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EFFECT OF DICHLOROISOPRENALINE ON THE PERIPHERAL VASCULAR RESPONSES TO ADRENALINE IN MAN

BY

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In suitable doses dichloroisoprenaline blocks the initial transient vasodilatation, but leaves unchanged the subsequent vasoconstriction, normally seen during intra-arterial infusion of adrenaline to the human forearm. Dichloroisoprenaline blocks both the initial transient large vasodilatation, and the subsequent sustained modest vasodilatation, normally seen in the forearm when adrenaline is infused intravenously. Dichloroisoprenaline abolishes the dilator effects of intra-arterial isoprenaline. These findings are consistent with the hypothesis that the difference between the responses to intra-arterial and intravenous adrenaline is due to the conversion in the body, elsewhere than in the forearm, of adrenaline to an isoprenaline-like substance.

When adrenaline is infused into the brachial artery in man there is first an initial large transient increase in blood flow through the forearm (Duff & Swan, 1951). With doses of the order 0.1 μg/min or less this is followed by a rapid return of flow to about the resting level, but with greater doses a reduction in blood flow follows. De la Lande & Whelan (1959) have suggested that this biphasic response of the forearm vessels represents a balance between the vasoconstrictor and vasodilator actions of adrenaline. Thus after the introduction of chlorpromazine or phenoxybenzamine into the forearm the constrictor effect of adrenaline is reduced or abolished, and a sustained dilator effect is unmasked. Recently, a compound, dichloroisoprenaline, has been described, which, in animals, blocks some of the inhibitory but not the excitatory effects of adrenaline (Powell & Slater, 1958). The effect of this substance on the response of the forearm vessels to intra-arterial infusions of adrenaline is now reported.

During a constant intravenous infusion of adrenaline at rates of 10 to 20 μg/min (which correspond approximately to intra-arterial doses of 0.1 to 0.2 μg/min) there is a different pattern of response in the forearm vessels (Allen, Barcroft & Edholm, 1946). There is, as with an intra-arterial infusion, an initial transient increase in flow, but this is often followed by a smaller and sustained increase in flow. Both these increases in flow are much greater than the simultaneous rise in arterial pressure and indicate a vasodilatation in the forearm. The reason for the difference between the responses of the forearm vessels to intra-arterial and intravenous infusions of adrenaline is not fully understood. Whelan (1952) proposed that since the sustained vasodilatation is not seen when adrenaline is given intra-arterially and

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is not affected by acute sympathectomy, it may be due to a circulating vasodilator substance other than adrenaline.

We have further tested this hypothesis by studying the effect of dichloroisoprenaline on the response of the forearm vessels to intravenous infusions of adrenaline.

METHODS

Twenty-five experiments were carried out on seventeen healthy male subjects, who lay supine on a couch in a laboratory maintained at a temperature between 20 and 22° C. Forearm blood flow was measured by venous occlusion plethysmography. A needle was inserted into the left brachial artery in the antecubital fossa and through this 0.9% sodium chloride solution containing 0.003% ascorbic acid was infused throughout the experiment at the rate of 4 ml./min. The ascorbic acid delays the oxidation of adrenaline and noradrenaline (Gaddum, Peart & Vogt, 1949). Dilutions of the drugs in ascorbic acid saline were prepared with the dose for 1 min contained in 4 ml. Adrenaline was given as L-adrenaline hydrochloride (Parke-Davis), noradrenaline as L-noradrenaline bitartrate (Bayer), and isoprenaline as the hydrochloride (Winthrop). In five experiments adrenaline and noradrenaline were infused into an antecubital vein of the opposite arm through an indwelling catheter at the rate of 10 μg/min for periods of up to 5 min. We are indebted to Eli Lilly & Co. for generous supplies of dichloroisoprenaline (compound 20522).

