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CARDIOVASCULAR ACTIONS OF PHENOXYBENZAMINE

BY

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Phenoxybenzamine increased the force of contraction and rate of the heart and lowered the blood pressure of dogs in pentobarbitone anaesthesia. This was preceded by depression of cardiac contractile force and a rise in blood pressure when phenoxybenzamine was injected following ganglion-blocking drugs or atropine. The positive inotropic and chronotropic and the hypertensive effects of phenoxybenzamine were prevented by pretreatment with reserpine or guanethidine.

It has previously been found that phenoxybenzamine increases the concentration of adrenaline and noradrenaline in urine and plasma of dogs in barbiturate anaesthesia (Benfey, Ledoux & Melville, 1959; Benfey, Ledoux & Segal, 1959; Millar, Keener & Benfey, 1959). It was observed in these studies that the usual quick fall in blood pressure did not occur when the drug was injected during an infusion of hexamethonium. Further studies have now shown that it is possible to obtain a rise in blood pressure by injecting phenoxybenzamine following ganglion-blocking agents or atropine, and it appears that the drug is related to reserpine, which releases endogenous adrenaline and noradrenaline and lowers the blood pressure but has a transient hypertensive action when injected following ganglion-blocking drugs (Maxwell, Ross, Plummer & Sigg, 1957). However, this is hard to reconcile with the fact that phenoxybenzamine is an antisympathomimetic agent. Preliminary reports of parts of this work have appeared (Benfey, 1960; Benfey, Ledoux & Melville, 1960).

METHODS

Dogs anaesthetized with sodium pentobarbitone (30 mg/kg) were used in these experiments. The cord was transected between C1 and C2 in the spinal dogs. The contractile force of the exposed heart was recorded by a Cushny myocardiograph. Artificial respiration was given to the spinal and open-chest animals. The blood pressure was recorded from the carotid artery, and the following drugs were injected intravenously.

Phenoxybenzamine (Dibenzyline hydrochloride) and dibenamine hydrochloride were kindly supplied by Smith, Kline & French, Montreal. They were dissolved in 2 ml. of ethanol, and 8 ml. of physiological saline was added immediately before injection. Reserpine (Serpasil), guanethidine (Ismelin), and phentolamine (Rogitine hydrochloride), kindly supplied by Ciba Company, Montreal. Pentolinium tartrate (Ansolysen) and hexamethonium bromide, kindly supplied by Poulenc, Montreal. Dichloroisoproterenol (compound No. 20522), kindly supplied by Eli Lilly & Co., Indianapolis. Iproniazid (Marsilid), kindly supplied by Hoffmann-La Roche, Montreal. Adrenaline (Adrenalin chloride solution, Parke, Davis & Co.).

RESULTS

The intravenous injection of 20 mg/kg of phenoxybenzamine in a dog under pentobarbitone anaesthesia had the following effects (Fig. 1). There was an

