Brit. J. Pharmacol. (1965), **25**, 126–133.

THE EFFECT OF SYMPATHOMIMETIC AMINES ON FEMORAL ARTERIAL BLOOD FLOW IN THE CAT

BY

A. KOLIN AND G. ROSS

WITH THE TECHNICAL ASSISTANCE OF S. AUSTIN

From the Department of Biophysics and Nuclear Medicine, University of California, Los Angeles, California, U.S.A.

(*Received November* 3, 1964)

The effects of adrenaline and noradrenaline on blood flow in the limbs of man and animals have been extensively investigated (Folkow, 1955; Green & Kepchar, 1959; Barcroft, 1963). Local intra-arterial injections of small doses of adrenaline usually increase while larger doses usually decrease femoral blood flow. When given intravenously, adrenaline may produce a greater femoral flow increase than any intra-arterial dose (Celander, 1954). Local intra-arterial injection of all doses of noradrenaline decreases femoral blood flow but when given intravenously noradrenaline may increase flow. A considerable body of evidence indicates that the increased blood flow in the limbs produced by intravenous adrenaline and noradrenaline is due to vasodilatation mediated via a neural pathway (Gayet, Gayet & Quivy, 1933; Gruhzit, Freyburger & Moe, 1954; Bowman, 1959a). Few studies on the blood flow changes produced in the limbs by other sympathomimetic amines have been reported. The scanty information available has been derived mainly from dogs using methods which themselves produce variable and possibly significant disturbances of the vascular bed and which have usually involved arterial cannulation. The present paper reports the use of the gated sine-wave electromagnetic flowmeter (Kolin, 1960) to determine the effects of intra-arterial and intravenous injection of adrenaline, noradrenaline, isoprenaline, phenylephrine, metaraminol, methoxamine, mephentermine and methylamphetamine on the blood flow through the unopened femoral arteries of anaesthetized cats.

METHODS

Twenty-two adult cats of either sex weighing between 2 and 5 kg were used. Pregnant animals were excluded. Anaesthesia was induced by intraperitoneal pentobarbitone sodium (30 mg/kg) and maintained by supplementary intravenous doses as required. Mean aortic pressure was measured by means of a Sanborn physiological pressure transducer from a cannula introduced into a common carotid artery. Blood flow in the unopened femoral artery was measured by means of the gated sine-wave electromagnetic flowmeter (Kolin, 1960) using 1-mm or 1.5-mm-diameter probes (Cox, Arora & Kolin, 1963). The baseline was established by occluding the artery distal to the probe for a few seconds and adjusting the phase control until mechanical and electrical zeros coincided. All wounds were closed with Michel clips and the flow probe leads were securely positioned with adhesive tape so as to minimize any movement of the probe on the artery. When these precautions were taken, the baseline drift was negligible but nevertheless zero

checks were made at not less than hourly intervals. Calibration was performed at the end of each experiment by inserting the probe into a soft rubber tube connected to a Mariotte bottle containing 0.9% saline which was allowed to run through the lumen of the probe into a graduated measuring flask. Intravenous injections were given through a polyethylene catheter in an external jugular vein. In those experiments in which drugs were injected intra-arterially, flow probes were placed on both femoral arteries and one limb was skinned. A 25 Gauge needle with the haft removed was connected to a microsyringe by a small length of polyethylene tubing and inserted into the abdominal aorta just above its bifurcation. A preliminary experiment showed no differences in the patterns of responses obtained from injections made at this site or directly into the femoral arteries. In some animals, the hind-limb was denervated by sectioning the sciatic and femoral nerves as high in the limb as possible.

Drugs were made up in 0.9% saline and three or four drugs were administered in random order in each experiment. Each drug was the first to be injected in at least one animal. Ample time was allowed for recovery between injections. The drugs used were adrenaline hydrochloride (Parke-Davis), noradrenaline bitartrate (Levophed, Winthrop), phenylephrine hydrochloride (Neo-synephrine, Winthrop), metaraminol bitartrate (Aramine, Merck), methoxamine hydrochloride (Methedrine, Burroughs Wellcome), mephentermine sulphate (Wyamine sulphate, Wyeth) and isoprenaline hydrochloride (Isuprel, Winthrop). Concentrations are expressed in terms of salts.

RESULTS

Control values

The mean values and standard deviations of flow, pressure and resistance in the twenty-two cats were as follows: femoral arterial flow (ml./min)$=10.6\pm3.2$; mean aortic pressure (mm Hg)$=148\pm15.6$; femoral vascular resistance (mean aortic pressure divided by mean femoral arterial flow, in mm Hg/ml./min)$=15.3\pm4.8$.

