Brit. J. Pharmacol. (1949), 4, 373.

THE ACTION OF *NOR*ADRENALINE

BY

J. H. BURN AND D. E. HUTCHEON

From the Department of Pharmacology, University of Oxford

(Received October 12, 1949)

Several investigations of the properties of *nor*-adrenaline (arterenol) have been published since the original observations of Barger and Dale (1910). As a list of these is given in the recent paper by Luduena, Ananenko, Siegmund, and Miller (1949) no attempt will be made to summarize previous work here, though the observations of others will be discussed in describing our own experiments. These have been carried out in order to investigate more closely the vascular action of *nor*-adrenaline, especially its vasodilator properties, to study further the effect of denervation upon its action, and also the variation in the relative potency of adrenaline and *nor*adrenaline in different organs. We have had at our disposal synthetic *l*-adrenaline and also a sample of *dl-nor*adrenaline kindly given to us by Dr. M. L. Tainter.

The cardiovascular system

Although it has long been known that agents like ergotoxine which reverse the pressor action of adrenaline fail to reverse that of *nor*adrenaline (Barger and Dale, 1910), hitherto there has been no demonstration in an animal corresponding to the results of Goldenberg, Pines, Baldwin, Greene, and Roh (1948) in man. These authors found that when the two substances were infused intravenously, changes occurred which enabled them to calculate that adrenaline caused a decrease of the general peripheral resistance, whereas *nor*-adrenaline caused an increase. Barcroft and Konzett (1949) infused the two substances intravenously in man, and found that, whereas *nor*-adrenaline caused a rise in systolic and diastolic pressure with a slowing of the heart rate, adrenaline caused a smaller rise in the systolic pressure and a fall in the diastolic pressure with a quickening of the heart rate.

Action on blood pressure.—The depressor action of adrenaline described by Moore and Purinton (1900) can be most easily observed in the cat when the animal is anaesthetized with ether and the vagi are cut. Under these conditions the blood pressure is usually high. When adrenaline is infused into a vein at a slow rate, there is a fall of blood pressure. When 5 μg. *l*-adrenaline were infused during 2 min., the fall recorded in Fig. 1*a* was produced. When 10 μg. *dl-nor*-adrenaline were infused during 2 min., there was a slight rise of blood pressure. The effects were then repeated in (*c*) and (*d*).

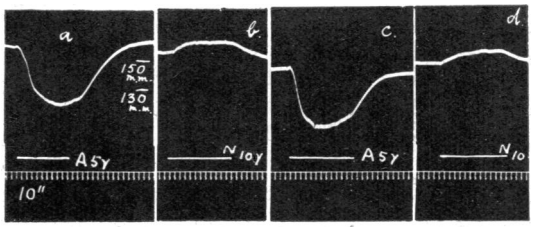

FIG. 1.—Cat blood pressure under ether anaesthesia after section of both vagi. (*a*) Shows depressor action of adrenaline when 5 μg. were slowly infused during 2 min. (*b*) Shows slight pressor action of *dl-nor*adrenaline when 10 μg. were similarly infused. (*c*) is a repetition of (*a*), and (*d*) is a repetition of (*b*).

The volume of one hindleg was also recorded in this experiment by using a plethysmograph, but except for an increase in volume pulse during adrenaline infusion no change was observed. Dale and Richards (1918) showed that if the hindleg was denervated by section of the sciatic nerve seven days previously the infusion of adrenaline caused a dilatation of the hindleg. By section of the nerves the reflex change in vascular tone resulting from a change in blood pressure was excluded. Three cats were therefore prepared by sciatic section and the final experiment in one of these is illustrated in Fig. 2. The infusion of 10 μg. *l*-adrenaline during 30 sec. produced a fall of blood pressure and dilatation of the denervated leg. The infusion of 20 μg. *dl-nor*adrenaline during 30 sec. produced a rise of blood pressure and constriction of the leg. The results, which were repeated several

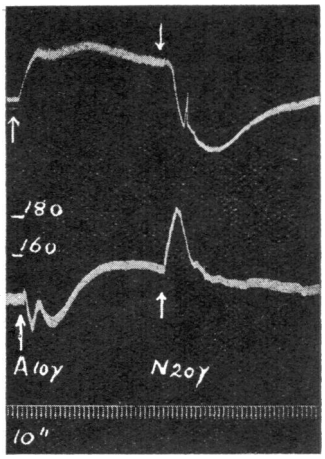

FIG. 2.—Cat under ether; vagi cut. L. sciatic nerve cut 8 days previously. Upper record is volume of the left hindleg and lower record is blood pressure. At the first arrow 10 μg. adrenaline was infused in 30 sec., and at the second arrow 20 μg. *dl-nor*adrenaline was infused in 30 sec. The first injection caused dilatation of the limb volume; the second caused constriction.

times in each of the cats, show that *l*-adrenaline caused peripheral dilatation but that *dl-nor*adrenaline caused peripheral constriction, the changes in the blood pressure being due to these effects.