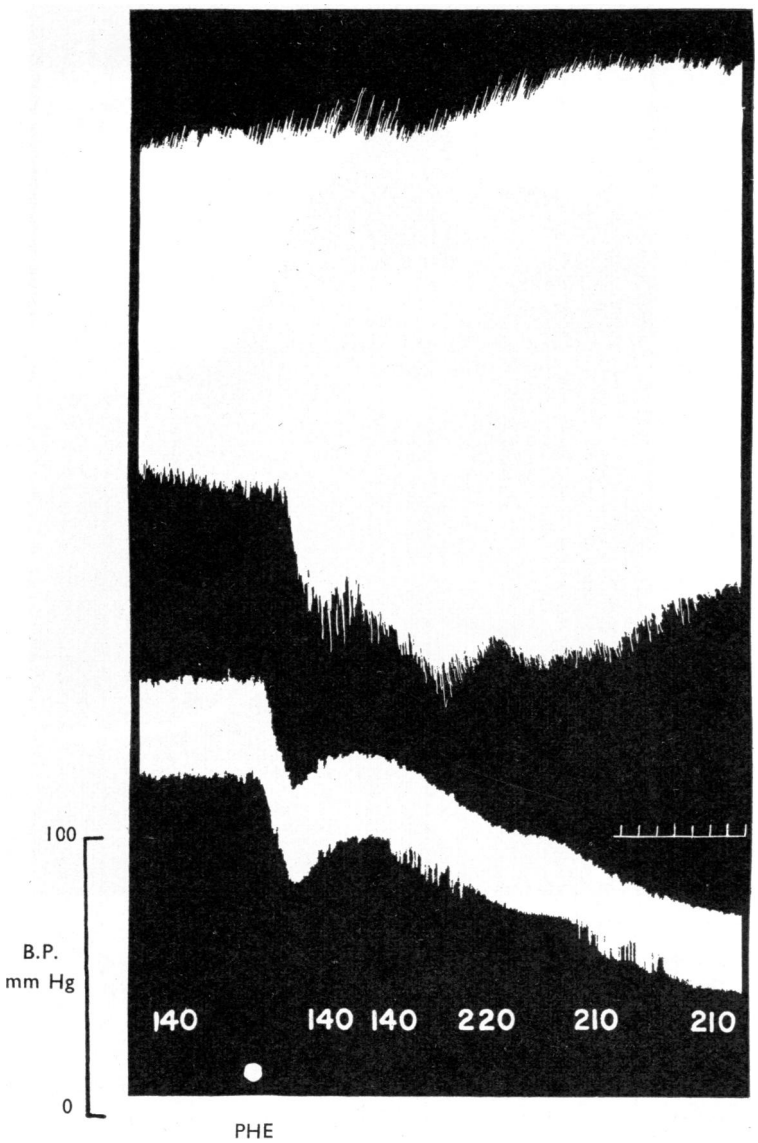

Fig. 1. Cardiac contractility and heart rate (upper record) and blood pressure (lower record) of a dog (9.8 kg) anaesthetized with pentobarbitone. Time in min. PHE: 20 mg/kg of phenoxybenzamine injected intravenously.

immediate increase in cardiac contractile force, there was a rise in heart rate 10 to 15 min later, and there was a fall in blood pressure. These inotropic, chronotropic and hypotensive effects were still present when the experiment was terminated after 3 hr.

Fig. 2 shows the actions of phenoxybenzamine in a dog treated with a ganglion-blocking drug. Ten mg/kg of pentolinium had little influence on cardiac contrac-