RESULTS

The effect of dichloroisoprenaline on the response to intra-arterial adrenaline. On the basis of animal experiments, the total dose of dichloroisoprenaline used in the first experiment was 32 mg. The results of this experiment are shown in Fig. 1. The infusion of 1.0 μg/min adrenaline produced a typical response consisting of an initial increase in flow followed by a fall to below the resting level. Dichloroisoprenaline was then infused into the brachial artery at the rate of 8 mg/min for 4 min. This caused a large transient increase in forearm blood flow on the infused side, which was associated with a warm feeling in the forearm. Flow on this side

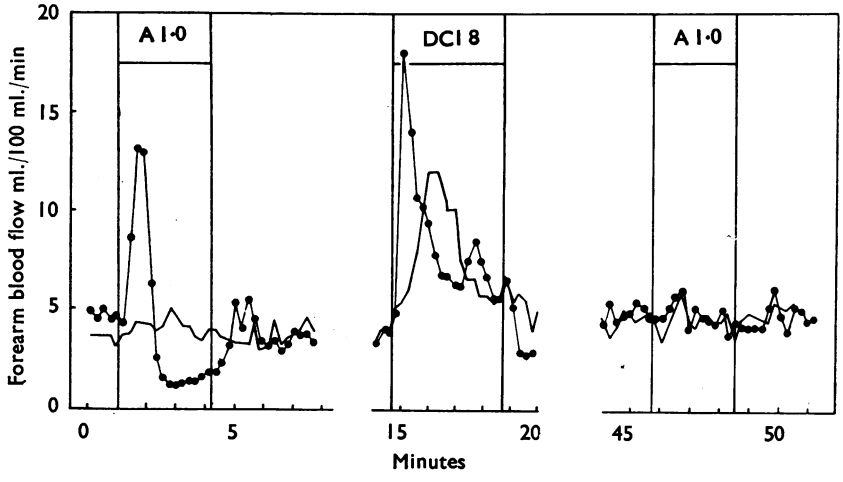

Fig. 1. The response of forearm blood flow to intra-arterial adrenaline (1.0 μg/min) before and after the intra-arterial infusion of DCI (8 mg/min). —— Control side; ●—— ● infused side.

returned quickly towards the resting level, but remained above it until the end of the infusion. Two minutes after the dichloroisoprenaline infusion commenced the subject complained of a feeling of apprehension, palpitations and an increase in respiration; he described the sensations as being similar to those accompanying an intravenous infusion of adrenaline. Blood flow to the control forearm increased rapidly at this time, but both this rise in flow and the symptoms subsided before the end of the infusion. Twenty-seven minutes after the end of the dichloroisoprenaline infusion the flow was the same on both sides and the intra-arterial infusion of adrenaline was repeated. This time the adrenaline produced no change in flow; the dichloroisoprenaline had abolished both the dilator and constrictor actions of adrenaline.

In the experiment illustrated in Fig. 2 the effects of a smaller dose of dichloroisoprenaline, 8 mg given over 4 min, are shown. During the dichloroisoprenaline

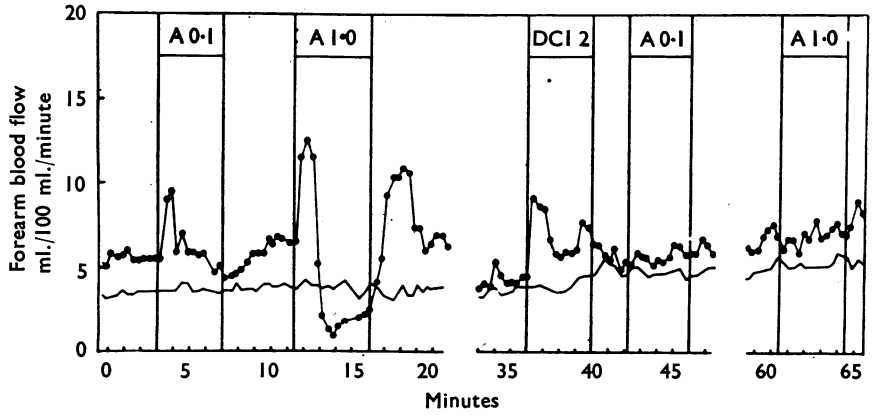

Fig. 2. The response of forearm blood flow to intra-arterial adrenaline (0.1 μg/min and 1.0 μg/min) before and after the intra-arterial infusion of DCI (2 mg/min). —— Control side; ● —— ● infused side.