Rabbit ear vessels.—In the rabbit ear vessels it is possible to study not only the vasoconstrictor action of adrenaline but also its vasodilator action which Gowdey (1948) showed was exerted during perfusion with Locke's solution containing 2-benzylimidazoline in a concentration 0.2×10^{-3}. We have therefore used the rabbit ear to compare the action of *nor*adrenaline with that of adrenaline in the presence of this reversing agent. The constrictor action of *nor*adrenaline on the vessels of the rabbit ear has been examined by Luduena *et al.* (1949) and also by Gaddum, Peart, and Vogt (1949). The former found that the ratio of equiactive amounts of *l-nor*adrenaline and *l*-adrenaline was 1.5–2.5; the latter found the ratio was 1.0–3.0. We made 21 comparisons and found the ratio was 1.0–4.0. All these findings agree in showing that as a rule *nor*adrenaline is a less potent constrictor than adrenaline for rabbit ear vessels, though the variation is from 25 to 100 per cent. In one experiment in which the dog hindleg was perfused with blood by a pump, we found that 4 μg. adrenaline and 8 μg. *dl-nor*adrenaline were equally active.

We found that perfusion of the rabbit ear with 2-benzylimidazoline converted the vasoconstrictor

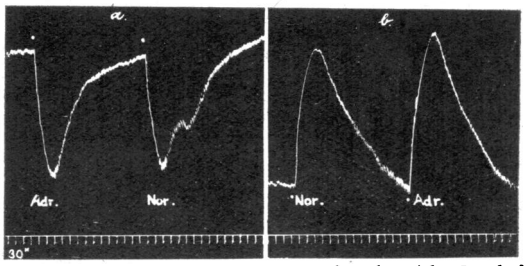

FIG. 3.—Rabbit ear vessels perfused with Locke's solution. Outflow recorded with Stephenson's recorder. (*a*) Shows equal constrictor effects of 0.04 μg. adrenaline and of 0.25 μg. *dl-nor*adrenaline. (*b*) Shows effects obtained during perfusion with Locke containing 0.2×10^{-3} benzylimidazoline. Equal dilator effects were exerted by 0.5 μg. *dl-nor*adrenaline and 0.15 μg. adrenaline.

action of *nor*adrenaline into a vasodilator action; this conversion is shown in Fig. 3, in which (*b*) shows that 0.16 μg. *l*-adrenaline caused a dilatation similar to that caused by 0.5 μg. *dl-nor*adrenaline. The vasodilator ratio of *l-nor*adrenaline to *l*-adrenaline was therefore about 1.5. The vasoconstrictor ratio in Fig. 3*a* was 3.0. The results of a series of observations are given in Table I. These indicated that the relative dilator action is similar to the relative constrictor action in the majority of ears; only in occasional ears like No. 5 in Table I is the dilator action of *nor*adrenaline very feeble. The conditions in the

TABLE I

COMPARISON OF DILATOR ACTION OF ADRENALINE WITH THAT OF *nor*ADRENALINE IN RABBIT EAR VESSELS DURING PERFUSION OF 2-BENZYLIMIDAZOLINE

Exp.	Equidilator doses		Ratio *l-nor*adrenaline/ *l*-adrenaline
	l-adrenaline μg.	*dl-nor*adrenaline μg.	
1	0.16	0.48	1.5
2	0.1	0.2	1.0
3	0.3	1.0	1.67
4	0.2	0.4	1.0
5	0.1	10.0	50.0
6	1.0	2.0	1.0

rabbit ear appear to be the opposite of the conditions in the cat, judged by the depressor action, seen after giving ergotoxine or ergotamine. In the majority of cats the depressor action of *nor*adrenaline is feeble or absent unless large doses are given (West, 1949), but in occasional cats it is just as great as that of adrenaline, as is shown in Fig. 4.

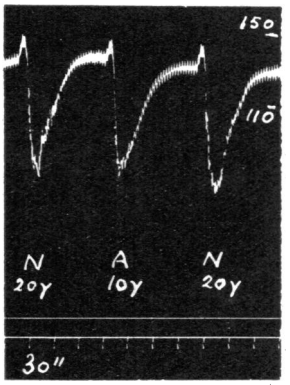

FIG. 4.—Cat, spinal preparation, eviscerated. Blood pressure record. Ergotoxine ethane sulphonate was injected in order to reverse action of adrenaline. 20 μg. *dl-nor*adrenaline was injected causing a depression similar to that caused by 10 μg. adrenaline. This result was exceptional.