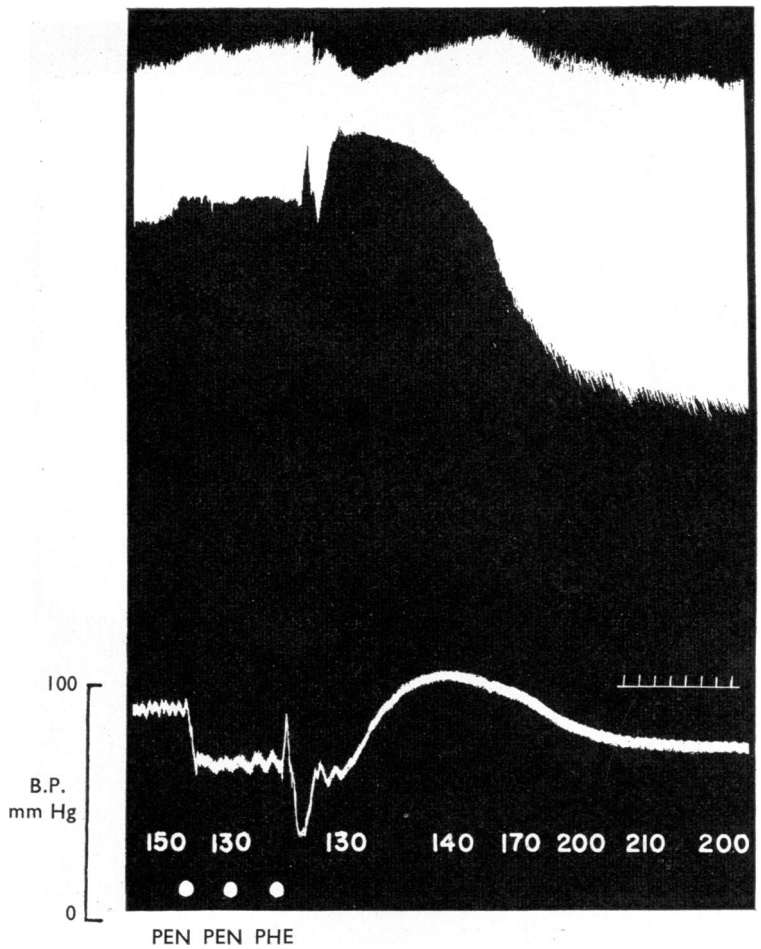

Fig. 2. Cardiac contractility and heart rate (upper record) and blood pressure (lower record) of a dog (7.2 kg) anaesthetized with pentobarbitone. Time in min. PEN: 5 mg/kg of pentolinium; PHE: 20 mg/kg of phenoxybenzamine injected intravenously.

tility, reduced the heart rate slightly, and lowered the blood pressure. Before it stimulated contractility and rate of the heart, phenoxybenzamine first depressed cardiac contractility for a period of approximately 10 min. While cardiac contractility was depressed the blood pressure rose to a peak and then fell when cardiac contractility began to increase.

The hypertensive action of phenoxybenzamine after ganglion-blocking drugs was variable and seemed to depend on the condition of the animal. When the blood pressure was normal, when few surgical procedures were carried out, and when the animal was kept warm, phenoxybenzamine could elevate the blood pressure to 200 mm Hg and keep it high for periods of more than 45 min. However, the rise was usually small and brief in an animal with a low blood pressure. Reserpine, a hypotensive agent with a transient hypertensive action in ganglionic blockade

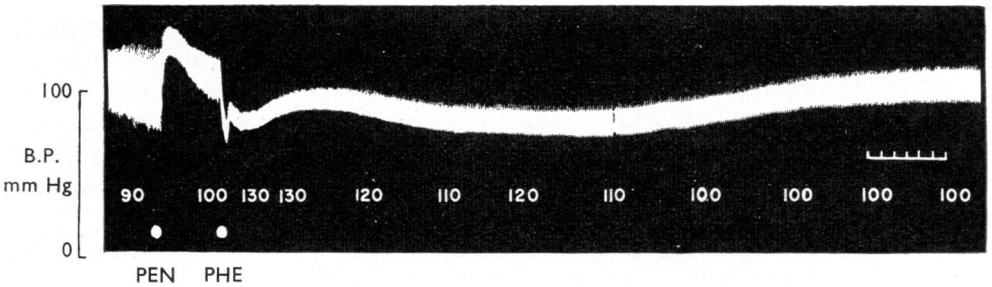

Fig. 3. Blood pressure and heart rate of a dog (8.1 kg) anaesthetized with pentobarbitone. Time in min. Reserpine (1 mg/kg) injected subcutaneously 24 hr before. PEN: 5 mg/kg of pentolinium ; PHE: 20 mg/kg of phenoxybenzamine injected intravenously.

(Maxwell *et al.*, 1957), was similarly found to have a poor hypertensive effect in dogs with a low blood pressure.

The dose of phenoxybenzamine required for the hypertensive effect (10 to 20 mg/kg) exceeded that sufficient for antisympathomimetic action (2 mg/kg). The time of injection was less than 1 min. Pentolinium was used in amount of 5 to 10 mg/kg and mostly given in two divided doses. Other ganglion-blocking drugs could be substituted for pentolinium and were all given in two divided doses, for example, tetraethylammonium (60 mg/kg), hexamethonium (30 mg/kg), pempidine (5 mg/kg). Atropine (4 mg/kg) had a similar action. The vagus nerves were cut only in the experiments in which atropine was given. Cutting the vagi did not enhance the hypertensive effect of phenoxybenzamine after ganglion-blocking drugs ; however, no experiments were carried out with atropine in animals whose vagus nerves were intact.

