow was the same in both arms.

The results of the remaining eight experiments are more briefly illustrated in Fig. 2. In these the average blood flow in the control arm rose from a resting value of 3·3 ml./100 ml. tissue/min to 13.8 ml./100 ml. tissue/min when the flow ceased to rise during the phase of body heating. In the treated arms the

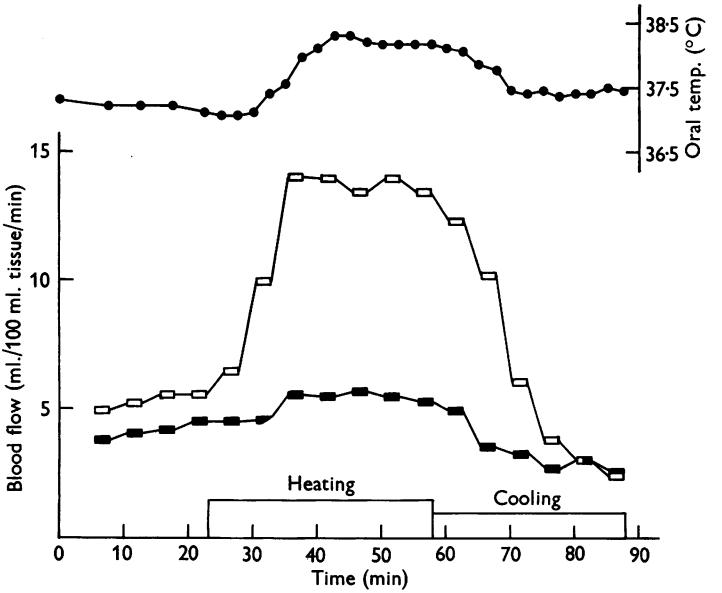

Fig. 1. The effect of cutaneous nerve block on the blood flow in the forearm during body heating and subsequent cooling. The right (■) forearm was anaesthetized and the left (□) was the control. The oral temperature is also shown.

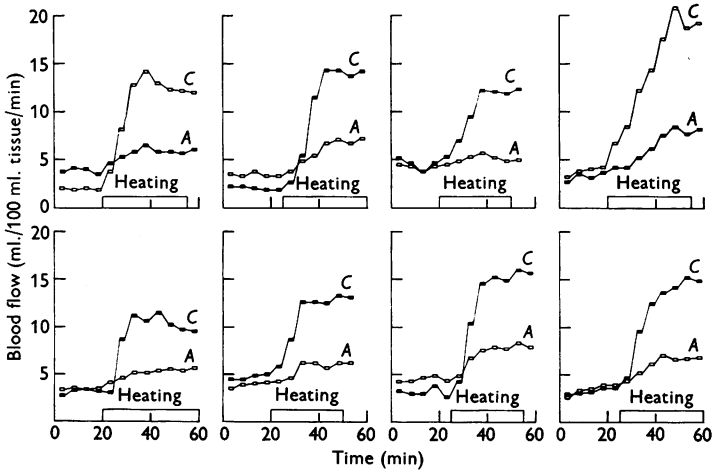

Fig. 2. The results of eight further experiments similar to that illustrated in Fig. 1. The symbols ■ and □ represent right and left forearm as before, and *A* the anaesthetized and *C* the control forearm.

average blood flow before body heating was 3·6 ml./100 ml. tissue/min and during body heating 6·5 ml./100 ml. tissue/min. In control experiments in which saline with adrenaline was substituted for lignocaine with adrenaline, the increase in blood flow on body heating was the same in the treated as in the untreated arm.

Cutaneous nerve block during body heating

The third type of experiment, in which cutaneous nerve block was performed on one forearm during the stage of increased blood flow accompanying body heating, presented a number of technical difficulties, the chief of which was ensuring that anaesthesia of the forearm was complete. There was no means of checking this during the course of the experiment as the forearm remained in the plethysmograph and anaesthesia could not be tested until it was withdrawn at the conclusion of the experiment. Although in all cases there was a substantial decrease in the blood flow in the treated arm it was never possible to reduce it completely to the level existing before heating. Furthermore, in two of four control experiments in which saline with adrenaline was used there was a definite fall in blood flow in the treated arm, although in a further three experiments in which saline only was used there was no change.

It was considered that attempting to anaesthetize the forearm skin whilst the forearm was in the plethysmograph was an unsatisfactory procedure, and further experiments were performed in which, during the stage of body heating, both arms were withdrawn from the plethysmographs and one was injected either with lignocaine and adrenaline or with saline and adrenaline. The arms were then returned to the plethysmographs and further readings taken. The results of six such experiments, three using lignocaine and adrenaline and three using saline and adrenaline, are shown in Fig. 3. It will be seen that the injection of lignocaine and adrenaline produced a substantial fall in the blood flow, an effect which was not produced by the injection of saline and adrenaline.

