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THE MECHANISM OF ADRENALINE-INDUCED INHIBITION OF SYMPATHETIC PREGANGLIONIC ACTIVITY

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When the blood pressure is raised the efferent discharge in many sympathetic nerve fibres is reduced and may disappear. This has been inferred from experiments on vascular reflexes (Heymans & Ladon, 1924) and established by direct electrical recording of impulses in both pre- and post-ganglionic sympathetic fibres, originally by Adrian, Bronk & Phillips (1932). Bronk, Ferguson & Solandt (1934) demonstrated that the inhibition could arise reflexly from the carotid sinus; the greater part of the effect can be abolished by cutting the carotid sinus nerves and the depressor nerves (Pitts, Larrabee & Bronk, 1941; Alexander, 1945), or the vagi and the sinus nerves (Gernandt, Liljestrand & Zotterman, 1946). There is a variable susceptibility to inhibition by a rise in blood pressure among different preganglionic fibres (Iggo & Vogt, 1960) which may be related to differences in function. Two principal methods have been used to raise the blood pressure in previous investigations, either the injection of pressor drugs or the mechanical obstruction of the aorta. Recently Marguth, Raule & Schaefer (1951) reported that intravenously-injected adrenaline was more effective than aortic obstruction in depressing sympathetic discharge, even when adrenaline caused a smaller rise in the blood pressure. This result suggested the possibility that adrenaline may inhibit sympathetic discharge not only on account of its pressor activity but also by some additional action either on the brain and spinal cord or directly on the baroreceptors. This latter possibility is suggested by the work of Palme (1944) and of Landgren, Neil & Zotterman (1952), which has shown that adrenaline, and also noradrenaline and Pitressin, can enhance the responsiveness of the baroreceptors when they are painted on the carotid sinus. However, the high concentrations of these substances required to alter the response of the baroreceptors raise some doubt as to whether intravenous injections have such a direct action. There is also some doubt about an action of adrenaline on the central nervous system, since intracarotid injections were less effective and had a longer latency of action than had

intravenous injections of the same amounts (Fischer, Raule & Seraphin, 1955). However, an action of adrenaline divorced from its pressor effects was postulated by the latter authors to account for the reduction in sympathetic discharge following the injection of adrenaline into adrenalectomized animals, in which adrenaline lacked its usual pressor activity. The theory was put forward that adrenaline acts directly on the spinal cord.

The present experiments were designed to compare quantitatively the relative effectiveness of injections of adrenaline and of other methods of raising the blood pressure in reducing sympathetic efferent activity. Observations were made before and after denervation of the baroreceptors and chemoreceptors. The results do not indicate that adrenaline has any potent inhibitory activity unrelated to its pressor effects.

METHODS

Experimental procedure. The six cats used were anaesthetized with ether, after a subcutaneous injection of atropine (0·25 mg/kg); anaesthesia was continued with an intravenous injection of chloralose (80 mg/kg) and supplemented with smaller doses of chloralose at intervals of several hours, as required. The arterial pressures were recorded from the femoral or brachial arteries by a mercury manometer recording on a kymograph paper, and simultaneously by an electrical transducer manometer recorded photographically with a double-beam oscilloscope. The second beam of the oscilloscope was used to display the amplified preganglionic action potentials picked up from small strands dissected from the cervical sympathetic nerve. The methods were the same as those used previously (Iggo & Vogt, 1960). All the injections were made into the right femoral vein and were washed into the circulation with 0·9 % NaCl solution. The substances used for injection were L-adrenaline (Burroughs Wellcome) 5–100 μg, L-noradrenaline (levo-Arterenol dextro-bitartrate, Bayer Products Ltd, dose expressed in weight of the base) 1–5 μg and vasopressin (Pitressin, Parke Davis and Co.) 2-6 i.u. To expand the circulatory volume blood was infused which had been collected from a donor cat by bleeding under ether into a flask containing heparin.

