RESEARCH PAPERS

THE EFFECT OF MUSCLE CONTRACTION ON THE BLOOD FLOW AND ON THE VASCULAR RESPONSES TO ADRENALINE, NORADRENALINE AND ISOPRENALINE IN INDIVIDUAL SKELETAL MUSCLES OF THE CAT

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The effect of muscle contraction on the rate of venous outflow and on the vascular responses to adrenaline, noradrenaline and isoprenaline was studied in individual muscles of the hind limbs of cats under chloralose anaesthesia. The maximum hyperaemia arising from contraction was produced when maximal twitches were elicited at frequencies which varied in different experiments from 1 to 8 per second, that is, frequencies well below those required to produce tetanus. During prolonged tetanic contractions the tension in the muscles soon fell to become constant at a lower level. This fall in tension reduced the mechanical impedance to flow and allowed vasodilatation to occur. In the tibialis anterior muscle the maximum hyperaemia was reached during the constant tension phase of the tetanus but in the soleus, the tension of which is maintained at a higher level, mechanical compression impeded the flow throughout the contraction. Both local vasodilator and vasoconstrictor actions of the sympathomimetic amines were reduced during the hyperaemia of muscle contraction. During contraction the muscle blood flow was markedly influenced by changes in mean arterial pressure. Thus isoprenaline, although a dilator substance in resting muscle, often passively reduced the blood flow through a contracting muscle, when injected intravenously, because of its hypotensive action. The reverse occurred with intravenously administered adrenaline and noradrenaline. The rise in blood pressure produced by these amines often forced more blood through the contracting muscle despite a weak local constrictor action.

THERE are a number of examples of published work in which conclusions concerning the effects of drugs on skeletal muscle contractions have been based on a preconceived knowledge of the vascular responses to the drugs in resting muscle. Particularly is this so in studies of the effects of sympathomimetic amines on the contractions of skeletal muscle. The effect of a drug on the blood flow through a contracting muscle may, however, be different from that in a resting muscle. For example, it has been shown that the local vasoconstrictor effect of adrenaline may be reduced[1–4], or abolished[5] during the hyperaemia accompanying a sustained tetanus. It was, therefore, considered of interest to study the effects of muscle contraction on the local vascular responses to other sympathomimetic amines as well as to adrenaline. Noradrenaline and isoprenaline were chosen for study because they are known to possess opposite actions on the blood flow through resting muscles[6–11]. In addition, a comparison was made of the effects of muscle contraction itself on the circulation through a slow (soleus) and a fast (tibialis anterior) contracting muscle.

The results emphasise the possible fallacies that may arise in drawing conclusions in the absence of a concomitant blood flow recording for during the vasodilatation accompanying muscle contraction, the local vascular actions of intravenously administered drugs may be completely masked by passive changes in flow resulting from alterations in mean arterial pressure.

METHODS

Cats were anaesthetised with chloralose only (80 mg./kg.) injected into the subcutaneous vein of the fore-limb. The preparation for the simultaneous recording of the contractions of and the venous outflow from the tibialis anterior, the gastrocnemius-plantaris or the soleus muscle was as previously described[9,12]. Shielded silver electrodes were placed on the sciatic nerve which was tightly ligated central to the electrodes. Contractions of the muscle were excited by rectangular pulses of 0·2 msec. duration and of twice the voltage necessary to evoke a maximal twitch. Blood pressure was recorded from a carotid artery, a blood pressure stabiliser[13,14] being connected when required. Drugs were injected intravenously through a cannula in a jugular vein or intra-arterially from a micro-syringe through a cannula in the cut central end of a branch of the femoral artery (for further details see Bowman[9]). The drugs used were (−)-adrenaline bitartrate, (−)-noradrenaline bitartrate and isoprenaline sulphate. The doses quoted refer to the quantity calculated as base. Solutions were prepared in 0·9 per cent w/v NaCl solution.