infusion there was an increase in flow on the infused side only, and there were no general or local symptoms. This dose abolished both the dilator action of 0.1 and 1.0 μg/min adrenaline and the constrictor effect of 1.0 μg/min.

Fig. 3 contains the results of an experiment in which even smaller doses of dichloroisoprenaline were infused. Initially 1.0 μg/min adrenaline produced a typical response. The administration of 0.1 mg dichloroisoprenaline in 1 min reduced but did not abolish the initial vasodilatation of 1.0 μg/min adrenaline infused 1.5 min later; but after 20 min this blocking action of dichloroisoprenaline had worn off and adrenaline gave a normal response. A similar transient blocking action was seen after the dose of dichloroisoprenaline had been increased to 0.5 mg. Dichloroisoprenaline, 0.05 mg/min, was then infused continuously for a period of 20 min. This produced a small increase in flow in the infused forearm. Adrenaline 1.0 μg/min was added to the infusion of dichloroisoprenaline on two occasions. Each time the dilator effect of adrenaline was abolished, but the

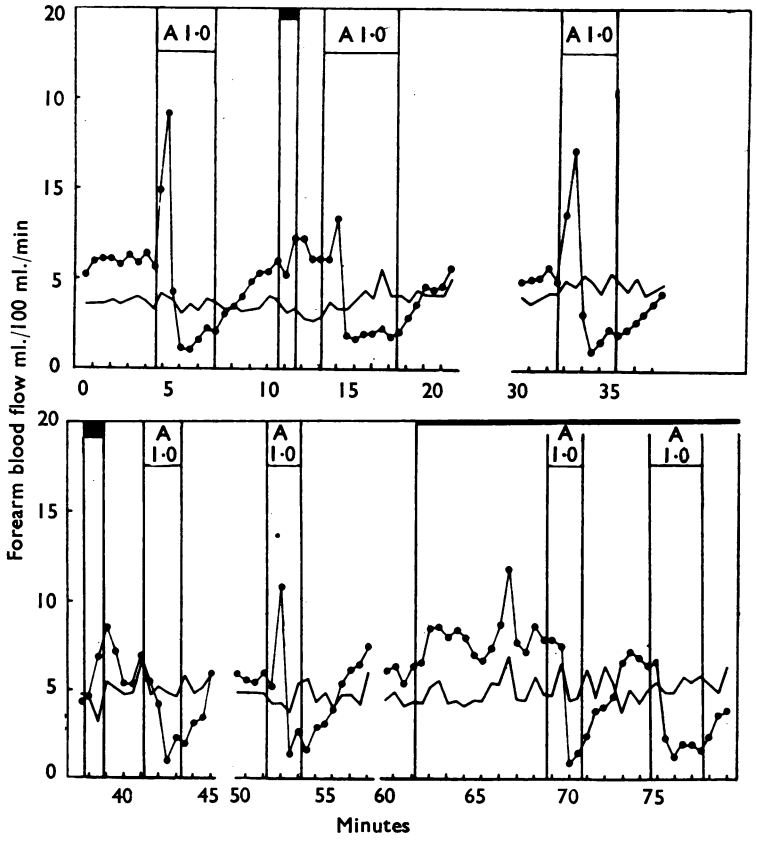

Fig. 3. The response of forearm blood flow to intra-arterial adrenaline 1.0 μg/min. Black rectangles represent periods during which DCI was infused, 11th min, 0.1 mg; 38th min, 0.5 mg; from 61st min, 0.05 mg/min for 20 min. —— Control side; ● —— ● infused side.

constrictor effect was as great as it had been before the administration of dichloroisoprenaline.