In two experiments the abdominal aorta was dissected free in order to occlude it when required with a polythene 'choker' (Hume & Nelson, 1954). In the first experiment it was approached through the thorax. In the second experiment, which was more successful because it avoided the need for artificial respiration, the aorta was exposed in the abdomen and 'chokers' were placed around it, one above the coeliac artery and one just below the superior mesenteric artery.

Denervation of the arterial baroreceptors and chemoreceptors. The carotid sinus nerves were dissected and identified near their entry into the sinus, and the depressor nerves were dissected out where they leave the superior laryngeal nerves. This approach may have left intact the baroreceptor innervation of the common carotid artery (Green, 1953). The cervical vagi were exposed high in the neck several millimetres below the origin of the superior laryngeal nerve. The nerves were cut in the following order: sinus nerve and depressor nerve on one side, then in the same order the corresponding nerves on the other side, and then the cervical vagi. Since atropine was injected subcutaneously at the beginning of each experiment there was no change in heart rate on vagotomy and one possible complicating factor in comparing the pre- and post-denervation activity of the sympathetic system was avoided.

Figures. The values for sympathetic efferent discharge in the graphs were obtained by measuring the total outflow during intervals of at least 5 and usually 10 sec or longer. This

was necessary because of the irregular nature of the discharge. When possible, the activity was measured for time intervals which corresponded to multiples of the respiratory cycle. This was done because the discharge frequently showed a respiratory rhythm. In the graphs the sympathetic activity is expressed as a percentage of the resting activity.

RESULTS

The activity of the sympathetic system was sampled by recording electrically from fine strands dissected from the cervical sympathetic nerve in the mid-cervical region and choosing a strand which contained a number of active sympathetic fibres (Fig. 1). The type of activity has been reported previously (Iggo & Vogt, 1960). The basal blood pressure in most experiments was 110–130 mm Hg when recorded with the mercury manometer.

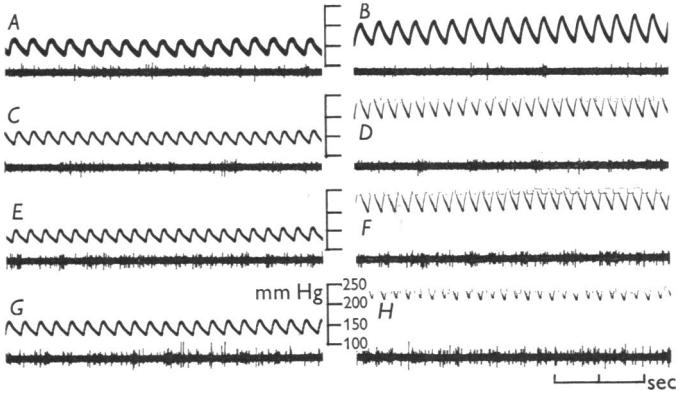

Fig. 1 (Cat 3). The effect of progressive denervation of the major baroreceptor and chemoreceptor regions on electrical activity in preganglionic sympathetic fibres of the cervical sympathetic nerve. The upper tracing in each record shows the femoral arterial blood pressure and the lower tracing the impulses in a strand of the cervical sympathetic nerve. *A*, intact cat; *B*, after the injection of 1·5 μg noradrenaline; *C*, basal activity after cutting the carotid sinus and depressor nerves bilaterally; *D*, injection of 5 μg noradrenaline; *E–H*, after cutting both vagi; *F*, injection of 5 μg noradrenaline and *H*, injection of 100 μg adrenaline. In *H* the blood pressure has risen to such a high level that the systolic pressure is off the top of the paper.

Comparison of different pressor agents

Intact cats. The following methods of raising the blood pressure were compared: intravenous injection of adrenaline, noradrenaline and Pitressin, transfusion of blood, and temporary obstruction of the abdominal aorta. The three drugs have in common that they increase vascular tone and that their local application sensitizes the sinus region to rises of blood pressure; no such effects are produced by the mechanical means used for raising the

blood pressure; these procedures distend rather than constrict the vessel walls while the pressure is rising.