RESULTS

Preliminary experiments showed that stimulation of the sciatic nerve with the voltages and frequencies used in these experiments was without effect on the blood flow through muscles paralysed by decamethonium. It was concluded, therefore, that concomitant stimulation of sympathetic nerves in the sciatic trunk did not influence the results to be described.

The Effect of Contraction on Venous Outflow

A series of maximal twitches, either of the tibialis anterior or of the soleus, produced an increase in the venous outflow from the contracting muscle. This effect was evident with rates of stimulation as low as once every 10 seconds (Fig. 1). The rate of flow at first increased as the frequency of stimulation was increased and a linear relation existed between the two until the flow reached a maximum at frequencies which varied from 1 to 8 per second in different experiments, but which were usually in the range of 2 to 4 per second. The increase in flow began immediately the rate of stimulation was speeded and usually reached a steady level within 30 seconds. The return of the flow to a slower, steady rate on reducing the frequency was more gradual, often taking as long as 8 to 10 minutes.

A few instances were recorded where the vessels of the resting muscle temporarily acquired a state of rhythmical activity. That is, they began to dilate and constrict alternately. McDowall[15] also experimenting on

cats, recorded a similar response. The rhythm was abolished during the hyperaemia which ensued when the muscles were made to contract, but often recurred on stopping the stimulation. Figure 2 shows rhythm of this type in the muscle vessels which was not accompanied by corresponding changes in mean arterial pressure.

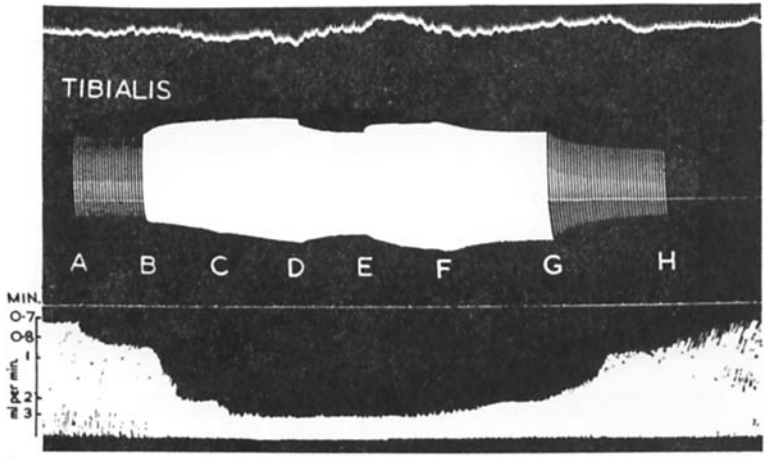

FIG. 1. Cat, 3·4 kg. The effect of a series of maximal twitches on the venous outflow from the tibialis anterior muscle. Upper record:—blood pressure; middle record:—indirectly excited maximal twitches; lower record:—venous outflow. Stimulation frequencies:—Between A and B and G and H, once every 10 sec.; between B and C and F and G, once per sec.; between C and D and E and F, twice per sec.; between D and E, four times per sec.

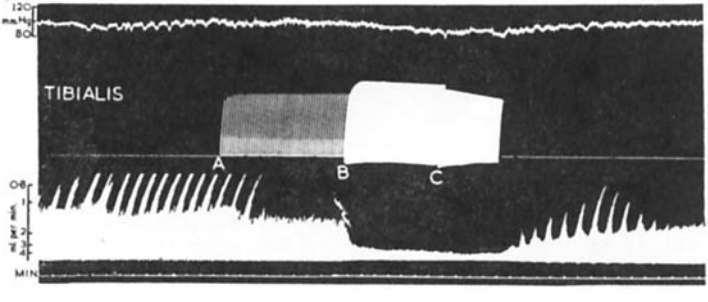

FIG. 2. Cat, 4 kg. Rhythmical activity of the blood vessels. Maximal twitches elicited, between A and B, once very 10 sec., between B and C, once per sec. and beginning at C, twice per sec.