The blockade of the dilator action of adrenaline by a steady infusion of 0.05 mg/min dichloroisoprenaline is again shown in the experiment in Fig. 4 ; 1.0 μg/min adrenaline added to the infusion of dichloroisoprenaline 4 min after it had been started still caused a slight initial increase in flow. However, when adrenaline was again given 6 min later it produced only a fall in flow. Dichloroisoprenaline had no effect on the constrictor action of 1.0 μg/min noradrenaline. It appears that the action of dichloroisoprenaline is cumulative and that in this dose it must be given for several minutes before it abolishes completely the dilator action of adrenaline.

This is further demonstrated in Fig. 5. Dichloroisoprenaline, 0.025 mg/min, and adrenaline, 0.1 μg/min, were infused simultaneously and the initial vasodilator response to adrenaline was obtained. The infusion of adrenaline was stopped and

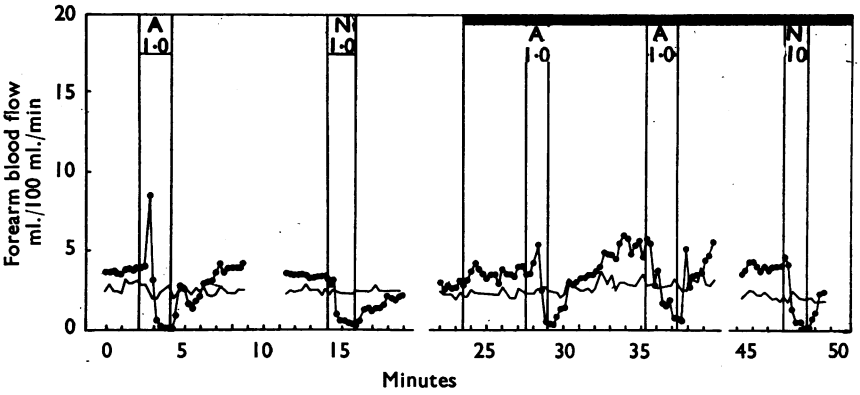

Fig. 4. The response of forearm blood flow to intra-arterial adrenaline (1.0 μg/min) and noradrenaline (1.0 μg/min). DCI 0.05 mg/min was infused during the time represented by the black rectangle. —— Control side; ● —— ● infused side.

