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NORADRENALINE POSTINFUSIONAL HYPOTENSION

by

Nasreen Javaid, M.B.,B.S.

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J. Mazurkiewicz, Ph.D.
Supervisor

Nasreen Javaid
Candidate

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INTRODUCTION

The treatment of shock resulting from varying causes has presented a challenge to clinicians and research workers for many years. The term "shock" is widely used to convey different meanings and has no universally accepted definition. From the clinical point of view the term is most commonly used when reference is made to "acute systemic arterial hypotension" with signs and symptoms of pallor, cold clammy extremities, tachycardia and extreme weakness. In order to counteract the phenomena of hypotension associated with shock, clinicians have long advocated the use of the vasopressor agent, noradrenaline. This sympathomimetic amine gained an important position in the treatment of shock, and in order to obtain a continuous effect it was administered as an intravenous drip. Goldenberg (1949) was the first to publish a report on the beneficial effects of noradrenaline in raising the blood pressure in conditions of shock. However, it was observed by many workers, both in the clinical field and in animal research, that following an infusion of noradrenaline, an intense fall in blood pressure resulted after the infusion was arrested, and that blood pressure remained at this low level for considerable periods. This marked fall in blood pressure after the termination of infusion is referred to as

"Noradrenaline Postinfusional Hypotension" (N.P.H.). It is difficult to determine if this in itself is a secondary form of shock; it certainly endangers the life of the patient whose blood pressure is already very low.

A number of reports on noradrenaline postinfusional hypotension have appeared in the literature. Previous workers have not adequately explained the details involved in the production of hypotension (N.P.H.). In the first part of this thesis the influence of an increase in dose, duration of infusion, and dose and duration of noradrenaline infusion on the postinfusional hypotension has been investigated. Tolerance to the pressor effects of noradrenaline has been reported by Welch (1954), Davies (1957), Hellar (1961), Rosenthale and Dipalma (1962) and others.

The second part of this study involved the effect of repeating the infusion in the same animal not only on the pressor effect of noradrenaline but on tolerance development and on noradrenaline postinfusional hypotension.

Modification of the noradrenaline pressor response following adrenergic nerve blockade and after depletion of catecholamine stores was shown by Hilton (1964). The third phase of this dissertation describes an investigation of such an adrenergic blockade and catecholamine depletion on the development of noradrenaline postinfusional hypotension.

HISTORICAL REVIEW

Clinical Use of Noradrenaline in Shock of Different Etiology

The use of noradrenaline infusions in the treatment of shock of varying etiology was advocated by many authors for almost 16 years.

A. Surgical Shock

Goldenberg and co-workers (1949) published the first account on the usefulness of intravenous drip of noradrenaline in acute hypotension during and after thoraco-lumbar sympathectomy; 22 out of 23 patients showed a satisfactory response. They also showed that noradrenaline infused in the concentration of 4 µg/ml (4 mg of noradrenaline diluted with 1 liter of isotonic saline) was effective in raising blood pressure to normotensive levels in haemorrhagic shock. After response to the initial dose of 0.1 µg/kg/minute was obtained the rate was adjusted to maintain a desired level of blood pressure.

The beneficial effects of intravenous noradrenaline drip during and after splanchnectomy and dorsal sympathectomy were investigated by Deterling and Apgar (1951). They found that noradrenaline when administered in the dose of 2.27 - 2.77 mg at the rate of 0.1-0.3 µg/kg/minute over a period of 7-96 hours returned blood pressure to normotensive levels.

The use of noradrenaline for maintaing blood pressure during surgical procedures was also advocated by Churchill-Davidson (1951) who infused the drug at a concentration of 4 µg/ml at a rate of 20 µg/minute for a

period of 5 minutes to 6 hours. In 69 cases submitted to different surgical operations, satisfactory pressor response was obtained in all cases including mitral valvotomy.

Similar beneficial results of noradrenaline infusion in surgical cases resulting in hypotension have been reported by Ghose (1952), Barlow and co-workers (1953), Freemont and co-workers (1954) and Gilmour (1955). Noradrenaline was infused in a concentration of 4-8 µg/ml at a rate adequate to sustain blood pressure at required levels.

Crawford and Haynes (1953) administered noradrenaline to subjects suffering from infections after surgery, peritonitis, extensive sympathectomy, removal of pheochromocytoma and splanchnic block in acute pancreatitis. They confirmed that noradrenaline 4 µg/ml given intravenously at a rate of 10-60 drops/minute did help their patients maintain adequate blood pressure levels.

Welch (1954) subjected 30 patients suffering from neurogenic or surgical shock to infusion of noradrenaline. Substantial pressor effects were obtained when the drug was infused at a rate of 20-40 drops/minute for 12-36 hours in a concentration of 4 µg/ml. This author also studied the effects of a different pressor agent, neosynephrine, in patients undergoing shock. Difficulty was experienced after discontinuation of the drug since the arrest of the infusion caused the blood pressure to fall to a low level. These

difficulties were circumvented by the use of corticotrophin (25 mg in 1 liter of 5% glucose) along with noradrenaline infusion before the termination of the latter.

Davies (1957) administered noradrenaline in a dose of 4-32 μg/ml at a rate of 60-80 drops per minute for 40-60 hours to 3 patients suffering from intestinal and peptic perforations associated with profound shock. Two of the three recovered and one showed an immediate response but died 12 days later.

These above-mentioned reports indicate that noradrenaline given as an intravenous drip has proved of value in raising the blood pressure in certain conditions of surgical shock.

B. Myocardial Infarction (Cardiogenic Shock)

Many clinicians claim noradrenaline to be the most beneficial agent in the treatment of shock resulting from myocardial infarction.

Calenda, Uricchio and Friedman (1953) administered noradrenaline to 13 cases suffering from myocardial shock; the dose used was 4 μg/ml at a rate determined by the pressor response obtained. Noradrenaline was found life-saving in only 4 cases. These authors did not believe that noradrenaline was of significant value in treatment of shock resulting from myocardial infarction.

Gazes and co-workers (1953) reported 14 cases of severe shock due to myocardial infarction, 7 of whom were

treated with neosynephrine, 6 with noradrenaline and one with a combination of both drugs. Noradrenaline when administered in a dose of 4 µg/ml at a rate sufficient to maintain the systolic pressure at 120 mm Hg (range 5-100 drops per minute), brought about total recovery from shock in 5 out of 6 patients; on the other hand only 2 out of 7 patients emerged from shock when neosynephrine was administered in a dose of 10-20 mg/liter, i.e., 10-20 µg/ml for 6-30 hours at a rate sufficient to raise the blood pressure to 120 mm Hg (5-100 drops/minute). The patient treated with combined therapy recovered. In trained nonanaesthetized dogs, these authors reported that noradrenaline injection (1 µg/kg) or infusion of noradrenaline (10 µg/kg/minute for 15 minutes) induced an increase in the force of myocardial contraction measured by a Walton-Brodie strain gauge. This increase in the force of myocardial contraction was minimal with 15 mg/kg of phenylephrine (Neosynephrine), 1 mg/kg of mephentermine (Wyamine) and 10 mg/kg of methoxamine (Vasoxyl). Gazes and co-workers concluded that the higher rate of recovery from shock resulting with noradrenaline administration was directly attributable to its dynamic effect on the cardiac contractile force.

Sampson and Zipser (1954) reported survival in 20 out of 30 patients treated with noradrenaline during shock of cardiogenic etiology. The average dose infused was 7.5 µg/kg/minute for a period of 3-136 hours; 10 patients died during the administration of noradrenaline.

Smith and Guz (1953) observed survival in 4 out of 6 cases of cardiogenic shock treated with noradrenaline, 5-40 μg/minute for 48 hours to 5 days. A drip rate of 36-60 drops/minute was maintained.

Successful treatment with noradrenaline (4 μg/ml) at a rate of 20 drops/minute for 18 hours was reported by Ruprechet (1956) in a case of shock due to myocardial infarction associated with atrioventricular block.

Siglin (1956) also administered noradrenaline (16 mg/liter) to maintain blood pressure in a case of shock due to myocardial infarction. Noradrenaline was infused for a period of 14 days with a total of 402 mg of noradrenaline. The rate of flow was adjusted to maintain blood pressure at 90-120 mm Hg. It should be pointed out that the author had concurrently administered cortisone so that the recovery of the patient could not have been entirely due to noradrenaline.

Heyer (1960) found a mortality rate of 45% in cases of myocardial infarction accompanied with shock and treated with noradrenaline. The dose used was relatively high (8 mg/liter, i.e., 8 μg/ml at a rate of 6-40 drops/minute) and it was even increased to 32 μg/ml when found necessary.

Noradrenaline was also found useful in cardiogenic shock by Hellar (1961) who administered 4 μg/ml at a rate of 7 drops/minute for an average of 1-6 days; the drip was not removed abruptly but was followed by an infusion of 5% dextrose for 12-24 hours. This procedure of weaning away the

drug was also recommended by Miller and Kaplan (1961) who used noradrenaline infusion (4-8 μg/ml) for variable periods of time in hypotensive shock following myocardial infarction.

C. Shock of Varying Etiology

The beneficial effects of noradrenaline in states of shock arising from different causes have been reported in many publications.

Skelton and co-workers (1952) administered noradrenaline to 17 patients suffering from shock as a result of: myocardial infarction (6); postoperative state (4); heart failure (2); peripheral vascular collapse (1); infections (4). All but one responded with an elevation of blood pressure; 9 recovered completely without showing signs of residual renal impairment. These authors found no deleterious effects on the cardiovascular and renal systems in 8 normal subjects to whom noradrenaline infusion (4 μg/ml in 5% dextrose) was administered.

The effectiveness of noradrenaline administration in shock was particularly striking in patients treated by Kurland and Malach (1952). The response was considered as satisfactory in 12 out of 17 episodes of shock due to myocardial infarction, and 18 out of 20 episodes of shock due to other causes. The dose used was 4 μg/ml in 5% glucose and the infusion was given from 4 to 74 hours at a rate of 20-30 drops/minute. The maximum duration of infusion was 6 days during which period a total of 62 mg of noradrenaline was infused.

Livesay and Chapman (1953) administered noradrenaline (4 μg/ml in glucose) at a rate determined by monitoring the pressor response, to 22 patients in shock resulting from acute pulmonary embolism, myocardial infarction, incompatible blood transfusion, overdose of hexamethonium, extensive burns, acute leukaemias, coronary insufficiency, acute cor pulmonale, and acute barbiturate intoxication. Out of 22 patients treated only two did not show a definite pressor response. Tachyphylaxis to the drug was noted.

Miller and co-workers (1953) reported excellent pressor response to noradrenaline infusion in 25 of 32 patients suffering from various types of shock associated with barbiturate intoxication, bulbar poliomyelitis, virus pleuro-pericarditis, ruptured ectopic pregnancy and empyema of the gall bladder. The dose of administered noradrenaline was 4 μg/ml infused at a rate of 10-15 drops per minute for 30 minutes to 36 hours. Overt myocardial side effects were not noticed. Concentrations of noradrenaline as high as 32 μg/ml, infused at a rate of 100 drops per minute, produced no undesirable side effects.

Moyer and co-workers (1953) treated patients suffering from shock due to myocardial infarction (14 cases), overwhelming infection (9), hypotension secondary to medication (6) and surgical shock (15). A satisfactory response in all but 2 of 44 patients who were given noradrenaline infusion at an average dose of 6 μg/ml was observed. The

rate of infusion was adjusted to maintain blood pressure at desirable levels.

Eckenoff and Dripps (1954) administered noradrenaline infusion (8 µg/ml in saline) to 75 civilian and military cases suffering from profound cardiovascular collapse, regardless of etiology (myocardial infarction, haemorrhage during operation, perforation of the bowel and peritonitis, etc.). The rate of administered noradrenaline was 1-2 µg per minute, but in certain instances 20-40 µg/kg were required. A total dose of 16 mg/kg during a 4 hour period was used. Such therapy proved adequate in maintaining blood pressure at required levels.

Hall (1955) reported a case of severe shock, of unknown etiology, in which noradrenaline was administered intravenously for 22 days (a total of 1452 mg), the rate of infusion being adjusted to maintain blood pressure between 90-120 mm Hg. The patient recovered completely without displaying any untoward effects.

From this review one can see that noradrenaline has been commonly utilized in the clinical treatment of shock. However, Nickerson (1961) pointed out that, "Although all these clinical reports provided evidence as to the value of vasopressor therapy, in that the blood pressure could be raised in a high percentage of cases and the patient might temporarily look and feel better, there was little reliable

evidence that survival was equally favourably affected."

Undesirable effects of noradrenaline infusion were reported in the literature. Bearn and co-workers (1952) determined the changes in hepatic blood flow by using their radio-opaque catheterization technique. They observed a slight decrease in hepatic blood flow induced by noradrenaline infusion at a rate of 0.10-0.20 μg/kg/minute for 30 minutes.

Grayson and Johnson (1952) have shown in animal studies that noradrenaline and adrenaline had a marked constrictor effect on the terminal branches of the hepatic artery. According to the authors the preservation of blood pressure at the cost of long periods of relative ischaemia of the liver is a hazardous procedure, and the infusion of noradrenaline should not be administered for more than one hour as it could be potentially dangerous.

Miller and co-workers (1955) have shown that electrocardiographic changes are associated with an infusion of noradrenaline in human subjects. Intravenous noradrenaline, 1 μg/ml in 5% dextrose was begun at a slow rate and gradually increased until the arterial blood pressure was raised to significantly higher levels. In 5 subjects arrhythmias of supraventricular origin were observed and 4 patients showed bradycardia.

Littler and McKendrick (1957) also presented clinical evidence of noradrenaline-induced cardiac

arrhythmias in 22 patients suffering from shock due to myocardial infarction. Noradrenaline infusion, 20-100 µg/ml in 5% dextrose for a period lasting up to 8 days, induced a pressor response in 10 out of 22 patients; however, none survived. Twelve other patients showed no pressor response whatever. Four cases showed cardiac arrhythmias associated with the infusion. The rate of the infusion was adjusted according to the blood pressure response. In animal investigations on dogs and monkeys (anaesthetized with pentobarbitone), after injection of 0.5 µg/kg of noradrenaline ventricular extrasystoles were observed. Doses of 6-12 µg/kg induced cardiac arrhythmias (nodal rhythm), transient auricular-ventricular dissociation, multifocal extrasystoles and paroxysms of ventricular tachycardia.

Clinically some evidence of renal damage induced by noradrenaline was shown by Boughton and Sommers (1957). Microscopic degenerative changes in the epithelium of convoluted tubules were found on post mortem examination in 8 patients, who had been given noradrenaline therapy from 3-48 hours with a total dose of 16-144 mg.

Yoe (1954) evaluated the effects of noradrenaline in cases of shock due to haemorrhagic fever; the dose administered was 10-30 µg/minute at a rate adjusted to maintain the blood pressure between 100-115 mm Hg. The duration of infusion varied from 20-101 hours. Out of 12 patients treated, 5 died. Yoe stated, "Noradrenaline is a useful

procedure in treatment of shock due to haemorrhagic fever, pressor therapy however alone rarely suffices. The response to noradrenaline is transient and does not prevent development of renal failure."

Other undesirable phenomena of noradrenaline administration in shock are tolerance development to the pressor response during the infusion (see Davies, 1957 and Livesay and Chapman, 1953) and the hypotension which ensues after the cessation of the infusion (see Welch, 1954; Hellar, 1961; and Miller and Kaplan, 1961); blood pressure often falls below the preinfusional level and remains at this "hypotensive level" for a considerable period of time. The occurrence of this "Noradrenaline Postinfusional Hypotension" (N.P.H.) seriously endangers the life of the patient as his preinfusional blood pressure is already low.

Studies on the mechanisms involved in noradrenaline postinfusional hypotension have been undertaken by many investigators, and different theories have been postulated to explain this phenomena. A detailed resume of the various theories subserving the phenomena of N.P.H. follows.

A. Release of Vasodilator Substance

Blackettand co-workers (1950) administered a continuous infusion of noradrenaline for a period of 8 days to unanaesthetized rabbits; a marked fall in blood pressure was observed when the infusion was replaced with saline. During

the infusion of noradrenaline haemoconcentration was not seen. Inactivation of noradrenaline through oxidation was excluded since no change in the blood pressure fall was observed after replacement from an old to a fresh noradrenaline infusion. These workers postulated that prolonged infusion of noradrenaline caused a release into the circulation of a vasodilator substance, and that this release continued for some time after the infusion had ceased, and was responsible for N.P.H.

Lever and Mowbray (1961) infused noradrenaline to normal nonanaesthetized recumbent adults and to dogs and rabbits anaesthetized with pentobarbitone. The human subjects received the infusion for 1-2 hours (10-30 μg/minute); and dogs, 15 μg/minute for 6 hours. A few minutes after the infusion was commenced an increase in the muscle blood flow was observed in man and animals, which continued in the postinfusional phase. A similar increase in muscle blood flow was observed in denervated gracilus muscle of the rabbit; this excluded the possibility of any neurogenic component being involved in increased blood flow. This increase in the muscle blood flow could possibly have been due to release of some vasodilator substance in the blood stream. On the basis of the above evidence these authors suggested that N.P.H. was induced by a vasodilator substance released into the blood stream during the late stage of infusion and during the postinfusional phase.

Eakins and Lockett (1961) investigated the effects of intravenous injection of adrenaline (6 μg/kg) in adrenalectomized cats pretreated with hexamethonium and anaesthetized with ether and chloralose. Plasma was withdrawn throughout the response of mean arterial pressure after the administration of adrenaline. It was purified and bioassayed for vasodilator activity utilizing the rat blood pressure technique. They claimed to have found an isoprenaline-like substance in the plasma extract. In cats pretreated with monoamine oxidase inhibitors an increase in the isoprenaline-like substance was found; however no such increase was detected after pretreatment with pyrogallol, a catechol-O-methyl transferase inhibitor. Eakins and Lockett therefore suggested that the isoprenaline-like activity may be due to the presence of a vasodilator substance formed from adrenaline by the action of catechol-O-methyl transferase and probably metabolized by amine oxidase. The liver seemed to be the main site of production of this substance, as isoprenaline-like activity in the plasma was increased after stimulation of hepatic nerves. The authors were not able to detect such a substance in plasma withdrawn during pressor response to noradrenaline injection (2.7-7 μg/kg).

Duner and Von Euler (1957) infused noradrenaline (0.2-0.8 μg/kg for 10 minutes) in cats anaesthetized with pentobarbitone. Marked noradrenaline-induced postinfusional

hypotension (N.P.H.) was observed after the infusion was terminated. They proposed that N.P.H. could be divided into two phases which were induced by different mechanisms: a) the immediate, short-lasting phase which occurred immediately after the arrest of infusion was believed to be due to a release of a vasodilator substance and was abolished by ergotoxin administration, and b) the second long-lasting phase which was ascribed to a partial sympathetic ganglionic blockade. In 1959 these same authors, in cats anaesthetized with pentobarbitone, infused noradrenaline (1.6-2.2 μg/kg/minute for 10 minutes), and observed a decrease in the blood flow in the hind part of the cat during the post-infusional hypotensive phase. This decrease in blood flow was suggested to be the result of peripheral vasodilatation which led to pooling of blood on the venous side and a consequent decrease in the circulating blood volume. When noradrenaline was infused under conditions of reduced ventilation, the blood pressure rise was of less intensity, but there was a marked increase in the pressor response to carotid occlusion. At the termination of infusion no secondary fall in blood pressure occurred in these experiments. The increased response to carotid occlusion under conditions of reduced ventilation was explained by the authors to be due to either increased outflow of catecholamines from the suprarenal gland or increased sensitivity of the receptors of the heart and the blood vessels to the endogenous transmitter.

Melville (1951) demonstrated that the pressor response induced by a continuous infusion of noradrenaline (0.1 mg/minute for 5 minutes) in spinal cats could be reversed by superimposed injection of ergotoxin, hydergine, ergotamine, dihydroergotamine, dibenamine or benzodiaxone (Compound F 933). A similar "noradrenaline reversal" was shown in cats pretreated with atropine and anaesthetized with either ether, chloralose or pentobarbitone, thus eliminating the possibility of any implication of either anaesthetic or surgical procedure employed. When noradrenaline infusion (0.1 mg/minute for 5 minutes) was administered in cats anaesthetized with chloralose and pretreated with atropine, the "noradrenaline reversal" was considerably diminished by infusion of pituitary extract (20 pressor units/minute for 8 minutes). Also during continuous infusion of pituitary extract "noradrenaline reversal" was replaced by a pressor response. In dogs anaesthetized with pentobarbitone and pretreated with ergotoxin, noradrenaline infusion (0.2 mg/kg/minute for 5 minutes) produced a depressor response; little change was observed when the dog was pretreated with atropine. Similar results were obtained with adrenalectomized dogs under pentobarbitone anaesthesia, except that after noradrenaline infusion was terminated the animals' blood pressure fell progressively. Melville suggested that the observed noradrenaline reversal was due to peripheral vasodilatation.

B. Ganglionic Blockade

Ganglionic blockade as a result of noradrenaline administration has been postulated as a possible mechanism of noradrenaline-induced postinfusional hypotension by many authors.

The effects of noradrenaline and adrenaline on ganglionic transmission have been reported by many workers.

Bulbring (1944) showed in cats anaesthetized with chloralose that intravenous injection of 0.1 μg of adrenaline produced increase of, and 0.5 μg of adrenaline caused a depression of ganglionic transmission in the superior cervical ganglion as evidenced by changes in the height of contraction of nictitating membrane which was stimulated preganglionically.

Posternak and Larabee (1950) reported that short periods of carotid occlusion in cats induced a depression in transmission of the stellate ganglion, which was believed to be due to an inhibitory action of noradrenaline released from the adrenal gland during carotid occlusion.