Changes in venous outflow during tetanic contractions depended on the muscle under study, the duration of the tetanus and the tension produced. There was always an initial short-lasting increase in venous outflow as the muscle first contracted (Figs. 3B, 4, 5, 6). This was followed by a decrease in flow which lasted as long as the muscle tension

remained at its maximum. The extent of the decrease in flow depended on the magnitude of the tension produced (Fig. 3A). In these experiments the muscles were unable to maintain the initial tension which soon relaxed to a lower level where it was maintained for several minutes.

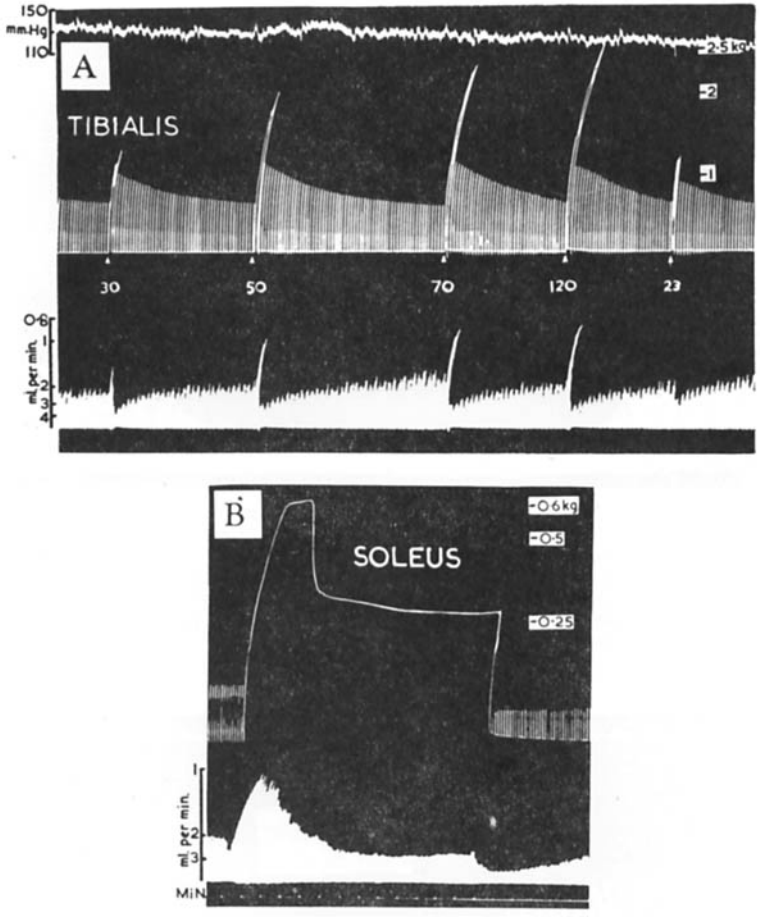

FIG. 3. The effect of tetanic contractions on venous outflow.
A.—cat, 3·6 kg. Maximal twitches elicited once every 10 sec. and tetani of 3 sec. duration interpolated. The figures below the middle record show the frequency of tetanic stimulation per sec.
B.—cat, 3·9 kg. Maximal tetanus of soleus muscle of 12½ min. duration elicited by stimulation at a frequency of 70 per sec.

As the tension fell, the blood flow increased until it reached a constant level at the same time as the tension reached its constant level (Figs. 3B to 6). The initial tension was maintained longer by the soleus at all rates of stimulation than it was by the tibialis anterior muscle. Maximum tetanic tension of the soleus muscle was produced by rates of stimulation of 50 to 75 per second and the initial tension was maintained for 30 to 90

seconds. Maximum tetanic tension of the tibialis anterior muscle was produced by rates of stimulation of 100 to 120 per second and the initial tension was maintained for 15 to 20 seconds. The tension of the tibialis anterior in a maximum tetanus usually became constant at $\frac{1}{4}$ to $\frac{1}{3}$ of the initial tension, whereas the tension of the soleus in a maximum tetanus became constant at $\frac{1}{2}$ to $\frac{2}{3}$ of the initial tension. The hyperaemia which