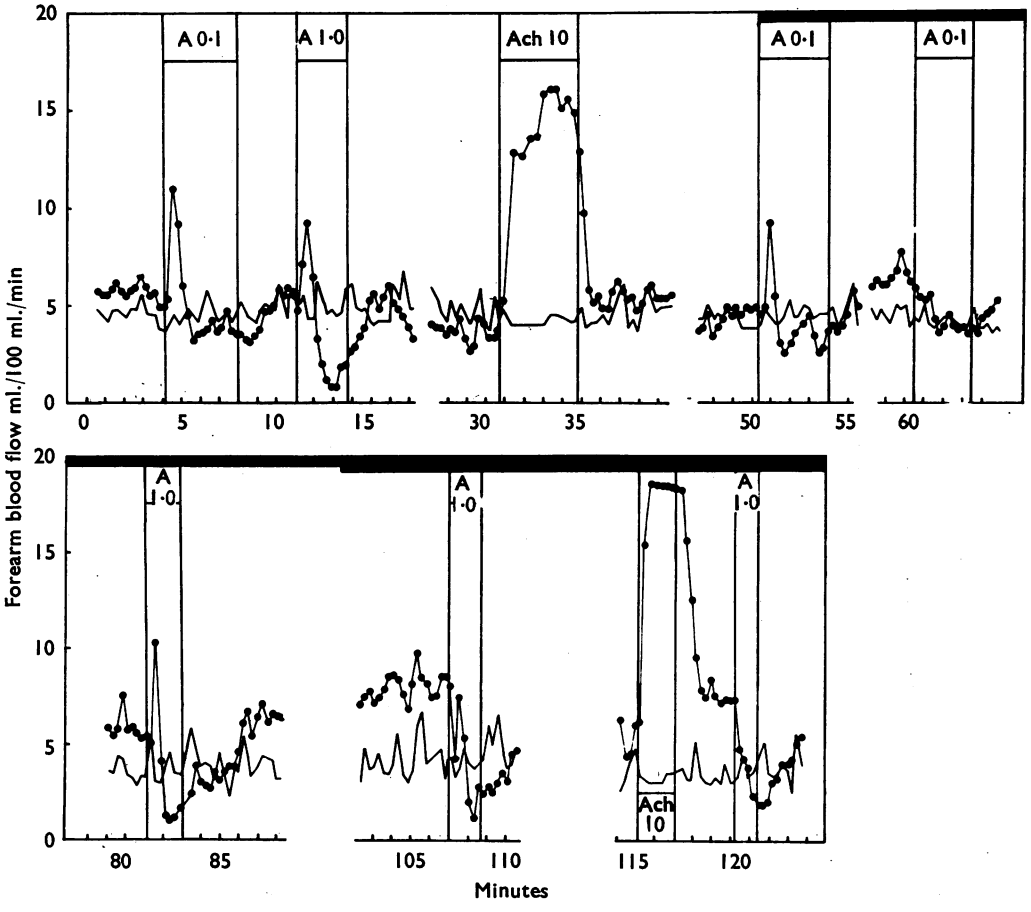

Fig. 5. The response of forearm blood flow to intra-arterial adrenaline (0.1 and 1.0 μg/min) and acetylcholine (10.0 μg/min). DCI was infused during the time represented by the black rectangle. From 50 to 101 min, 0.025 mg/min; from 101 min to end, 0.1 mg/min. —— Control side; ● —— ● infused side.

that of dichloroisoprenaline was continued. When adrenaline was again given 6½ min later its dilator action was abolished. However, even after 30 min this dose of dichloroisoprenaline did not block the initial vasodilator response to 1.0 μg/min adrenaline. The rate of infusion of dichloroisoprenaline was then increased to

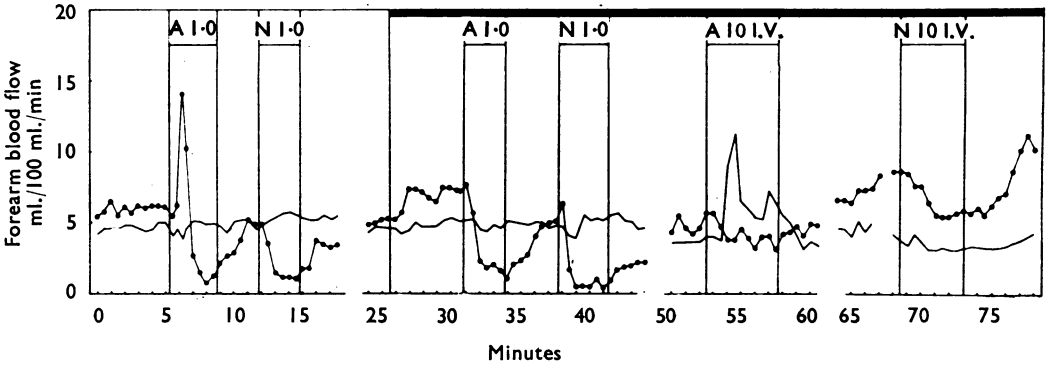

Fig. 6. The response of forearm blood flow to intra-arterial adrenaline (1.0 μg/min) and noradrenaline (1.0 μg/min), and to intravenous adrenaline (10 μg/min) and noradrenaline (10 μg/min). DCI 0.05 mg/min was infused intra-arterially during the time represented by the black rectangle. —— Control side; ● —— ● side receiving arterial infusion.