Intestinal vessels.—Plethysmograph experiments were carried out on loops of the intestine of the cat under chloralose anaesthesia using the method described by Bülbring and Burn (1936). It was found that the injection of a small dose of *dl-nor*adrenaline caused dilatation of the intestinal loop just as did the injection of a similar dose of adrenaline, as shown in Fig. 5. *Nor*adrenaline caused some rise of blood pressure, though this passed off as the dilatation came on. However, to exclude the blood pressure rise as a cause of the dilatation, some experiments were done in which the blood pressure was kept constant by attaching the carotid cannula to a large vessel containing Ringer's solution at constant pressure. The same dilatation of the intestinal loop was observed when *nor*adrenaline was injected, although the blood pressure did not change.

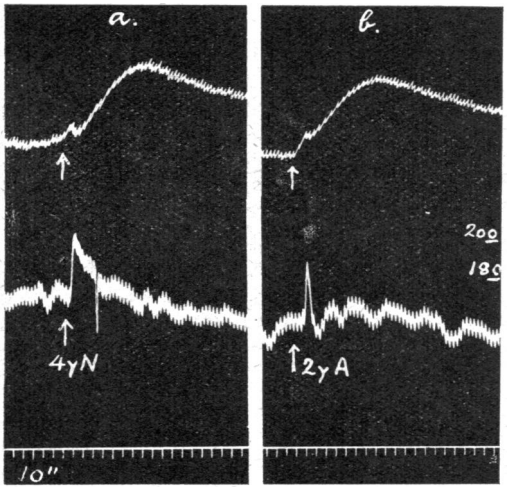

FIG. 5.—Cat, chloralose. Upper record shows volume of intestinal loop; lower record is blood pressure; (*a*) shows dilatation of intestinal vessels when 4 μg. *dl-nor*adrenaline was injected; (*b*) shows similar dilatation when 2 μg. adrenaline was injected.

Action on the heart.—Since *nor*adrenaline lacks the vasodilator action of adrenaline in the muscle vessels, it was of interest to discover the effect of *nor*adrenaline on the coronary vessels. Observations were first made on the coronary flow, the rate, and the amplitude of the cat heart perfused with Ringer-Locke by Langendorff's method. Fig. 6 shows the changes in coronary flow with Stephenson's recorder (1948). The effects of the two substances in the doses given were almost identical on the amplitude and coronary flow, though *dl-nor*adrenaline had less effect on the rate, increasing it by 54 beats per min., while adrenaline

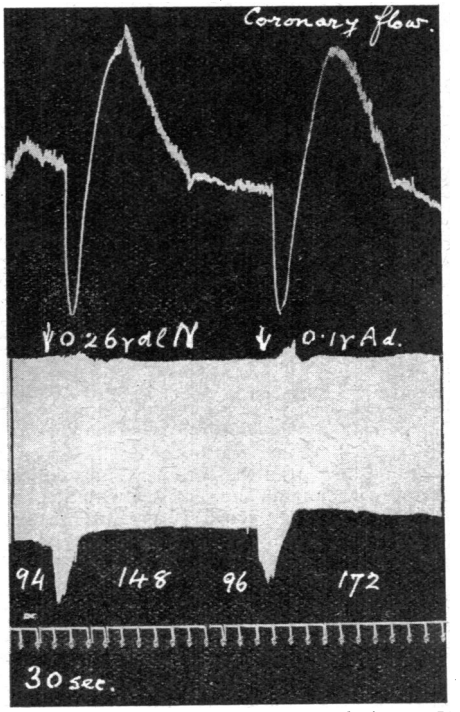

FIG. 6.—Cat heart, Langendorff perfusion. Upper record was coronary flow by Stephenson's method; middle record was amplitude of contractions; heart rate given in figures below. The effects of injecting into the cannula 0.26 μg. *dl-nor*adrenaline and of 0.1 μg. adrenaline were similar on the coronary flow and amplitude. *Nor*adrenaline had a smaller action on the heart rate.

increased it by 76 beats per min. When half these doses were used, the effect on the rate was the same for both, and, as there was less increase in force of contraction, the initial diminution of coronary flow was absent. Marsh, Pelletier, and Ross (1948) also observed that arterenol had the same effect on the rate, contraction, and coronary flow as *dl*-epinephrine in the perfused rabbit and cat heart. In the heart-lung preparation of the dog, observations were very kindly made for us by our colleagues Drs. J. M. Walker and E. M. Lourie in the course of another investigation. Fig. 7 shows the similar effect of 2 μg. *l*-adrenaline