Intra-arterial injections

In common with other workers (Dörner, 1954; Bowman, 1959a), it was frequently observed that control injections of more than 0.02 ml. of 0.9% saline produced a transient vasodilatation. Drug injections were, therefore, always given in volumes smaller than this. Vasodilatation was inferred when a flow increase occurred in the presence of an unchanged or decreased blood pressure while a decreased flow with an unchanged or increased blood pressure was attributed to vasoconstriction. However, it should be noted that only the largest doses of each drug produced any blood pressure alteration. On the basis of the responses obtained, the drugs could be divided into three groups. Table 1 shows these groups and also the range of doses studied.

Group A: *vasoconstrictors.* Phenylephrine, metaraminol, methoxamine and methylamphetamine produced only vasoconstriction in normal and skinned limbs. Noradrenaline usually behaved similarly but in one animal a small secondary dilatation followed the initial constriction. The descending order of vasoconstrictor potency was noradrenaline —phenylephrine—metaraminol—methoxamine—methylamphetamine.

Group B: *vasoconstrictors and vasodilators.* Adrenaline and mephentermine gave rise to variable effects in both normal and skinned limbs. In two of four animals adrenaline (0.01 to 2.0 μg) produced dilatation only, while larger doses produced dilatation followed by constriction (Table 1). In the other two animals even the smallest effective doses produced the latter type of response. Doses above 4 μg produced constriction followed by a secondary dilatation in all animals. Mephentermine also gave variable responses. In four cats, doses under 150 μg produced dilatation or dilatation followed by constriction.

TABLE 1

FEMORAL ARTERIAL FLOW CHANGES PRODUCED IN NORMAL LIMBS BY INTRA-ARTERIAL SYMPATHOMIMETIC AMINES

+ = Increase; +− = increase followed by decrease; − = decrease; −+ = decrease followed by increase

Group	Drug	Dose range (μg)	No. of cats	No. of cats showing flow responses			
				+	+−	−	−+
A: Vasoconstrictors	Noradrenaline	0·02– 4	7	0	0	6	1
	Phenylephrine	0·1 – 6	4	0	0	4	0
	Metaraminol	0·1 – 2	4	0	0	4	0
	Methoxamine	1 – 4	4	0	0	4	0
	Methylamphetamine	2 –200	5	0	0	5	0
B: Vasoconstrictors and vasodilators	Adrenaline	0·01– 2	4	2	2	0	0
		2 – 4	4	0	2	0	2
		4 – 8	4	0	0	0	4
	Mephentermine	1 –150	5	1	3	1	0
C: Vasodilator	Isoprenaline	0·04– 2	4	4	0	0	0

This secondary constriction became more prominent as the dose was increased. In one cat, all effective doses produced constriction only. Mephentermine differed from adrenaline in the following respects: the maximum dilatation was always of lesser magnitude and of shorter duration; vasodilatation alone (that is, not followed by constriction) was only rarely obtained; and, when vasoconstriction occurred, it was not followed by vasodilatation.

Group C: vasodilator. Isoprenaline produced only vasodilatation in all the animals studied.

In groups A and B, vasoconstriction was greater in the normal limb than in the skinned limb. In group B, doses of adrenaline which produced only dilatation in the skinned limb produced constriction followed by dilatation in the normal limb. In groups B and C, dilator responses were considerably smaller in denervated limbs presumably because the vessels were already near their state of maximum dilatation.

Intravenous injections

The doses used and the resistance changes produced by the groups cited above are shown in Table 2.

Group A. These drugs increased systemic arterial pressure and femoral arterial flow. The calculated vascular resistance at the peak of the pressor response usually ranged from

TABLE 2

FEMORAL VASCULAR RESISTANCE CHANGES PRODUCED IN NORMAL LIMBS BY INTRAVENOUS SYMPATHOMIMETIC AMINES

Changed resistances are expressed as percentages of preinjection values, and ranges are given

Drug	Dose range (μg/kg)	No. of cats	Femoral vascular resistance (%)	
			At pressure peak	At flow peak
Noradrenaline	0·02– 15	13	71– 97	40– 97
Phenylephrine	2 – 83	7	76–116	42–116
Metaraminol	4 – 40	4	93–110	55–110
Methoxamine	17 –100	6	86–102	86–102
Methylamphetamine	6 –160	5	83– 95	83– 95
Mephentermine	15 –240	5	75–104	75–104
Adrenaline	0·03– 3	8	80–107	49–107
Isoprenaline	0·02– 4	4	—	45–103

80 to 100% of the preinjection level although exceptionally values as low as 70% and as high as 116% were obtained (Table 2). After methoxamine and methylamphetamine, pressure and flow reached maximum levels at the same time, after which flow then returned to or below the original level while the pressure remained elevated and the calculated resistance increased.