Lundberg (1952) found that an intravenous injection of adrenaline (1-10 μg) caused a noticeable inhibition of transmission in sympathetic ganglia (superior cervical and stellate) of cats anaesthetized with pentobarbitone.

The depressor effects of noradrenaline on ganglionic transmission were confirmed in 1956 by Matthews in decerebrate cats. Depression of postganglionic potentials

in the superior cervical ganglion during submaximal preganglionic stimulation was observed. The dose of noradrenaline administered was 5 μg/kg intravenously. Adrenaline was found to be three times more potent than noradrenaline in this respect.

Duner and Von Euler (1957) induced noradrenaline postinfusional hypotension in cats anaesthetized with pentobarbitone. Noradrenaline 0.2-2.6 μg/kg/minute for 10 minutes was administered. The response obtained after carotid occlusion was diminished during and after the infusion. Pretreatment of cats with tetraethyl-ammonium bromide, a ganglionic blocking agent, abolished the long-lasting phase of postinfusional hypotension. These authors suggested that the long lasting-phase of noradrenaline-induced hypotension may be due to a partial blockade of the "peripheral vasomotor system." It was observed that buffer nerve section aggravated the N.P.H. The authors interpreted that when buffer nerves were cut, no counter regulation was effective, and therefore noradrenaline postinfusional hypotension was aggravated. They explained that since the postinfusional hypotension was abolished after tetraethyl-ammonium bromide (TEA), it might be possible that after the ganglionic transmission was already blocked by TEA, noradrenaline administration did not cause a further ganglionic blockade, and hence did not produce noradrenaline postinfusional hypotension. However the authors' interpretation is not clear, for if

buffer nerve section aggravated the N.P.H., this would mean that the reflexes were still operating during the hypotensive phase, and maintained the blood pressure at a higher level; if so, then with ganglionic blockade when such reflexes are abolished the postinfusional hypotension should be increased and not abolished.

Ganglionic blockade as a mechanism of N.P.H. was questioned by Mazurkiewicz and Murnaghan (1964). Noradrenaline 8 μg/kg/minute for 5 minutes was infused in cats anaesthetized with pentobarbitone. Ganglionic transmission was not impaired during N.P.H. as shown by the unchanged contractions of the nictitating membrane elicited by preganglionic stimulation. It was further shown that N.P.H. was absent not only in hexamethonium-treated cats, but also in normal cats when their preinfusional blood pressure was lowered (by bleeding) to a level similar to that seen in the former animals. On the other hand despite ganglionic blockade produced by hexamethonium administration, N.P.H. did occur when the low preinfusional blood pressure was raised by a continuous infusion of angiotensin previous to noradrenaline administration. Moreover in animals whose preinfusional blood pressure was lowered by bleeding N.P.H. was absent; however restoration of normal preinfusional blood pressure by reinfusion of blood resulted again in N.P.H. It was suggested, therefore, that absence of N.P.H. after tetraethyl-ammonium bromide observed in the experi-

ments of Duner and Von Euler could have been due to the low preinfusional blood pressure seen in these animals. Mazurkiewicz and Murnaghan (1964) also found no difference in the intensity of N.P.H. in eviscerated cats, which seemed to indicate that N.P.H. could be linked with vasodilatation in regions other than the mesentery. In eviscerated preparations the main blood supply of the liver was excluded (by ligation of both hepatic artery and femoral vein), thereby suggesting that liver was not the source of the vasodilator substance as proposed by Eakins and Lockett (1961). Moreover chromatographic studies of plasma withdrawn during N.P.H. did not reveal any isoprenaline-like substance (personal communication).

Condon and Sheenan (1963) showed a secondary depressor response after single injections of noradrenaline (0.1-0.7 µg/kg intravenously) in dogs. Pentobarbitone, thiopentone sodium (pentothal) and barbitone were used as anaesthetics. Baroreceptor denervation abolished this secondary depressor response. These authors also showed that after pretreatment with dibenzyline (phenoxybenzamine) 15 mg/kg, both the pressor and depressor response to noradrenaline injection disappeared; it was therefore suggested that the secondary fall in blood pressure represents an over compensation by the baroreceptor mechanism for the initial elevation of blood pressure. A decrease in the total peripheral resistance was suggested either by a direct "inhibitor

action of noradrenaline on the blood vessel wall" or by a reflex mechanism involving the vasomotor centre. It should be pointed out that studies of Duner and Von Euler (1957) and Condon and Sheenan drew attention to the role of baro-receptor reflexes in producing the secondary fall in blood pressure after noradrenaline infusion. Whereas, Duner and Von Euler (1957) reported that baroreceptor denervation aggravated the N.P.H., Condon and Sheenan showed the nor-adrenaline depressor response to be abolished by baro-receptor denervation. The discrepancy in the results of these authors could have been due to the fact that Duner and Von Euler used dogs and administered noradrenaline in-fusion (total dose 6 μg/kg), while Condon and Sheenan used cats and administered noradrenaline injections (0.1-0.17 μg/kg), and used much smaller doses.

In 1959 Kendrick reported that ganglionic blocking drugs could modify the peripheral vascular effects of adrenaline and noradrenaline. The author used "totally perfused" dogs in whom the heart was replaced by a pump capable of maintaining a constant flow output against pressure heads up to 200 mm Hg. This procedure eliminated the cardiac effects of adrenaline and noradrenaline so that the responses in the perfused animal reflected only the change in resistance of the peripheral vascular system. Ganglionic blockade with hexamethonium converted the di-phasic response of noradrenaline to a monophasic response.

The author considered the after-fall in the blood pressure response to noradrenaline as "possibly due to a change in the vasoconstrictor tone because of either an increased activity of the presso-receptor reflexes or a direct inhibition of the sympathetic system by these pressor amines." This assumption was based on the observation that the after-fall in blood pressure response to noradrenaline was abolished, after administration of the ganglionic blocking agent, hexamethonium.

Burn and Rand (1959) observed tolerance development to the pressor response of noradrenaline in spinal cats. N.P.H. ensued after an infusion of 6.5 μg/minute for 30 minutes. The authors suggested that during an infusion of noradrenaline, adrenergic receptors in the blood vessels become increasingly insensitive to its pressor action. It is quite possible that the blood vessels take up the infused noradrenaline, store it and then slowly discharge it on the receptors, leaving a few receptors free on which circulating noradrenaline can act. Ganglionic blockade was also suggested to be responsible for the lack of sympathetic tone and the secondary fall in blood pressure. Noradrenaline postinfusional hypotension was shown to be reversed immediately after administration of ephedrine or after injection of other indirectly acting sympathomimetic amines such as methedrine, aramine, vasoxine and propadrine.

C. Decreased Blood Volume

It is well known that sympathetic over-activity causes haemoconcentration and decreased cardiac output. Bainbridge and Trevan (1917) slowly infused noradrenaline intravenously in anaesthetized dogs for 20 minutes or longer at a rate sufficient to maintain the arterial pressure at "supra normal" levels. During the infusion a rise in the portal pressure was observed, while systemic pressure was significantly altered. A steady decrease in the plasma volume relative to the corpuscular volume and an increase in the viscosity of blood was observed. On discontinuing the infusion, arterial blood pressure fell below pre-infusional level, while the portal pressure remained high; turgidity of the liver was noted. The fall in arterial pressure was attributed to cardiac output failure resulting from defective venous inflow caused by reduction in circulating blood volume.

Erlanger and Gasser (1919) administered 6-11 ml of 1:1000 adrenaline (1 μg/ml) intravenously for 21-90 minutes to dogs anaesthetized with ether. After the infusion was terminated there was a marked fall in blood pressure followed by a slow return to the preinfusional level. The secondary hypotension observed in these experiments was associated with haemoconcentration and a reduction of 28.8% in blood volume. An increase in the portal pressure was also observed, but it was suggested that this was not

the causative factor of shock since blocking the portal radicles of the liver with lycopodium spores (these plug the vessels proximal to the point where they break up into capillaries) resulted in an increase in portal pressure, but did not induce a change in blood pressure.

In cats anaesthetized with Dial (Diallyl barbituric acid, Ciba) Freeman (1933) showed that prolonged hyperactivity of the autonomic sympathetic system induced by either adrenaline infusion (3.35 μg/kg/minute for 97 minutes) into the jugular vein or by "spontaneous emotional activity in pseudo effective states" (a condition produced by decortication via orbitus, under ether, leading to increased hyperactivity of sympathetic system) resulted in a decreased blood volume of 13.4%, the plasma volume decreased to a greater extent than cell volume (there was a rise in haematocrit value).

Freeman and co-workers (1941) repeated some of the above experiments in unanaesthetized trained dogs. Adrenaline was infused at a rate of 3.35 μg/kg/minute for a period of 1-1.5 hours. A fall in arterial blood pressure, beginning during the infusion and reaching to low levels after termination of the infusion was observed; this was accompanied by a decrease in peripheral blood flow and great haemoconcentration.

Schmutzer, Ekkhari and Maloni (1961) investigated the relationship between blood volume changes and noradrenaline postinfusional hypotension, in mongrel dogs subjected

to prior splenectomy and anaesthetized with pentobarbitone. Infusion of noradrenaline (4 μg/kg/minute for 10 minutes) led to N.P.H. associated with striking diminution of plasma volume (average 26.8%). The fall in blood pressure seen at the termination of the infusion was prevented by infusion of dextran or whole blood. This procedure of infusing dextran at the end of noradrenaline infusion was also found effective in a number of patients suffering from shock who were treated with noradrenaline infusion. The authors also reported clinically that hypovolaemic state associated with haemorrhagic shock was aggravated further by noradrenaline infusion.

Rosenthale and Dipalma (1962) observed acute tolerance development to the pressor effect of noradrenaline when infusion of 4 μg/kg/minute was administered over a period of 3 hours to mongrel dogs under urethane anaesthesia. This tolerance development was associated with haemoconcentration, decreased blood volume, decreased cardiac output and acidosis. Restoration of plasma volume with dextran (20 ml/kg) produced a dramatic, though temporary reversal of tolerance. On the other hand splenectomy, adrenalectomy and correction of acidosis did not affect the development of tolerance. As no change in the development of tolerance was seen after pretreatment with hexamethonium or in spinal and decerebrated cats, any involvement of the autonomic reflexes in the tolerance develop-

ment was ruled out. At the time tolerance to noradrenaline had developed plasma levels of noradrenaline were high and monoamine oxidase activity in the liver was not increased, which indicated that there was no enhancement of noradrenaline catabolism.

Nickerson and Sutter (1964) infused angiotensin (0.5 μg/kg/minute) or noradrenaline (0.2 μg/kg/minute) to dogs under light pentobarbitone anaesthesia for a period of 60 minutes. The effects of these infusions on intravascular fluid volume were assessed by changes in plasma protein concentration. Iodine 131 labelled serum albumin was injected intravenously and its concentration in the plasma measured prior to, during, and after the infusion of these pressor agents. During the infusion of equipressor doses of angiotensin and noradrenaline a comparable loss of relatively protein-free fluid was observed.

The above-mentioned experiments reveal that decreased blood volume was observed during and after infusion of noradrenaline; haemoconcentration was often reported. It is possible, therefore, that noradrenaline postinfusional hypotension may be in part or wholly related to these changes.

D. Beta Receptor Activation

It is known that on blood pressure noradrenaline produces its excitatory response (pressor effect) by its action on the alpha adrenergic receptors, and its inhibitory

response (depressor effect) by acting on the beta adrenergic receptors. The postinfusional hypotension may be a result of activation of beta receptors, and hence vasodilatation and a marked fall in blood pressure.

Karim (1964) demonstrated a secondary depressor response after injection of noradrenaline (5-20 μg) in cats anaesthetized with pentobarbitone. Such a fall in blood pressure was not seen in eviscerated animals, and the suggestion was made that dilatation (of the splanchnic blood vessel) was a factor involved in the depressor response. The author also claimed success in abolishing this depressor response with noradrenaline by beta receptor blockade induced by administration of pronethalol (5 mg/kg intravenously).

E. Histamine Release

Copola and Dipalma (1962) showed tolerance development to the pressor effect of noradrenaline in mongrel dogs anaesthetized with Dial-urethane mixture (Diallylbarbituric acid, Ciba). Tolerance development was associated with a progressive increase in plasma histamine level (47.8 $\pm$ 5.9 (S.E.) μ/liter to 89.6 $\pm$ 7.5 (S.E.) μ/liter) during the three hour infusion period. The average dose of noradrenaline during the three hour infusion period was 13.3 μg/kg/minute. If histamine stores were depleted by administration of Compound 48/80, tolerance to noradrenaline was no longer produced. The mean initial dose of noradrenaline to raise the blood pressure was 12.6 μg/kg/minute;

after injection of Compound 48/80 the mean dose of noradrenaline required to raise the blood pressure to the same level was 5.3 μg/kg/minute. These authors suggested that histamine may be a causative factor in producing tolerance to the pressor effects of noradrenaline. However Nickerson and Goodman (1947) showed that dibenamine-induced reversal of adrenergic vasopressor effects in cats anaesthetized with pentobarbitone was not altered by atropine, benadryl or pyribenzamine, suggesting that the blood pressure "reversal" was probably not due to a release of histamine.

West (1949) showed that in ergotoxin-treated spinal cats, and in cats under urethane and chloralose anaesthesia, a fall in blood pressure was elicited by noradrenaline injections (250 μg). Antihistaminics (benadryl and antistine) administered prior to the injection of ergotoxin did not affect the noradrenaline reversal, which indicated that the vasodepressor response induced by a large dose of noradrenaline was not due to liberation of histamine. West postulated that the mechanism of the fall in blood pressure induced by noradrenaline was due to activation of a presso-receptor reflex arising in the pulmonary artery. The activation of this reflex was attributed to being secondary to an increase in the pulmonary artery pressure (a rise in pulmonary vessel pressure has been shown to induce a fall in systemic circulation by Parin in 1947).

F. Changes in Peripheral Resistance

Weglarz and Killip (1963) in their experiments on dogs under pentobarbitone anaesthesia observed that infusion of noradrenaline (1.2 μg/kg for 10 minutes) caused a decline in the peripheral resistance towards the end of infusion. This decline persisted for 10 minutes after the infusion was arrested. No significant reduction in cardiac output during the decline in peripheral resistance was observed. N.P.H. and tolerance to the pressor effects of noradrenaline were attributed to a decline in the peripheral resistance.

G. Tissue Hypoxia

Yard and Nickerson (1956) infused large doses of noradrenaline (2 μg/kg/minute for 4 hours) to dogs under light pentobarbitone anaesthesia. Such an infusion produced a marked fall in blood pressure resulting in intense shock followed by death in 10 out of 11 animals. Post mortem examination revealed haemorrhages in the intestinal lumen and on the mucosal surface, suggesting the possibility of tissue hypoxia which resulted from prolonged vasoconstriction; possibly this hypoxia may be the cause of shock and pathological lesion.

H. Changes in Cardiac Output

Gilbert and Hohf (1964) administered noradrenaline infusion to dogs under pentobarbitone anaesthesia. Noradrenaline was administered in 5% dextrose in amounts sufficient to

raise the blood pressure by 50 mm Hg. for a period of 120 minutes. The average infusion rate used was 8 μg/kg/minute at the beginning of the experiment and it was raised to 18 μg/kg/minute towards the end of infusion. Cardiac output was measured by the indicator dilution method. A loss of pressor response was evident after 10 minutes of infusion at which time a low cardiac output without a decrease in the total peripheral resistance was observed. According to the authors the loss of pressor responsiveness probably resulted from a progressive decrease in myocardial function. Two out of nine animals died of low blood pressure and low cardiac output before the end of the two hour infusion period.

Page and Olmsted (1961) infused noradrenaline (4-16 μg/minute) to unanaesthetized dogs for one hour. The authors observed a rise in arterial pressure associated with a fall in cardiac output at the beginning of the infusion. With a constant rate of infusion (4 μg/minute for 1 hour) the arterial pressure level tended to fall and a continued depression of cardiac output was observed.

I. Direct Effects on the Myocardium

Some evidence of the deleterious effects of noradrenaline on the myocardium was presented by Szakacs and Cannon (1958). Continuous infusion of noradrenaline at a rate of 0.8-0.9 μg/minute for 107 to 336 hours was administered to dogs sedated with morphine (2 mg/kg). Focal myocarditis was revealed on post mortem examination. Necro-

tising arteritis of the gastrointestinal tract was also observed. The autopsy of two clinical fatal cases of shock treated previously with noradrenaline infusion also showed focal myocarditis and haemorrhagic lesions of the pericardium and endocardium.

Maling and Highman (1958) administered an intravenous infusion of a total dose of 0.51 mg/kg of noradrenaline to unanaesthetized dogs at a rate of 6.2 µg/kg/minute for 83 minutes. During and after the infusion, tolerance developed to the pressor effect of noradrenaline and on termination of infusion a fall in blood pressure below the preinfusional level ensued. The heart was sensitized to catecholamines, as small doses of these amines induced ventricular tachycardia. In dogs killed one day after infusion, fatty changes in the heart were seen.

Szakacs, Dimmette and Cowart (1959) infused noradrenaline in dogs pretreated with morphine (2 mg/kg). Different concentrations of noradrenaline (corresponding to the therapeutic doses in man) were infused for varying periods. At a dose level of 1-1.5 µg/kg/minute for 24 hours, there was a mean rise in arterial blood pressure of 30 mm Hg. Two-thirds of the animals showed gross myocardial changes after ten hours of such continuous infusion. An infusion of 0.8 µg/kg/minute continued for several days resulted in focal areas of myocarditis. In doses of 10-15 µg/kg/minute for one hour, severe mechanical injuries to the mitral valve were seen. Further experimental work on

the cardiotoxic effects of noradrenaline was done by Szakacs and Mehlman (1960). Dogs were sedated with morphine (2 mg/kg) and infused with noradrenaline 0.5-15 mg/kg. Death occurred when 10 mg/kg was infused from 0.5-3 hours or 5 mg/kg for 6 hours. The cause of death was cardiac haemorrhage and pulmonary oedema. Autopsy showed medial necrosis and degeneration of the conducting system of the heart.

Binder (1965) studied the haemodynamic effects of noradrenaline and metaraminol in 10 patients suffering from severe shock due to acute myocardial infarction. He observed that these haemodynamic effects were dependent on the patient's condition. With an initially low cardiac output and an elevated peripheral resistance, these drugs elevated the cardiac output, but produced little change in the latter; when however, the peripheral resistance was initially normal or low and the cardiac output low, moderately reduced or normal, noradrenaline increased the peripheral resistance significantly but reduced the cardiac output. This author expressed the opinion, that vasopressor drugs are of limited value in the treatment of shock due to myocardial infarction. In 15 patients treated, pressor response to noradrenaline or metaraminol was obtained in 14 cases, yet only three survived.

Shubin and Weil (1965) observed for 327 hours, 10 patients who were suffering from shock due to acute myocardial infarction and treated them with noradrenaline and metaraminol. Beneficial haemodynamic effects of these drugs were seen

when administered in moderate amounts. When mean arterial pressure increased from 57-80 mm Hg there was an increase in cardiac output (32%) above the pretreatment values; this increase was remarkably associated with a decrease in peripheral resistance. However these authors further showed that additional elevation of blood pressure was not accompanied by an increase in the cardiac output; on the contrary when mean arterial pressure was raised to levels exceeding 90 mm Hg cardiac output fell and peripheral resistance was increased. Their work indicated that pressor amines have detrimental effects when clinicians use them for maintaining "normal blood pressure."

Sambhi and co-workers (1964) measured cardiac output by the dye dilution technique of Nicholson and Wood in 15 patients suffering from shock and treated with metaraminol and noradrenaline. These authors concluded that the vasopressor amines did not reduce the cardiac output, in 14 out of 15 patients treated.

Moss, Vittands and Schenk (1966) investigated the effects of sustained infusions of noradrenaline in dogs anaesthetized with pentobarbitone. To 3 groups of animals graded doses of 1, 2 and 4 µg/kg/minute of noradrenaline for 4 hours were administered. During the first 15 minutes of infusion the cardiac performance was augmented, but this effect was not sustained; the cardiac output declined, and the magnitude of this decline was related to the dose rate

of noradrenaline infused. The mean arterial pressure returned to, or was slightly below the control level. Electrocardiographic changes (elevation of ST segment, diminution of QRS amplitude, and Q wave abnormalities) indicated a progressive deterioration of electrical activity of the myocardium. Sustained hypovolaemia was not seen during prolonged infusion of noradrenaline and severe acidosis (pH<7.20) was inconstant. The investigators suggested that prolonged infusion of noradrenaline may produce a dissociation between myocardial oxygen supply and demand, and the end result of this sequence of events appears to be the development of hypoxic myocardial lesions and cardiac dysfunction.

Schenk and Moss (1966) investigated the cardiovascular effects of sustained infusions of noradrenaline in rabbits, cats and dogs, and demonstrated that the major toxic effect was exerted on the myocardium. The rabbits were infused a dose of 0.4, 0.8 to 1, 2 and 1.5 to 3 µg/kg/minute for 1-15 hours. Cats received 1, 2 or 4 µg/kg/minute for 4 hours and the dogs 0.5, 1, 2 or 4 µg/kg/minute for 4 hours. These doses are comparable to clinical doses. The cardiac lesions consisted of focal degeneration, necrosis of myocardium and subendocardial haemorrhage.

In spite of the vast amount of experimental work done the exact mechanism of noradrenaline postinfusional hypotension remains obscure. The experimental evidence

regarding the role of ganglionic blockade, histamine release or the presence of a circulating vasodilator substance is very conflicting. However most workers in this field do believe that a decrease in blood volume and in cardiac output is associated with the hypotension induced by an infusion of noradrenaline. An interpretation of the data published in the literature is difficult in view of the wide ranges in the dose of infused noradrenaline; a variety of animals under different anaesthetic conditions; and an equally baffling number of experimental techniques were utilized by different workers.