If a comparison among different pressor agents is to have any value, it is necessary first to establish whether repetition of the same procedure gives reproducible results. Adrenaline (10 μg) was injected four times in one animal with the following increases in arterial pressure from the same base line: 63, 65, 66 and 68 mm Hg. The efferent activity was reduced by 65, 86, 80 and 40 % respectively. This variability in reduction of sympathetic discharge rules out any precise comparisons of the potency of different pressor agents.

In Fig. 2 the reduction in efferent activity, expressed as a percentage, is plotted (open signs) against the peak amplitude of the blood pressure change following the injection of adrenaline, noradrenaline and Pitressin in cat No. 3. On the whole, the greater the rise in blood pressure the greater was the inhibition of activity. There is no indication that adrenaline was more potent than either noradrenaline or Pitressin. The results of a similar, more detailed, comparison of intravenous adrenaline and aortic occlusion in cat No. 6 are shown in Fig. 3. Over a range of pressure rises of 20–105 mm Hg there was no indication that adrenaline was more potent than occlusion of the aorta. The time course of the changes in arterial pressure and in sympathetic activity following the injection of adrenaline and aortic obstruction are shown in Fig. 4. The blood pressure change was more abrupt with occlusion, and in some trials the arterial pressure was falling again at a time when the pressor response to an infusion of adrenaline had not yet reached its peak. This difference in the rate of change of pressure may account for the partial recovery of efferent discharge sometimes seen early during the occlusion and occurring only later after an injection of adrenaline. However, after prolonged (2–5 min) elevation of the blood pressure, by continued infusion of adrenaline or by persistent obstruction of the abdominal aorta, the inhibitory strengths of the two procedures were similar (Fig. 4).

When the attempt was made to raise the blood pressure by transfusing blood taken from a donor cat the results were not really comparable with the other procedures. Even after the infusion of 120 ml. of blood the arterial pressure did not rise higher than 145 mm Hg from a basal level of 115 mm Hg. Furthermore, the rate of rise of arterial pressure was slow compared to the response to intravenous adrenaline. The first infusion of 20 ml. of blood raised the arterial pressure from 115 to a peak of 140 mm Hg over 3 min and there was a further brief rise of 4–5 mm Hg with each additional 20 ml. of blood to give a final value of 145 mm Hg. The sympathetic discharge was reduced to 45 % with a 30 mm rise in blood pressure after the infusion of approximately 50 ml. of blood, whereas a similar

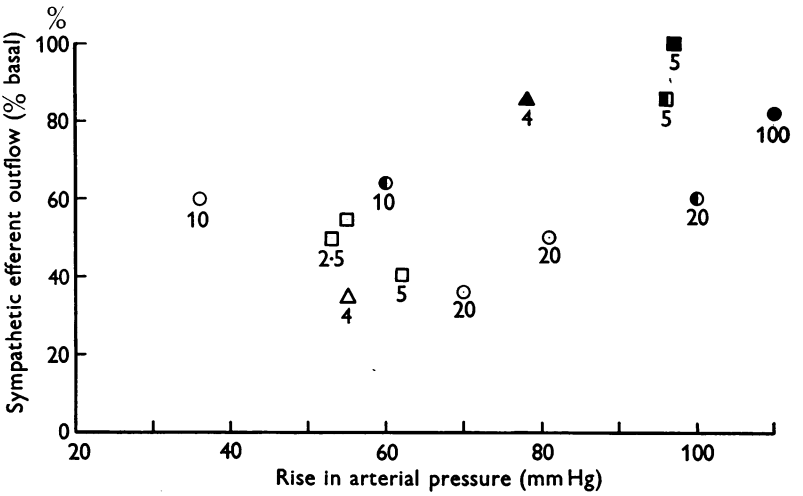

Fig. 2 (Cat 3). The reduction in sympathetic efferent activity by different pressor agents. The peak in arterial pressure above the basal level is plotted along the abscissa and the efferent activity expressed as a percentage of the resting level is plotted on the ordinate. The open symbols refer to the intact animal, the half-filled symbols to trials with the sinus and depressor nerves cut bilaterally, and the filled symbols to trials with both vagi also cut. The figures under the symbols indicate the dose of catecholamines (μg) and of Pitressin (i.u.). ○ adrenaline; □ noradrenaline; △ Pitressin.

