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LOCAL VASOMOTOR RESPONSES TO RUBEFACIENTS AND ULTRA-VIOLET RADIATION

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The increase in blood flow produced by radiant heating of proximal areas of the forearm has been found to be associated with concurrent vaso-dilatation in the distal portion of the limb (Crockford & Hellon, 1959). This phenomenon is not dependent on central-nervous-system connexions since it occurs in subjects with complete brachial-plexus tears as well as in individuals with nerve blocks between the heated area and the spinal cord (Crockford, Hellon & Parkhouse, 1962). The centrifugal spread of the vaso-dilatation is prevented, however, by subcutaneous injection of either adrenaline or lignocaine immediately distal to the heated area. It was suggested on the basis of these studies that the spread of the vaso-dilatation may be conducted directly through the muscle walls of the subcutaneous arterial plexus. The present work attempts to determine whether the cutaneous erythema caused by rubefacients or by ultra-violet radiation is associated with changes in blood flow in the forearm similar to those produced by heating.

METHODS

Local areas of erythema were produced on the forearm of three healthy male subjects by the application of either a 5 % cream or a 20 % aqueous-glycerine mixture of Trafuril (tetra-hydro-furfuryl nicotinic acid ester, Ciba Laboratories, Ltd). This rubefacient was rapidly applied to an area 7 cm in width encircling the forearm just below the antecubital fossa. Within 5–10 min the rubefacient produced a sharply demarcated zone of bright erythema sometimes associated with sensations of mild burning and warmth. The cutaneous irritation subsided within a few hours after the material was washed off, and as a rule only slight erythema was visible on the following day. The effects of the rubefacient were also studied in three subjects with severe brachial plexus injuries. Each of them had paralysis of one arm with total sensory loss and muscle wasting. The site of the traction lesion was thought to be distal to the dorsal root ganglia, because of the absence of intradermal histamine flares and cold vasodilatation reactions (Bonney, 1959). The skin temperature of the denervated arm in each of these individuals was lower than that of the normal arm. Since the erythematous action of Trafuril is thought to be diminished by cooling of the skin surface (Nassim & Banner, 1952), warm air was carefully blown on the arm to relax the superficial vaso-constriction.

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An attempt was made in each normal subject to prevent the extension of vasodilatation into the distal portion of the forearm by the local injection of a 1:200,000 solution of adrenaline or 1% lignocaine (Crockford *et al.* 1962). Immediately before each experiment began approximately 10–15 ml. of each solution was injected subcutaneously in a ring encircling the mid portion of the forearm, approximately 3 cm distal to the area of rubefaction. Each normal subject also received a similar injection of isotonic saline as a control test.

Measurements of the forearm blood flow were made for a period of 5–10 min before application of Trafuril, and for 20–30 min afterwards. The blood-flow measurements were made every 15 sec with the strain-gauge plethysmographic technique described by Whitney (1953). One gauge was placed about the forearm in the mid portion of the erythema, and one or two others at a distance of 3 or 6 cm distal to the erythematous margin. In each experiment control blood-flow measurements were made simultaneously in the contralateral arm with a single gauge. The position of the arms, the room temperature and the details of the plethysmographic technique have been described previously (Crockford & Hellon, 1959).

Cutaneous erythema was also produced in each normal subject by ultra-violet radiation. Three mercury arc lamps fitted with aluminium foil reflectors were placed radially about the arm at a distance of 23–41 cm from the skin. These lamps were of the medium pressure (MB) type, and had a loading of 125 W. An area of the forearm similar in size and position to that described in the rubefacient studies was exposed to ultra-violet light from this source for periods of 12–25 min. Erythema usually appeared within 2–3 hr, and remained for a day or more. Blood-flow measurements lasting for 10 min were begun within an hour after ultra-violet exposure and were repeated at hourly intervals for approximately 6–8 hr. Because of the long duration of each experiment careful control measurements were necessary, and for this purpose two gauges were placed in corresponding positions on the contralateral arm. The amount of ultra-violet exposure required to produce erythema varied for each subject and multiple trials had to be carried out to determine the optimal erythematous dose. Because of the difficulty in predicting the time of onset of the increase in blood flow no attempt was made to block the distal vasodilatation by subcutaneous injection of lignocaine or adrenaline. The subjects with brachial plexus injuries were not used in these ultra-violet studies.