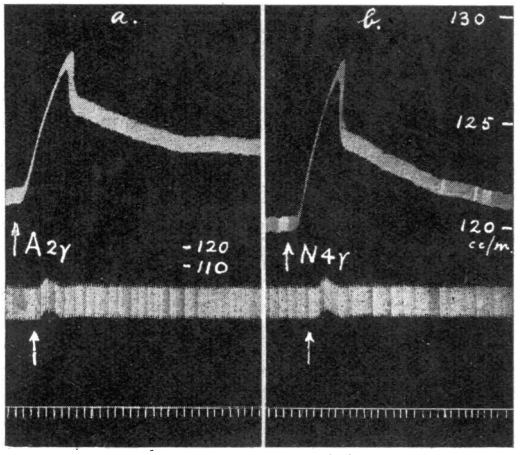

FIG. 7.—Heart-lung preparation of dog. Upper record is the outflow from the coronary sinus collected by a Morawitz cannula and recorded with Stephenson's recorder. Lower record is pressure in brachiocephalic artery. In (*a*) the dilator effect of injecting 2 μg. adrenaline into the s. vena cava is shown, and in (*b*) the similar effect of 4 μg. *dl-nor*adrenaline. Note that the effect of adrenaline was more prolonged. (Experiment of J. M. Walker and E. M. Lourie.)

and of 4 μg. *dl-nor*adrenaline on the outflow from the coronary sinus collected by a Morawitz cannula and recorded by Stephenson's method (1949). The record shows that the effect of adrenaline was more prolonged; this was repeatedly observed. Folkow, Frost, and Uvnäs (1949) have also found that *nor*adrenaline exerts a dilator action on the coronary vessels of the dog.

Renal vessels.—Because renal ischaemia causes hypertension, we examined the effect of *nor*-adrenaline on renal blood flow to see if it caused a greater diminution than adrenaline. The action was studied in cats under chloralose anaesthesia in which the adrenal glands were excluded from the circulation and to which an injection of heparin had been given. A cannula tied into one renal vein conducted the blood through a rubber tube back into the external jugular vein, and the rate of flow through the tube was measured by collecting the blood by a T-piece in the tube during a period of 10 or 15 sec. In one experiment the blood pressure was maintained constant by connecting the femoral artery to a reservoir of blood under an air pressure equal to that in the blood. The results, shown in Table II, indicated that *nor*-adrenaline has not a greater constrictor action on the renal vessels than adrenaline, but that, if anything, the constrictor action of *nor*adrenaline is less. This result is in agreement with that of Gaddum, Peart, and Vogt (1949) on the perfused renal vessels of the rabbit. They found that *l-nor*-adrenaline was equal in constrictor action to *l*-adrenaline when given in 2.5 times as great a dose.

TABLE II

COMPARISON OF CONSTRICTOR ACTION OF ADRENALINE AND *nor*ADRENALINE IN RENAL VESSELS

	Venous outflow c.c./sec.		Fall in flow c.c./sec.
	Before	After	
16 μg. *dl-nor*adrenaline ...	0.47	0.33	0.14
8 μg. *l*-adrenaline ...	0.6	0.38	0.22
4 μg. *l*-adrenaline ...	0.72	0.59	0.13
8 μg. *dl-nor*adrenaline ...	0.92	0.82	0.10
4 μg. *l*-adrenaline ...	1.02	0.88	0.14

In another experiment the renal blood outflow was measured during the continuous intravenous infusion first of adrenaline and then of *nor*-adrenaline; in this experiment a compensating reservoir to maintain a constant blood pressure was not used. The rate of infusion was chosen so that the renal flow could be measured at the same blood pressure with the two substances. The results are given in Table III, which shows that the rates of renal flow for a given blood pressure were the same whichever substance was infused.

Summary of results.—The results on the cardiovascular system show that the one important difference between adrenaline and *nor*adrenaline is in the action on the vessels of skeletal muscle, where the former is dilator but the latter constrictor. On the intestinal vessels of the cat, on the coronary vessels of the cat and the dog, on the vessels of the rabbit ear during perfusion with 2-benzylimidazoline, *nor*adrenaline is dilator when adrenaline is dilator. No evidence was found that

TABLE III

RENAL BLOOD FLOW

Substance	Rate of infusion μg./min.	Duration of infusion min.	Height of blood pressure mm.	Renal flow c.c./min.
l-adrenaline ...	3.4	10	150	0.5
,, ...	3.4		140	0.53
,, ...	3.4		130	0.47
*dl-nor*adrenaline	15.4	11	136	0.47
,,	15.4		128	0.47
,,	15.4		124	0.48
l-adrenaline ...	7.5	6	136	0.45
,, ...	7.5		120	0.47

*nor*adrenaline has a greater constrictor action than adrenaline on the renal vessels.