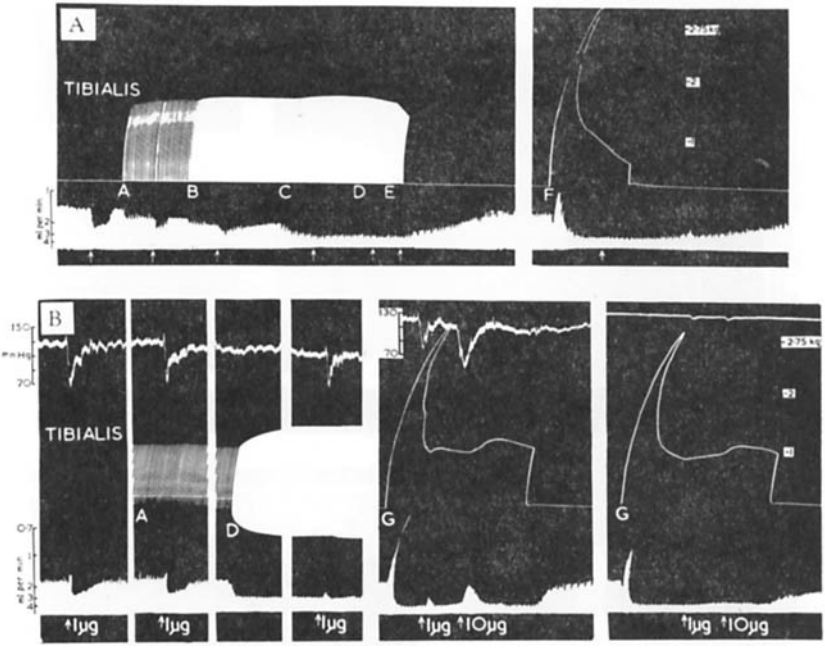

FIG. 4. The effect of muscle contraction on the local vasodilatation produced by isoprenaline.
A.—cat, 3·8 kg. At the arrows, 0·4 μg. isoprenaline administered intra-arterially. Stimulation frequencies:—between A and B, once every 10 sec.; between B and C, once every 5 sec.; between C and D, once every 2 sec.; between D and E, once per sec. Beginning at E, twice per sec. and at F, 50 per sec.
B.—cat, 4·2 kg. At the arrows isoprenaline administered intravenously. Stimulation frequencies:—between A and D, once every 10 sec.; beginning at D, once per sec. and at G, 120 per sec. The record on the extreme right shows the effect of isoprenaline after stabilising the blood pressure.

occurred during the constant tension phase of the tetanus was relatively greater in the tibialis anterior than in the soleus muscle. However, a further increase in flow from the soleus muscle occurred after the tetanus (Fig. 3B) whereas the hyperaemia reached its maximum during tetanus of the tibialis anterior and did not increase afterwards (Figs. 4A, 5, 6). The maximum rate of blood flow during a tetanus of the tibialis anterior, or immediately after a tetanus of the soleus muscle, did not exceed the greatest hyperaemia produced by a rapid series of single twitches, but was usually of equal value (Figs. 4A, 5, 6).

The Effect of Muscle Contraction on the Blood Flow Responses to Adrenaline, Noradrenaline and Isoprenaline

In the resting muscle, adrenaline and noradrenaline may produce an increase in flow, a decrease in flow or a compound response depending