METHODS

Experimental Procedure

Cats of both sexes weighing 2-4.5 kg were used. Sodium pentobarbitone 35 mg/kg administered intraperitoneally was used as the anaesthetic agent in all experiments. Some animals required an additional dose of pentobarbitone 10 mg/kg before operative procedures could be commenced. During the course of the experiment 3 mg/kg of pentobarbitone was given intravenously as required. Heparin 10 mg/kg intravenously was used as the anticoagulant.

After the animal was anaesthetized, it was placed in the supine position on a heated table; the trachea was exposed by a midline incision and a cannula inserted. The animals were permitted to breathe spontaneously. Both femoral veins were cannulated with polyethylene catheters; the right vein was used for the administration of all drugs administered in this investigation. Each drug injection was washed into the circulation with 1.5 ml of physiological saline. Noradrenaline was infused through the left femoral vein, using a Palmer slow infusion apparatus. The left carotid artery was cannulated and connected to a mercury manometer. Blood pressure changes were continuously recorded on a smoked kymograph. In some of the experiments blood pressure

changes were monitored on a Grass polygraph by the use of a Statham pressure transducer.

Lead II of the electrocardiogram was continuously monitored via a Grass polygraph. E.C.G. readings were taken as follows.

1) Before noradrenaline infusion (control reading).

2) At one minute intervals during the infusion.

3) At one minute intervals for 10 minutes after the arrest of noradrenaline infusion, and

4) Every 10 minutes for 80-90 minutes after the infusion was terminated.

Heart rate changes were calculated from the electrocardiograph record. Since cardiac irregularities developed during the noradrenaline infusion, heart rate during this period was calculated from the intermittent periods of regular beats and represents, therefore, approximate values only.

After the noradrenaline infusion was arrested, postinfusional hypotension of long duration ensued. In view of the fact that in some experiments recovery of the blood pressure to the preinfusional level did not ensue within the experimental period, it was necessary to introduce the following terms:

1) "Lowest blood pressure" (L.B.P.) represents the lowest blood pressure reached following termination of infusion.

2) "Midpoint of recovery of blood pressure" (M.P.R.) represents the level of mean blood pressure in mm Hg reached when recovery of 50% was attained from the lowest blood pressure (L.B.P.). M.P.R. was calculated by taking the difference between the control preinfusional mean blood pressure value and L.B.P. value and adding 50% of this difference to the L.B.P. value.

3) "Maximum recovery of blood pressure" (M.R.) represents the mean blood pressure in mm Hg when the maximum recovery of blood pressure from the postinfusional hypotensive phase was reached within the experimental period used in this investigation (90-120 minutes).

Time in minutes to reach these three parameters (L.B.P., M.P.R. and M.R.) was estimated in all experiments. It gives some indication of the duration of noradrenaline postinfusional hypotension.

Experimental Design

Part I

In the first group of experiments a "control dose" of noradrenaline (8 μg/kg/minute for 5 minutes) was administered repeatedly to the same animal (Group I, 6 cats). Since a full recovery from N.P.H. did not occur within our experimental period of time, in the next group of experiments only one single noradrenaline infusion was administered to each animal. The following parameters that could affect the intensity and duration of N.P.H. were investigated:

an increase in the dose of noradrenaline infused; (Group II).

an increase in the duration of noradrenaline infusion; (Group III).

an increase in both dose and time of infusion; (Group IV).

In Group II, the following doses of noradrenaline were infused.

a) 8 μg/kg/minute for 5 minutes, i.e., 40 μg/kg (total dose) (6 cats); Group IIa.

b) 16 μg/kg/minute for 5 minutes, i.e., 80 μg/kg (total dose) (6 cats); Group IIb.

c) 32 μg/kg/minute for 5 minutes, i.e., 160 μg/kg (total dose) (6 cats); Group IIc.

In the third group of experiments (18 cats), the total dose of infused noradrenaline was kept constant at 40 μg/kg, but it was infused for varying time periods:

a) 8 μg/kg/minute for 5 minutes; total dose 40 μg/kg (6 cats); Group IIIa.

b) 4 μg/kg/minute for 10 minutes; total dose 40 μg/kg (6 cats); Group IIIb.

c) 2 μg/kg/minute for 20 minutes; total dose 40 μg/kg (6 cats); Group IIIc.

In the fourth group of experiments (18 cats), both the dose and time of noradrenaline infused were increased.

a) 8 μg/kg/minute for 5 minutes, i.e., total dose 40 μg/kg/minute in 5 minutes (6 cats); Group IVa.

b) 8 μg/kg/minute for 10 minutes, i.e., total dose 80 μg/kg/minute in 10 minutes (6 cats); Group IVb.

c) 8 μg/kg/minute for 20 minutes, i.e., total dose 160 μg/kg/minute in 20 minutes (6 cats); Group IVc.

Part II

The second part of this study was concerned with the effects of depletion of noradrenaline stores on the intensity and duration of noradrenaline postinfusional hypotension.

The catecholamine-depleting agents studied were: Reserpine (Group V, 6 cats), alpha methyldopa (Group VI, 6 cats) and guanethidine (chronic) (Group VII, 6 cats).

Part III

The effects of peripheral sympathetic blockade induced by bretylium and guanethidine (acute administration) were investigated in the next two groups of experiments; Group VIII (7 cats) and Group IX (6 cats) respectively.

Part IV

In view of the beneficial effect of quindonium bromide in experimental haemorrhagic shock (Melville, 1964),

the effects of quindonium bromide on noradrenaline post-infusional hypotension were investigated in Group X, consisting of 6 cats.

In all of the experiments performed in the second and third part of this study (Group V to X) the dose of noradrenaline infused was 8 µg/kg/minute for 5 minutes, and the total volume of fluid infused was 8 ml.

For statistical significance the student's "t" test was applied (Bryant, 1966). In this study statistically significant means $P < 0.05$.

Drugs

Noradrenaline (Levarterenol bitartrate, Winthrop)

Stock solutions of noradrenaline were made in 0.001 N hydrochloric acid to obtain a concentration of 1 mg/ml. Fresh stock solutions were made every week. To obtain the required concentration of the drug for infusion, solutions were made freshly before each experiment by diluting the stock solution in ascorbic acid-saline (1% ascorbic acid was diluted with 0.9% saline to give a final concentration of 0.005%). In most of the experiments the dose of noradrenaline infused, expressed as free base, was 8 µg/kg/minute at a rate of 1.6 ml/minute, i.e., total volume of 8 ml was infused.

Reserpine (Serpasil, Ciba)

Reserpine was given in a dose of 5 mg/kg intraperitoneally, 24-48 hours before the experiment. The

solution was made in a concentration of 5 mg/ml, by dissolving 100 mg of reserpine powder in 0.6 ml of glacial acetic acid and making it up to a volume of 20 ml with sterile water.

Alpha-methyldopa (Aldomet, Merck Sharpe and Dohme)

Alpha-methyldopa powder (100 mg/kg) was dissolved in 2 ml of saline, and injected intraperitoneally for three consecutive days before the experiment was started.

Guanethidine (Ismelin, Ciba)

Ampoules containing 20 mg of guanethidine were used. In acute experiments 1 mg/kg of guanethidine was administered intravenously 30-50 minutes before the infusion of noradrenaline was started. In chronic experiments guanethidine was administered in a dose of 5 mg/kg intraperitoneally daily for 7 days before the experiment was commenced.

Bretylium tosylate (Darenthin, Burroughs Wellcome)

Bretylium tosylate powder (5 mg/kg) was dissolved in saline (1.5 ml) and administered 1/2-1 hour before the infusion of noradrenaline was started.

Quindonium bromide (W3366A, Warner)

In one group of experiments consisting of 6 cats, quindonium bromide powder dissolved in saline was administered in the dose of 10 mg/kg intravenously very slowly, 30 minutes before the infusion of noradrenaline was started.

RESULTS - PART I

The Effects of Repeated Noradrenaline Infusions

In the first group of experiments (Group I) 6 cats under pentobarbitone anaesthesia were used. Infusion of noradrenaline (8 μg/kg/minute) was administered for 5 minutes; the same infusion was repeated twice at suitable intervals (60-90 minutes) in the same animal.

First Noradrenaline Infusion (Ii)

Changes in Blood Pressure

In this group of experiments the control preinfusional mean arterial blood pressure was 146 ± 10 mm Hg. During the first minute of infusion intense hypertension ensued and the blood pressure rose to 240 ± 10 mm Hg; however the blood pressure did not maintain itself at this level, and a gradual decline in blood pressure ensued in spite of the continuation of infusion. At the end of infusion the blood pressure level was 192 ± 10 mm Hg. After the arrest of the infusion the blood pressure fell far below the preinfusional level; the lowest blood pressure level (L.B.P.) reached was 77 ± 8 mm Hg and was reached in 5 ± 2 minutes (see Figure 3). However a slow recovery from this hypotension ensued, and the "midpoint of recovery of blood pressure" 111 ± 8 mm Hg was reached in 40 ± 6 minutes (see Figure 3). The maximum

recovery (M.R.) of blood pressure obtained during this experimental period was 136 ± 11 mm Hg and was reached in 86 ± 12 minutes (see Figure 3).

Changes in Heart Rate

Preinfusional heart rate was 218 ± 13 beats/minute as seen in Figure 1. Bradycardia, possibly due to reflex vagal stimulation (161 ± 11 beats/minute), developed at the peak of blood pressure rise and persisted during the noradrenaline infusion. At the end of infusion heart rate was 198 ± 16 beats/minute. At the lowest blood pressure level (L.B.P.) reached after the arrest of infusion, heart rate decreased again to 159 ± 12 beats/minute, and although it was slightly higher at the midpoint of recovery of blood pressure (M.P.R.) (179 ± 12 beats/minute), it was still markedly decreased as compared to the preinfusional rate in spite of the hypotensive phase. At maximum recovery of blood pressure heart rate was 206 ± 13 beats/minute, i.e., still below the preinfusional rate.

Second Noradrenaline Infusion (Iii)

Changes in Blood Pressure

The preinfusional mean arterial blood pressure before the second noradrenaline infusion was administered, was 134 ± 11 mm Hg. The peak blood pressure rise after the administration of infusion was 225 ± 8 mm Hg, however the

Ii

Iii

Iiii

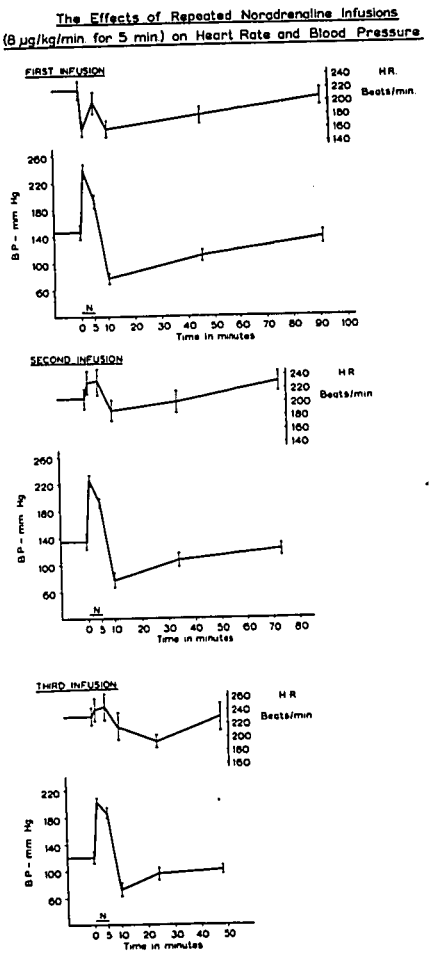

Figure 1

Heart rate and blood pressure changes induced by repeated infusions of noradrenaline administered in the same animal at suitable intervals.

N represents time of noradrenaline infusion.

Ii (upper record) represents first infusion of noradrenaline (8 µg/kg/minute for 5 minutes);

Iii (middle record) represents second infusion of noradrenaline (8 µg/kg/minute for 5 minutes); and

Iiii (lower record) represents third infusion of noradrenaline (8 µg/kg/minute for 5 minutes), administered to the same animal.

Mean ± S.E.M. from 6 experiments, except for M.P.R. in Group Iiii which represents Mean ± S.E.M. from 4 experiments, (see Text) are represented.

blood pressure declined in spite of the continuation of the infusion and at the end of infusion blood pressure level was 192 ± 6 mm Hg. After the arrest of the infusion a marked fall in blood pressure was seen and the L.B.P. reached was 76 ± 11 mm Hg in 5 ± 2 minutes (see Figure 3). M.P.R. of blood pressure level was 105 ± 10 mm Hg and was reached in 28 ± 7 minutes (see Figure 3) after the infusion was arrested. M.R. seen within our experimental period was 122 ± 9 mm Hg and was reached in 68 ± 3 minutes (see Figure 3).

Changes in Heart Rate

Preinfusional heart rate before the second infusion was 206 ± 13 beats/minute. Bradycardia during the infusion as seen with the first infusion was not observed, instead a tachycardia ensued during the administration of noradrenaline and persisted during the infusion. At the end of 5 minute infusion heart rate was 232 ± 18 beats/minute. After the arrest of infusion heart rate decreased with the fall in blood pressure. At L.B.P. heart rate declined to 187 ± 15 beats/minute, but returned gradually to the preinfusional level and even higher during the hypotensive phase. At M.P.R. of blood pressure level reached in 28 ± 7 minutes, (see Figure 3) heart rate was 199 ± 16 beats/minute and at M.R. of blood pressure level reached in 68 ± 3 minutes (see Figure 3) heart rate was higher than the preinfusional rate (229 ± 14 beats/minute).

Third Noradrenaline Infusion (Iiii)

Changes in Blood Pressure

Before the third infusion preinfusional mean arterial blood pressure was 120 ± 9 mm Hg. When infusion was administered blood pressure rose to 203 ± 7 mm Hg, however the blood pressure was not maintained at this level in spite of the continuous administration of infusion and at the end of infusion blood pressure dropped to 186 ± 7 mm Hg. After the termination of infusion a marked fall in blood pressure was observed; L.B.P. was 71 ± 10 mm Hg reached in 5 ± 2 minutes (see Figure 3). M.P.R. of blood pressure level was 96 ± 9 mm Hg reached in 19 ± 13 minutes (see Figure 3) after the arrest of infusion, however M.P.R. was not reached in 2 out of 6 experiments performed, and for this reason the mean of only 4 experiments is represented in the figure. M.R. of blood pressure seen in this experimental period was 102 ± 6 mm Hg and was reached in 43 ± 6 minutes (see Figure 3).

Changes in Heart Rate

Preinfusional heart rate in this group of experiments was 229 ± 14 beats/minute. Here again no bradycardia developed during the noradrenaline infusion, instead a tachycardia ensued and persisted during the 5 minutes of infusion. At the end of infusion heart rate was 243 ± 19 beats/minute.

After arrest of infusion heart rate dropped with the fall in blood pressure and at L.B.P. of blood pressure level heart rate was 213 ± 20 beats/minute. At M.P.R. of blood pressure, in contrast to that observed in the first and second infusion, heart rate was further decreased to 192 ± 9 beats/minute. As pointed out before M.P.R. was reached in only 4 out of 6 experiments. At M.R. of blood pressure level seen in our experimental period heart rate was 230 ± 20 beats/minute which is close to the preinfusional value.

Changes in E.C.G.

Figure 2 represents examples of electrocardiographic changes induced by repeated infusions of noradrenaline (8 μg/kg/minute for 5 minutes) in the same animal.

During noradrenaline infusion bradycardia was observed during the first infusion; during the second infusion bradycardia was absent. Third infusion of noradrenaline induced only slight transient slowing of the heart rate followed by tachycardia. In this cat cardiac irregularities developed during the period of noradrenaline infusion during all three infusions, but disappeared when the infusion was arrested.

In order to compare the duration of noradrenaline postinfusional hypotension in this group of experiments, the values for times to reach L.B.P., M.P.R., and M.R. of blood pressure were calculated in minutes and represented in Figure 3.

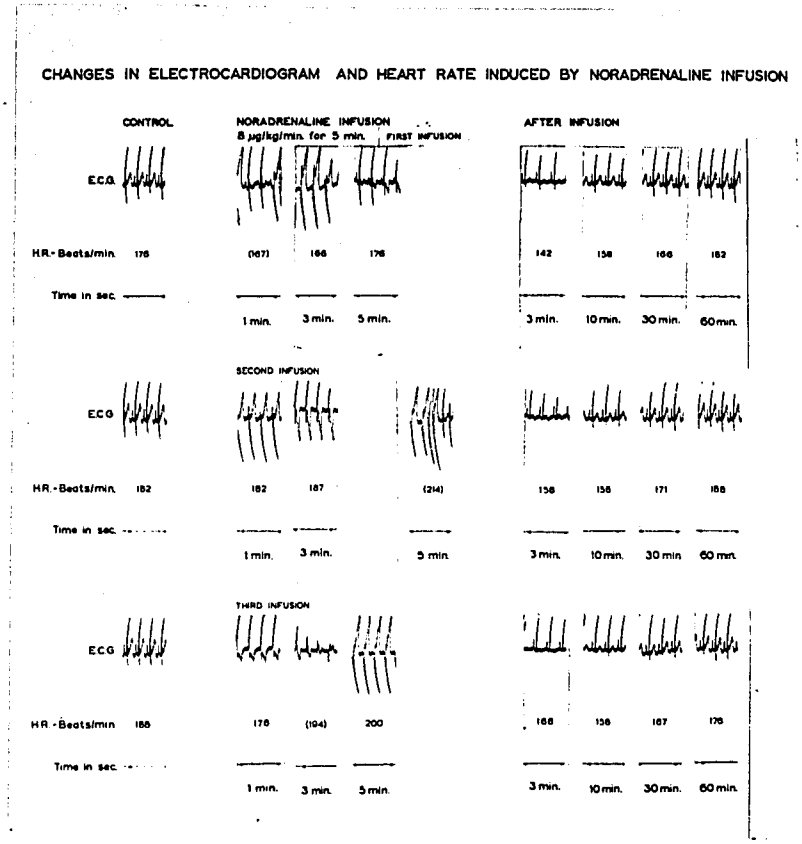

Figure 2

E.C.G. changes induced by 3 noradrenaline infusions, (8 µg/kg/minute for 5 minutes) administered to the same cat, male 3.25 kg, anaesthetized with pentobarbitone.
Upper tracing represents an example of E.C.G. tracing seen during the first infusion.
Middle tracing represents an example of E.C.G. changes seen during the second infusion.
Lower tracing represents E.C.G. changes seen during the third infusion.
Heart rate calculated during the period of cardiac irregularities, represents approximate values only.

The time to reach L.B.P. of blood pressure level was 5 ± 2 minutes in all the three infusions. Time to M.P.R. of blood pressure was shortened after the second and third infusion; it was 40 ± 6 minutes, 28 ± 7 minutes and 19 ± 13 minutes after the first, second and third infusions respectively. However statistical analysis (t test) showed the difference to be nonsignificant ($P < 0.05$). Similarly time to M.R. of blood pressure was reduced after repeated infusion. It was 86 ± 12 minutes after the first infusion, 68 ± 3 minutes after the second infusion and 43 ± 6 minutes following the third infusion. The difference between the first and third infusions and between the second and third infusions was statistically significant.

These results indicate that when the same dose of noradrenaline is infused for the same period of time in the same animal at suitable intervals, the duration of N.P.H. is reduced after repeated infusions.

In summary then, repetition of the same noradrenaline infusion in the same animal at suitable intervals (Group I) resulted in a decreased pressor response during the first minute of infusion. However, the second and third noradrenaline infusions were administered at different preinfusional blood pressure levels since full recovery of blood pressure after the arrest of infusion was not reached within our experimental period of time.

The Effect of Repeated Infusions of Noradrenaline in the Same Animal on Time to L.B.P., M.P.R. and M.R.

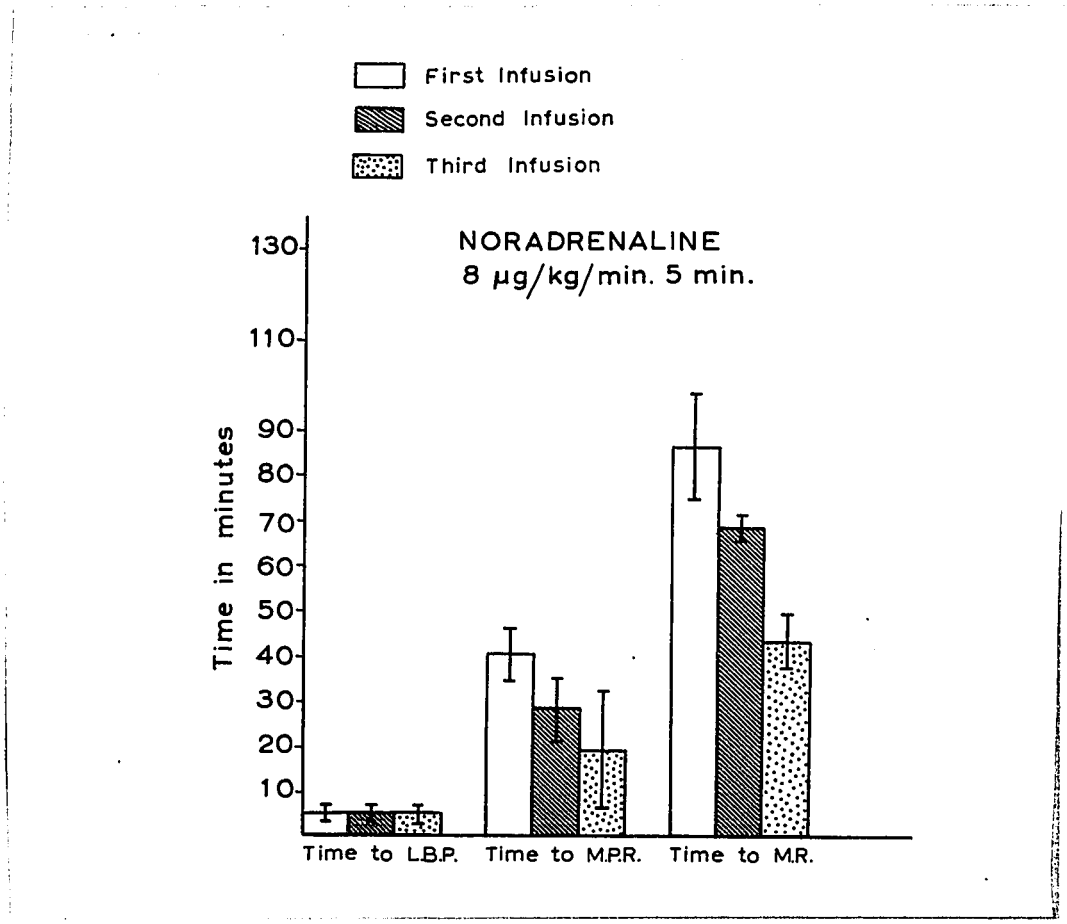

Figure 3

Summary of results obtained in Group I. Noradrenaline infusion (8 µg/kg/minute for 5 minutes) was administered 3 times to the same animal.
Time to L.B.P., M.P.R. and M.R. were calculated in minutes.
Mean ± S.E.M. of 6 experiments are represented, except for time to M.P.R. after the third infusion which represents the mean of 4 experiments.