Temperature changes and vasoconstrictor release

The observation that in subject 3 cutaneous nerve block was consistently followed by a small but definite increase in blood flow suggested that in this subject cutaneous anaesthesia resulted in the release of vasoconstrictor tone. Fig. 4 sets out the results of three of the fourth group of experiments which were performed in order to determine whether, by altering the experimental conditions (e.g. the temperature of the bath, room, or plethysmograph), this phenomenon could be more generally demonstrated.

Cooling the water in the plethysmograph to 28° C failed to evoke any release of vasoconstrictor tone following anaesthesia (Fig. 4*a*) and indeed suppressed

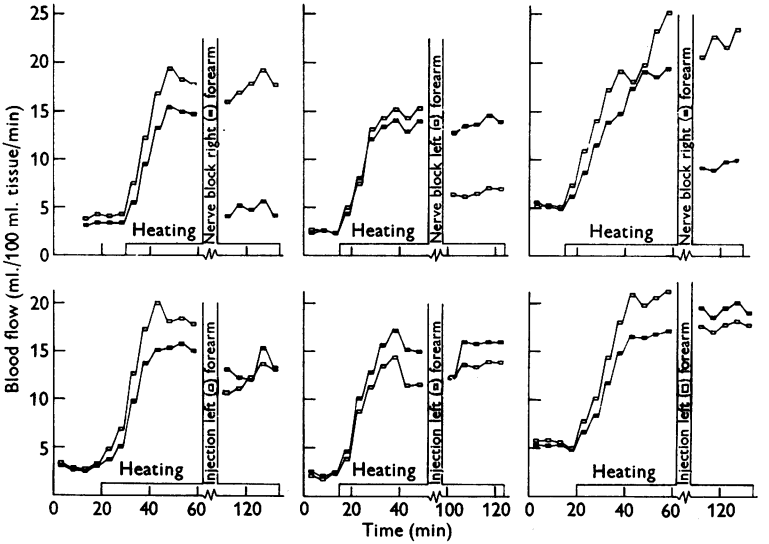

Fig. 3. The upper three figures show the effect in three subjects of cutaneous nerve block performed during the phase of increased blood flow which accompanies body heating. The corresponding lower three figures show, for the same subjects, the effect of substituting saline with adrenaline for lignocaine with adrenaline.

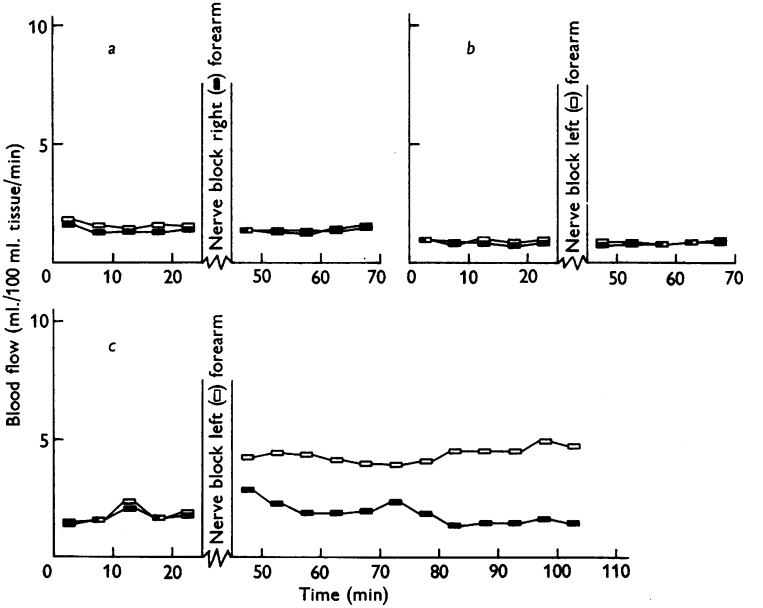

Fig. 4. The effect of cutaneous nerve block on forearm blood flow at lower plethysmograph, bath and room temperatures. In *a* (subject 6) and *b* (subject 3) the plethysmograph temperature was reduced to 28° C. In *c* (subject 3) the plethysmograph temperature was maintained at 34° C and the room and bath temperature lowered.

it in the single subject in whom it was known to occur (Fig. 4*b*). Lowering the bath temperature, though in general without effect, appeared to accentuate the release of vasoconstrictor tone in subject 3 (Fig. 4*c*).