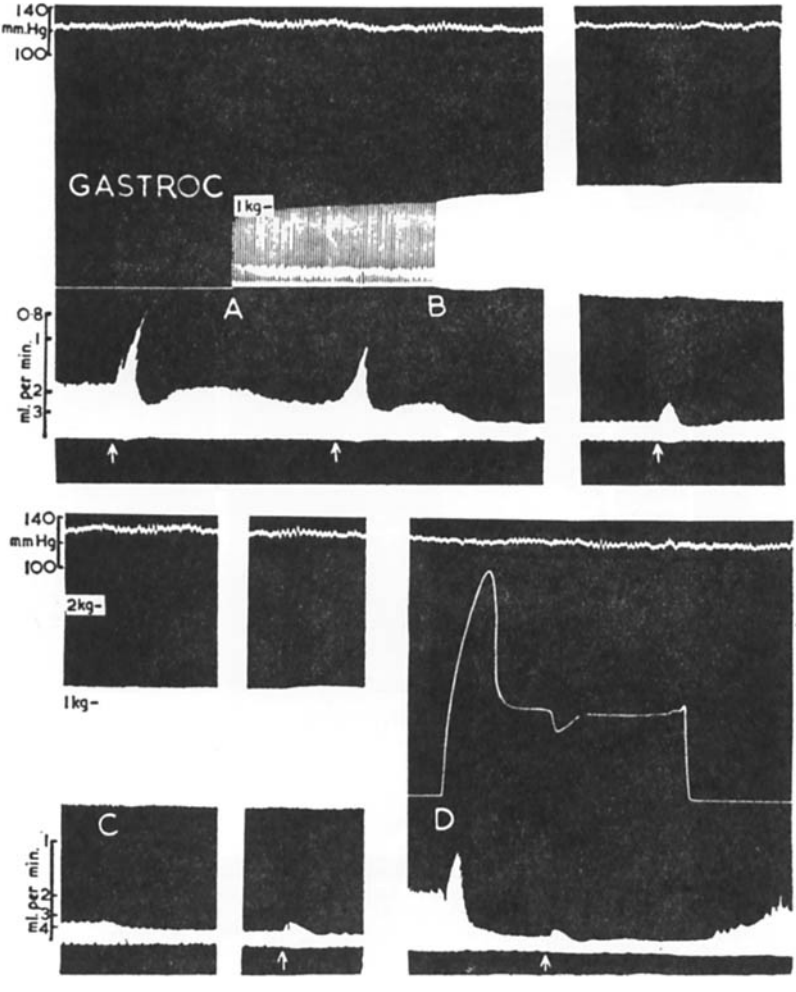

FIG. 5. Cat, 3·4 kg. The effect of muscle contraction on the local vasoconstriction produced by intra-arterially administered adrenaline. At the arrows, 3 μg. adrenaline injected intra-arterially. Stimulation frequencies:—between A and B, once every 10 sec.; between B and C, once every 3 sec.; beginning at C, once every 1·5 sec. and at D, 50 per sec.

on the dose administered, the route of injection, the general arterial blood pressure and the vasomotor tone in the muscle[9]. Isoprenaline always causes vasodilatation[11].

The increase per cent in the rate of blood flow produced by isoprenaline

or by dilator doses of adrenaline was reduced during the hyperaemia accompanying muscle contraction. The greater the rate of stimulation, the greater the hyperaemia and the greater the reduction in the effect of these amines. When the maximum vasodilatation arising from muscle contraction had been obtained it was impossible to produce any further dilatation with intra-arterially administered isoprenaline (0·002 to 0·4 μg.) or adrenaline (0·001 to 0·05 μg.), both amines then being completely without effect on the blood flow. Figure 4A illustrates the effect of increasing the frequency of stimulation on the dilator response to intra-arterially administered isoprenaline. When the muscle vessels were at, or approaching the stage of maximum dilatation arising from muscle