The effect of denervation

The nictitating membrane.—The normally innervated nictitating membrane of the cat is much less affected by *nor*adrenaline than by adrenaline, but after removal of the superior cervical ganglion and postganglionic degeneration the membrane becomes equally sensitive to both substances. Thus nerve degeneration brings about a small increase in sensitivity to adrenaline, but a large increase to *nor*adrenaline (Bülbring and Burn, 1949).

The pupil dilator muscle.—We have examined the changes produced by degeneration of the sympathetic fibres to the iris. About eight days after extirpation of the ganglion on one side, the cat was anaesthetized with urethane, and the pupils were examined under a bright light during injection of adrenaline and of *nor*adrenaline. The minimum amounts of each substance which caused a dilatation of (*a*) the denervated and (*b*) the normal pupil were determined, and results in three cats are given in Table IV, which shows

TABLE IV

RELATION OF ACTION ON NORMAL AND DENERVATED PUPIL

Cat	Minimal dilating dose	Normal μg.	Denervated μg.	Ratio
1	*l*-adrenaline	2	1	2
	*l-nor*adrenaline	30	1	30
2	*l*-adrenaline	2	0.1	20
	*l-nor*adrenaline	25	0.4	62
3	*l*-adrenaline	7.5	0.5	15
	*l-nor*adrenaline	100	2.0	50

that the dose calculated in terms of *l-nor*adrenaline just sufficient to dilate the normal pupil was found to be 12–15 times greater than for *l*-adrenaline. Denervation increased the sensitivity to *nor*-adrenaline much more than to adrenaline, and in one cat the denervated pupil was equally sensitive to both. The behaviour of the pupil was thus similar to that of the nictitating membrane. It was always observed that injections of *nor*-adrenaline, too small to cause dilatation of the normal pupil, caused constriction of the pupil.

Greer, Pinkston, Baxter, and Brannon (1938) have also investigated the action of adrenaline and *nor*adrenaline on the normal and on the denervated pupil. They wished to compare the effect of *nor*adrenaline with that of hepatic nerve stimulation, and they drew no conclusions about the modification of the pupil response by denervation. Their photographs, however, agree with our findings.

Action in other organs

The spleen.—The relative activity of adrenaline and *nor*adrenaline in causing contraction of the cat spleen perfused *in situ* has been stated by Gaddum, Peart, and Vogt (1949) to be 0.5–1.0, this being the ratio of the dose of *l-nor*adrenaline to *l*-adrenaline. Our results in spinal cats using a spleen plethysmograph gave a wider range. Thus

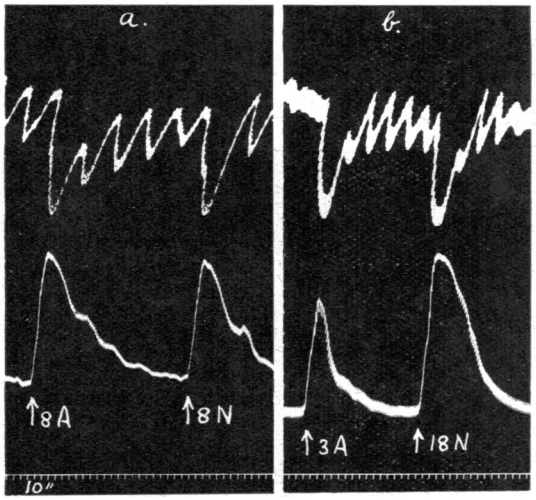

FIG. 8.—Cat, spinal preparation. Upper record spleen volume, lower record blood pressure. The figure illustrates the decline in sensitivity to *nor*adrenaline, and the increase in sensitivity to adrenaline. Early in the experiment 8 μg. adrenaline was equal in action to 8 μg. *dl-nor*adrenaline. Late in the experiment 3 μg. adrenaline was equal to 18 μg. *dl-nor*adrenaline.

in one cat *l-nor*adrenaline was found to be twice as active as *l*-adrenaline, and in another only one-fifth as active. Even in the same cat the relative potency changed in the course of the experiment, *dl-nor*adrenaline decreasing from equivalence to *l*-adrenaline to one-sixth the potency. The initial and final observations in this experiment are shown in Fig. 8. While the sensitivity to *nor*-adrenaline greatly declined, that to adrenaline slightly increased. The various results in different experiments are given in Table V.