DISCUSSION

In studies of vasomotor control in the human skin, the hand has been used more frequently than other regions of the body, not only on account of its accessibility but also because in it the ratio of skin to other tissues is particularly high; and it has been generally assumed that the vasoconstrictor mechanism so clearly demonstrated in the skin of the hand (Lewis & Pickering, 1931; Warren, Walter, Romano & Stead, 1942; Sarnoff & Simeone, 1947; Arnott & Macfie, 1948; Gaskell, 1956) is the means whereby the blood flow is controlled in the skin elsewhere in the body. Grant & Holling (1938), who used the skin temperature of the forearm as a measure of the changes in cutaneous blood flow, showed however that blocking the cutaneous nerves by local anaesthesia did not cause either flushing or warming of the skin, and that a similar cutaneous nerve block performed during body heating produced pallor and cooling in the anaesthetized area. They concluded from these findings that, in the forearm skin, vasodilatation is due to the action of vasodilator nerves. These findings were later confirmed by Doupe, Cullen & Macaulay (1943) but do not appear to have received general acceptance (Uvnäs, 1954; Folkow, 1955).

The extent to which the forearm skin blood flow in the neutral or normal body temperature state (that is, when the bath and plethysmograph temperatures are maintained at 34° C) is the result of vasoconstrictor tone maintained by vasoconstrictor nerves is demonstrated by the results of the first type of experiment performed. These results show clearly that blocking the cutaneous nerves does not produce a consistent increase in blood flow in the forearm skin, hence the low level of blood flow in the normal or neutral body temperature state cannot be the result of vasoconstrictor tone.

Evidence that the increase in forearm blood flow with body heating is produced by an active vasodilator mechanism, mediated by nerve fibres contained in the cutaneous nerves supplying the forearm skin, is provided by the second type of experiment, in which the normal response to body heating was either abolished or greatly reduced in the anaesthetized forearm (Figs. 1, 2). The presence of an active vasodilator mechanism is further demonstrated by the fall in the forearm blood flow which accompanied cutaneous nerve blocks performed after the blood flow had been raised by body heating (Fig. 3). These results confirm the findings of Grant & Holling (1938).

Early in this investigation, however, it was noticed that one subject differed from the others in consistently exhibiting an increase in forearm blood flow when the nerve block was performed in the neutral or normal body-temperature

state. In three experiments on this subject the mean blood flow in the control forearm was 2·4 ml./100 ml. tissue/min as compared with 4·2 ml./100ml. tissue/min in the anaesthetized forearm, suggesting the release of vasoconstrictor tone. Evidence that a vasoconstrictor component is present in most subjects has been provided by Roddie, Shepherd & Whelan (1957*a*). They measured the oxygen saturation of the blood in a superficial vein and observed that blocking the cutaneous nerves increased the degree of saturation, indicating that the blood flow to the skin had been increased and hence that

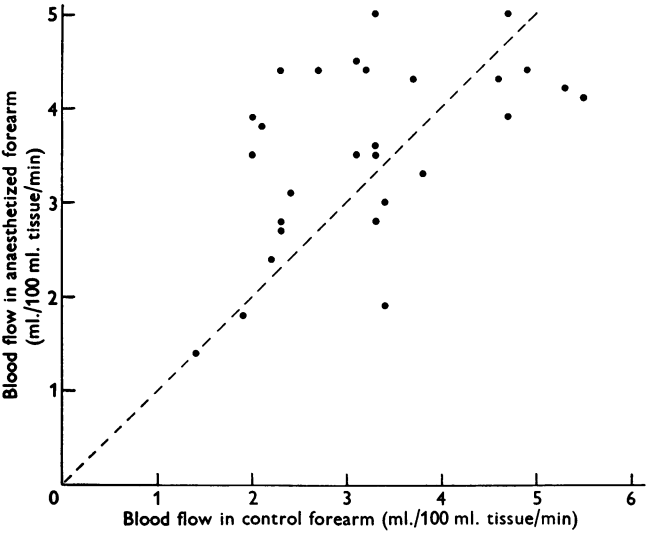

Fig. 5. The relation between the blood flow in the anaesthetized forearm and that in the contralateral (control) forearm following cutaneous nerve block at neutral temperature conditions (plethysmograph 34° C, bath 34° C, room 26°–28° C). The line drawn represents a 1:1 relation.

there had been some release of vasoconstrictor tone. Furthermore, they observed (Roddie, Shepherd & Whelan, 1957*b*) that on heating the body there is an initial small increase in the blood flow in the forearm which they attribute to the release of vasoconstrictor tone.

There is evidence, however, that their subjects might have been considerably cooler than ours. They are described (Roddie *et al.* 1957*a*) as being lightly clad in a room at 16°–18° C. It was considered possible, therefore, that the difference between our results and theirs might be explained by some systematic difference in the local or general temperature conditions employed. Moreover, if in those experiments in which the subjects were maintained at the 'normal' or neutral temperature condition the blood flow in the anaesthetized arm is plotted against that in the control (contralateral) arm, it can be seen (Fig. 5) that there was a tendency for the forearm blood flow to be

greater as the result of cutaneous nerve block if the blood flow in the control arm was less than 4 ml./100 ml. tissue/min and to be less if the flow in the control arm was above that level.