Tolerance development to the pressor effect of noradrenaline was seen during the first, second and third noradrenaline infusions; however, the decline in blood pressure was somewhat less intense after consecutive infusions.

Reflex vagal bradycardia ensued during the first infusion, while tachycardia was observed during the second and third infusions.

During the secondary postinfusional hypotensive phase which ensued after each of the three consecutive noradrenaline infusions bradycardia persisted; it was however, most marked after the first infusion and the least intense after the second.

Within our experimental period of time heart rate recovered gradually toward the preinfusional level after each infusion while blood pressure stayed below preinfusional level in each case.

Cardiac arrhythmias were observed during all three consecutive noradrenaline infusions but disappeared after the arrest of infusion. They were present in 5 out of 6 experiments during the first infusion; during the second infusion they ensued in 5 out of 6 cats, and during the third infusion they were again present in 5 out of 6 experiments.

Time to reach L.B.P. was identical after each of the three infusions (5 minutes); however, the preinfusional

blood pressure was different each time. After each consecutive infusion, time to reach M.P.R. of blood pressure was shorter.

Time to M.R. of blood pressure within the experimental period of time was significantly shorter after the third than after the first infusion and significantly shorter after the third than after the second.

In view of the fact that some kind of tolerance seemed to develop both to the pressor and to the depressor response induced by noradrenaline infusion, in further groups of experiments only one single infusion of noradrenaline was administered to each animal.

The following parameters were investigated:

1. The effects of an increase in dose of administered noradrenaline on the pattern of N.P.H. (Group II).
2. The effects of an increase in the duration of noradrenaline infusion while the dose remained constant. (Group III).
3. The effects of an increase both in dose and time of noradrenaline administration. (Group IV).

GROUP II

Single noradrenaline infusion was administered in a dose of 16 µg/kg/minute or 32 µg/kg/minute. The duration of infusion was 5 minutes and this time factor was kept constant throughout this group of experiments. For each dose investigated, 6 different cats under pentobarbitone anaesthesia were used. The results obtained are represented in Figure 4.

Noradrenaline Infusion (8 µg/kg/minute)(IIa)

For the sake of comparison, the results described previously in Group Ii are included in Figure 4.

Noradrenaline Infusion (16 µg/kg/minute)(IIb)

Changes in Blood Pressure

In this group of cats the preinfusional mean arterial blood pressure level was 155 ± 6 mm Hg. The peak blood pressure level reached after the administration of the infusion was 253 ± 8 mm Hg; however, the blood pressure declined in spite of the continuation of the infusion, and at the end of the infusion blood pressure reached the level of 206 ± 10 mm Hg. After the arrest of infusion a marked fall in blood pressure was seen and the lowest blood pressure was 89 ± 8 mm Hg reached in 16 ± 3 minutes (see Figure 6).

IIa

IIb

IIc

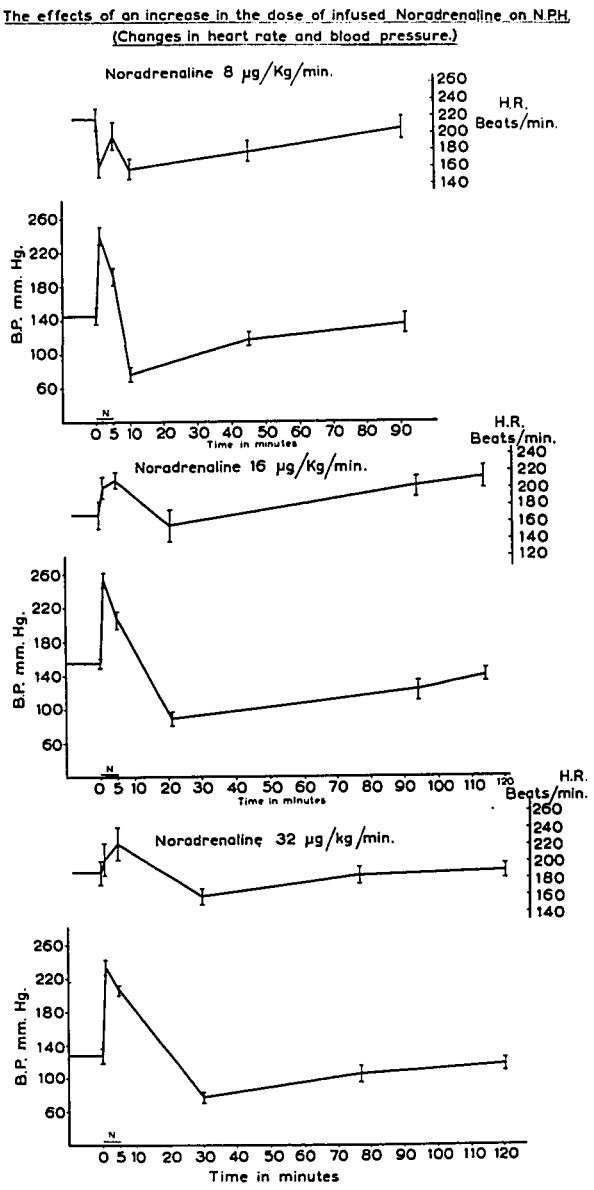

Figure 4

Heart rate and blood pressure changes induced by noradrenaline infusion in cats under pentobarbitone anaesthesia.
N represents time of noradrenaline infusion.
Group IIa (upper record) represents noradrenaline infusion, 8 µg/kg/minute for 5 minutes, and is included for the sake of comparison.
Group IIb (middle record) represents noradrenaline infusion, 16 µg/kg/minute for 5 minutes.
Group IIc (lower record) represents noradrenaline infusion, 32 µg/kg/minute for 5 minutes.
Six cats were used in each group. Mean ± S.E.M. are represented.

At M.P.R. blood pressure was at 122 ± 7 mm Hg and was reached after 89 ± 12 minutes since the arrest of noradrenaline infusion (see Figure 6). M.R. seen within our experimental period of time (90-120 minutes) was 129 ± 9 mm Hg and was reached in 109 ± 11 minutes (see Figure 6).

Changes in Heart Rate

The preinfusional heart rate in this group of experiments (IIb) was 170 ± 16 beats/minute. Bradycardia during the infusion did not develop; on the contrary, tachycardia (202 ± 13 beats/minute) ensued during the first minute of infusion and persisted throughout the 5 minutes of infusion. Heart rate was 211 ± 9 beats/minute at the end of infusion. Heart rate decreased gradually after the arrest of infusion when the blood pressure declined. At L.B.P. heart rate fell down to 157 ± 19 beats/minute, but returned gradually to the preinfusional value and even higher during the hypotensive phase. At M.P.R. of blood pressure, which was reached in 89 ± 12 minutes, (Figure 6), the heart rate was higher than the control value (203 ± 12 beats/minute) and at M.R. of blood pressure level, which was reached in 109 ± 11 minutes, (Figure 6) it was further increased to 213 ± 16 beats/minute.

Noradrenaline Infusion (32 µg/kg/minute)(IIc)

Figure 4 (lower record) represents the heart rate and blood pressure changes induced by a single noradrenaline infusion of 32 µg/kg/minute for 5 minutes. Mean ± S.E.M. of 6 experiments are presented (Group IIc). A total of 9 experiments was performed in this group; however in 3 experiments the M.P.R. was not reached within the experimental period (80-120 minutes) and therefore these experiments were not included in the represented data.

Changes in Blood Pressure

The control mean arterial preinfusional blood pressure level was 137 ± 7 mm Hg.. During the first minute of infusion the blood pressure rose to 251 ± 14 mm Hg; but as in the previous groups of experiments blood pressure was not maintained at this level and a gradual fall in pressure occurred in spite of continuous infusion for 5 minutes. At the end of infusion blood pressure was 201 ± 8 mm Hg. The L.B.P. reached was 78 ± 6 mm Hg, 25 ± 6 minutes after the arrest of infusion (Figure 6). M.P.R. of blood pressure was 108 ± 7 mm Hg and was reached in 72 ± 10 minutes (Figure 6). Maximum recovery of blood pressure within the present experimental period of time (90-120 minutes) was 107 ± 5 mm Hg reached in 115 ± 13 minutes (see Figure 6).

Changes in Heart Rate

The preinfusional heart rate was 186 ± 14 beats/minute. Tachycardia developed during the first minute of infusion (202 ± 19 beats/minute) and continued during the period of infusion. At the end of infusion, heart rate was 229 ± 17 beats/minute. Heart rate decreased toward the control value after the arrest of infusion. At L.B.P. it was below preinfusional rate (174 ± 14 beats/minute), but it gradually returned to control rate during the hypotensive phase. At the M.P.R. of blood pressure the heart rate was 183 ± 10 beats/minute, i.e., almost identical with the control rate, and at the time of M.R. of blood pressure the heart rate was 189 ± 9 beats/minute, i.e., only slightly above the preinfusional value.

Changes in E.C.G.

Figure 5 represents examples of E.C.G. changes induced by different doses of infused noradrenaline.

During noradrenaline infusion of 8 μg/kg/minute for 5 minutes bradycardia was observed during first and second minute of infusion, while infusion of 16 μg/kg/minute for 5 minutes and of 32 μg/kg/minute for 5 minutes induced no bradycardia but instead increased the heart rate.

Cardiac irregularities developed during the period of noradrenaline infusion but consistently disappeared after the infusion was arrested. With the 8 μg dose, cardiac

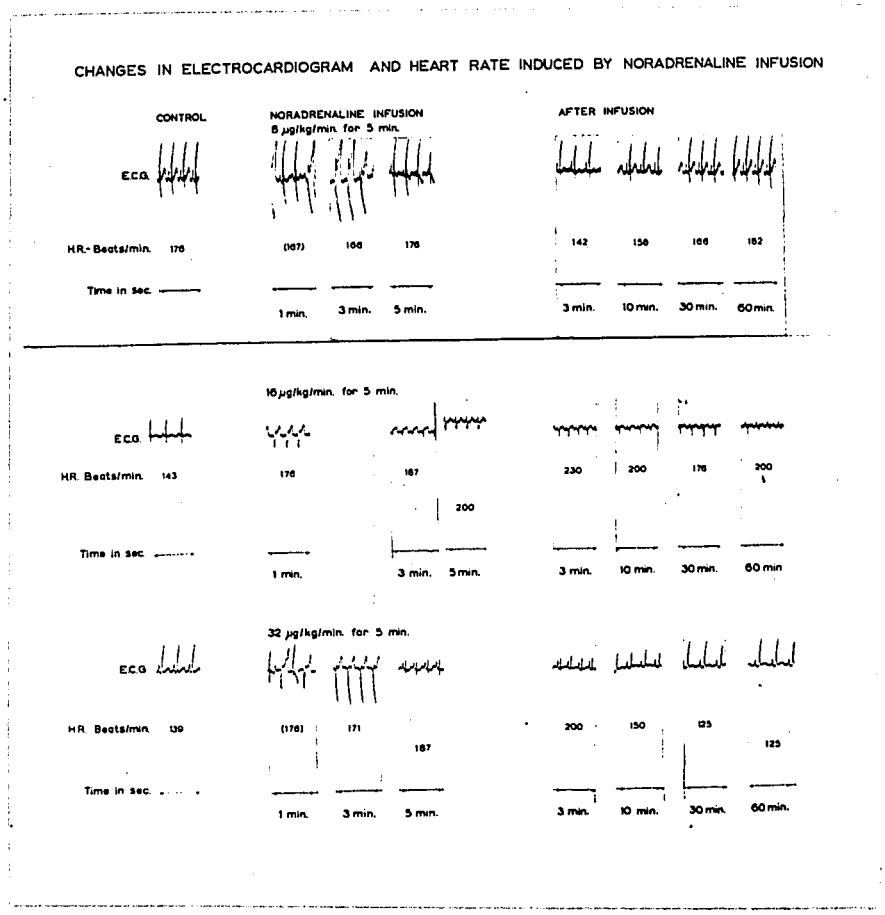

Figure 5

Changes in E.C.G. induced by a single noradrenaline infusion in cats under pentobarbitone anaesthesia.
Upper tracing: 8 µg/kg/minute for 5 minutes infused in cat, female 3.25 kg.
Middle tracing: 16 µg/kg/minute for 5 minutes infused in male cat, 3.0 kg.
Lower tracing: 32 µg/kg/minute infused in female cat, 2.7 kg.
Heart rates calculated during period of cardiac arrhythmias represent approximate values only.

irregularities appeared in 5 out of 6 experiments. With 16 μg/kg/minute irregularities developed in 3 out of 6 experiments, and with 32 μg/kg/minute for 5 minutes cardiac irregularities developed in all of the 6 experiments performed.

In order to compare the effects of the three doses of noradrenaline infused in this study on subsequent patterns of N.P.H. the values for times to reach L.B.P., M.P.R. and M.R. of blood pressure were calculated in minutes and are represented in Figure 6. The times to reach L.B.P., M.P.R. and M.R. of blood pressure increased with an increase in the dose infused. Times to L.B.P. were 5 ± 2 minutes, 16 ± 3 minutes and 25 ± 6 minutes, after doses of 8 μg/kg/minute for 5 minutes, 16 μg/kg/minute for 5 minutes and 32 g/kg/minute for 5 minutes respectively. Statistical analysis (t test) showed that time to L.B.P. was significantly ($P < 0.05$) increased after infusion of 16 μg/kg/minute as compared to 8 μg/kg/minute and after 32 μg/kg/minute as compared to 8 μg/kg/minute. However there was no significant difference between time to reach L.B.P. after 16 μg/kg/minute and after 32 μg/kg/minute. Time to reach M.P.R. of blood pressure was also increased with an increase in the dose of infused noradrenaline; it was 40 ± 6 minutes, 89 ± 12 minutes, and 72 ± 10 minutes after 8 μg/kg/minute, 16 μg/kg/minute and 32 μg/kg/minute, respectively. Time to reach M.P.R. of blood pressure was significantly shorter for 8 μg/kg/minute when compared to the 16 μg/kg/minute and

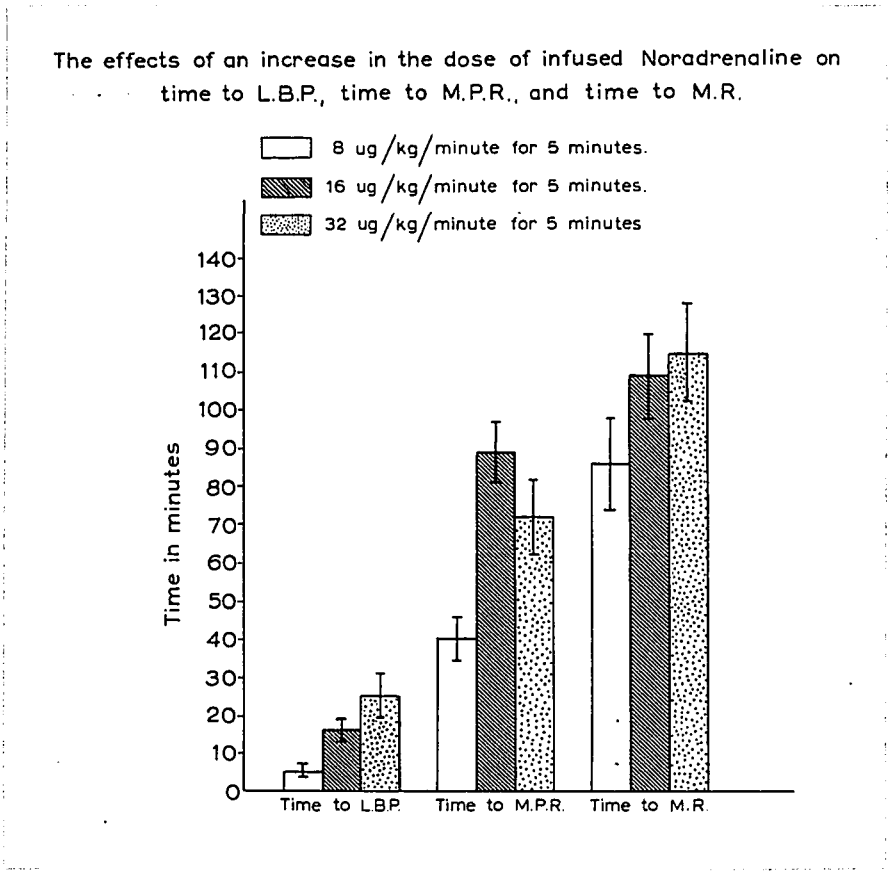

Figure 6

Combined results from Group IIa, IIb and IIc. Single noradrenaline infusion was administered to cats under pentobarbitone anaesthesia, 6 cats were used for each dose.
Total dose infused was 40 μg/kg, 80 μg/kg and 160 μg/kg respectively. Time of infusion was constant (5 minutes). Time to L.B.P., M.P.R. and M.R. is calculated in minutes. Mean ± S.E.M. are shown.

significantly shorter when compared to the 32 μg/kg/minute, but no significant difference was observed between time required after 16 μg/kg/minute and 32 μg/kg/minute. Time to reach M.R. was 86 ± 12 minutes, 109 ± 11 minutes and 115 ± 13 minutes after 8 μg/kg/minute, 16 μg/kg/minute, and 32 μg/kg/minute, respectively. Statistical analysis utilizing the t test showed that difference in time to reach M.R. after 8 μg/kg/minute as compared to 16 μg/kg/minute was not significant, nor was there any significant difference after 16 μg/kg/minute and 32 μg/kg/minute, and after 8 μg/kg/minute and 32 μg/kg/minute.

These experiments showed that an increase in the dose of infused noradrenaline resulted in increase in duration of N.P.H. The recovery toward preinfusional level was slower. After the highest dose, blood pressure only slightly recovered from the prolonged postinfusional hypotensive phase.

In summary then, doubling the dose of noradrenaline infused to 16 μg/kg/ minute (duration of infusion being kept constant) did not result in a much greater rise in blood pressure during the first minute of noradrenaline infusion; however a four-fold increase to 32 μg/kg/minute produced a considerably greater pressor response.

Increase in the dose of infused noradrenaline did not influence tolerance development to the pressor effect

during noradrenaline infusion. Blood pressure declined similarly whether a double or a four-fold dose was infused during the same period of time.

Reflex vagal bradycardia ensued during an infusion of a single dose of noradrenaline, but tachycardia was observed during an infusion of a double and a four-fold dose.

During the secondary postinfusional hypotensive phase, bradycardia persisted whether a single (8 μg/kg/minute), double or four-fold dose of noradrenaline was infused during a period of 5 minutes; however, it was most intense after 8 μg/kg/minute for 5 minutes. At M.P.R. of blood pressure heart rate returned to preinfusional rate after an infusion of 16 μg/kg/minute, and it was almost at control rate after an infusion of 32 μg/kg/minute, while bradycardia persisted at M.P.R. when 8 μg/kg/minute of noradrenaline was infused. After the arrest of infusion within our experimental period of time, heart rate returned to preinfusional value when a double or four-fold dose of noradrenaline was infused, while it was slightly below preinfusional rate when 8 μg/kg/minute was administered.

In each case whether a single, double or four-fold dose of noradrenaline was infused, after the arrest of infusion the blood pressure remained still below preinfusional level when complete or almost complete recovery of heart rate toward preinfusional value ensued. Cardiac arrhythmias were present in 5 out of 6 experiments when

8 µg/kg/minute of noradrenaline was infused, but surprisingly only in 3 out of 6 experiments when 16 µg/kg/minute was infused. After an infusion of 32 µg/kg/minute, cardiac arrhythmias appeared in all the experiments. In each case cardiac irregularities disappeared immediately after the arrest of noradrenaline infusion.

The blood pressure declined more slowly below pre-infusion level when the dose of noradrenaline infused was increased. Time to reach L.B.P. was significantly increased after 16 µg/kg/minute as compared with 8 µg/kg/minute, and there was a significant increase in time to reach L.B.P. after 32 µg/kg/minute as compared with 8 µg/kg/minute. Although there was also an increase in time to reach L.B.P. after 32 µg/kg/minute as compared with 16 µg/kg/minute the difference was not statistically significant.

An increase in the dose of noradrenaline infused also resulted in an increase in time to reach M.P.R. of blood pressure. The increase in time was significantly increased after 16 µg/kg/minute as compared with 8 µg/kg/minute.

There was an increase in time to reach M.R. of blood pressure after double and four-fold doses of noradrenaline, as compared to a single dose (8 µg/kg/minute); however, the increase was not statistically significant. One should stress that M.R. does not represent full recovery of blood pressure, but only a stabilized low blood pressure level after the arrest of noradrenaline infusion.