Pretreatment of the animals with reserpine or guanethidine prevented the inotropic, chronotropic and hypertensive actions of phenoxybenzamine in animals treated with ganglion-blocking agents ; this appears to indicate that they depend on the presence of endogenous adrenaline and noradrenaline. Fig. 3 shows that, in a dog pretreated subcutaneously with 1 mg/kg of reserpine 24 hr before, phenoxybenzamine given after pentolinium merely produced a slight and transient

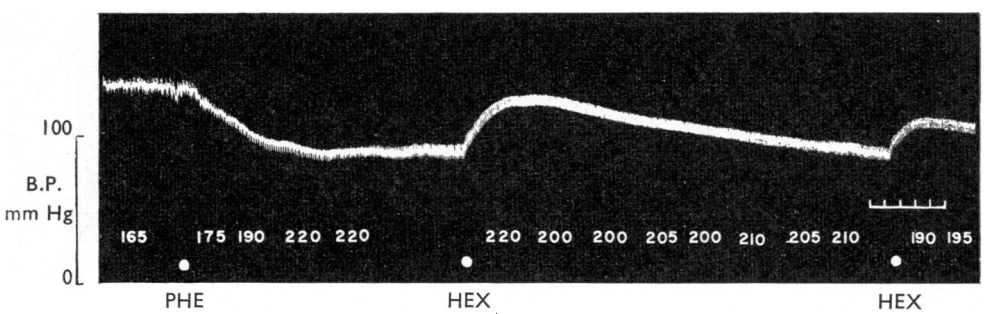

Fig. 4. Blood pressure and heart rate of a dog (11.6 kg) anaesthetized with pentobarbitone. Time in min. PHE: 20 mg/kg of phenoxybenzamine; HEX: 1 mg/kg of hexamethonium injected intravenously.

rise in heart rate and small fluctuations in blood pressure. The intravenous injection of 15 mg/kg of guanethidine 24 hr previously similarly prevented the stimulant actions of phenoxybenzamine after ganglion-blocking drugs. Cardiac contractility was depressed for a prolonged period and never increased, cardiac rate remained unchanged, and the blood pressure was rather stable. Pretreatment with guanethidine also abolished the inotropic, chronotropic and hypertensive actions of 0.5 to 1 mg/kg of reserpine given intravenously after ganglion-blocking drugs.

Ganglion-blocking drugs led to a rise in blood pressure in unanaesthetized dogs treated with reserpine (Maxwell *et al.*, 1957). A similar effect is shown in Fig. 4.