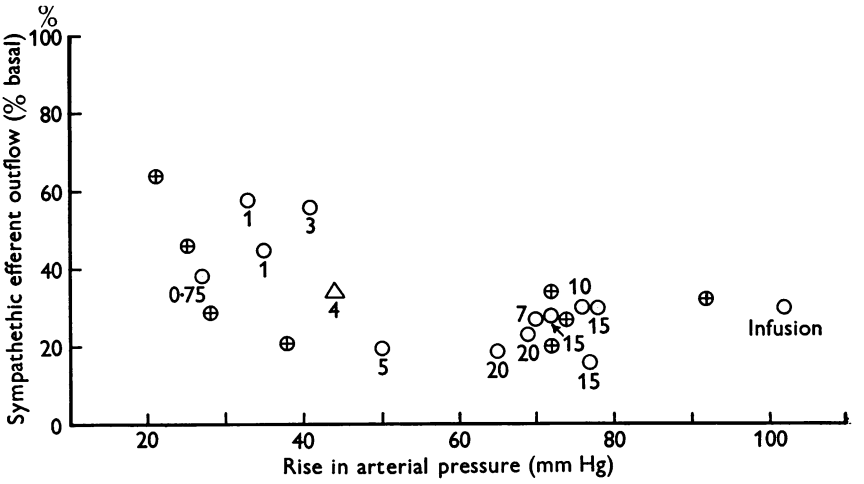

Fig. 3 (Cat 6). Comparison of the effects of adrenaline, Pitressin and aortic occlusion in a cat with the buffer nerves intact. Results plotted in the same way as Fig. 2. The figures under the symbols indicate the dose of adrenaline (μg) and of Pitressin (i.u.). ○ intravenous adrenaline; △ intravenous Pitressin; ⊕ occlusion of abdominal aorta.

reduction in activity after 10 μg adrenaline required about twice the rise in arterial pressure in the same cat. During 20 min of elevated blood pressure, caused by transfusion, the sympathetic efferent discharge returned slowly to about 60 % of the original value. After the blood transfusion the contour of the blood pressure pulse was flattened, the systolic peak being prolonged to a plateau (Fig. 5*d*). This would lead to a more