GROUP III

In the next group of experiments (Group III) the effects of an increase in the time of noradrenaline infused, the dose of noradrenaline remaining constant, were studied.

Group III consisted of 3 groups of experiments in each of which 6 cats were used. In Group IIIa the dose of infused noradrenaline was 8 μg/kg/minute for 5 minutes. Noradrenaline infusion, 8 μg/kg/minute for 5 minutes, is represented in Group IIIa; the results of this group of experiments were already described (see Group Ii) and are included for the sake of comparison in Figure 7. In Group IIIb the dose of noradrenaline infused was 4 μg/kg/minute for 10 minutes. In Group IIIc the dose of noradrenaline infused was 2 μg/kg/minute for 20 minutes. The results obtained are represented in Figure 7.

Noradrenaline Infusion (4 μg/kg/minute for 10 minutes)(IIIb)

Changes in Blood Pressure

In this group of experiments preinfusional blood pressure level was 140 ± 8 mm Hg. The peak of blood pressure rise induced by noradrenaline infusion was 207 ± 9 mm Hg, however the blood pressure was not maintained during the period of infusion and a decline from 207 ± 9 mm Hg to 173 ± 7 mm Hg at the end of 10 minutes infusion ensued. After the termination of infusion, the secondary hypotension

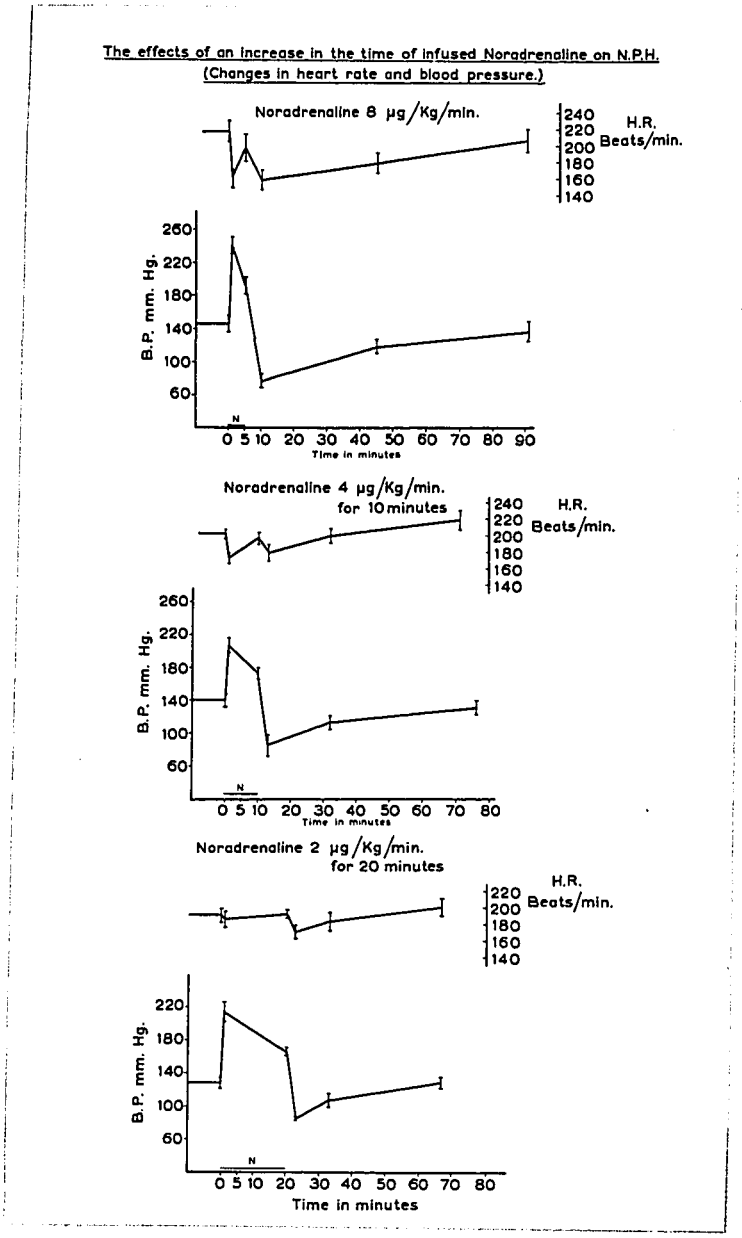

Figure 7

Heart rate and blood pressure changes induced by noradrenaline infusion in cats under pentobarbitone anaesthesia.
N represents time of noradrenaline infusion.
Group IIIa (upper record) represents noradrenaline infusion 8 µg/kg/minute for 5 minutes.
Group IIIb (middle record) represents noradrenaline infusion 4 µg/kg/minute for 10 minutes.
Group IIIc (lower record) represents noradrenaline infusion 2 µg/kg/minute for 20 minutes.
Six cats were used in each group. Mean ± S.E.M. are represented.

was less intense as compared to that in control experiments and L.B.P. was 85 ± 13 mm Hg reached in 3 ± 2 minutes (see Figure 9). (L.B.P. reached in control experiments was 77 ± 8 mm Hg). M.P.R. of blood pressure level was 113 ± 8 mm Hg and was reached in 22 ± 10 minutes (Figure 9). M.R. of blood pressure level was 132 ± 8 mm Hg and was reached in 66 ± 15 minutes (see Figure 9).

Changes in the Heart Rate

The preinfusional heart rate was 203 ± 5 beats per minute. During noradrenaline infusion bradycardia possibly due to vagal reflex similar to that observed in control experiments was obtained, and at the peak of blood pressure rise heart rate declined to 173 ± 6 beats/minute. At the end of infusion heart rate was still below the preinfusional value, 197 ± 7 beats/minute. A progressive decrease in the heart rate associated with the fall in blood pressure was observed after the termination of infusion. At L.B.P. the heart rate was 179 ± 10 beats/minute. A gradual recovery of heart rate towards the control value was seen during the hypotensive phase. At M.P.R. of blood pressure the heart rate was 200 ± 9 beats/minute and at M.R. of blood pressure the heart rate was 219 ± 12 beats/minute, which was slightly higher than the preinfusional heart rate. This is in contrast to control experiments in which heart rate remained decreased during the whole period of the secondary hypotensive phase.

Noradrenaline Infusion (2 µg/kg/minute for 20 minutes)(IIIc)

Changes in Blood Pressure

In this group of experiments the preinfusional blood pressure level was 128 ± 7 mm Hg. The peak of blood pressure rise after administration of noradrenaline infusion was 214 ± 12 mm Hg. During the period of infusion the height of blood pressure response was not maintained and at the end of infusion blood pressure declined to 166 ± 5 mm Hg. After the infusion was arrested, blood pressure fell below the pre-infusional level (which was 128 ± 7 mm Hg) to 85 ± 2 mm Hg (L.B.P.) reached in 3 ± 2 minutes (see Figure 9). This fall in blood pressure was considerably less than that in control experiments, where a fall in blood pressure below the pre-infusional blood pressure level (146 ± 10 mm Hg) to 77 ± 8 mm Hg was observed. M.P.R. of blood pressure level was 107 ± 8 mm Hg and was reached in 13 ± 5 minutes (see Figure 9) after the arrest of infusion. M.R. of blood pressure was 128 ± 7 mm Hg, and occurred 47 ± 18 minutes after cessation of the infusion (see Figure 9).

Changes in the Heart Rate

The preinfusional heart rate was 191 ± 8 beats/minute. At the peak of blood pressure rise heart rate was slightly decreased to 186 ± 10 beats/minute, but returned to preinfusional level (192 ± 5 beats/minute) at the termination

of infusion. At L.B.P. the heart rate decreased to 171 ± 8 beats/minute and at M.P.R. of blood pressure it was still at 183 ± 11 beats/minute. The heart rate slightly increased with the recovery of blood pressure and at M.R. of blood pressure it was 200 ± 11 beats/minute.

Changes in E.C.G.

Examples of changes in the E.C.G. induced by noradrenaline infusion when the time of infusion was increased (dose of noradrenaline infusion being constant) are represented in Figure 8.

The upper tracing shows changes in the E.C.G. induced by noradrenaline 8 μg/kg/minute for 5 minutes; the middle tracing represents E.C.G. changes induced by noradrenaline 4 μg/kg/minute for 10 minutes; and the lower tracing represents changes in E.C.G. induced by noradrenaline 2 μg/kg/minute for 20 minutes. A different cat was used for each infusion. Bradycardia was observed in upper and middle tracings; the lower tracing shows a slight decrease in heart rate during the first minute of infusion. Cardiac irregularities were seen in 5 out of 6 experiments during infusion of noradrenaline 8 μg/kg/minute for 5 minutes; in 3 out of 6 experiments during 4 μg/kg/minute for 10 minutes; and in none of the 6 experiments when 2 μg/kg/minute for 20 minutes was infused. After cessation of infusion cardiac irregularities were absent in both former groups (IIIa and IIIb).

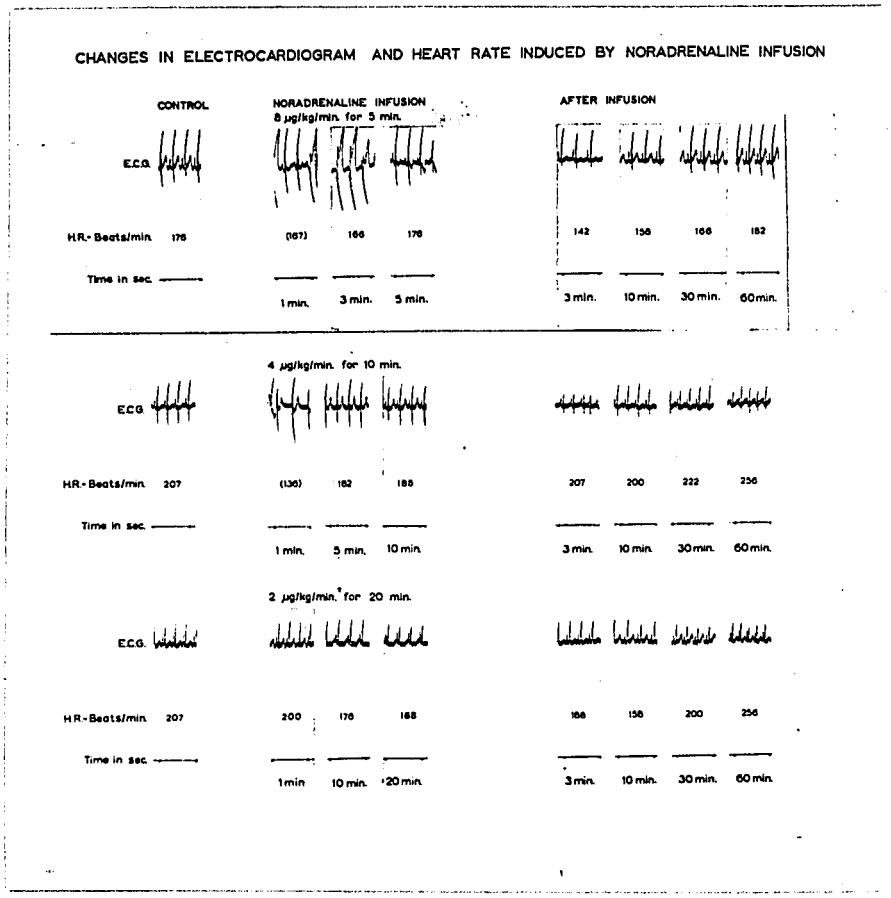

Figure 8

Changes in E.C.G. induced by single noradrenaline infusion in cats under pentobarbitone anaesthesia.
Upper tracing: 8 µg/kg/minute for 5 minutes infused in female cat, 3.2 kg;
Middle tracing: 4 µg/kg/minute for 10 minutes infused in male cat, 4 kg;
Lower tracing: 2 µg/kg/minute for 20 minutes infused in male cat, 3 kg.
Total dose infused was 40 µg/kg in each case.
Heart rates calculated during the period of cardiac arrhythmias induced by noradrenaline and represent approximate values only.

Time in minutes to reach L.B.P., M.P.R. and M.R. of blood pressure level in Group III of experiments was calculated and is represented in Figure 9.

Increasing the duration of noradrenaline infusion caused no difference in the time to reach L.B.P. which remained at 5 ± 2 minutes, 3 ± 2 minutes and 3 ± 2 minutes for 8 μg/kg/minute, 4 μg/kg/minute and 2 μg/kg/minute respectively. However the time to reach M.P.R. of blood pressure and M.R. of blood pressure showed a decrease on increasing the time of infusion. Time to reach M.P.R. of blood pressure level was 40 ± 6 minutes, 22 ± 10 minutes and 13 ± 5 minutes when the time of infusion was 5 minutes, 10 minutes and 20 minutes respectively. Time to M.R. of blood pressure level was 86 ± 12 minutes, 66 ± 15 minutes and 47 ± 18 minutes when the time of infusion was increased from 5 to 10 and thereafter to 20 minutes respectively.

Statistical analysis (t test $P < 0.05$) showed no significant difference in time to reach L.B.P. after all three different infusions. Time to reach M.P.R. of blood pressure level after 4 μg/kg/minute for 10 minutes was not significantly different from time to reach M.P.R. of blood pressure level after 8 μg/kg/minute for 5 minutes. There was no significant difference between time to reach M.P.R. of blood pressure level after 4 μg/kg/minute for 10 minutes and 2 μg/kg/minute for 20 minutes. However a significant decrease in time to M.P.R. of blood pressure level was

The effects of an increase in time of infused Noradrenaline on time to L.B.P., time to M.P.R., and time to M.R.

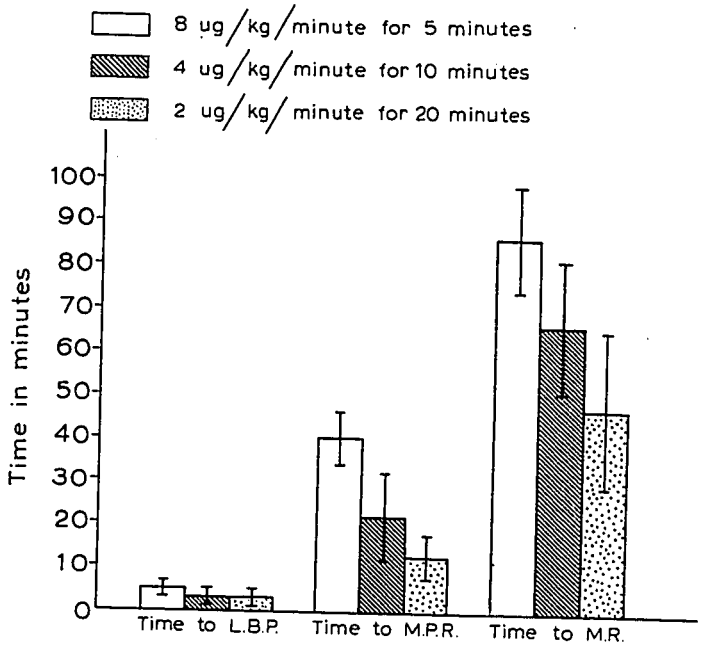

Figure 9

Combined results from Group IIIa, IIIb and IIIc. Single noradrenaline infusion was administered in cats under pentobarbitone anaesthesia, 6 cats were used for each dose.
Total dose infused was 40 μg/kg infused during 5 minutes,
40 μg/kg infused during 10 minutes and 40 μg/kg infused during 20 minutes.
Time to L.B.P., M.P.R. and M.R. is calculated in minutes.
Mean ± S.E.M. are represented.

observed after 2 μg/kg/minute for 20 minutes as compared to 8 μg/kg/minute for 5 minutes. Time to reach M.R. of blood pressure level showed no significant decrease between 8 μg/kg/minute for 5 minutes and 4 μg/kg/minute for 10 minutes or between 4 μg/kg/minute for 10 minutes and 2 μg/kg/minute for 20 minutes. However significant reduction in time to M.R. of blood pressure level was observed between 8 μg/kg/minute for 5 minutes and 2 μg/kg/minute for 20 minutes.

These results demonstrate that the same dose of noradrenaline infused for a longer period of time shortens significantly the recovery period of the hypotensive phase.

In summary then, an increase in the time of noradrenaline administration (while the dose was identical, 40 μg/kg) resulted in less intense rise in blood pressure when the rate was 4 μg/kg/minute for 10 minutes.

Tolerance development to the pressor effect of noradrenaline during the infusion was not affected when the same dose of noradrenaline was administered at a slower rate.

Reflex vagal bradycardia was observed during the infusion of 8 μg/kg/minute for 5 minutes of noradrenaline; a decrease in the heart rate persisted during the hypotensive phase. When the time of noradrenaline infused was increased to 10 minutes, reflex vagal bradycardia was less intense and after arrest of infusion there was also a more rapid recovery

of the heart rate toward the preinfusional value. Heart rate during the infusion was almost unchanged when the same dose of noradrenaline was infused for 20 minutes, and only a slight and short-lasting decrease in heart rate was seen during the secondary hypotensive phase.

When the infusion was administered for 10 or 20 minutes at M.R. of blood pressure heart rate was above pre-infusional value. Cardiac arrhythmias occurred only in 3 out of 6 experiments when the same dose of noradrenaline was infused for 10 minutes instead of 5 minutes. (They were present in 5 out of 6 experiments during 5 minutes of noradrenaline infusion.) Cardiac arrhythmias were absent during the slowest rate of noradrenaline infusion (2 μg/kg/minute for 20 minutes).

Time to reach L.B.P., i.e., the onset of N.P.H. was not significantly changed. It seems, therefore, that when the same dose of noradrenaline was infused for a longer period of time the secondary hypotensive phase was less intense.

Time to reach M.P.R. was decreased when the duration of infusion was increased; however a significant change was observed only between 8 μg/kg/minute for 5 minutes as compared with 2 μg/kg/minute for 20 minutes.

Time to reach M.R. of blood pressure was also decreased when the duration of noradrenaline infusion was increased but the change was not statistically significant.

GROUP IV

The effects of simultaneous increase in the dose and time of noradrenaline infusion were investigated in Groups IVa, IVb, and IVc.

Group IV consisted of 3 groups of experiments. Six cats were used for each group. In the first group (IVa) noradrenaline was infused in a dose of 8 μg/kg/minute for 5 minutes. In the second group (IVb) noradrenaline was infused in a dose of 8 μg/kg/minute for 10 minutes. In the third group of experiments (IVc) noradrenaline was infused in a dose of 8 μg/kg/minute for 20 minutes. The results obtained are represented in Figure 10.

Noradrenaline infusion (8 μg/kg/minute for 5 minutes) is represented in Group IVa. The results of this group of experiments were already described (see Group Ia) and are included in Figure 10 for the sake of comparison.

Noradrenaline Infusion (8 μg/kg/minute for 10 minutes)(IVb)

Changes in Blood Pressure

The preinfusional blood pressure in Group IVb was 138 $\pm$ 4 mm Hg and the peak of blood pressure rise induced by noradrenaline infusion was 237 $\pm$ 12 mm Hg. The blood pressure was not maintained during the period of the infusion and it fell to a low of 171 $\pm$ 6 mm Hg at the end of infusion. An intense drop in blood pressure was observed after the infusion

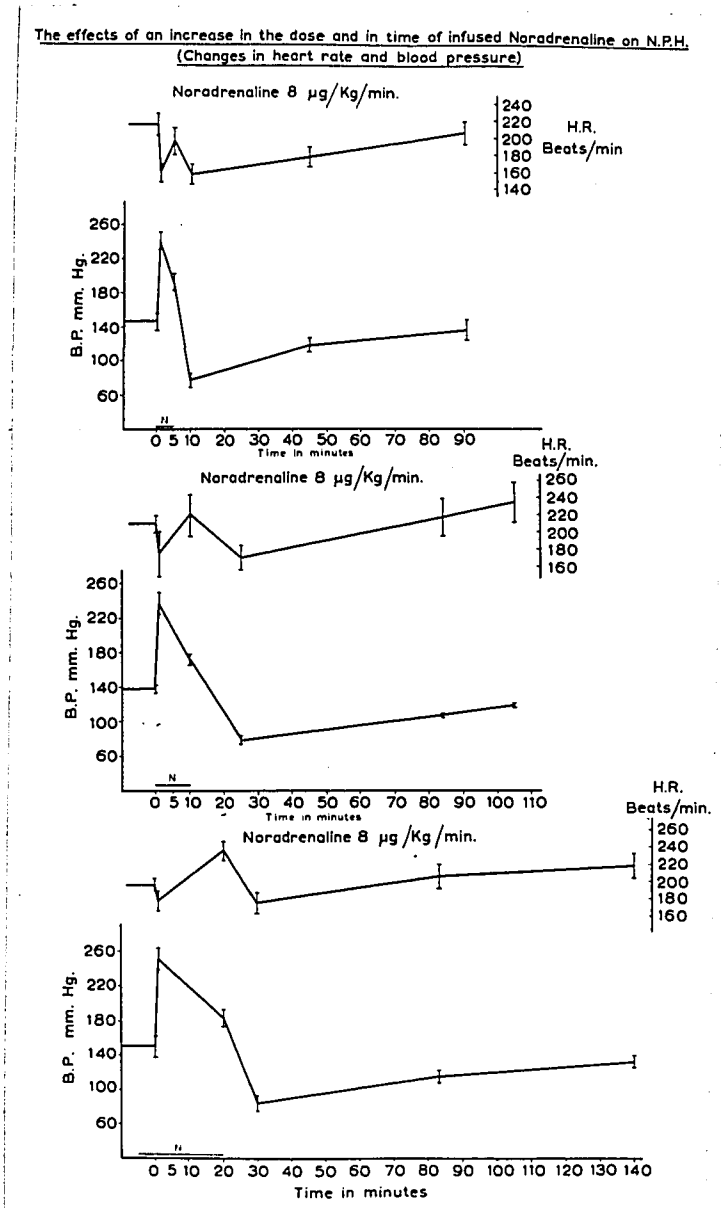

Figure 10

Heart rate and blood pressure changes induced by noradrenaline infusion in cats under pentobarbitone anaesthesia.
N represents time of noradrenaline infusion.
Group IVa (upper record) represents noradrenaline infusion 8 µg/kg/minute for 5 minutes.
Group IVb (middle record) represents noradrenaline infusion 8 µg/kg/minute for 10 minutes.
Group IVc (lower record) represents noradrenaline infusion 8 µg/kg/minute for 20 minutes.
Six cats were used in each group. Mean ± S.E.M. are represented.

was arrested; L.B.P. was 78 ± 4 mm Hg reached in 15 ± 2 minutes (see Figure 12). M.P.R. of blood pressure level was 108 ± 2 mm Hg and it was reached in 74 ± 12 minutes (see Figure 12). M.R. of blood pressure level was 119 ± 2 mm Hg and was reached in 95 ± 10 minutes (see Figure 12).