Following the intravenous injection of noradrenaline, phenylephrine and metaraminol, however, a further reduction of vascular resistance to as low as 40% of the preinjection value frequently occurred during the period when the pressor response was declining (Fig. 1,*a* and *d*). Subsequently resistance increased to control or above control levels. The two-stage reduction of resistance failed to occur in some animals (Fig. 1,*c*), and the responses then resembled those induced by methoxamine and methylamphetamine.

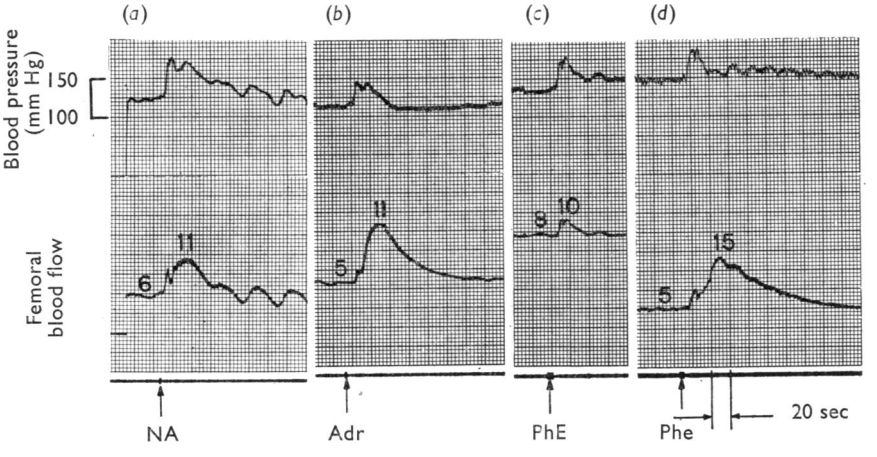

Fig. 1. Effects of intravenous injection (at arrows) of 3 μg of noradrenaline (NA, *a*), 5 μg of adrenaline (Adr, *b*) and 30 μg of phenylephrine (PhE, *c* and *d*) on femoral arterial flow in four different cats. The numbers above the flow records indicate ml./min. Note that in one animal phenylephrine produced only a 25% increase in flow (*c*) while, in another, the same dose produced a similar pressure rise but a 200% increase in flow occurring in two distinct stages (*d*).

Group B. In three animals mephentermine had a weak pressor effect which was accompanied by a small femoral flow increase and a reduction of less than 30% in the vascular resistance. In one of these animals, the flow then fell to below control values even though the pressure remained elevated. A fall in arterial pressure occurred in two animals in one of which femoral flow increased while in the other it decreased. Adrenaline also gave variable flow responses. In one animal, all effective doses produced vasoconstriction; in another the smallest doses produced vasoconstriction and larger doses vasodilatation. A primary reduction of resistance to as low as 40% of the control values occurred in six animals. In two of these, the resistance subsequently increased to above control levels.

Group C. Isoprenaline invariably produced a fall in arterial pressure accompanied by an initial reduction in flow. During this phase, the calculated resistance was unchanged or slightly increased. After 15 to 20 sec, the blood pressure began to recover and the flow then rose rapidly to above control levels indicating vasodilatation. In the dose range used, the maximum reduction in resistance observed was 55%.

In four experiments, vagotomy and atropinization were performed without significant alteration of the femoral flow responses to either the intra-arterial or intravenous injection of any of the sympathomimetic amines used.

DISCUSSION

Our finding that adrenaline, phenylephrine, metaraminol and methoxamine produce vasoconstriction and that isoprenaline produces vasodilatation in the hind-limb when injected into the femoral artery is in accord with the observations of others (Bowman, 1959a, b; Aviado, 1959; Johnson, Green & Lanier, 1953; Folkow, Frost & Uvnäs, 1948). In dogs, however, methylamphetamine has been reported to produce vasodilatation (Aviado, 1959) and vasodilatation followed by constriction (Frumin, Ngai & Papper, 1952), while mephentermine has been observed to produce femoral vasodilatation (Aviado, 1959) and vasoconstriction (Levy, Phillips & Brind, 1954). In cats, we find methylamphetamine to be a pure femoral vasoconstrictor while mephentermine may dilate or constrict depending partly on the dose used and partly on individual variation.