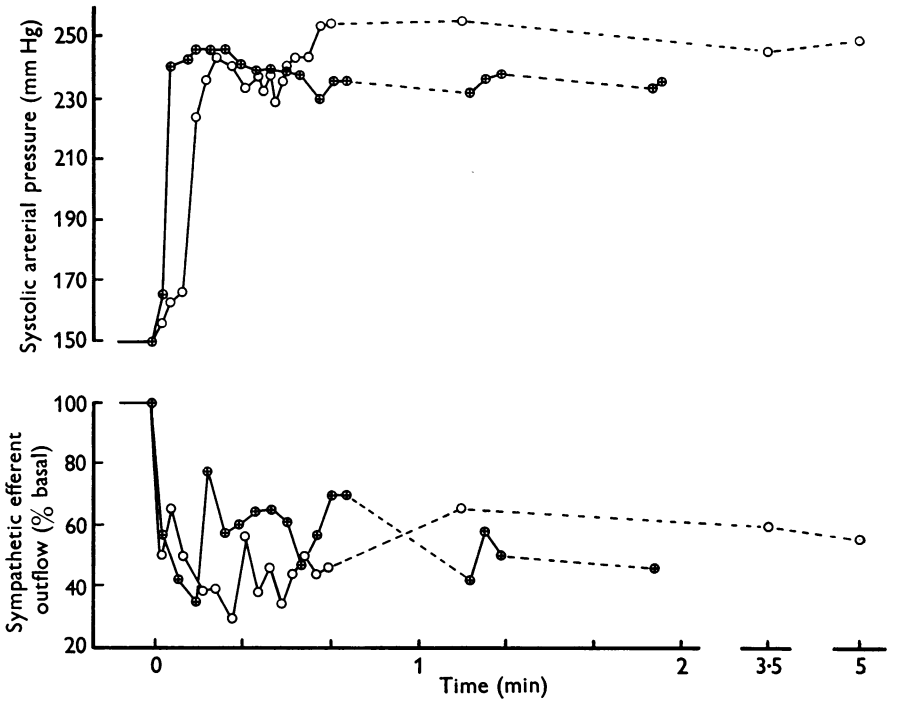

Fig. 4 (Cat 6). The effect of (*a*) an intravenous infusion of adrenaline, O—O, and (*b*) prolonged aortic occlusion, ⊕—⊕, on the brachial arterial pressure (upper curves) and the cervical sympathetic activity, expressed as a percentage of resting activity (lower curves). A total of 70 μg adrenaline was infused over a period of 5 min.

persistent high-frequency inflow of impulses from the baroreceptors and may account for the greater inhibitory action of the transfusion at a lower mean level of blood pressure. Transfusion after cutting the carotid sinus and depressor nerves and the cervical vagi did not inhibit the sympathetic discharge, although a similar flattening of the arterial pressure pulse occurred.

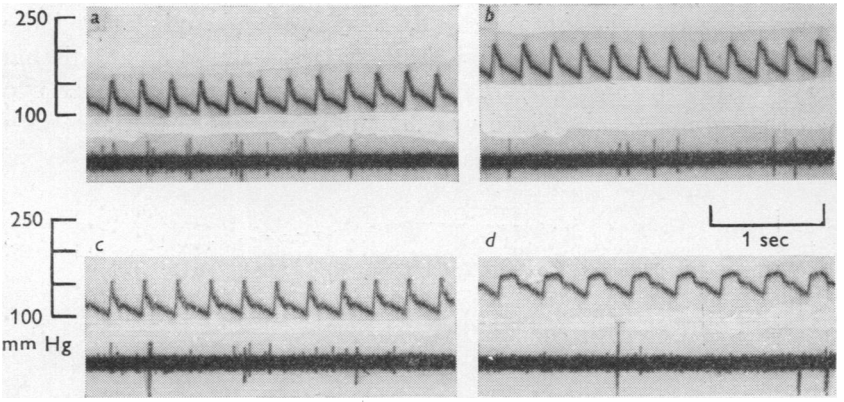

Fig. 5 (Cat 4). A comparison of the changes in contour of the arterial pressure wave following the I.V. injection of adrenaline and the transfusion of blood. Records show (*a*) before and (*b*) after the injection of 10 μg adrenaline; (*c*) before and (*d*) after the transfusion of 50 ml. blood. Note the prolonged systolic plateau in (*d*). The transfusion was as effective in reducing the sympathetic outflow (lower tracing in all records) as the I.V. adrenaline, even though the rise in arterial pressure was less. The B.P. calibrations are at the left-hand side. Time (1 sec) applies to all records.

Effect of denervation of baroreceptors and chemoreceptors

These experiments were done primarily in order to see whether adrenaline exerted an effect on sympathetic outflow by means other than by an action through the baroreceptors and chemoreceptors. They also gave some additional information on the afferent pathways involved in the depression of sympathetic activity.

To test the completeness of the carotid sinus denervation after section of the sinus nerve the effect on the arterial blood pressure of occluding the common carotid artery was examined. Only in one of the four cats was there, on one side, a small residual rise in blood pressure when the common carotid artery was clamped after cutting the nerve.