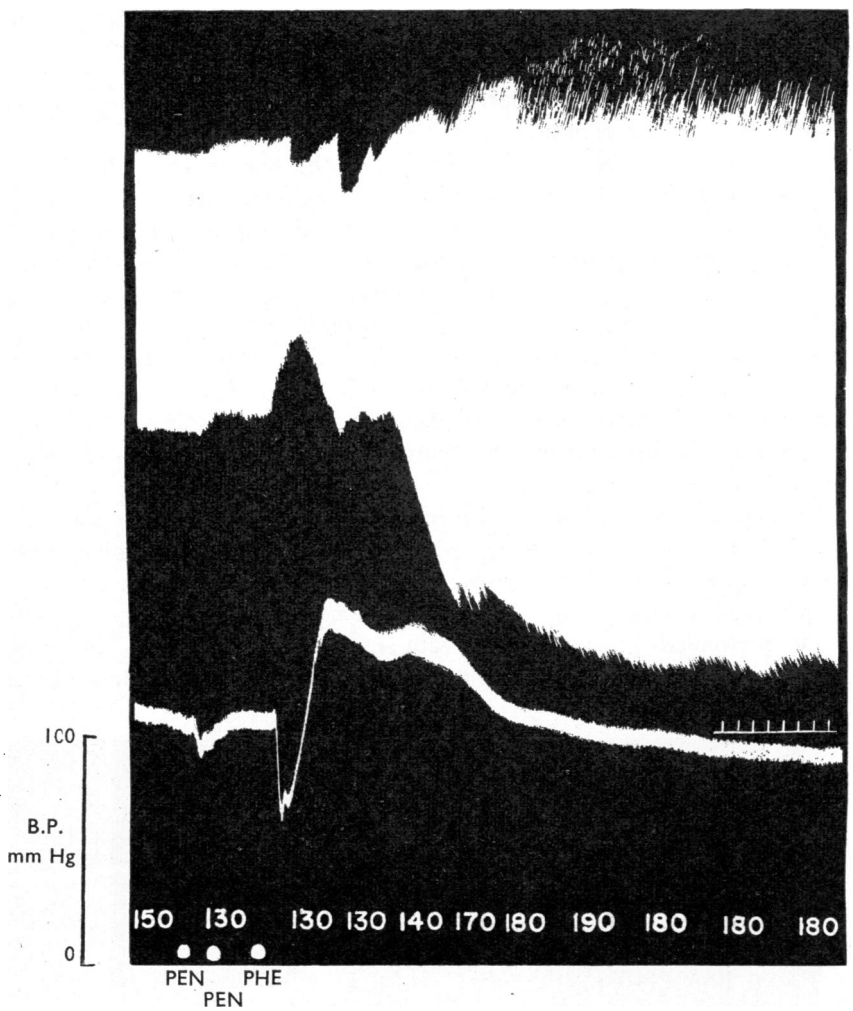

Fig. 5. Cardiac contractility and heart rate (upper record) and blood pressure (lower record) of a dog (9.2 kg) anaesthetized with pentobarbitone. Time in min. Phenoxybenzamine (20 mg/kg) injected intravenously 24 hr before. PEN: 2.5 mg/kg of pentolinium; PHE: 20 mg/kg of phenoxybenzamine injected intravenously.

One mg/ml. of hexamethonium produced a rise in blood pressure in an animal treated with 20 mg/kg of phenoxybenzamine.

Cocaine can potentiate actions of adrenaline and noradrenaline. The intravenous injection of 5 mg/kg of cocaine in ganglionic blockade greatly potentiated the hypertensive action of 0.5 to 1 mg/kg of reserpine injected intravenously 10 to 20 min later. Cocaine prevented the initial negative inotropic action of phenoxybenzamine in ganglionic blockade, but there was a poor hypertensive effect. The monoamine oxidase inhibitor iproniazid (20 mg/kg given intravenously 1 hr before) did not prevent the negative inotropic effect of phenoxybenzamine, and there was no rise in blood pressure in ganglionic blockade.

Reserpine elevates the blood pressure of a spinal dog (Maxwell *et al.*, 1957); phenoxybenzamine, however, caused a prolonged fall. An attempt was made to obtain a blood pressure rise with phenoxybenzamine in spinal dogs in ganglionic blockade by infusing small amounts of noradrenaline (10 to 50 ng/kg/min). However, there was no success although the blood pressure could be kept fairly high.