Changes in Heart Rate

Preinfusional heart rate was 209 ± 10 beats/minute. Bradycardia, possibly due to vagal reflex, was observed and heart rate decreased to 174 ± 26 beats/minute when the peak of blood pressure rise during the noradrenaline infusion was reached. At the end of infusion the heart rate increased to 219 ± 24 beats/minute, i.e., above the preinfusional value. At L.B.P. the heart rate decreased again to 170 ± 14 beats/minute, i.e., below the preinfusional value; it recovered gradually and increased to 217 ± 22 beats/minute at M.P.R. of blood pressure level. At M.R. of blood pressure it was 235 ± 23 beats/minute which was above the preinfusional rate.

Noradrenaline Infusion (8 µg/kg/minute for 20 minutes)(IVc)

Changes in Blood Pressure

In Group IVc preinfusional blood pressure was 150 ± 12 mm Hg. The peak rise in blood pressure achieved during noradrenaline infusion was 251 ± 13 mm Hg; however the blood pressure response was not maintained during the

infusion and blood pressure declined from 251 ± 13 mm Hg to 183 ± 10 mm Hg. After arrest of the infusion blood pressure fell far below the preinfusional level; L.B.P. was 84 ± 9 mm Hg reached in 10 ± 3 minutes (see Figure 12). M.P.R. of blood pressure level was at 115 ± 7 mm Hg and was reached in 63 ± 10 minutes (see Figure 12). M.R. of blood pressure obtained within the experimental period of time (90-120 minutes) after infusion was 132 ± 7 mm Hg, and was reached in 120 ± 15 minutes (see Figure 12).

Changes in Heart Rate

Preinfusional heart rate was 197 ± 7 beats/minute. At the peak blood pressure rise during the infusion, a transient decrease to 178 ± 11 beats/minute was observed. However the heart rate increased gradually, and at the end of 20 minutes of infusion it was 236 ± 11 beats/minute, i.e., above the preinfusional value. After the arrest of infusion at L.B.P. the heart rate decreased to 175 ± 12 beats/minute. A gradual recovery of the heart rate associated with a recovery of blood pressure was observed. At M.P.R. heart rate was 206 ± 14 beats/minute, i.e., almost identical with the control value. At M.R. of blood pressure the heart rate was 219 ± 14 beats/minute, i.e., above the preinfusional rate.

Changes in E.C.G.

As shown in Figure 11 although an initial decrease in heart rate was observed in all cases, the heart rate increased during the late phase of infusion of 8 μg/kg/minute for 10 minutes, and during the later phase of infusion of 8 μg/kg/minute for 20 minutes. It remained decreased or unchanged during 8 μg/kg/minute for 5 minutes. Cardiac irregularities ensued in 5 of 6 experiments during the infusion of 8 μg/kg/minute for 5 minutes of noradrenaline but disappeared after the infusion was terminated. 8 μg/kg/minute of noradrenaline infused for 10 minutes induced arrhythmias in all 6 experiments. During the infusion of 8 μg/kg/minute for 20 minutes arrhythmias were observed in 5 out of 6 experiments. In both cases cardiac irregularities were absent after the arrest of infusions.

The time to reach L.B.P., M.P.R. and M.R. of blood pressure levels when simultaneous increase in dose and time of noradrenaline infusion was investigated is summarized in Figure 12.

Time to L.B.P. was increased as compared to 8 μg/kg/minute when the dose and time of infused noradrenaline were increased. Time to L.B.P. was 5 $\pm$ 2 minutes and 15 $\pm$ 2 minutes with 8 μg/kg/minute for 5 minutes and 8 μg/kg/minute for 10 minutes respectively. The increase between these two groups was statistically significant ($P < 0.05$). With increase in dose and time of noradrenaline infusion to

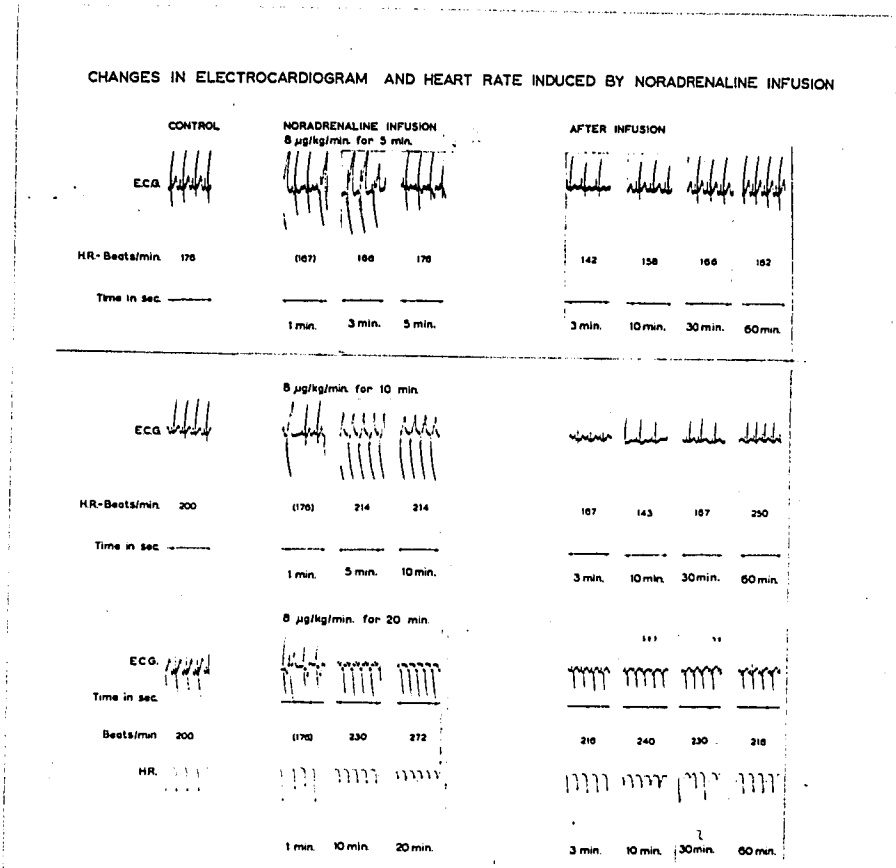

Figure 11

Changes in E.C.G. induced by single noradrenaline infusion, in cats under pentobarbitone anaesthesia.
Upper tracing: 8 µg/kg/minute for 5 minutes infused in female cat, 3.2 kg;
Middle tracing: 8 µg/kg/minute for 10 minutes infused in male cat, 3.6 kg;
Lower tracing: 8 µg/kg/minute for 20 minutes infused in female cat, 3.4 kg.
Heart rates calculated during the period of cardiac arrhythmias represent approximate values only.

The effects of an increase in dose and time of infused Noradrenaline on time to L.B.P., time to M.P.R., and time to M.R.

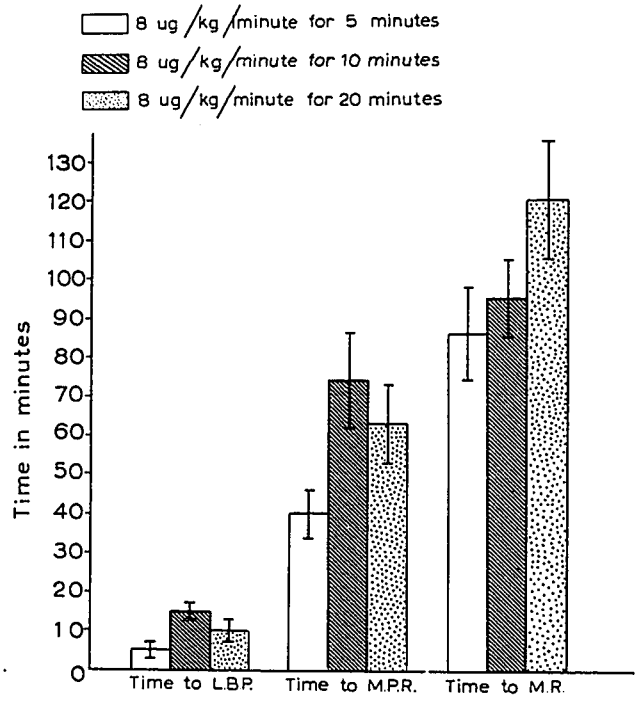

Figure 12

Combined results from Group IVa, IVb and IVc. Single noradrenaline infusion was administered in cats under pentobarbitone anaesthesia, 6 cats were used for each dose. Total dose infused was 40 μg/kg during 5 minutes, 80 μg/kg during 10 minutes and 160 μg/kg during 20 minutes. Time to L.B.P., M.P.R. and M.R. are calculated in minutes. Mean $\pm$ S.E.M. are shown.

8 μg/kg/minute for 20 minutes, time to L.B.P. was 10 ± 3 minutes. This was not significantly different from that of 8 μg/kg/minute for 5 minutes or of 8 μg/kg/minute for 10 minutes.

Time to M.P.R. of blood pressure level was significantly increased from 40 ± 6 minutes with 8 μg/kg/minute for 5 minutes to 74 ± 12 minutes with 8 μg/kg/minute for 10 minutes. At 8 μg/kg/minute for 20 minutes, time to M.P.R. of blood pressure level was 63 ± 10 minutes. The difference between 8 μg/kg/minute for 5 minutes and 8 μg/kg/minute for 10 minutes was statistically significant, but there was no statistically significant difference between 8 μg/kg/minute for 10 minutes and 8 μg/kg/minute for 20 minutes, however the difference was significant between 8 μg/kg/minute for 5 minutes and 8 μg/kg/minute for 20 minutes.

Time to M.R. of blood pressure level was increased with an increase in dose and time of noradrenaline infusion. It was 86 ± 12 minutes, 95 ± 10 minutes and 120 ± 15 minutes after 8 μg/kg/minute for 5 minutes, 8 μg/kg/minute for 10 minutes and 8 μg/kg/minute for 20 minutes respectively. The difference was only statistically significant between 8 μg/kg/minute for 5 minutes and 8 μg/kg/minute for 20 minutes; all the other differences were nonsignificant.

These results indicate that the hypotensive phase following noradrenaline infusion is increased when both the dose of noradrenaline and duration of noradrenaline infusion are increased.

In summary then, an increase in the dose and time of infused noradrenaline did not seem to influence significantly the pressor effect of noradrenaline. Tolerance development, i.e., the decline in blood pressure during noradrenaline infusion, was more intense after the larger doses of noradrenaline (8 μg/kg/minute for 10 minutes and 8 μg/kg/minute for 20 minutes).

Reflex vagal bradycardia during the infusions was most intense and prolonged after the dose of 8 μg/kg/minute for 5 minutes, and decreased in duration and intensity after consecutive increase in dose and time of noradrenaline infused. At the end of an infusion of 8 μg/kg/minute for 20 minutes, heart rate was markedly increased.

During the secondary postinfusional phase at M.P.R. the heart rate was below preinfusional value after 8 μg/kg/minute for 5 minutes, while it was almost back to normal preinfusional rate when the time and dose of noradrenaline were increased to 8 μg/kg/minute for 10 minutes or 8 μg/kg/minute for 20 minutes.

Similarly to the previous groups of experiments (I-III) the recovery of the heart rate was observed at a time when blood pressure was well below preinfusional level.

Cardiac arrhythmias were observed in 5 out of 6 experiments with a single dose of noradrenaline infused (8 μg/kg/minute) during 5 minutes and in all 6 experiments when the dose of noradrenaline and time of infusion were

doubled. They occurred in 5 out of 6 experiments when the dose of noradrenaline infused was 8 μg/kg/minute for 20 minutes. Cardiac irregularities disappeared after the arrest of noradrenaline infusion in each case.

Time to reach L.B.P., i.e., the onset of N.P.H. was increased although the increase was not statistically significant. In spite of the increase in dose and time of noradrenaline infusion, the values reached for L.B.P. were similar.

An increase in the dose of noradrenaline from 8 μg/kg/minute for 5 minutes to 8 μg/kg/minute for 10 minutes resulted in a significant increase in the time to reach M.P.R. There was also a significant increase in time to reach M.P.R. after 8 μg/kg/minute for 10 minutes as compared with 8 μg/kg/minute for 20 minutes. The blood pressure level reached at M.P.R. was lower after each increase in dose and time of noradrenaline infused.

Time to M.R. of blood pressure within our experimental period of time was increased after each increase in dose and time of infused noradrenaline; however the increase was statistically significant only between 8 μg/kg/minute for 5 minutes as compared with 8 μg/kg/minute for 20 minutes.

RESULTS - PART II

EFFECTS OF CATECHOLAMINE DEPLETION ON N.P.H.

Reserpine

Reserpinized cats showed sedation and miosis. They suffered from diarrhoea, were weak and looked sick. Out of 21 cats reserpinized in this study, two died before the experiment was started, and one died during the first infusion of noradrenaline.

Figure 13 represents results obtained in 12 reserpinized cats (Group V)..

Changes in Blood Pressure

The preinfusional blood pressure level in reserpinized cats was lower (101 ± 3 mm Hg) than in control animals (142 ± 5 mm Hg). The peak of blood pressure rise reached during noradrenaline infusion was 224 ± 5 mm Hg in the reserpinized animals as compared to 232 ± 4 mm Hg in the controls; the difference between the peak blood pressure level reached and the preinfusional level of blood pressure was 123 ± 4 mm Hg in the treated animals as compared to 90 ± 5 mm Hg in the control animals, i.e., a greater pressor response to noradrenaline was observed in reserpinized animals.

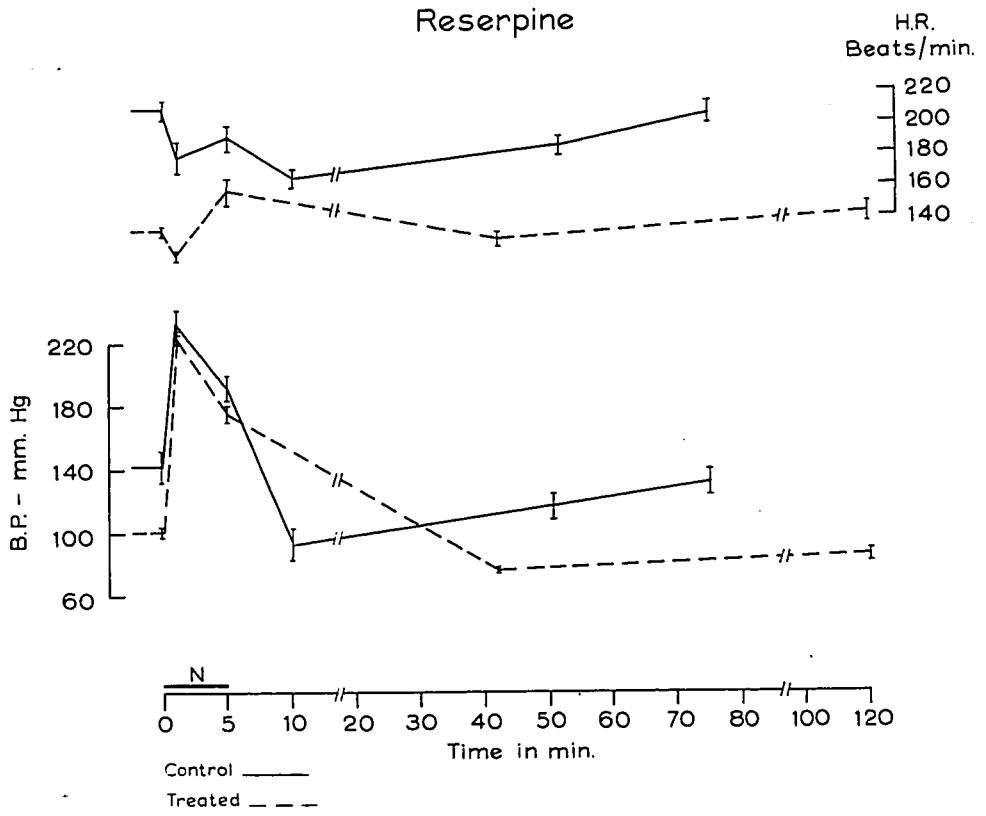

Figure 13

Heart rate and blood pressure changes (Mean ± S.E.M. of 12 experiments) induced by noradrenaline infusion (8 µg/kg/minute for 5 minutes) in reserpinized cats. Blood pressure level at 120 minutes after the termination of infusion is shown. Steady line represents Mean ± S.E.M. of 30 control experiments.
N indicates time of noradrenaline infusion.

In both pretreated and non-treated cats, tolerance to the pressor response developed during the continuous administration of noradrenaline infusion. The blood pressure declined from 224 ± 5 mm Hg to 177 ± 5 mm Hg at the end of infusion. This tolerance was quite similar to controls where a decline from 232 ± 4 mm Hg to 191 ± 10 mm Hg was seen.

When compared to controls, reserpinized cats showed a more gradual fall in blood pressure after the infusion of noradrenaline was arrested. Figure 23 shows that time to reach L.B.P. was longer (21 ± 9 minutes) than in controls (5 ± 2 minutes). This difference is statistically significant. Time to reach M.P.R. of blood pressure (66 ± 15 minutes) was significantly longer than in controls. In 50% of the experiments, the M.P.R. of blood pressure level was not reached. Time to reach M.R. of blood pressure (85 ± 13 minutes) was also increased over that attained in control experiments, though the difference was not statistically significant. Full recovery was never reached in our experimental period of time (120 minutes).

Changes in Heart Rate

Preinfusional heart rate was very slow in the reserpinized animals (132 ± 3 beats/minute) as compared to the control animals (210 ± 6 beats/minute). During the early phase of noradrenaline infusion, at the peak of blood pressure rise, decrease in the heart rate was observed

(116 ± 6 beats/minute); this was much less than that observed in the control experiments where heart rate decreased from 210 ± 6 beats/minute to 178 ± 9 beats/minute. At the end of infusion heart rate increased above preinfusional values (157 ± 8 beats/minute). After the arrest of infusion of noradrenaline, heart rate decreased, and at L.B.P. it was 127 ± 4 beats/minute, close to the preinfusional value, and stayed at this rate during the hypotensive phase; whereas in the control experiments heart rate at L.B.P. (165 ± 6 beats/minute) was far below the preinfusional heart rate (210 ± 6 beats/minute). At M.R. of blood pressure heart rate was increased to 144 ± 6 beats/minute, i.e., above the preinfusional rate. This is different from the controls where heart rate returned to the preinfusional rate when M.R. of blood pressure was reached.

Changes in E.C.G.

Figure 14 represents an example of changes in E.C.G. seen during noradrenaline infusion in control cats (upper tracing) and in reserpinized cats (lower tracing). In the treated animals a markedly slower preinfusional heart rate was observed. Cardiac irregularities ensued during noradrenaline infusion in both groups of experiments, but disappeared after the infusion was arrested in both cases. Cardiac arrhythmias during noradrenaline infusion were more intense in reserpinized cats than in

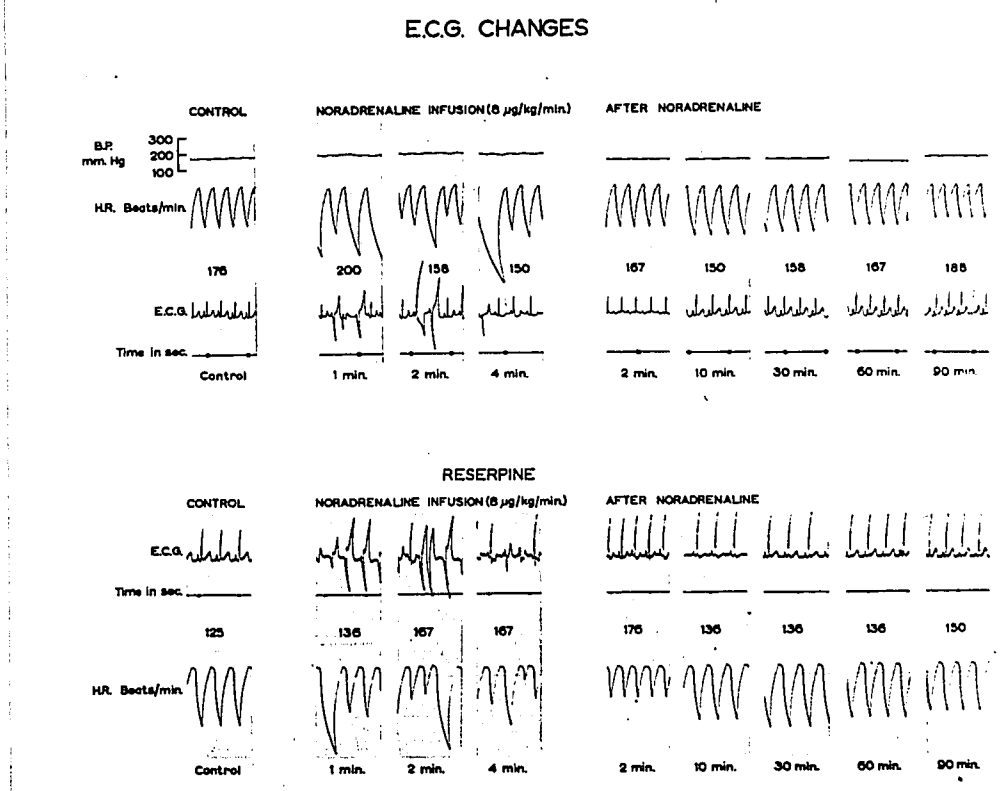

Figure 14

Upper record: Cat 3.0 kg, male. In descending order are represented changes in blood pressure, heart rate and electrocardiogram induced by noradrenaline infusion (8 µg/kg/minute for 5 minutes) in control animals.