RESULTS

Studies of rubefacient action

The effect of Trafuril on peripheral blood flow in the forearm was studied in 14 experiments, 8 with the 5% cream preparation and 6 with the 20% aqueous-glycerine mixture. In each instance there was a significant increase in blood flow in the erythematous zone. This was associated with a simultaneous rise in blood flow in the distal part of the forearm, shown by both gauges (Fig. 1). In both the proximal and distal areas of the limb, there was an increase in blood flow from base-line values of 2–4 ml. to approximately 6–8 ml./100 ml./min.

These changes appeared 4–5 min after Trafuril was applied, and remained for the duration of the experiment, up to 30 min. Although the erythema sometimes extended a few millimetres beyond the treated area, redness of the skin was never observed in the region near the distal strain gauge.

These experiments were repeated after subcutaneous injection of

lignocaine in a ring round the forearm distal to the treated area. In all three subjects there was the usual increase in blood flow in the treated area, but the ring of anaesthetic prevented extension of the vasodilatation to the distal portion of the forearm (Fig. 2). A ring of adrenaline injected at the same site in three other experiments likewise prevented the increase in blood flow in the distal portion of the forearm (Fig. 3). Subcutaneous injections of equal volumes of isotonic saline around the forearm, however,

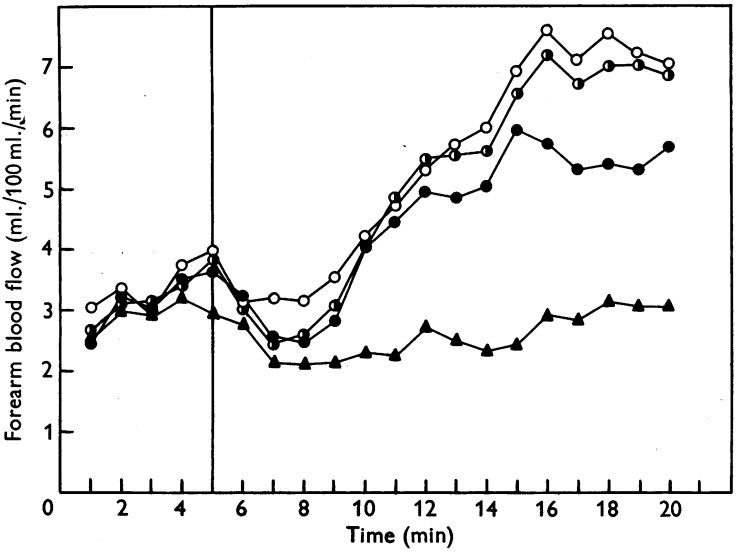

Fig. 1. Changes in forearm blood flow following application of rubefacient (at vertical line). The strain-gauge measurements are made within the area of erythema (○), 3 cm (◑), and 6 cm (●) distally, and on the contralateral arm (▲). Each point represents the mean of the four blood-flow readings taken during that minute.

had no comparable effect, and the lower segment of the limb showed an increase in blood flow similar to that observed with the rubefacient alone.

The effect of the rubefacient on peripheral blood flow was studied in three subjects with brachial-plexus injury. In these subjects the application of 30 or even 50 % solutions of Trafuril to the paralysed forearm failed to produce a significant degree of erythema during the 1 hr period of observation. No change in blood flow was observed in the portion of the arm to which Trafuril was applied, and no vasodilatation developed in the distal portion of the limb. In the normal arm of each of these subjects, however, the usual increase in local blood flow, spreading distal to the treated area, followed application of the rubefacient.