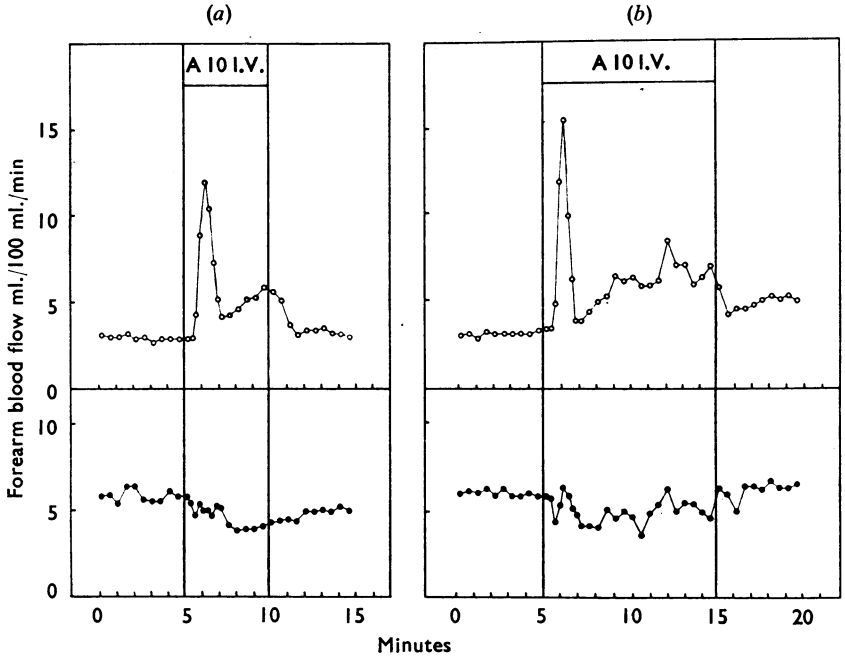

Fig. 7. The response of forearm blood flow to intravenous adrenaline (10 μg/min) infused for (a) 5 min and (b) 10 min. Average of 5 and 4 experiments respectively. DCI 0.05 mg/min was infused into one brachial artery throughout each experiment commencing at least 10 min before the adrenaline was given. Upper panels (○——○) control side. Lower panels (● —— ●) DCI infused side.