Our results confirm previous observations that intravenously administered adrenaline and noradrenaline dilate muscle vessels and indicate that this property is shared by other sympathomimetic amines.

The dilatation induced by group A drugs (Table 1) must be an indirect effect since these amines produce only vasoconstriction when given by local intra-arterial injection. Intravenous methoxamine, methylamphetamine and mephentermine produce only slight vasodilatation which is maximal at the peak of the arterial pressure rise. The reduction of vascular resistance rarely exceeds 15% and is probably a mechanical effect of the pressure increase similar to that described by Green, Lewis, Nickerson & Heller (1944). A similar dilatation accompanies the pressor response induced by the intravenous administration of adrenaline, noradrenaline, phenylephrine and metaraminol but, in contrast to the effects of methoxamine, methylamphetamine and mephentermine, a second phase of dilatation commonly occurs as the pressor response declines. During this latter period femoral vascular resistance may fall to as low as 40% of its initial value and the maximum reduction of resistance may occur as late as 20 sec after the peak of the pressure response (Fig. 1,*d*).

There have been many attempts to discover the mechanism of sympathomimetic vasodilatation. Cobbold & Vass (1953) found that intravenous noradrenaline failed to produce femoral vasodilatation when the rise in systemic arterial pressure was prevented by a compensating device. They therefore ascribed the reduction of femoral vascular resistance to a mere passive effect of the rise in systemic pressure. Bowman (1959a) and Gruhzit *et al.* (1954), on the other hand, found that a reflex dilatation occurred even when a pressure compensator was used. Our own results, showing a distinct temporal separation between the peak pressor effect and the maximum reduction of femoral vascular resistance, also exclude a purely passive mechanism. The hypothesis of Cobbold & Vass also fails to explain the dilatation produced by intravenous adrenaline. We have confirmed previous observations (Dörner, 1954; Bowman, 1959a) that when given by this route adrenaline may produce a greater dilatation than any local intra-arterial dose despite the fact that systemic arterial pressure often falls after the intravenous administration of this amine.

Many investigators (Tournade & Malmejac, 1933; Gayet *et al.*, 1933; Binet & Burstein, 1947; Taylor & Page, 1951; Gruhzit *et al.*, 1954; Bowman, 1959a) have used cross-

circulation and perfusion techniques to show that intravenous adrenaline and noradrenaline produce vasodilatation in skeletal muscle which is mediated via neural pathways. Taylor & Page (1951) suggested that the vasodilatation was due to central vasomotor inhibition. In their cross-circulation experiments, injection of 10 μg of adrenaline or noradrenaline into the dog's head circulation produced transient falls of blood pressure in the body which was isolated from the head except by the spinal cord. Tournade & Malmejac (1933) and Gayet *et al.* (1933) also attributed the femoral vasodilatation which they observed after the injection of 20 to 50 μg of adrenaline to a chemical action on the vasomotor centre. In our experiments, however, femoral vasodilatation was produced by doses as low as 0.1 μg and the effects were smaller and later when the drugs were given by intra-carotid arterial rather than by intravenous injection. Therefore, inhibition of vasomotor centres in the brain can play only a minor part in producing the vasodilatation we observed.

Marrazzi (1939) and Bülbring & Burn (1942) showed that adrenaline may inhibit ganglionic transmission but again this effect was produced only by doses greatly in excess of those required to produce femoral vasodilation.

Baroreceptor reflex activity may play some part in producing the vasodilatation but since the latter has been demonstrated after section of the vagi and carotid sinus nerves (Tournade & Malmejac, 1933) and after vagotomy and bilateral carotid occlusion (Jones & MacDowall, 1956) other factors must be involved.