Lower record: Changes in electrocardiogram and heart rate induced by the same noradrenaline infusion in reserpinized cat (3.8 kg male). Reserpine 5 mg/kg was administered intraperitoneally 24-48 hours before noradrenaline infusion.

Heart rate calculated during cardiac irregularities induced by noradrenaline infusion represent approximate values only (see Methods).

controls and were observed in all 12 reserpinized preparations. During noradrenaline infusion, in reserpinized cats, bradycardia (observed always in control experiments) was less intense and transient. In contrast to control experiments, in reserpinized cats, after the infusion of noradrenaline was arrested, heart rate was increased at L.B.P. and remained increased during the hypotensive phase. Ninety minutes after the arrest of noradrenaline infusion heart rate was above the preinfusional rate.

Alpha Methyldopa

In a further group of experiments the intensity and duration of N.P.H was investigated after depletion of catecholamines induced by chronic administration of alpha methyldopa (Group VI).

N.P.H. did not ensue in 2 out of 7 experiments. The data gathered in these two experiments are excluded from Figure 15 which is a summary of the results obtained.

Changes in Blood Pressure

Preinfusional blood pressure in cats pretreated with alpha methyldopa was lower (110 ± 4 mm Hg) than that seen in control animals (142 ± 5 mm Hg). The peak of blood pressure rise induced by noradrenaline infusion was 211 ± 8 mm Hg in the pretreated animal as compared to 232 ± 4 mm Hg in control experiments. The difference between the control

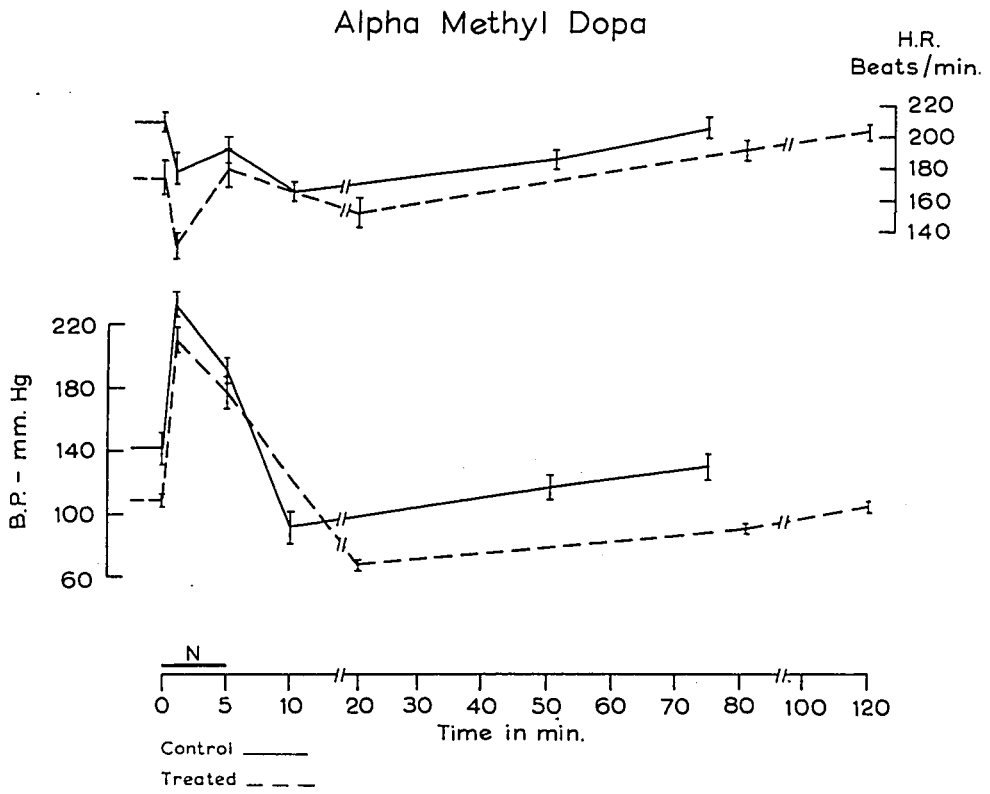

Figure 15

Changes in heart rate and blood pressure (Mean ± S.E.M. of five experiments) induced by noradrenaline infusion 8 µg/kg/minute for 5 minutes in cats pretreated chronically with alpha methyldopa.
N indicates time of noradrenaline infusion.

preinfusional blood pressure and the peak of blood pressure reached was 101 ± 8 mm Hg in the treated as compared to 90 ± 5 mm Hg in control experiments. In both pretreated and non-treated cats tolerance development to the pressor response was observed during continuous administration of noradrenaline infusion. In alpha methyldopa pretreated cats the blood pressure declined from 211 ± 8 mm Hg to 179 ± 10 mm Hg at the end of infusion. This decline in blood pressure was of less intensity than in control experiments where a decline from 232 ± 4 mm Hg to 191 ± 4 mm Hg was seen.

Alpha methyldopa pretreated cats showed a more gradual fall in blood pressure after the infusion of noradrenaline was arrested than that seen in control experiments. Figure 23 shows that times to reach L.B.P. (16 ± 6 minutes), M.P.R. (76 ± 5 minutes) and M.R. of blood pressure (110 ± 15 minutes) were significantly increased as compared to controls.

Changes in Heart Rate

Preinfusional heart rate was slower in cats pretreated with alpha methyldopa (173 ± 11 beats/minute) as compared to control animals (210 ± 6 beats/minute). In contrast to the results obtained in animals pretreated with reserpine, intense reflex bradycardia was observed at the peak of blood pressure rise induced by noradrenaline

infusion; heart rate decreased to 130 ± 16 beats/minute. At the end of the infusion heart rate increased to 180 ± 12 beats/minute, i.e., was close to preinfusional rate. After the arrest of infusion, heart rate steadily declined below preinfusional rate and at L.B.P. it was 152 ± 9 beats/minute; whereas in control experiments heart rate at L.B.P. was far below the preinfusional rate (165 ± 6 beats/minute as compared to 210 ± 6 beats/minute before the infusion). Heart rate and blood pressure then recovered simultaneously and at M.P.R. of blood pressure cardiac rate was 191 ± 7 beats/minute which was above the preinfusional value. At M.R. of blood pressure it was further increased to 203 ± 5 beats/minute. This increased heart rate was noted at the time when full recovery of blood pressure had not been reached. This is different from the control experiment where the heart rate was far below the preinfusional value during the hypotensive phase and returned to the preinfusional rate only when M.R. of blood pressure was reached, i.e., 70 ± 3 minutes after arrest of infusion.

Changes in E.C.G.

Figure 16 represents an example of E.C.G. changes seen during noradrenaline infusion in control cats (upper tracing) and in cats pretreated with alpha methyldopa (lower tracing). Cardiac irregularities ensued during noradrenaline infusion but disappeared after termination

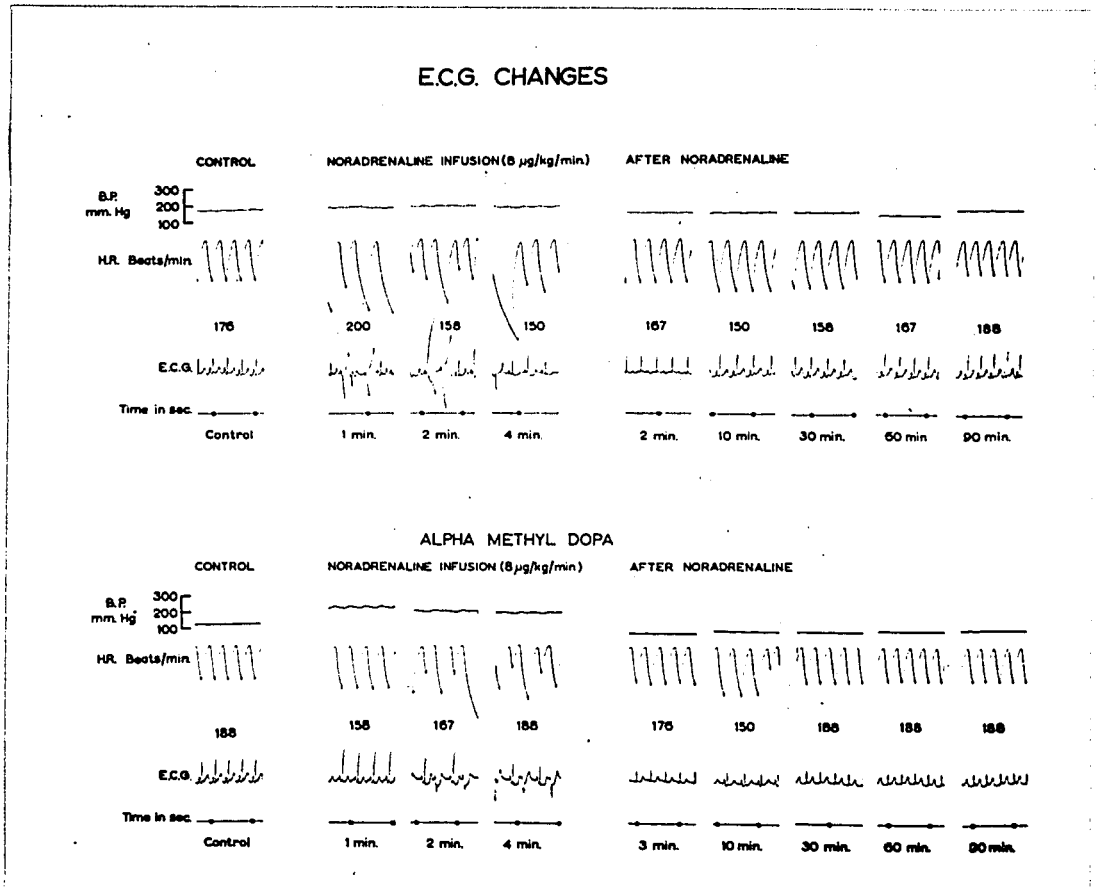

Figure 16

Upper record: Cat 3.0 kg male. In descending order are represented changes in blood pressure, heart rate and electrocardiogram induced by noradrenaline infusion (8 µg/kg/minute for 5 minutes) in control animals.

Lower record: Cat 2.4 kg female. Changes in blood pressure, heart rate and electrocardiogram induced by the same noradrenaline infusion in alpha methyldopa pretreated animals. Alpha methyldopa 100 mg/kg was administered intraperitoneally daily for 3 consecutive days before noradrenaline infusion was administered.

Heart rate calculated during cardiac irregularities induced by noradrenaline infusion represent approximate values only (see Methods).

of infusion in both control and treated cats. The usually observed bradycardia in control cats during noradrenaline infusion was also present in alpha methyldopa pretreated cats. Both control and treated cats showed a decrease in heart rate after the arrest of infusion but in alpha methyldopa pretreated cat heart rate returned to preinfusional value 30 minutes after the arrest of infusion, while it remained decreased 60 minutes after the infusion was arrested in control cat.

Guanethidine (chronic pretreatment)

It was considered of interest to investigate the effects of chronic pretreatment with guanethidine on the assumption that such a procedure would deplete catecholamine stores. Guanethidine was given in a dose of 5 mg/kg intraperitoneally daily for 7 days. A summary of the results obtained in 4 cats (Group VII) is represented in Figure 17.

Changes in Blood Pressure

Cats pretreated with guanethidine for 7 days showed a lower preinfusional blood pressure (105 $\pm$ 2 mm Hg) as compared to control animals (142 $\pm$ 5 mm Hg). The peak rise in blood pressure reached with noradrenaline infusion was lower (205 $\pm$ 10 mm Hg) in the treated animal than in controls (232 $\pm$ 4 mm Hg). The difference between the preinfusional blood pressure and the peak blood pressure

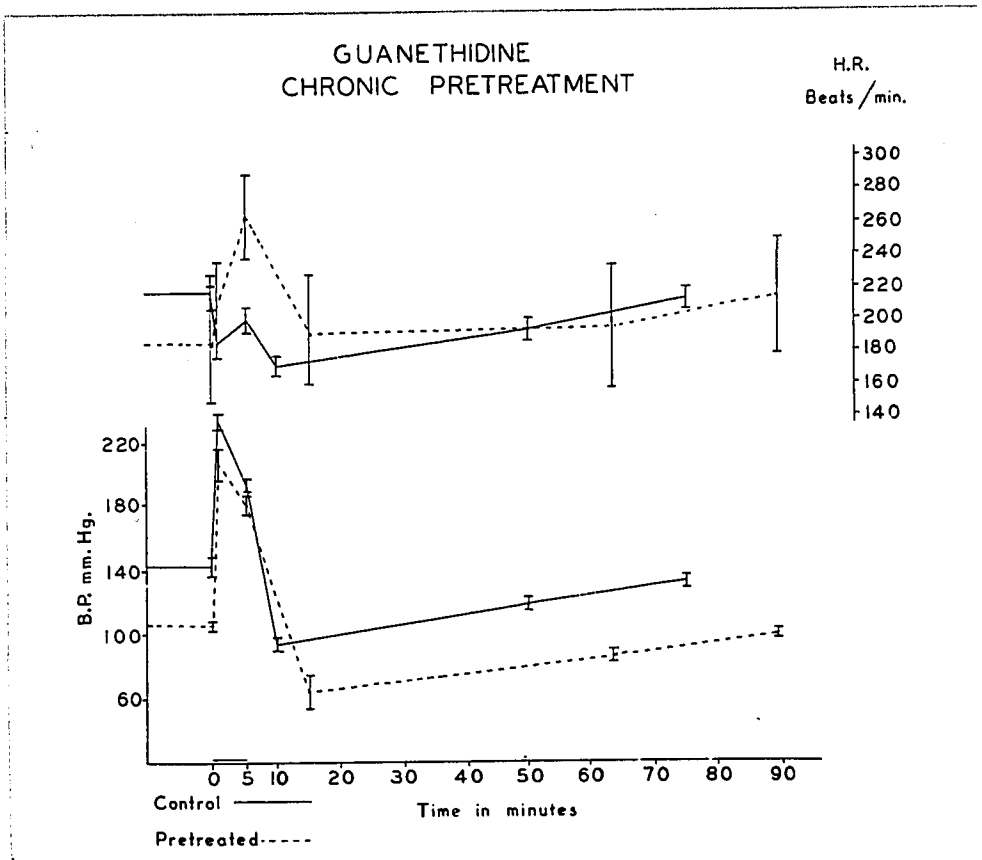

Figure 17

Changes in heart rate and blood pressure (Mean ± S.E.M. of four experiments) induced by noradrenaline infusion (8 µg/kg/minute for 5 minutes) in cats pretreated chronically with guanethidine.
N indicates time of noradrenaline infusion.

reached during the infusion was 100 ± 6 mm Hg in the treated animal and 90 ± 5 mm Hg in control cats, indicating a slightly increased pressor response to noradrenaline in the pretreated animals, possibly due to a lower preinfusional blood pressure level.

In both pretreated and non-treated animals tolerance development to the pressor response was observed during continuous administration of noradrenaline infusion. In the treated animals the blood pressure declined from 205 ± 10 mm Hg to 178 ± 7 mm Hg.

After the termination of noradrenaline infusion cats pretreated chronically with guanethidine showed a more gradual fall in blood pressure as compared to controls.

Figure 23 shows that the time to reach L.B.P. was 10 ± 3 minutes in the treated cats whereas in the controls it was 5 ± 2 minutes; the difference was statistically significant. Similarly time to M.P.R. (58 ± 8 minutes) and time to reach M.R. of blood pressure (84 ± 11 minutes) was significantly increased as compared to control experiments. This seems to indicate that similarly to pretreatment with reserpine and alpha methyldopa chronic guanethidine pretreatment resulted in a slower onset of N.P.H. and a slower recovery of blood pressure from the hypotensive phase. Full recovery of blood pressure was not reached within our experimental period of time (90-120 minutes).

Changes in Heart Rate

Preinfusional heart rate was much slower in the treated animals (178 ± 35 beats/minute) than in the control animals (210 ± 6 beats/minute), but it was very variable as shown by large S.E.M. During noradrenaline infusion, bradycardia which was usually seen in control experiments was not observed but a marked tachycardia ensued instead. At the last minute of infusion the heart rate increased to 257 ± 27 beats/minute, i.e., above the preinfusional rate. After arrest of the infusion heart rate decreased gradually towards control levels, and at L.B.P. it was 184 ± 31 beats/minute; this was still slightly above the preinfusional value. (However, in control experiments where preinfusional heart rate was 210 ± 6 beats/minute, at L.B.P. heart rate was 165 ± 6 beats/minute, far below the preinfusional value.) Heart rate remained steady at 184 ± 31 beats/minute during the hypotensive phase. At M.P.R. of blood pressure it was 188 ± 38 beats/minute. At M.R. of blood pressure heart rate was 199 ± 35 beats/minute, i.e., slightly above the preinfusional level. This is different from the control experiments where the heart rate was far below the preinfusional values during the hypotensive phase and returned to the preinfusional value only when M.R. of blood pressure was reached, i.e., at 75 minutes after the arrest of infusion. It should be pointed out that the standard error in this group of experiments was high possibly due to smaller number of experiments performed.

Changes in E.C.G.

An example of E.C.G. changes induced by noradrenaline in cats pretreated chronically with guanethidine is represented in Figure 18, (lower tracing). The upper tracing represents an example of E.C.G. changes induced by noradrenaline in control cats. Preinfusional heart rate in pretreated cat was slower than in control animals. Cardiac irregularities appeared during the infusion of noradrenaline in both cats, but disappeared after the infusion was terminated. Cardiac irregularities appeared in two out of 4 guanethidine experiments. Marked bradycardia seen in control cat during noradrenaline infusion was absent in guanethidine treated animal, and an increase in heart rate was seen during noradrenaline infusion; 30 minutes after the noradrenaline infusion was arrested heart rate decreased, slightly, but 90 minutes after the termination of infusion it was above the preinfusional value.

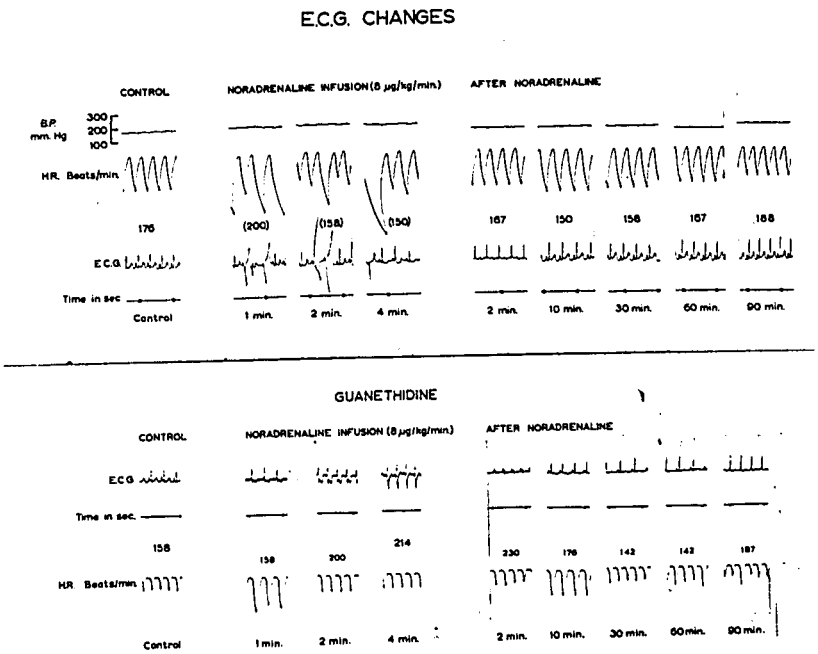

Figure 18

Upper record: Cat 3 kg male, in descending order are represented changes in blood pressure, heart rate and electrocardiogram induced by noradrenaline infusion (8 µg/kg/minute for 5 minutes) in control cat.

Lower record: Cat 3.2 kg male. Changes in electrocardiogram and heart rate induced by the same noradrenaline infusion in cat pretreated chronically with guanethidine. Guanethidine (5 mg/kg) was administered intraperitoneally daily for 7 days before noradrenaline infusion.

Heart rate calculated during cardiac irregularities induced by noradrenaline infusion represent approximate values only (see Methods).

RESULTS - PART III

EFFECTS OF PERIPHERAL ADRENERGIC BLOCKADE ON N.P.H.

Bretylium

In Part III of this study the effects of peripheral adrenergic blockade on the effects of noradrenaline infusion were investigated in the next group of experiments (Figure 19).

Boura and Green (1959) showed that bretylium, a quaternary benzyl salt, caused a specific peripheral adrenergic blockade, probably by impairing conduction of impulses in the adrenergic neurones.

Bretylium tosylate (5 mg/kg intravenously) was administered 15-30 minutes before the infusion of noradrenaline was started to 7 cats (Group VIII). This dose abolished the carotid occlusion response.