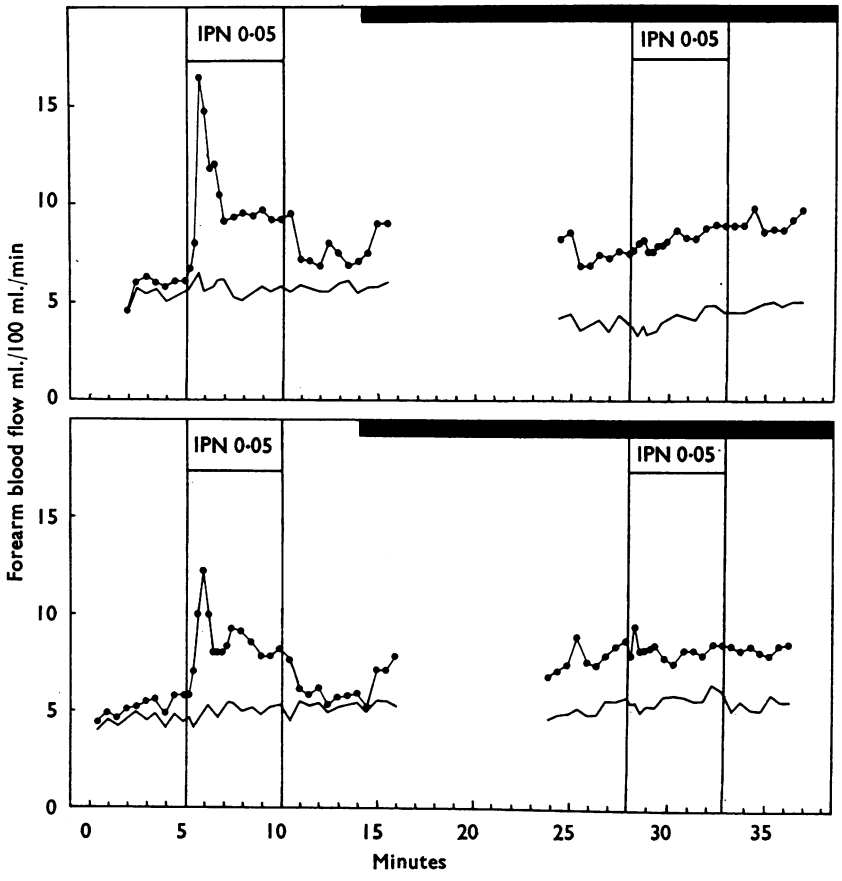

Fig. 8. The response of forearm blood flow to intra-arterial isoprenaline (0.05 μg/min) in two subjects. DCI 0.05 mg/min was infused during the time represented by the black rectangle. —— Control side; ● —— ● infused side.

0.1 mg/min and this abolished the dilator action of this larger dose of adrenaline on each of two occasions. Infusions of 10 μg/min acetylcholine were given before and during the infusion of 0.1 mg/min dichloroisoprenaline. The dilator action of acetylcholine was unaffected at a time when the dilator response to adrenaline was abolished.

The effect of dichloroisoprenaline on the response to intravenous adrenaline. This was studied in 9 experiments. In the experiment illustrated in Fig. 6 the constant infusion of 0.05 mg/min dichloroisoprenaline abolished the dilator action of adrenaline, 1.0 μg/min, without affecting the constrictor action of this dose of adrenaline or noradrenaline, 1.0 μg/min, both infused intra-arterially.

Adrenaline, 10 μg/min, was then given intravenously for 5 min. This produced a characteristic response on the control side, but caused a slight fall in flow on the side which was receiving dichloroisoprenaline. In four similar experiments 10 μg adrenaline was given intravenously for 5 min. The results of these 4 experiments

and the experiment illustrated in Fig. 6 have been averaged, and are shown in Fig. 7a. In 4 other experiments the intravenous adrenaline was continued for 10 min, and the averaged results of these experiments are shown in Fig. 7b. The results in these two groups of experiments are qualitatively similar. Dichloroisoprenaline has clearly abolished both the initial transient and the smaller sustained vasodilatation.

In two experiments 10 μg/min noradrenaline was also given intravenously. This produced a fall in blood flow which was slightly more marked on the side which was receiving dichloroisoprenaline than on the control side. One of these infusions is illustrated in Fig. 6.

In five additional experiments we have shown that dichloroisoprenaline blocks the vasodilator action of intra-arterial isoprenaline in the human forearm. Two of these experiments are illustrated in Fig. 8.

DISCUSSION

It is clear from the present experiments that dichloroisoprenaline can exert a potent modifying effect on the peripheral vascular actions of adrenaline. With large doses (8 to 32 mg) given intra-arterially over a short period, there is abolition of both the dilator and constrictor responses to 1.0 μg/min adrenaline infused into the brachial artery. Smaller doses (0.1 to 0.5 mg given in 1 min) blocked only the dilator effect of adrenaline, but their action was brief. Very small doses of dichloroisoprenaline, such as 0.05 mg/min, given as a continuous infusion, were able after the first few minutes to block consistently the dilator response to 0.1 and 1.0 μg/min adrenaline. The time taken for this blocking action to develop suggests that it depends on the accumulation of a sufficient amount of dichloroisoprenaline in the forearm. This may explain some of the observed individual variation in susceptibility to the drug.