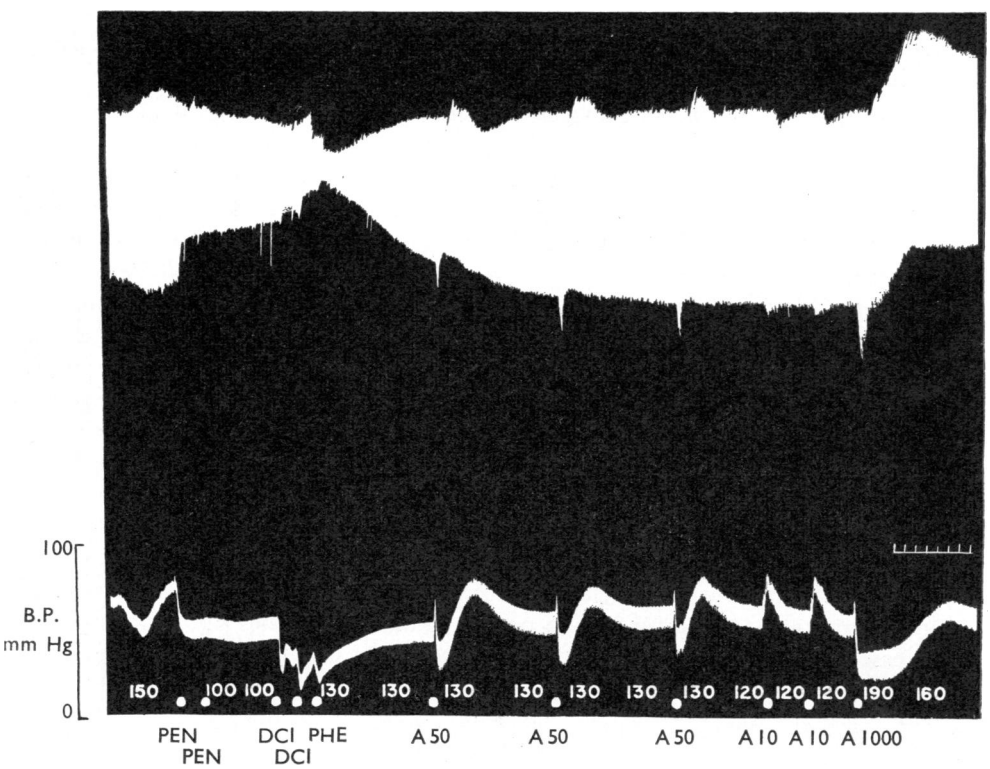

Fig. 6. Cardiac contractility and heart rate (upper record) and blood pressure (lower record) of a dog (7.2 kg) anaesthetized with pentobarbitone. Time in min. Phenoxybenzamine (20 mg/kg) injected intravenously 24 hr before. PEN: 2.5 mg/kg of pentolinium; DCI: 2.5 mg of dichloroisoproterenol; PHE: 20 mg/kg of phenoxybenzamine; A 50: 50 μg/kg of adrenaline; A 10: 10 μg/kg of adrenaline; A 1000: 1 mg/kg of adrenaline injected intravenously.

When phenoxybenzamine was injected in anaesthetized dogs after ganglion-blocking drugs during an infusion of adrenaline or noradrenaline (1 μg/kg/min), there was an immediate and deep fall in blood pressure. It appears that following phenoxybenzamine greatly increased amounts of circulating adrenaline and noradrenaline act strongly on the vasodilator receptors.

Antisympathomimetic drugs abolish the hypertensive action of reserpine (Maxwell *et al.*, 1957); however, pretreatment with phenoxybenzamine (20 mg/kg given intravenously 24 hr before) did not interfere with the typical actions of another dose of the drug after pentolinium (Fig. 5). This was surprising in view of the fact that phenoxybenzamine appeared to exert its hypertensive action through endogenous adrenaline and noradrenaline, but it was not possible to obtain a rise in blood pressure with injected adrenaline or noradrenaline 24 hr after phenoxybenzamine.

However, Fig. 6 shows that when a dog treated with 40 mg/kg of phenoxybenzamine in a period of 24 hr was given dichloroisoproterenol which interferes with the action of adrenaline on the heart and on vasodilator receptors, a small dose of adrenaline (10 μg/kg) could produce a rise in blood pressure, while a large dose (1 mg/kg) caused a blood pressure fall and an intermediate dose (50 μg/kg) had a mixed effect. The hypertensive effect of the small dose of adrenaline may have been due to an increase in cardiac output; however, little, if any, increase in cardiac contractility and no change in heart rate were demonstrable.

Dichloroisoproterenol could not be used satisfactorily to demonstrate sympathomimetic actions of phenoxybenzamine on the heart by blocking them because, although interfering with the effects of injected adrenaline, it strongly stimulated the contractile force and rate of the heart after ganglion-blocking drugs for a prolonged period of time. But Fig. 6 shows that when phenoxybenzamine was injected before the dichloroisoproterenol effects developed, there was only a small rise in cardiac contractility and rate, and adrenaline could further increase cardiac contractile force. In the absence of dichloroisoproterenol phenoxybenzamine generally stimulated cardiac contractility to such an extent that adrenaline could not further increase it. Dichloroisoproterenol also appeared to stimulate vasodilator receptors which prevented the blood pressure rise after phenoxybenzamine.

Certain other antisympathomimetic drugs did not have a hypertensive action following ganglion-blocking drugs. Twenty to 50 mg/kg of dibenamine, which is closely related to phenoxybenzamine, lowered the blood pressure and depressed cardiac contractile force for a long period of time. Five mg/kg of phentolamine depressed the heart so much that several injections of adrenaline were needed to re-establish its function.