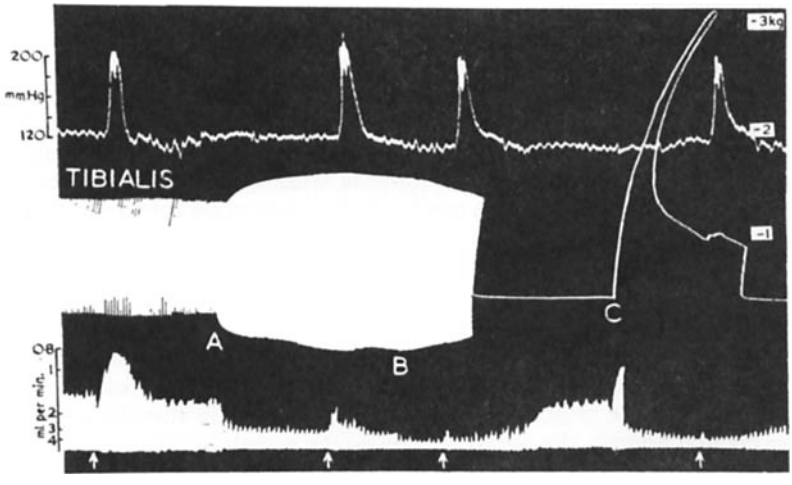

FIG. 6. Cat, 3·9 kg. The effect of muscle contraction on the local vasoconstriction produced by intravenously administered noradrenaline. At the arrows, 10 μg. noradrenaline injected intravenously. Stimulation frequencies:—initially once every 10 sec.; between A and B, once per sec.; beginning at B, twice per sec., and at C, 50 per sec.

contraction, the intravenous administration of isoprenaline (0·25 to 2·5 μg./kg.) usually caused a marked reduction in venous outflow from the muscle. The intravenous administration of dilator doses of adrenaline (0·25 to 2·5 μg./kg.), on the other hand, still caused some increase in the rate of blood flow. The use of the blood pressure stabiliser showed that both of these responses were passive effects caused by the changes in mean arterial pressure. Figure 4B illustrates the effects of intravenously administered isoprenaline.

Vasoconstriction produced by adrenaline or noradrenaline (1 to 3 μg. i.a. or 2·5 to 5 μg./kg. i.v.) was reduced during the hyperaemia of muscle contraction. The greater the rate of stimulation, the smaller the vasoconstriction became. Even when maximum dilatation arising from contraction had been produced, further increase in the frequency of stimulation caused a further reduction in the vasoconstrictor action of adrenaline

and noradrenaline. Figures 5 and 6 illustrate these effects with intra-arterially administered adrenaline and intravenously administered noradrenaline respectively. The intravenous administration of small doses of adrenaline and noradrenaline which caused a weak vasoconstriction in the resting muscles, frequently caused only an increase in blood flow during the hyperaemia of contraction. When, by means of the blood pressure stabiliser, the blood pressure was prevented from rising, the same doses were either without effect or again caused a weak vasoconstriction in the contracting muscles.

Discussion

It has long been established that muscle contraction is accompanied by vasodilatation[1,2,16 to 25], and the present experiments show that in the experimental animal anaesthetised with chloralose the maximum effect occurs at stimulation frequencies well below those required to produce tetanus. During tetanic contractions there is an initial sharp increase in venous outflow as the muscle contracts. No initial increase in flow occurred, however, in some earlier experiments in which the femoral artery flow was recorded and in common with others[2,26], it is concluded that this effect is simply due to mechanical compression forcing out blood from the muscle. Subsequent to the initial increase in venous outflow, a short period occurs during which the flow from the muscle is decreased. This is considered by many workers[2,16,17,21 to 28] to be due to the mechanical compression of the muscle vessels impeding the flow and the present results support this view, since the extent and duration of the decrease in flow proved to be dependent on the extent and duration of the initial high tension in the muscle. During prolonged tetanic stimulation in the experimental animal, the initial tension in the muscle soon falls, probably at least partly as a consequence of the reduced blood flow. It then becomes constant at a lower level. During the fall in tension, the venous outflow increases to a level 2 to 6 times that of the flow from the resting muscle. It appears, therefore, that vasodilatation is made possible by the fall in tension and the consequent reduction in mechanical compression. Kramer and Quensel[21] were of the opinion that 5 seconds was the longest duration of the mechanical impedance to flow. But, in the present experiments this impedance lasted as long as the initial tension was maintained, which in turn depended on the muscle under study and the frequency of stimulation. Since different muscles maintain the initial tension for different periods, vascular changes can accurately be related to tension changes, only when, as in the present experiments, the blood flow from individual muscles is recorded.