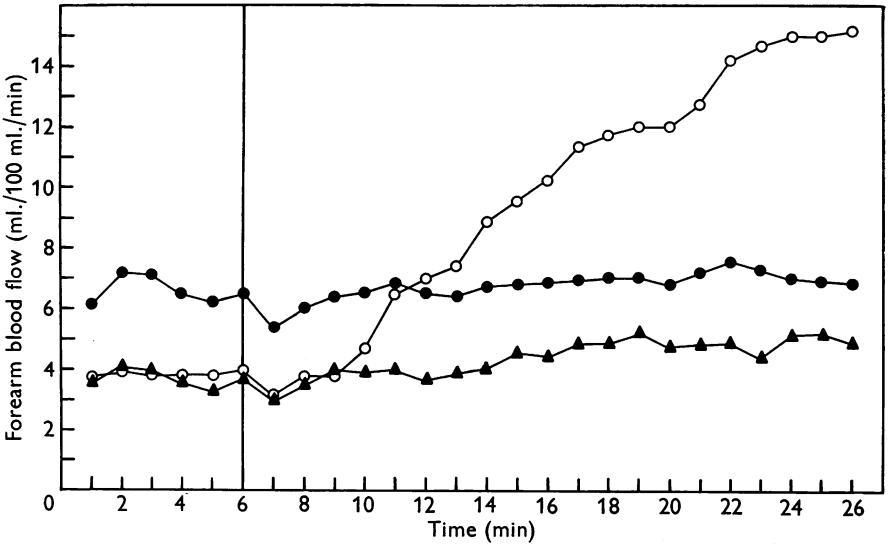

Fig. 2. Effect of subcutaneous ring of 1 % lignocaine, injected at mid forearm, on change of distal blood flow after application of Trafuril (at vertical line) proximally. Flows measured in proximal (○), and distal (●) regions of ipsilateral forearm, and in contralateral (▲) forearm. Each point represents the mean of the four blood-flow readings taken during that minute.

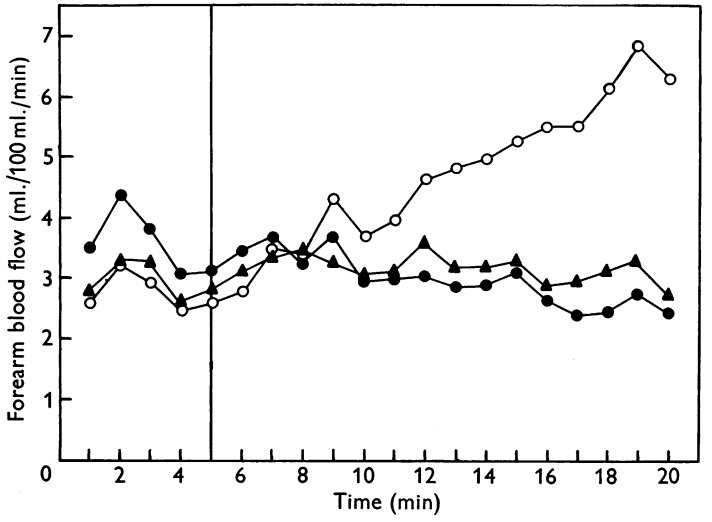

Fig. 3. Effect of subcutaneous ring of adrenaline (1:200,000) injected at mid-forearm region on change of distal blood flow after application of rubefacient (at vertical line) proximally. Flows measured in proximal (○), and distal (●) regions of ipsilateral forearm, and in contralateral (▲) forearm. Each point represents the mean of the four blood-flow readings taken during that minute.

Studies with ultra-violet radiation

The changes in forearm blood flow after various degrees of exposure to ultra-violet light were studied in 16 experiments in three subjects. In seven of these no changes in blood flow were observed for a period of 7–8 hr after exposure, even though a definite area of erythema appeared within 4–5 hr. In the other 9 experiments the subjects were exposed for longer periods to ultra-violet light, averaging 20–25 min, with distances

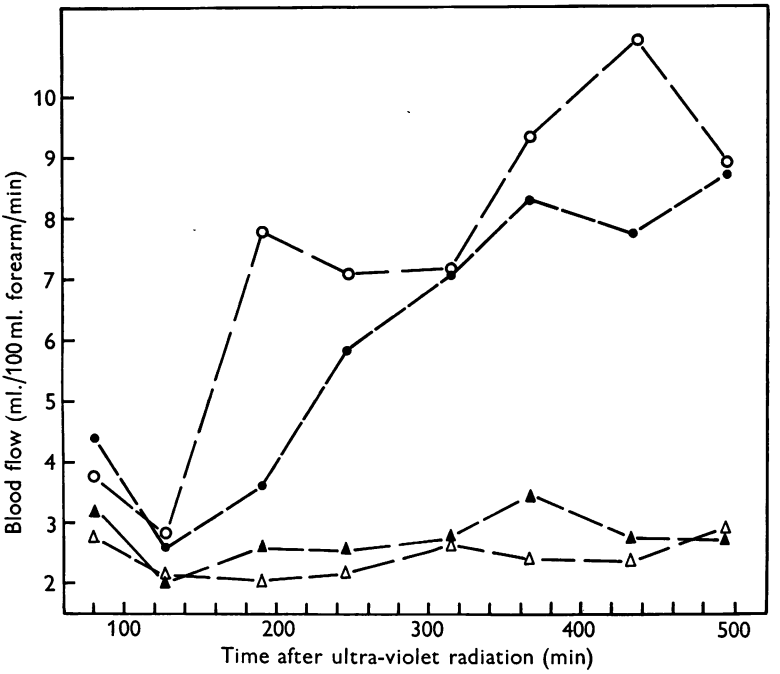

Fig. 4. Responses of forearm blood flow following ultra-violet radiation to the proximal area of the limb (○) and in the non-exposed area 6 cm distally (●). Control measurements were made on the contralateral limb at comparable positions on the proximal (△) and distal (▲) forearm. Each point represents the mean of 40 determinations made in a 10 min period at the time indicated.