TABLE V

CONSTRICTOR EFFECTS IN SPLEEN

Cat	Equivalent doses in μg.		Ratio *l-nor*adr./*l*-adren.
	*dl-nor*adr.	*l*-adren.	
1	20	2	5.0
2	8	3	1.3
3	3	1	1.5
4(*a*)	8	8	0.5
4(*b*)	18	6	1.5
4(*c*)	18	3	3.0
5	80	10	4.0
6	10	1.25	4.0
7	10	1.8	2.7
			Range 0.5–5.0

Bronchioles.—At least two comparisons on the bronchioles have already been made. Tainter, Pedden, and James (1934) found that *dl-nor*-adrenaline had one-seventh of the activity of adrenaline in perfused guinea-pig lungs in relaxing

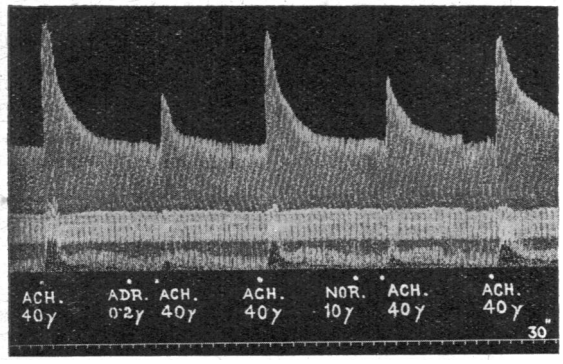

FIG. 9.—Bronchiolar constriction recorded by method of Konzett and Roessler in guinea-pig anaesthetized with urethane. Figure shows constrictor action of 40 μg. acetylcholine, and also the diminished action when 0.2 μg. adrenaline was injected beforehand. The effect of this amount of adrenaline is shown to be slightly greater than the effect of 10 μg. *nor*adrenaline. (Experiment of N. K. Dutta.)

TABLE VI

AMOUNTS WHICH INHIBIT BRONCHOCONSTRICTION EQUALLY

Exp.	Constrictor agent	*l*-adren. μg.	*dl-nor*adren. μg.	Ratio $\frac{l\text{-}nor.}{l\text{-}adr.}$
1	Histamine	10.0	>40	>2
2	,,	0.5	>20	>20
3	,,	0.2	>80	>200
4	,,	5.0	120	12
5	Acetylcholine	0.2	15	37.5

the contraction caused by histamine or pilocarpine. Luduena, Ananenko, Siegmund, and Miller (1949) found a smaller activity—namely, that *l-nor*-adrenaline had one-seventeenth the activity of adrenaline. Our thanks are due to our colleague Dr. N. K. Dutta for making comparisons in anaesthetized guinea-pigs by the method of Konzett and Roessler (1940). The result in one experiment is shown in Fig. 9 and the different results are given in Table VI.

In these experiments there is again evidence of a very variable relationship between adrenaline and *nor*adrenaline. In all experiments *nor*-adrenaline was weaker than adrenaline as a bronchodilator, but it was difficult to quote a single figure as expressing the mean. Some unknown factor appeared to modify the relative activity.

Inhibition of cat intestine.—Many workers have used the inhibitory action of *nor*adrenaline on isolated loops of rabbit intestine as a means of estimation. The inhibition of the movements of the cat intestine *in situ* by *nor*adrenaline was observed by Greer *et al.* (1938). They attached considerable importance to it because they felt that it rendered untenable the view that hepatic sympathin or sympathin E was purely motor. We have obtained similar results to those of Greer and his colleagues, an example being given in Fig. 10, in which 5 μg. *dl-nor*adrenaline produced a slightly shorter inhibition of the duodenal contractions than 1.25 μg. *l*-adrenaline.

Effect in skeletal muscle.—Adrenaline has an action in skeletal muscle which was demonstrated by Bülbring and Burn (1942). If the sciatic nerve of a cat (anaesthetized with chloralose) is stimulated by maximal single shocks at rates up to 15 per min., the tension developed by each twitch of the gastrocnemius can be recorded on the drum. When a dose of neostigmine, too small by itself to modify the tension, is first injected a following injection of adrenaline causes an increase in tension. An example of this action is shown in

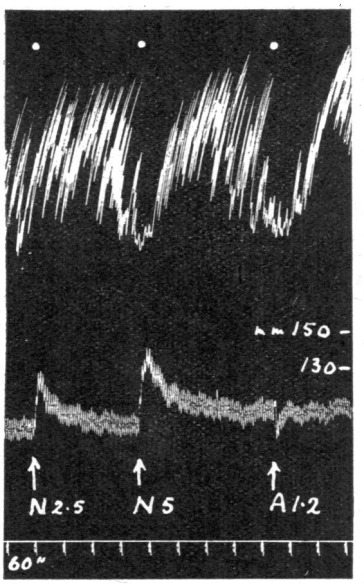

FIG. 10.—Cat, chloralose. Upper record of volume of balloon in the duodenum. Lower record of blood pressure. At N 2.5, 2.5 μg. *dl-nor*adrenaline; at N 5, 5.0 μg. *dl-nor*adrenaline; at A 1.2, 1.25 μg. adrenaline was injected intravenously. Note that N 5 produced slightly shorter inhibition than A 1.2.