A voluntary muscular contraction is the algebraic sum of the contractions and relaxations of the large number of motor units, each of which is contracting irregularly, asynchronously and intermittently. In an experimental electrically produced tetanus, on the other hand, all the muscle fibres involved are in sustained synchronous contraction. Since the blood flow changes during a tetanus are influenced by the tension in the muscles, the results obtained during experimental electrically produced

tetani cannot be truly related to the changes which occur in voluntary muscular movements. Presumably, during voluntary contractions, there will be vasodilatation in those motor units which are relaxed and mechanical compression in those which are contracted. The overall changes in the rate of blood flow will not, therefore, be so marked as those seen in the experimental animal.

The results obtained with sympathomimetic amines emphasise the fact that it is impossible accurately to predict the effect of a drug on the blood flow through a contracting muscle, from a knowledge of its action in resting muscle. As might be expected, the effects of vasodilator doses of the drugs are relatively smaller when the vessels are already widely dilated due to contraction. The vasoconstrictor actions of adrenaline and noradrenaline are also reduced during muscle activity. This result with adrenaline confirms that of other workers[1 to 5].

During contraction the muscle blood flow is markedly influenced by changes in mean arterial pressure. Since both local dilator and constrictor actions of the drugs are reduced during muscle activity, the changes in blood flow after intravenous administration will be mainly a consequence of the effect on the general arterial blood pressure. Thus isoprenaline, although a dilator substance in resting muscles, may passively reduce the flow through contracting muscles because of the fall in blood pressure produced. The reverse is true with adrenaline and noradrenaline. The rise in blood pressure produced by these amines may force more blood through the contracting muscles because of the weakened local constrictor action.

References

1. Rein, *Klin. Wschr.*, 1930, **9**, 1485.
2. Bülbring and Burn, *J. Physiol.*, 1939, **95**, 203.
3. Rein and Schneider, *Z. Biol.*, 1931, **91**, 13.
4. Wakim and Essex, *Circulation*, 1952, **5**, 370.
5. Mertens, Rein and Valdecassas, *Pflüg. Arch. ges. Physiol.*, 1936, **237**, 454.
6. Folkow, Frost and Uvnäs, *Acta physiol. scand.*, 1948, **15**, 412.
7. Cobbold and Vass, *J. Physiol.*, 1953, **120**, 105.
8. Dörner, *Arch. exp. Path. Pharmak.*, 1954, **221**, 286.
9. Bowman, *J. Pharm. Pharmacol.*, 1959, **11**, 104.
10. Chen, Portman, Russell and Ensor, *J. Amer. pharm. Ass., Sci. Ed.*, 1951, **40**, 273.
11. Bowman, *J. Pharm. Pharmacol.*, 1959, **11**, 143.
12. Bowman and Zaimis, *J. Physiol.*, 1958, **144**, 92.
13. Krayer and Verney, *Arch. exp. Path. Pharmak.*, 1936, **180**, 75.
14. Ginzel and Kottegoda, *J. Physiol.*, 1954, **123**, 277.
15. McDowall, *ibid.*, 1950, **111**, 1.
16. Gaskell, *J. Anat. Lond.*, 1876–77, **11**, 360.
17. Gaskell, *ibid.*, 1876–77, **11**, 720.
18. Verzar, *J. Physiol.*, 1912, **44**, 243.
19. Keller, Loeser and Rein, *Z. Biol.*, 1930, **90**, 260.
20. Rein, Mertens and Schneider, *Pflüg. Arch. ges. Physiol.*, 1935, **236**, 636.
21. Kramer and Quensel, *ibid.*, 1937, **239**, 620.
22. Grant, *Clin. Sci.*, 1938, **3**, 157.
23. Barcroft and Millen, *J. Physiol.*, 1939, **97**, 17.
24. Barcroft and Dornhurst, *ibid.*, 1949, **109**, 402.
25. Hilton, *ibid.*, 1953, **120**, 230.
26. Anrep, Blalock and Samaan, *Proc. roy. Soc. B.*, 1933, **114**, 223.
27. Dolgin and Lehman, *Arbeitsphysiologie*, 1930, **2**, 248.
28. Anrep and von Saalfield, *J. Physiol.*, 1935, **85**, 375.