Gruhzit *et al.* (1954) showed that adrenaline and noradrenaline produced a reflex vasodilatation in perfused leg preparations of dogs only after traversing the heart and that this reflex failed to occur after exclusion of the thoracic aorta from the circulation. They postulated that mechanoreceptors along the course of the thoracic aorta activated by the inotropic cardiac action of the amines were the source of this reflex. This hypothesis was supported by their finding that phenylephrine, which has much less inotropic activity than adrenaline (Goldberg, Cotten, Darby & Howell, 1953), failed to cause any significant reflex dilatation. In cats, however, intravenous phenylephrine produced substantial reduction of femoral vascular resistance (Fig. 1,*d*) while mephentermine and methylamphetamine which have pronounced inotropic actions (Goldberg *et al.*, 1953) failed to produce significant vasodilatation. Bowman (1959a) in cross-circulation experiments also failed to elicit reflex femoral vasodilatation with isoprenaline, which has a powerful inotropic action (Lands & Howard, 1952). Mohme-Lundholm (1953) has suggested that the dilatation produced in muscle by adrenaline is due to the release of lactic acid, and Celander (1954) suggests that the greater dilating effect of intravenous adrenaline is due to a general release of lactic acid from the entire skeletal musculature. However, in man, de la Lande & Whelan (1962) showed that intra-arterial infusion of sodium lactate or of lactic acid buffered to a *p*H as low as 3.3 had no effect on forearm blood flow although they produced increases in the lactic acid content of the venous effluent greatly in excess of those produced by adrenaline. Moreover, Glover & Shanks (1963) have shown that dichloroisoprenaline prevented both the initial and after-dilatations produced by adrenaline but did not prevent the rise in venous lactic acid concentration. The fact that intra-arterial mephentermine produces dilatation is also against Lundholm's hypothesis since this amine has little metabolic activity (Eckfeld, Abell & Seifter, 1954).

It must be concluded that none of the extant hypotheses accounts fully for the flow changes produced by intravenous sympathomimetic amines.

SUMMARY

1. Changes in the blood flow through the unopened femoral arteries of anaesthetized cats after the local intra-arterial and intravenous injection of adrenaline, noradrenaline, phenylephrine, metaraminol, methylamphetamine, mephentermine, methoxamine and isoprenaline have been determined by an electromagnetic method. The simultaneous recording of mean aortic pressure enabled changes in femoral vascular resistance to be calculated.

2. Local intra-arterial injection of isoprenaline reduced, while noradrenaline, phenylephrine, metaraminol, methoxamine and methylamphetamine increased, femoral vascular resistance. Adrenaline and mephentermine produced variable resistance changes.

3. Those agents which increased femoral vascular resistance when given intra-arterially frequently reduced resistance when given intravenously. This reduction accompanied the rise in systemic arterial pressure, but in many animals adrenaline, noradrenaline, phenylephrine and metaraminol frequently induced a further reduction in resistance as the pressor effect declined.

4. These observations are discussed in relation to the current theories of the mechanism of vasodilatation produced by sympathomimetic amines.

This work was supported by a grant (No. H 3092) from the U.S. Public Health Service and assisted by a grant from the Office of Naval Research.

REFERENCES

AVIADO, D. M. (1959). Cardiovascular effects of some commonly used pressor amines. *Anesthesiology*, **20**, 71–97.

BARCROFT, H. (1963). In *Handbook of Physiology*, ed. HAMILTON, W. F., Section 2, Vol. II, *Circulation*, p. 1353. Washington: American Physiological Society.

BINET, L. & BURSTEIN, M. (1947). Sur la vasodilatation périphérique d'origine adrénalique. *C.R. Soc. Biol. (Paris)*, **141**, 631–633.

BOWMAN, W. C. (1959a). A comparison between the vascular responses to adrenaline and noradrenaline in individual skeletal muscles of the cat. *J. Pharm. Pharmacol.*, **11**, 104–119.

BOWMAN, W. C. (1959b). The effect of isoprenaline on the blood flow through individual skeletal muscles in the anesthetized cat. *J. Pharm. Pharmacol.*, **11**, 143–149.

BÜLBRING, E. & BURN, J. H. (1942). An action of adrenaline on transmission in sympathetic ganglia, which may play a part in shock. *J. Physiol. (Lond.)*, **101**, 289–303.

CELANDER, O. (1954). The range of control exercised by the sympathico-adrenal system. *Acta physiol. scand.*, **32**, Suppl. 116.

COBBOLD, A. F. & VASS, C. C. N. (1953). Responses of muscle blood vessels to intra-arterially and intravenously administered noradrenaline. *J. Physiol. (Lond.)*, **120**, 105–114.

COX, P., ARORA, H. & KOLIN, A. (1963). Electromagnetic determination of carotid blood flow in the anesthetized rat. *IEEE, Tr. Biomed. Electr.*, BME-10, 171–173.

DE LA LANDE, I. S. & WHELAN, R. F. (1962). The role of lactic acid in the vasodilator action of adrenaline in the human limb. *J. Physiol. (Lond.)*, **162**, 151–154.