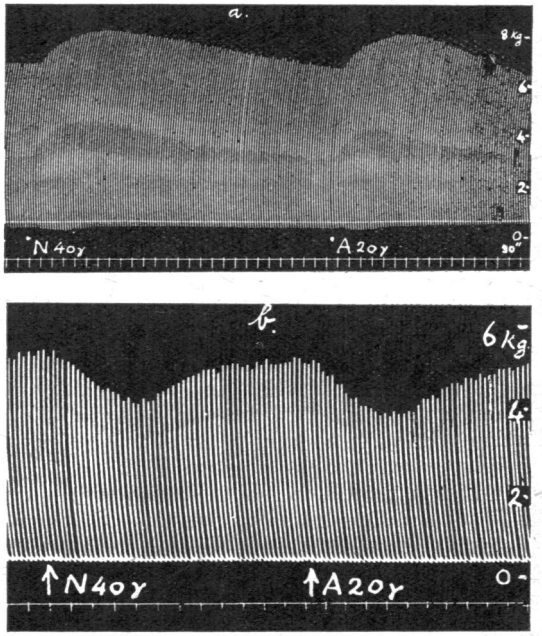

FIG. 11.—Cat, chloralose. Record of tension in gastrocnemius muscle in response to maximal single shocks applied to the sciatic nerve. (*a*) Shows the increase of tension produced by injecting first 40 μg. *dl-nor*adrenaline, and later 20 μg. adrenaline into the iliac artery. These injections were made 30 min. after the injection of 20 μg. neostigmine. (*b*) Shows a record in another cat in which the same injections caused a decrease in tension. These injections were made shortly after the injection of 30 μg. neostigmine. *Nor*adrenaline and adrenaline produce the same effect on the muscle tension.

Fig. 11*a* in which an identical effect exerted by *nor*adrenaline is also seen. When larger amounts of neostigmine are given, the injection of adrenaline may have the opposite effect, causing a decline in the tension. In these circumstances, too, *nor*adrenaline has the same action (Fig. 11*b*).

DISCUSSION

Adrenaline causes vasodilatation in two conditions; first in the cat under ether when the blood pressure is high because the vagi have been cut, and second in the cat to which ergotoxine or some other reversing agent has been given. There has always been discussion whether these two conditions are essentially the same. Our observations appear to indicate that they are not, because the observations show that *nor*adrenaline does not cause vasodilatation in the cat under ether, whereas it causes dilatation in the rabbit ear vessels in the presence of a reversing agent exactly as does adrenaline.

The vascular action of *nor*adrenaline thus differs from that of adrenaline because it does not dilate the vessels of the denervated hindleg of the cat, but rather it constricts them. The difference is probably confined to the muscle vessels. The action of *nor*adrenaline is similar to that of adrenaline (in similar doses) in dilating (*a*) the coronary vessels of the cat and the dog, (*b*) the intestinal vessels of the cat, and (*c*) the vessels of the rabbit ear in the presence of a reversing agent.

Denervation, in some tissues at least, produces a greater change in the reaction to *nor*adrenaline than to adrenaline. Bülbring and Burn (1949) demonstrated that this was true for the nictitating membrane, and used the observation to estimate the relative amounts of adrenaline and *nor*adrenaline present in a mixture. Our results show that the same change occurs in the reaction of the pupil. Only when large amounts of *nor*adrenaline are injected does the normal pupil dilate; but the denervated pupil is about equally sensitive to *nor*adrenaline and to adrenaline.

These observations prompt the suggestion that in some tissues the presence of the sympathetic nerve supply protects the end-organ against the action of *nor*adrenaline in the blood stream, though it

does not similarly protect the end-organ against adrenaline. If *nor*adrenaline is the chemical transmitter of the nervous impulse, such a protection might be useful from a teleological standpoint, as it would enable the nerve to have sole control of the end-organ except for the emergency when adrenaline was liberated.

The great increase in sensitivity to *nor*adrenaline after denervation may explain West's observation (1947) that pieces of intestine or uterus stored in the refrigerator for periods up to five days lose their sensitivity to adrenaline but do not lose it to *nor*adrenaline. Perhaps two processes go on side by side: a general failure of the tissue metabolism measured by the loss of sensitivity to adrenaline; a failure of the mechanism of innervation leading to a denervation and therefore an increase in sensitivity to *nor*adrenaline.