It was for this reason that the fourth type of experiment was performed in an attempt to find the optimum conditions for demonstrating a vasoconstrictor component in the vasomotor control of the forearm skin. The effects of altering the local and general temperature conditions were specially examined in the one subject (subject 3) found to exhibit such a response. Reducing the local temperature to 28° C abolished any rise in blood flow following cutaneous nerve block in this subject (Fig. 4*b*). There was evidence of a potentiation of the vasoconstrictor activity in this subject when the bath and room temperatures were both lowered but the local temperature was maintained at 34° C (Fig. 4*c*). The effects of local cooling (Fig. 4*a*) and general body cooling were also examined in subjects who did not normally show evidence of release of vasoconstrictor tone with cutaneous nerve block, but these manoeuvres failed to provide satisfying evidence of the existence of vasoconstrictor tone in these subjects.

Although the experiments which have been described show that vasodilatation in the skin of the forearm due to body heating is the result of an active vasodilator mechanism, they do not exclude the possibility that there is also a vasoconstrictor mechanism present. It could be that not only does the nervous mechanism involve some pathway other than the cutaneous nerves—for example the vascular plexuses (Mitchell, 1956)—but it might also subserve some purpose other than that of body temperature regulation. Evidence in support of the existence of such a vasoconstrictor mechanism is provided by the rise in temperature of the skin of the forearm which results from sympathectomy, and the great increase in blood flow which accompanies brachial plexus block. The increase observed following such a block is as great as the maximum blood flow obtained by body heating and much greater than the combined effects of blocking the radial, median and ulnar nerves together with the cutaneous nerves of the forearm (Barcroft, Edholm, Foster, Fox & Macpherson, 1956). The evidence provided by the use of ganglion blocking agents, however, would seem to indicate that vasoconstrictor release plays a relatively unimportant role in the control of forearm blood flow. Hamilton, Henley & Morrison (1954) showed that hexamethonium bromide produced a substantial change in hand and foot blood flow but only a small rise in calf and forearm flow.

Postulating a vasodilator mechanism at once raises the problem of its mode of action. Hilton & Lewis (1955*a*, *b*) demonstrated in the cat that the increased blood flow in the submandibular gland resulting from stimulation of the chorda tympani is due to the production of bradykinin-forming substance which, together with the plasma proteins in the extracellular fluid, produces the

powerful vasodilator polypeptide, bradykinin. A similar mechanism in which the sweat glands replace the submandibular gland could well explain the phenomena seen in the forearm skin, and Fox & Hilton (1956) demonstrated that the bradykinin-forming substance was present in sweat collected from the forearm, which strongly suggested that such a mechanism was involved. This hypothesis received further support when it was shown by Fox & Hilton (1957) that bradykinin could be demonstrated in the subcutaneous extracellular fluid following body heating but before the onset of sweating, thus explaining the vasodilatation which is observed to occur before the onset of sweating. These observations, by suggesting the mode of action of the vasodilator nerves, remove an important obstacle to the acceptance of the concept of control of skin blood flow by means of a vasodilator mechanism.

The difference between the vasomotor control of the human forearm and that of the hand raises the question of the mechanism of vasomotor control in the skin of the rest of the body. It is clear that this will now require investigation, but it seems that the skin of the rest of the body is likely to resemble that of the forearm rather than that of the hand.

SUMMARY

1. Experiments were performed in which the blood flows in both forearms were measured simultaneously by means of water-filled venous-occlusion plethysmographs while the subject reclined in a bath, the temperature of which could be accurately controlled.

2. In experiments performed at 'normal' or neutral temperature conditions (bath and plethysmograph at 34° C) blocking the cutaneous nerves in one forearm with 2% lignocaine containing 1:67,000 adrenaline did not produce any significant change in the blood flow of the treated forearm, except in one subject who consistently showed a small increase.

3. If the bath temperature was subsequently raised until the oral temperature of the subject was 38° C the large increase in blood flow in the control forearm (which has previously been shown to be confined to the skin), did not occur in the treated forearm.

4. When the cutaneous nerves of the forearm were anaesthetized during the phase of increased blood flow which accompanies body heating, the blood flow in the treated forearm fell to a value close to that observed in the neutral temperature condition.

5. Control experiments in which saline with adrenaline was substituted for the lignocaine with adrenaline gave negative results.

6. Attempts to demonstrate (by varying the temperature of the bath and plethysmograph) the release of vasoconstrictor tone in subjects other than the one in whom it had been observed did not succeed.

7. It is concluded that the blood flow in the skin of the human forearm is regulated mainly by a vasodilator mechanism and not, as in the skin of the hands and feet, mainly by the release of vasoconstrictor tone.

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