DÖRNER, J. (1954). Zur Frage der Gefassdilatation nach Adrenalin. *Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak.*, **221**, 288–298.

ECKFELD, D. K., ABELL, L. L. & SEIFTER, J. (1954). Pharmacological properties of mephentermine, a sympathomimetic amine. *J. Amer. pharm. Ass., Sci. Ed.*, **43**, 705–708.

FOLKOW, B. (1955). Nervous control of the blood vessels. *Physiol. Rev.*, **35**, 629–663.

FOLKOW, B., FROST, J. & UVNÄS, B. (1948). Action of adrenaline, noradrenaline and some other sympathomimetic drugs on the muscular, cutaneous and splanchnic vessels of the cat. *Acta physiol. scand.*, **15**, 412–420.

FRUMIN, M. J., NGAI, S. H. & PAPPER, E. M. (1952). The mechanism of action of desoxyephedrine on the vascular bed in the limb of the dog. *J. Lab. clin. Med.*, **40**, 131–135.

GAYET, R., GAYET, T. & QUIVY, D. (1933). Sur les réactions vaso-dilatatrices du muscle à l'adrénaline et leur processus déterminant. *C.R. Soc. Biol. (Paris)*, **114**, 619–624.

GLOVER, W. E. & SHANKS, R. G. (1963). Observations on the relation between the vasodilator and metabolic action of adrenaline in the human forearm. *J. Physiol. (Lond.)*, **167**, 280–287.

GOLDBERG, L. I., COTTEN, M. DE V., DARBY, T. D. & HOWELL, E. V. (1953). Comparative heart contractile force effects of equipressor doses of several sympathomimetic amines. *J. Pharmacol. exp. Ther.*, **108**, 177–185.

GREEN, H. D., LEWIS, R. N., NICKERSON, N. D. & HELLER, A. L. (1944). Blood flow, peripheral resistance and vascular tonus with observation on the relationship between blood flow and cutaneous temperature. *Amer. J. Physiol.*, **141**, 518–536.

GREEN, H. D. & KEPCHAR, S. H (1959). Control of peripheral resistance in major systemic vascular beds. *Physiol. Rev.*, **39**, 617–686.

GRUHZIT, C. C., FREYBURGER, W. A. & MOE, G. K. (1954). The nature of the reflex vasodilatation induced by epinephrine. *J. Pharmacol. exp. Ther.*, **112**, 138–150.

JOHNSON, H., GREEN, H. D. & LANIER, J. T. (1953). Comparison of adrenergic blocking action of ilidar (Ro 2–3248), tegitine (C–7337) and priscoline in the innervated saphenous arterial bed (skin exclusive of muscle) and femoral arterial bed (muscle exclusive of skin) of the anaesthetized dog. *J. Pharmacol. exp. Ther.*, **108**, 144–157.

JONES, J. J. & MCDOWALL, R. J. S. (1956). The action of adrenaline on the vasomotor mechanism. *J. Physiol. (Lond.)*, **134**, 8–9*P*.

KOLIN, A. (1960). In *Medical Physics*, ed. GLASSER, O., Vol. 3, p. 141. Chicago: Year Book Publishers.

LANDS, A. M. & HOWARD, J. W. (1952). A comparative study of the effects of l-arterenol, epinephrine and isopropylarterenol on the heart. *J. Pharmacol. exp. Ther.*, **106**, 65–75.

LEVY, M. N., PHILLIPS, F. A. & BRIND, S. H. (1954). The static limit of arterial blood pressure in the dog's hind limb. *Circ. Res.*, **2**, 509–515.

MARRAZZI, A. S. (1939). Electrical studies on the pharmacology of autonomic synapses. II. The action of a sympathomimetic drug (epinephrine) on sympathetic ganglia. *J. Pharmacol. exp. Ther.*, **65**, 395–404.

MOHME-LUNDHOLM, E. (1953). The mechanism of the relaxing effect of adrenaline on smooth muscle. *Acta physiol. scand.*, **29**, Suppl. 108.

TAYLOR, R. D. & PAGE, I. H. (1951). Peripheral vasomotor effects of adrenaline and noradrenaline acting upon the isolated perfused central nervous system. *Circulation*, **4**, 563–575.

TOURNADE, A. & MALMEJAC, J. (1933). Des effets vaso-dilatateurs qu'engendre, au niveau de la circulation périphérique (musculaire et rénale). L'action strictement centrale de l'adrénaline. *C.R. Soc. Biol. (Paris)*, **114**, 1247–1250.