After each of the nerves (carotid sinus nerve, depressor nerve, cervical vagus) was cut there was a rise in systemic arterial pressure which persisted for different times in the various animals. In the experiment illustrated in Fig. 1 the blood pressure fell almost to the initial level a few minutes after each nerve was cut. The largest and best sustained rises of arterial pressure after denervation were obtained in the animal in which the blood volume had been expanded by a transfusion of 120 ml. of blood. In this cat the pressure was 140 mm Hg after transfusion and just before denervation, and it became steady at 210 mm Hg after cutting the sinus nerves, depressor nerves and the cervical vagi.

The effects of total baroreceptor and chemoreceptor denervation on sympathetic activity were striking. As is shown in Fig. 1 there was a dramatic increase in the sympathetic outflow (compare Fig. 1*A* and *E*). In some animals there was a large change after cutting only the sinus and depressor nerves, but in the experiment illustrated in Fig. 1 the largest increase appeared only when the vagi were cut.

There was also a variable disturbance of the response to experimentally induced hypertension. In the experiment shown in Fig. 1 the basal efferent activity did not increase substantially on cutting the sinus and depressor nerves (compare Fig. 1*A* and *C*) yet the inhibition by a rise in blood pressure clearly seen in section *B* (before denervation of carotid sinus and aortic arch) was negligible in section *D* (after denervation). This was so in spite of the fact that 5 μg noradrenaline instead of 1·5 μg was injected and the rise in blood pressure therefore was 50 mm Hg higher than before. In other experiments the basal efferent discharge was enhanced by cutting the sinus and depressor nerves and the sympathetic activity was strongly inhibited when the blood pressure was raised. In all animals, however, the suppressing action of hypertension on sympathetic discharge was almost completely absent after cutting all the nerves (sinus nerves, depressor nerves and cervical vagi). Very high levels of blood pressure failed to depress the sympathetic discharge in cats with completely denervated baroreceptors and chemoreceptors, as seen in Fig. 1*H* and Fig. 2 (black signs). Of particular importance is the failure of adrenaline, even at a dose of 100 μg, to reduce sympathetic outflow.

In its effect on basal sympathetic discharge, baroreceptor and chemoreceptor denervation resembled somewhat the effect of 'chemical sympathectomy' produced by prolonged treatment with reserpine (Iggo & Vogt, 1960). The discharge was more continuous and lacking in respiratory rhythm, and some individual cells discharged impulses very regularly. Whereas in both conditions there was unimpaired sensitivity to stimuli such as sudden noise, the responses to experimentally induced changes in blood pressure were quite different. After section of the carotid sinus nerves, depressor nerves and vagi there was no response in contrast to the very brisk response in the reserpine-treated cat. In the latter the reflex arc was, of course, intact except for the lack of transmitter at the postganglionic nerve-endings.

DISCUSSION

The results described in this paper confirm earlier reports that a temporary rise in blood pressure will suppress most of the efferent sympathetic activity in intact cats. This suppression depends principally on the extent and the rate of the rise in pressure, and secondarily on factors such as the

depth of anaesthesia. It is absent after denervating the major arterial baroreceptor and chemoreceptor pathways. Four of the five methods used to raise the arterial pressure in the present work were, as far as could be judged, equally potent in reducing sympathetic discharge. The size of the blood-pressure change, rather than the nature of the pressor agent, seemed to determine the response. The exception was provided by blood transfusion, with which, however, the changes in pressure were gradual and the blood-pressure pulse had a prolonged and flattened systolic peak. It proved more potent than the other methods in relation to the pressure level achieved, possibly because of the change in shape of the arterial-pressure wave.