from the lamp of 23–30 cm. In these instances an increase in blood flow was noted in both the irradiated areas of the forearm and in the distal non-erythematous portion of the limb, comparable to the changes seen following the application of rubefacient. The erythema in these nine cases developed more rapidly and appeared within 1–2 hr after exposure. The increase in blood flow was evident between 2 and 6 hr after ultra-violet radiation, and remained elevated for 6–8 hr, at which time the experiment was ended (Fig. 4). In all but one experiment the onset of the vaso-

dilatation occurred at a time when flows were not being recorded. In this one instance the increase in blood flow appeared simultaneously in both the irradiated and non-irradiated sections of the arm exactly 252 min after exposure (Fig. 5). A definite zone of marked erythema, however, had been present for some 2 hr before the increase in blood flow developed.

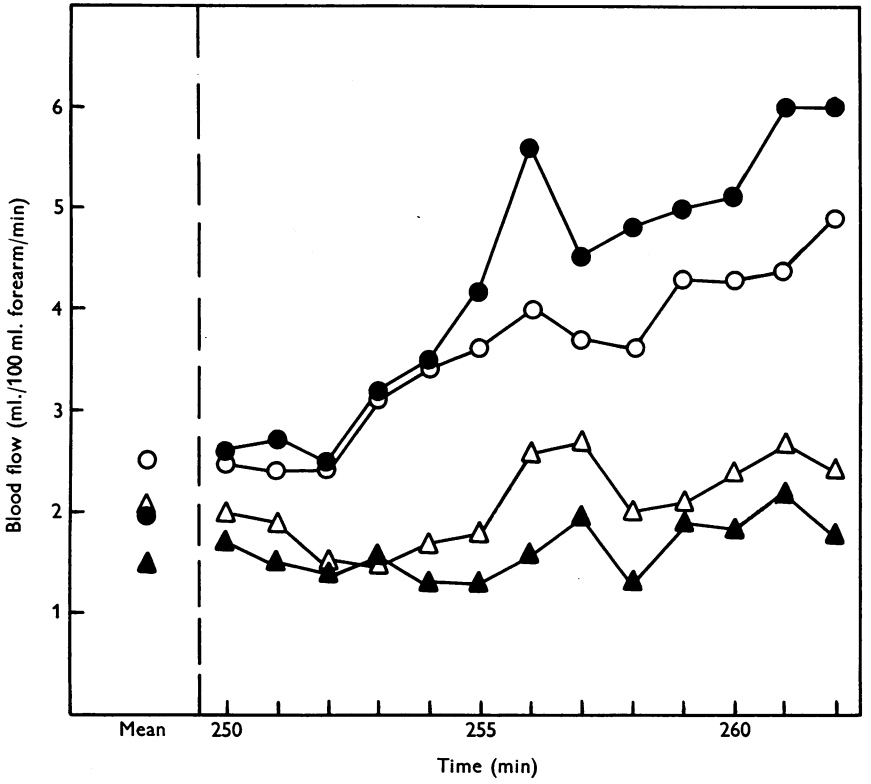

Fig. 5. Time of onset of increase in blood flow in the exposed portion of the forearm (○) and the non-erythematous distal segment (●) after ultra-violet radiation for 25 min. Control measurements were made on the opposite arm in comparable positions (△,▲). Mean blood-flow values are those obtained between 215 and 230 min after radiation. Each point from 250 min onwards is the mean of the four readings taken in that minute.

DISCUSSION

These experiments have shown that the erythema resulting from application of a rubefacient, or exposure to ultra-violet light, produces an increase in blood flow in forearm skin comparable in magnitude to that caused by radiant heat or the application of hot water. The vasodilatation caused by the ultra-violet light or the rubefacient in normal subjects extended beyond the erythematous area and produced a simultaneous

elevation of blood flow in the distal portion of the forearm, similar to that observed with local heating. Likewise the distal extension of the vasodilatation produced by the rubefacient was prevented by subcutaneous injection of a ring of adrenaline or local anaesthetic solution. Thus it would appear that the reaction of the vessels of the forearm to vasodilating influences is basically the same, whether initiated by local heating or by chemical irritation. Once these stimuli produced a vasodilatation it invariably spread distally to involve the non-erythematous or unheated portions of the arm. The delayed and unpredictable onset of the ultra-violet response made it impossible to study this stimulus, either with nerve-block techniques or on the patients with brachial plexus lesions. It is, however, suggested that a similar mechanism operates after ultra-violet as with the two other types of stimulus, particularly since both treated and untreated areas react together even after a delay of over 4 hr.