If such a protection is afforded by innervation against the effect of *nor*adrenaline, it evidently plays little part in the blood vessels, the heart, the spleen, and the intestines, though this is a problem for further investigation. Certainly the spleen may become increasingly insensitive to *nor*adrenaline in the course of a few hours in spite of the opposite change taking place in the reaction to adrenaline.

SUMMARY

1. An important difference between the vascular action of *nor*adrenaline and that of adrenaline is that, whereas the latter causes dilatation of the vessels of the denervated hindlimb of the cat, the former causes constriction. This difference is in the muscle vessels.

2. *Nor*adrenaline like adrenaline dilates the coronary vessels of the cat and dog and in small doses also the intestinal vessels. In the vessels of the rabbit ear, the constrictor action of *nor*adrenaline is just as easily converted to a dilator action by 2-benzylimidazoline as is that of adrenaline.

3. Denervation increases the action of *nor*adrenaline on the nictitating membrane and on the pupil much more than it increases that of adrenaline. We suggest that some mechanism exists to protect the nictitating membrane, the pupil, and probably other organs from *nor*adrenaline in the blood; this protection is less effective against adrenaline. When the nerves degenerate the protection disappears.

4. *Nor*adrenaline causes contraction of the spleen *in situ*. During the course of an experiment the spleen becomes less sensitive to *nor*adrenaline though it increases slightly in sensitiveness to adrenaline.

5. *Nor*adrenaline has a smaller constrictor action on renal blood flow than adrenaline.

6. *Nor*adrenaline inhibits intestinal movements recorded by a balloon in the duodenum. Its inhibitory action appears to be about half that of adrenaline, though the relation probably varies.

7. *Nor*adrenaline has the same effect as adrenaline on skeletal muscle previously treated with neostigmine, no matter whether the effect of adrenaline is to augment or to diminish the tension developed when shocks are applied to the sciatic nerve.

8. *Nor*adrenaline has much less effect than adrenaline in dilating the bronchioles, but the quantitative relation varies considerably.

We wish to thank Dr. N. K. Dutta for carrying out the experiments on the bronchioles and Mr. St. John Ives for doing many of the experiments on the rabbit ear. The work was done during the tenure by one of us (D.E.H.) of a Medical Research Fellowship awarded by the National Research Council of Canada.

REFERENCES

Barcroft, H., and Konzett, A. (1949). *Lancet*, **1**, 147.
Barger, G., and Dale, H. H. (1910). *J. Physiol.*, **41**, 19.
Bülbring, E., and Burn, J. H. (1936). *J. Physiol.*, **87**, 254.
Bülbring, E., and Burn, J. H. (1942). *J. Physiol.*, **101**, 224.
Bülbring, E., and Burn, J. H. (1949). *Brit. J. Pharmacol.*, **4**, 202.
Dale, H. H., and Richards, A. N. (1918). *J. Physiol.*, **52**, 110.
Folkow, B., Frost, H., and Uvnäs, B. (1949). *Acta physiol. scand.*, **17**, 201.
Gaddum, J. H., Peart, W. S., and Vogt, M. (1949). *J. Physiol.*, **108**, 467.
Goldenberg, M., Pines, K. L., Baldwin, E. de F., Greene, D. G., and Roh, C. E. (1948). *Amer. J. Med.*, **5**, 792.
Gowdey, C. (1948). *Brit. J. Pharmacol.*, **3**, 254.
Greer, C. M., Pinkston, J. D., Baxter, J. H., jun., and Brannon, E. S. (1938). *J. Pharmacol.*, **62**, 189.
Konzett, H., and Roessler, R. (1940). *Arch. exp. Path. Pharmak.*, **195**, 71.
Luduena, F. P., Ananenko, E., Siegmund, O. H., and Miller, L. C. (1949). *J. Pharmacol.*, **95**, 155.
Marsh, D. F., Pelletier, M. H., and Ross, C. A. (1948). *J. Pharmacol.*, **92**, 108.
Moore, B., and Purinton, C. O. (1900). *Pflüg. Arch.*, **81**, 483.
Stephenson, R. P. (1948). *J. Physiol.*, **107**, 162.
Stephenson, R. P. (1949). *J. Physiol.*, **108**, 102.
Tainter, M. L., Pedden, J. R., and James, M. (1934). *J. Pharmacol.*, **51**, 371.
West, G. B. (1947). *J. Physiol.*, **106**, 418.
West, G. B. (1949). *Brit. J. Pharmacol.*, **4**, 63.