DISCUSSION

The results suggest that the cardiovascular actions of phenoxybenzamine are probably mediated by adrenaline and noradrenaline. There was little change in cardiac contractility and rate and in blood pressure when pretreatment with reserpine or guanethidine had greatly reduced the amount of available adrenaline and noradrenaline. However, there was a fall in blood pressure when phenoxybenzamine was injected without pretreatment, and this was very marked in the presence of

infused adrenaline and noradrenaline. The increase in the plasma concentration and urinary excretion of adrenaline and noradrenaline caused by phenoxybenzamine (Millar *et al.*, 1959 ; Benfey *et al.*, 1959a and b) seems to contribute to the fall in blood pressure.

No rise in urinary catecholamine excretion was previously detected when phenoxybenzamine was injected during an infusion of hexamethonium or when the blood pressure fall was prevented by repeated injections of vasopressin. These results support the suggestion of Brown & Gillespie (1957) that phenoxybenzamine interferes with the inactivation of endogenous noradrenaline. An indirect action of phenoxybenzamine has also been reported by Hukovic (1959), who found an increased response of the isolated rabbit atrium to sympathetic stimulation.

The fact that phenoxybenzamine stimulated the heart in ganglionic blockade when sympathetic tone was greatly reduced may, however, indicate a direct action of the drug, that is, a release of adrenaline and noradrenaline in a manner similar to that of reserpine, although the methods of measuring urinary catecholamine output did not detect it. However, there are differences in the actions of the two drugs since a single dose of reserpine could prevent the cardiovascular effects of phenoxybenzamine and a single dose of phenoxybenzamine could not.

The blood pressure rise appears to be possible because the amount of circulating adrenaline and noradrenaline is low in ganglionic blockade. When signs of cardiac stimulation indicated an increase in circulating catecholamine, the blood pressure rise turned into a fall. The mechanism of the blood pressure rise following phenoxybenzamine is obscure. The rise in blood pressure was always followed by signs of cardiac stimulation. It is not likely that an increase in cardiac output produced the blood pressure rise because while it occurred cardiac contractility was depressed and the rate not changed. But sympathomimetic agents have not been reported to constrict blood vessels 24 hr after a full dose of phenoxybenzamine. It may be suggested that there is a difference between exogenous and endogenous catecholamine. When small amounts of adrenaline and noradrenaline are released in the body they may elevate the blood pressure by vasoconstriction in the presence of phenoxybenzamine and ganglion-blocking drugs. It has repeatedly been observed that ganglion-blocking drugs and atropine potentiate hypertensive actions of noradrenaline (Haas & Goldblatt, 1959). In the presence of phenoxybenzamine the greater amounts of adrenaline and noradrenaline released by reserpine act predominantly on vasodilator receptors.

It is, however, not necessary to assume that phenoxybenzamine releases adrenaline and noradrenaline. The drug may interfere with the inactivation of the transmitter substance of the sympathetic fibres and, in the presence of ganglion-blocking drugs or atropine, potentiate its action on the vasoconstrictor receptors instead of exerting its usual antisympathomimetic action.

A transient depressant effect on cardiac contractility became evident when phenoxybenzamine was given in ganglionic blockade. The related drug dibenamine had a very prolonged depressant action and never stimulated cardiac contractile force in ganglionic blockade. Dibenamine has been reported to have a negative inotropic action upon the heart-lung preparation of the dog and to diminish the rate of the isolated rabbit auricle (Acheson, Farah & French, 1949). Phentolamine

depressed the heart very strongly in ganglionic blockade. The drug was found to have a positive chronotropic action in dogs and cats; however, this was absent in the isolated heart (Gross, Tripod & Meier, 1951). Piperoxane had a quinidine-like action on the isolated rabbit auricle (Dawes, 1946). Thus, although previous studies in cats have shown that all of these antisympathomimetic agents increase the urinary output of adrenaline and noradrenaline in a manner similar to that of phenoxybenzamine (Benfey *et al.*, 1959b), it seems that strong depressant effects prevent a sympathomimetic stimulation of the heart.

Note added in proof

It has been found that in dogs subjected to transection of the cervical spinal cord and vagotomy phenoxybenzamine stimulated cardiac rate and contractility which were further increased by injecting reserpine an hour later; it has been concluded that phenoxybenzamine releases small amounts of catecholamines; and it has been suggested that the blockade of the adrenergic receptor involves both an impaired inactivation and a release of the sympathetic transmitter substance (Benfey & Varma, *Fed. Proc.*, in the press).

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