The present results do not support the view that adrenaline has a direct central inhibitory action on sympathetic discharge. The possibility that a central action was masked by the more powerful reflex response to hypertension is ruled out by the finding that, after denervating the major baroreceptor and chemoreceptor pathways, adrenaline, even in large doses, was just as ineffective as the other pressor agents. However, this argument would be invalid if the supposed central action of adrenaline were exerted on the intracerebral or spinal part of these very pathways and would therefore disappear when the peripheral part of the reflex arc is interrupted.

The possibility remains that high local concentrations of adrenaline somewhere else in the central nervous system may inhibit sympathetic activity; this idea we did not think worth testing, seeing that intravenously administered adrenaline penetrates only very slightly into the brain.

An important role of an increase in the sensitivity of the baroreceptors was unlikely because, as already mentioned, only high local concentrations of pressor substances produce an inhibitory effect. Furthermore, such a role was practically ruled out by the finding that, for the same increment in blood pressure, adrenaline was no more potent an inhibitor of sympathetic outflow than aortic occlusion, which does not alter baroreceptor sensitivity.

Another factor which may participate in the pressor-induced inhibition of sympathetic outflow could be a reduction in chemoreceptor discharge. Diamond & Howe (1956) have shown that the chemoreceptor discharge may be reduced by a rise in blood pressure when the arterial pressures are below 100 mm Hg and the animal is therefore suffering some degree of anoxia. The reduction is presumably due to the increased blood flow through the carotid and aortic bodies. Landgren (1958), in addition, has shown that even when a cat is breathing 100 % oxygen, and the blood is presumably saturated with oxygen, there may be a chemoreceptor discharge at very low arterial pressures, which disappears when the blood

pressure is raised. Such a fall in chemoreceptor discharge would reflexly diminish sympathetic outflow. It is unlikely to have occurred in the present experiments, in which the basal blood pressures were between 110 and 130 mm Hg, and the cats showed no signs of anoxia. However, in the absence of detailed information, this question must be left open.

The difference between these findings and those of Marguth *et al.* (1951), who consider adrenaline a more potent inhibitor of sympathetic activity than aortic occlusion, may possibly be caused by the different time course of the two responses and the fact that some degree of adaptation occurs with time. If only the degree of inhibition at 14 sec, for example, had been examined in the experiment of Fig. 4, adrenaline would have scored over aortic occlusion, but the reverse holds for the state at 115 sec, and when the experiment is viewed as a whole the effects are very similar. We therefore conclude that adrenaline, like the other pressor agents, inhibits the sympathetic outflow principally by a reflex action through the arterial baroreceptors.

The contribution to sympathetic stabilization provided by vagal afferent fibres other than the arterial baroreceptors cannot be gauged accurately by the present experiments. It is clear that although pressor doses of adrenaline and noradrenaline might be ineffective in inhibiting the activity of the sympathetic centres after bilateral denervation of the carotid sinuses and the aortic arch as in Fig. 1 *D*, yet there were, in the cervical vagi, additional afferent fibres with a powerful inhibitory action. This action can be inferred from the effect of cutting both vagi (Fig. 1 *E–H*), which released still further the basal efferent sympathetic discharge.

SUMMARY

1. Preganglionic sympathetic activity was recorded from strands of the cervical sympathetic trunk in cats anaesthetized with chloralose.

2. The effect of raising the blood pressure by intravenous injections of adrenaline, noradrenaline or Pitressin, and by transfusion of blood or temporary occlusion of the aorta was examined before and after section of the sinus nerves, depressor nerves, and cervical vagi.

3. For the same rise in blood pressure, aortic occlusion and injection of the three hormones were indistinguishable in their inhibitory effects on sympathetic preganglionic discharge. All effects were abolished by cutting the carotid sinus and depressor nerves and the cervical vagi. The finding that adrenaline is no more potent than aortic occlusion in inhibiting sympathetic discharge is at variance with observations reported in the literature, perhaps because the different time course of the effects has not always been taken into consideration.

4. Expansion of the circulatory volume caused greater inhibition per increment in blood pressure than injection of adrenaline, but the pressor effects were so slow in developing that a valid comparison cannot be made.

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