As has been noted by Crockford *et al.* (1962), the phenomenon resembles in many respects the dilatation of the femoral artery observed experimentally after contraction of the leg muscles of the cat (Hilton, 1959). This post-contraction dilator response is also blocked by the local application of adrenaline or cocaine, but is not affected by partial denervation such as sympathectomy or resection of the posterior or ventral spinal nerve roots. Hilton (1959) believes that this vasodilatation is probably conducted in the smooth muscle of the artery, and he suggests that the mechanism is responsible for a number of other vasodilator phenomena which are commonly considered to be caused by axon reflexes.

Cutaneous erythema and vasodilatation failed to appear after application of the rubefacient to the paralysed forearm in the three subjects with brachial-plexus injury. These same patients were used in the experiments of Crockford *et al.* (1962), in which it was shown that the response to infra-red heating in the paralysed forearm was the same as in normal individuals with distal spread of the vasodilatation beyond the heated area. Thus it appears that chronic denervation of the cutaneous blood vessels abolishes their response to this pharmacological stimulus, but leaves their reaction to a thermal stimulus unimpaired.

The increased blood flow in the forearm caused by rubefacients has been observed previously by Crismon, Fox, Goldsmith & Macpherson (1959). These workers found that application of a benzyl ester of nicotinic acid to the whole forearm produced an approximately twofold increase in blood flow, which could not be prevented by anaesthetic blockade of the cutaneous nerves to the area. Other rubefacients such as capsicin produced redness without increased blood flow, a reaction similar to that we observed after ultra-violet radiation.

To our knowledge there have been no previous plethysmographic

measurements of blood flow following exposure to ultra-violet light. An increase in temperature has been found, however, in the skeletal muscles underlying the skin area exposed to ultra-violet irradiation (Bing, 1943). This elevation of temperature was observed within 7 hr after exposure to the rays, and was thought to be due to an increased blood flow through the muscles. In our studies a similar period of time elapsed before the increase in blood flow appeared, even though cutaneous erythema had been present for several hours. This delay in the development of the vasodilator response to photochemical stimulus cannot be due solely to the time required for the elaboration of a dilating substance by the epidermis (Lewis & Zotterman, 1926), since the erythema was always observed some hours before any increase in blood flow. The very slow development of the increase in flow probably depends also on the rate of penetration of the dilating substance into the deeper layers of the tissues. As described by Blum (1955), an erythematous appearance of the skin after ultra-violet radiation is due to the dilatation of the fine capillaries in the corium and is not associated at first with a measurable increase in blood flow. In contrast, the erythema resulting from application of rubefacients develops simultaneously with an increased blood flow, which perhaps indicates differences between the mode of action of these two stimuli. Despite these differences in the onset of erythema and increased blood flow, once this increase develops it appears almost simultaneously in both the proximal and distal portions of the forearm in both the rubefacient and ultra-violet experiments. With the plethysmographic technique, however, it is not possible to make sufficiently rapid measurements of blood flow to permit an accurate estimate of the speed of the extension of the vasodilatation to the distal portion of the forearm. In the cat the rate of travel of the dilator response in the femoral artery after muscular contraction was found to be about 10 cm/sec, a speed too slow for a neural mechanism (Hilton, 1959).

SUMMARY

1. An investigation was made of the changes in blood flow in the forearm caused by local application of a rubefacient (tetra-hydro-furfuryl-nicotinic acid ester) and by exposure to ultra-violet light.

2. In normal subjects either of these agents produced a significant increase in blood flow in the area of erythema, as well as in the distal non-erythematous portion of the limb. Patients with complete brachial-plexus lesions showed no vasodilatation with the rubefacient, even when it was applied in high concentration.

3. The distal spread of vasodilatation in normal subjects was blocked by subcutaneous injection of adrenaline or lignocaine, but not by isotonic saline solution.

4. It is suggested that the spread of the vasodilatation is propagated as a wave of relaxation conducted in the smooth muscle of the subcutaneous arterial plexus.

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