Once present, this blocking action of dichloroisoprenaline persisted throughout its infusion. The smallest dose of dichloroisoprenaline tried in the present experiments was 0.025 mg/min; after it had been given for 10 min this blocked the dilator action of 0.1 μg/min of adrenaline but was without effect on 1.0 μg/min adrenaline. We have not tested whether or not a dose of dichloroisoprenaline which blocks the constrictor action of adrenaline has any effect on the constrictor action of noradrenaline, but the smaller doses which had a specific action on the dilator effect of adrenaline had no effect on the reactions to noradrenaline and acetylcholine. It seems likely that dichloroisoprenaline will be a valuable tool in elucidating the part played by adrenaline in peripheral vascular responses and in studying the mechanisms of its action.

Since the work of Dale in 1906 it has been known that adrenaline possesses two distinct actions—excitatory and inhibitory. Ahlquist (1948) has proposed that these actions result from adrenaline acting on specialized receptors which he has designated alpha and beta. Stimulation of the alpha receptors results in renal and cutaneous vasoconstriction and contraction of the nictitating membrane; actions which are readily antagonized by phenoxybenzamine. Stimulation of the beta receptors results in an increase in the rate and force of the heart, bronchial relaxation,

vasodilatation in skeletal muscle and glycogenolysis ; these effects can be prevented by dichloroisoprenaline (Powell & Slater, 1958 ; Moran & Perkins, 1961 ; Mayer, Moran & Fain, 1961). Levy & Ahlquist (1961) now consider that dichloroisoprenaline produces specific blockade of the beta receptors.

The presence of constrictor or alpha adrenaline receptors in the forearm has been clearly demonstrated by De la Lande & Whelan (1959) and by Allwood & Ginsburg (1961). By an indirect method Ginsburg & Cobbold (1960) have shown that beta receptors exist in the forearm. The present experiments are compatible with the hypothesis that stimulation of these receptors is responsible for the initial transient increase in flow seen during the intra-arterial infusion of adrenaline.

It has been suggested that the response of forearm vessels to adrenaline represents the summation of its vasodilator and vasoconstrictor actions (De la Lande & Whelan, 1959). If so, a drug which selectively blocks the dilator action would be expected to increase the constrictor response usually seen after the first minute of an adrenaline infusion. In none of the present experiments did the constrictor response to adrenaline appear to be augmented although more intense constriction was certainly possible. It is difficult to reconcile this finding with the observation that after drugs such as phenoxybenzamine or chlorpromazine the infusion of adrenaline gives rise to vasodilatation. We can offer no satisfactory explanation for these results which apparently lead to conflicting conclusions. The mechanism of the biphasic response to intra-arterial adrenaline therefore remains to be elucidated.

The present experiments demonstrate that a dose of dichloroisoprenaline which selectively blocks the dilator action of intra-arterial adrenaline also completely blocks the initial and the sustained dilator actions of intravenous adrenaline. Whelan (1952) has suggested that the sustained vasodilatation is due to a circulating vasodilator substance other than adrenaline ; the present experiments show that the action of this hypothetical substance is blocked by dichloroisoprenaline. Cobbold, Ginsburg & Paton (1960) have suggested that the hypothetical dilator substance may be isoprenaline, and Eakins & Lockett (1961) have shown that an isoprenaline-like substance appears in the blood during intravenous infusions of adrenaline in cats. In animals, dichloroisoprenaline blocks the activity of isoprenaline (Powell & Slater, 1958), and we have shown that dichloroisoprenaline blocks the vasodilator action of intra-arterial isoprenaline in the human forearm. Thus the present findings are consistent with the hypothesis that adrenaline administered intravenously leads to the appearance in the blood of isoprenaline, and that this substance is responsible for the sustained vasodilatation.

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