Changes in Blood Pressure

Bretylium tosylate administration alone induced an initial short-lasting rise in blood pressure from the mean control blood pressure of 129 ± 10 mm Hg to 173 ± 13 mm Hg; the mean rise was +44 ± 5 mm Hg, this rise was followed by a fall in blood pressure to 110 ± 10 mm Hg, (mean fall in blood pressure was 19 ± 4 mm Hg from the control

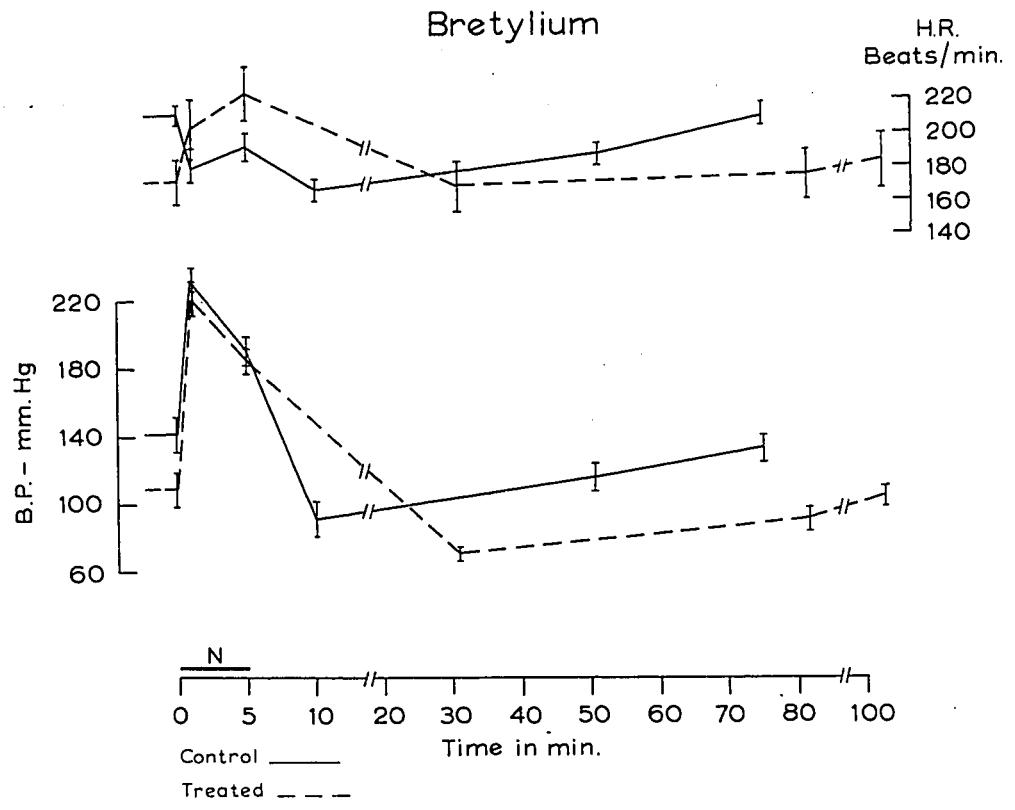

Figure 19

Heart rate and blood pressure changes (Mean ± S.E.M. of 6 experiments) induced by noradrenaline infusion (8 μg/kg/minute for 5 minutes) in cats pretreated with bretylium tosylate (10 mg/kgi.v.) 30 minutes before noradrenaline infusion was administered.
N indicates the time of noradrenaline infusion.

blood pressure level). Noradrenaline infusion was administered when blood pressure reached a steady level, i.e., about 30 minutes after bretylium administration.

As can be seen from the figure bretylium pretreated cats showed a lower preinfusional blood pressure than control animals (110 ± 10 mm Hg as compared to 142 ± 5 mm Hg). The maximum increase in blood pressure induced by noradrenaline infusion was 223 ± 10 mm Hg in the bretylium pretreated cats, as compared to 232 ± 4 mm Hg in the control animals. The difference between the control preinfusional blood pressure and the peak blood pressure rise induced by noradrenaline was quite similar; it was +93 ± 7 mm Hg in the treated cats and +90 ± 5 mm Hg in the control animals.

In both pretreated and control cats, tolerance development to the pressor response was observed during continuous administration of noradrenaline infusion. The blood pressure declined from 223 ± 10 mm Hg to 188 ± 7 mm Hg in bretylium pretreated animals. This tolerance was of slightly less intensity than in the control experiments where a decline from 232 ± 4 mm Hg to 191 ± 4 mm Hg was observed.

After infusion of noradrenaline was arrested, bretylium pretreated cats showed a more gradual decline in blood pressure than that seen in the control animals. Figure 19 and Figure 23 show that time to reach L.B.P. after

the arrest of infusion was 26 ± 4 minutes in the treated animals whereas in the control experiments L.B.P. was reached in 5 ± 2 minutes. The difference was statistically significant. Time to reach M.P.R. of blood pressure was significantly increased (78 ± 7 minutes) as compared to that seen in the controls (45 ± 3 minutes). Time to reach M.R. of blood pressure (105 ± 7 minutes) in the bretylium pretreated animals was also significantly longer than in the controls (70 ± 3 minutes). These results indicated that in bretylium pretreated cats, postinfusional hypotension developed more slowly and the recovery of blood pressure from the hypotensive phase was more prolonged than in the control experiments. Full recovery to the preinfusional blood pressure level was not reached within our experimental period of time (120 minutes). N.P.H. did not ensue in one out of 7 cats. This experiment was excluded from the data presented in Figure 19 and Figure 23.

Changes in Heart Rate

Preinfusional heart rate was much slower in cats pretreated with bretylium (173 ± 13 beats/minute) as compared to control animals (210 ± 6 beats/minute) (see Figure 19). During noradrenaline infusion bradycardia (which was usually seen in control experiments) was not observed but instead a marked tachycardia ensued. At the last minute of infusion heart rate was still elevated

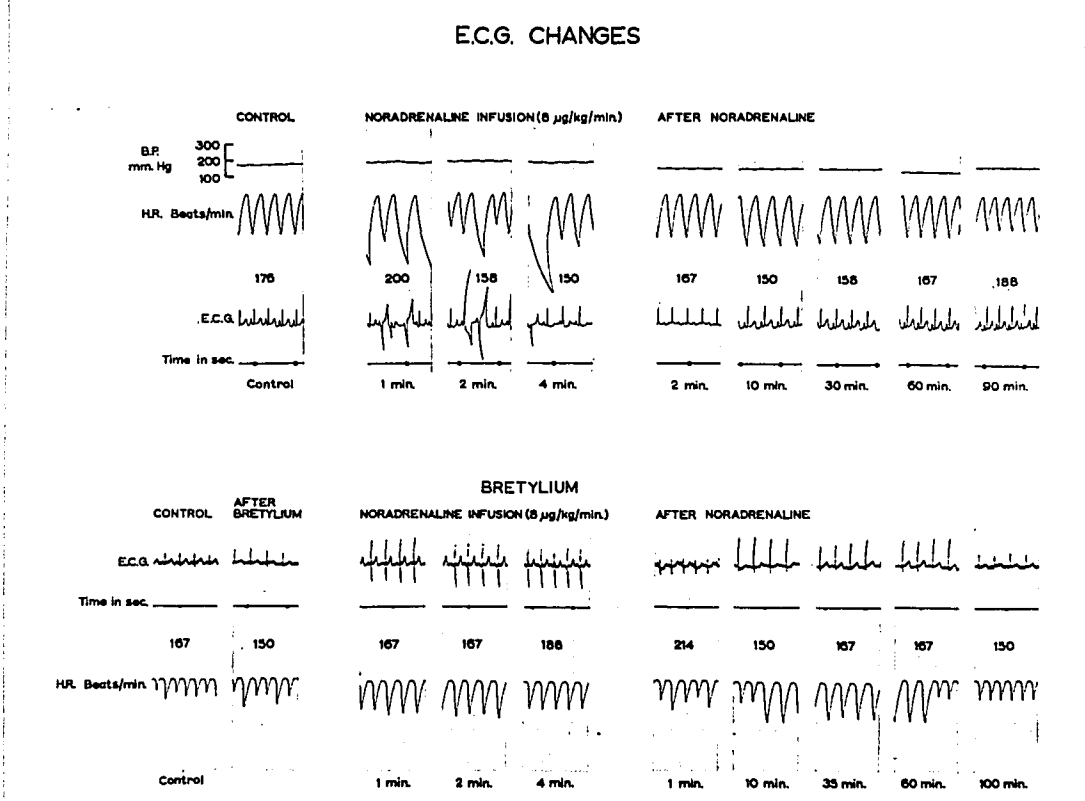

Figure 20

Upper record: Cat 3.5 kg male. In descending order are represented changes in blood pressure, heart rate and electrocardiogram induced by noradrenaline infusion (8 µg/kg/minute for 5 minutes) in control animal.

Lower record: Changes in electrocardiogram and heart rate induced by an identical noradrenaline infusion in bretylium pretreated cat (2.7 kg male). Bretylium tosylate (10 mg/kg intravenously) was administered 30 minutes before noradrenaline infusion.

Heart rate calculated during cardiac irregularities induced by noradrenaline infusion represent approximate values only (see Methods).

(224 ± 16 beats/minute). After the arrest of infusion heart rate gradually declined and at the time of L.B.P. it was almost identical with the preinfusional value (168 ± 15 beats/minute), whereas in control experiments the heart rate at L.B.P. was far below the preinfusional rate (165 ± 6 beats/minute as compared to 210 ± 6 beats/minute before infusion). In the pretreated animals heart rate remained close to preinfusional rate throughout the hypotensive phase until the M.P.R. of blood pressure was reached. It was slightly increased above the preinfusional value at M.R. of blood pressure (186 ± 16 beats/minute). This is different from the control experiment where the heart rate was far below the preinfusional values during the hypotensive phase and returned to the preinfusional rate only when M.R. of blood pressure was reached, i.e., at 75 minutes after the arrest of the infusion.

Changes in E.C.G.

Figure 20 represents an example of E.C.G. changes seen during noradrenaline infusion in control cats (upper tracing) and in bretylium pretreated cats (lower tracing).

Cardiac irregularities developed consistently during infusion of noradrenaline in the nonpretreated cats, but disappeared after the infusion of noradrenaline was arrested. Bretylium treated cats had a slower preinfusional heart rate than the controls. Cardiac irregularities did

not develop during noradrenaline infusion in 6 out of 7 cats pretreated with bretylium.

Figure 20 shows the absence of cardiac irregularities and bradycardia during noradrenaline infusion. Although the heart rate fluctuated slightly in this experiment, bradycardia (which was seen in the control experiment) during noradrenaline infusion was absent in bretylium pretreated animals.

Heart rate increased 10 minutes after the arrest of infusion but remained closed to the preinfusional value during the hypotensive phase and during the progressive recovery of blood pressure towards the control preinfusional level.

Guanethidine (Acute treatment)

The effects of peripheral adrenergic blockade induced by acute guanethidine administration (1 mg/kg intravenously) on intensity and duration of N.P.H. were investigated in Group IX of experiments (6 cats).

Guanethidine administration alone caused an initial rise of blood pressure, (mean being 35 ± 10 mm Hg) followed by a marked fall in blood pressure (mean fall of 52 ± 8 mm Hg) below the original control level. Infusion of noradrenaline (8 µg/kg/minute for 5 minutes) was administered when the blood pressure reached a steady level, i.e., 30-120 minutes after injection of guanethidine. The dose of guanethidine used in this investigation abolished carotid occlusion response.

Figure 21 represents changes in heart rate and blood pressure induced by noradrenaline infusion after acute pretreatment with guanethidine.

Changes in Blood Pressure

Guanethidine pretreated cats showed a lower preinfusional blood pressure level as compared to the control animals (101 ± 7 mm Hg as compared to 142 ± 5 mm Hg). The peak of blood pressure rise reached was lower (219 ± 11 mm Hg) in the treated animals as compared to the control experiments (232 ± 4 mm Hg), however when the differences between the preinfusional blood pressure and the peak of

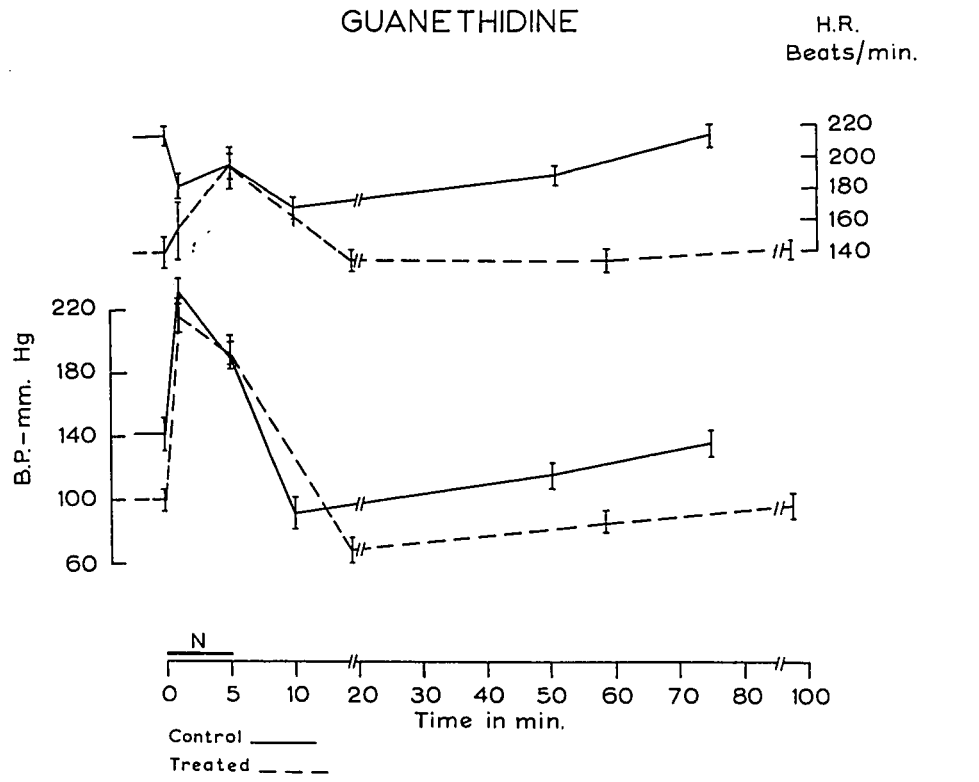

Figure 21

Heart rate and blood pressure changes (Mean ± S.E.M. of six experiments) induced by noradrenaline infusion, 8 µg/kg/minute for 5 minutes, in cats pretreated with guanethidine (1 mg/kg i.v.).
N indicates time of noradrenaline infusion.

blood pressure reached during noradrenaline infusion are compared the value was 122 ± 9 mm Hg in the treated animals as compared to 90 ± 5 mm Hg in the control experiment, i.e., in the pretreated animals the pressor response to noradrenaline was potentiated possibly due to a lower preinfusional blood pressure level.

In both pretreated and non-treated cats tolerance development to the pressor response was observed during continuous administration of noradrenaline infusion. In pretreated cats the blood pressure declined from 219 ± 11 mm Hg to 191 ± 11 mm Hg at the end of infusion. This tolerance was less than that observed in the control experiment where a decline from 232 ± 4 mm Hg to 191 ± 4 mm Hg was seen.

Guanethidine pretreated cats showed a more gradual fall in blood pressure after the infusion of noradrenaline was arrested than that seen in the control experiments. Figure 23 shows that time to reach L.B.P., M.P.R. and M.R. was 14 ± 6 minutes, 53 ± 16 minutes and 90 ± 22 minutes, respectively. All three values were increased as compared to controls but the differences were not statistically significant (t test).

Changes in Heart Rate

Preinfusional heart rate in guanethidine treated animals was much slower (137 ± 12 beats/minute) than in

control animals (210 ± 6 beats/minute). During noradrenaline infusion bradycardia was not observed but the heart rate increased from the preinfusional rate of 137 ± 10 beats/minute to 153 ± 18 beats/minute; at the last minute of infusion heart rate was 207 ± 16 beats/minute which was far above the preinfusional value. After the arrest of infusion heart rate gradually returned to the preinfusional rate and at L.B.P. it was 134 ± 7 beats/minute, i.e., almost identical with the preinfusional heart rate, this is different from the control experiments where the heart rate fell far below preinfusional values at L.B.P. Heart rate remained steady at 134 ± 7 beats/minute throughout the hypotensive phase. A very slight increase in heart rate (141 ± 6 beats/minute) was observed when M.P.R. of blood pressure was reached. At maximum recovery of blood pressure, reached during the experimental period (90-120 minutes) heart rate was 141 ± 6 beats/minute which was very close to the preinfusional value.

Changes in E.C.G.

Figure 22 (lower tracing) represents an example of E.C.G. changes induced by noradrenaline infusion in cat acutely pretreated with guanethidine. The upper tracing shows E.C.G. changes seen during noradrenaline infusion in control cat. Guanethidine treated cat had a slower preinfusional heart rate than control animal. Two minutes

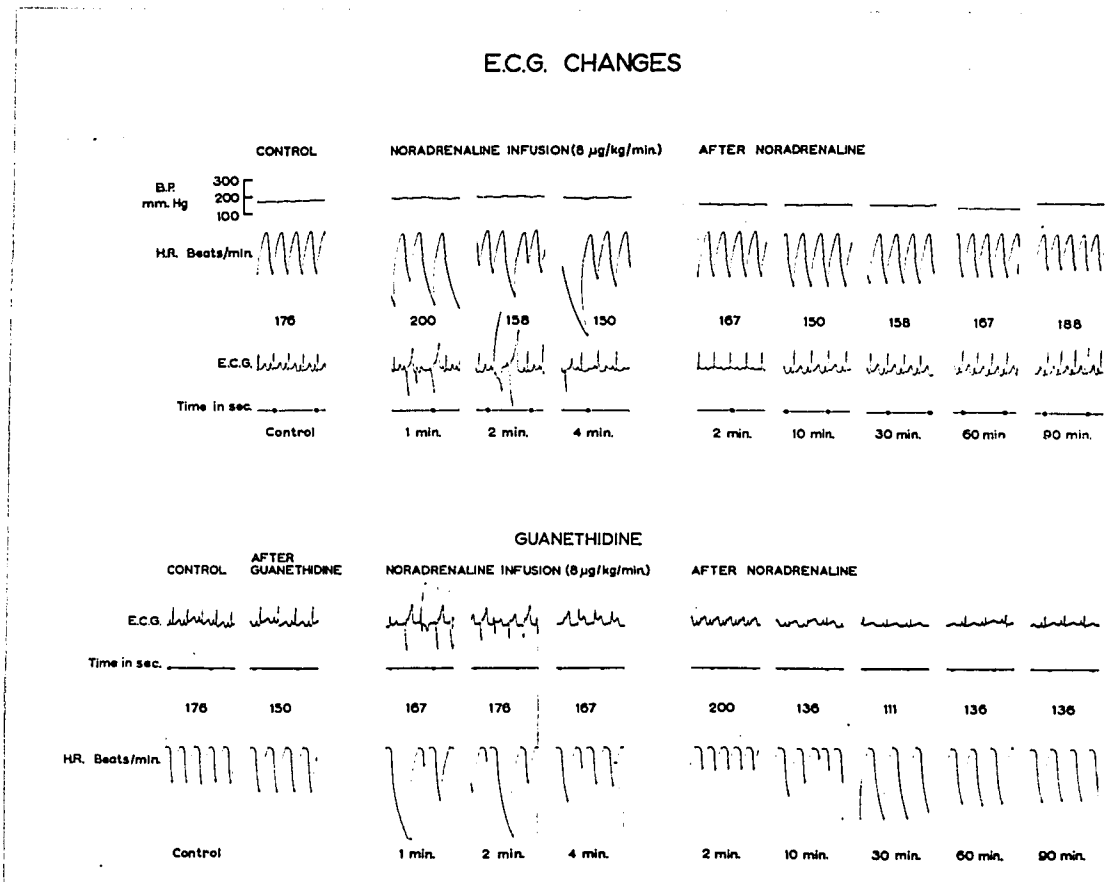

Figure 22

Upper record. Cat 3.0 kg male. In descending order are represented changes in blood pressure, heart rate and electrocardiogram induced by noradrenaline infusion (8 µg/kg/minute for 5 minutes) in control animals.
Lower record. Cat 4.1 kg. Changes in electrocardiogram and heart rate induced by noradrenaline infusion administered to guanethidine pretreated animal. Guanethidine 1 mg/kg intravenously was administered 30 minutes before noradrenaline infusion was started.
Heart rate calculated during cardiac irregularities induced by noradrenaline infusion represent approximate values only (see Methods).

after arrest of noradrenaline infusion heart rate increased in guanethidine treated cats but was then decreased during the hypotensive phase. Cardiac irregularities during the period of noradrenaline infusion were seen in all 6 guanethidine pretreated cats.

Absence of bradycardia during noradrenaline infusion is evident in the guanethidine pretreated animal (Figure 22).

In the control animals cardiac arrhythmias disappeared after the infusion of noradrenaline was arrested. However in the guanethidine pretreated experiments irregularities often persisted 10-15 minutes after the arrest of infusion.

Figure 23 summarizes the results obtained after depletion of catecholamine stores by reserpine, alpha methyldopa and guanethidine (chronic treatment) and after peripheral adrenergic blockade induced by bretylium, and guanethidine (acute administration). Time to reach L.B.P., M.P.R. and M.R. of blood pressure level is represented in minutes (Mean $\pm$ S.E.M.).

In control cats time to reach L.B.P. was 5 ± 2 minutes. It was 21 ± 9 minutes, 16 ± 6 minutes, 10 ± 3 minutes, 26 ± 4 minutes and 14 ± 6 minutes, in reserpinized, alpha methyldopa treated, guanethidine (chronic treatment), bretylium treated, and guanethidine (acute treatment) pretreated cats, respectively. The increase in time to L.B.P.

The Effects of Catecholamine Depletion and of Peripheral Adrenergic Blockade on N.P.H.

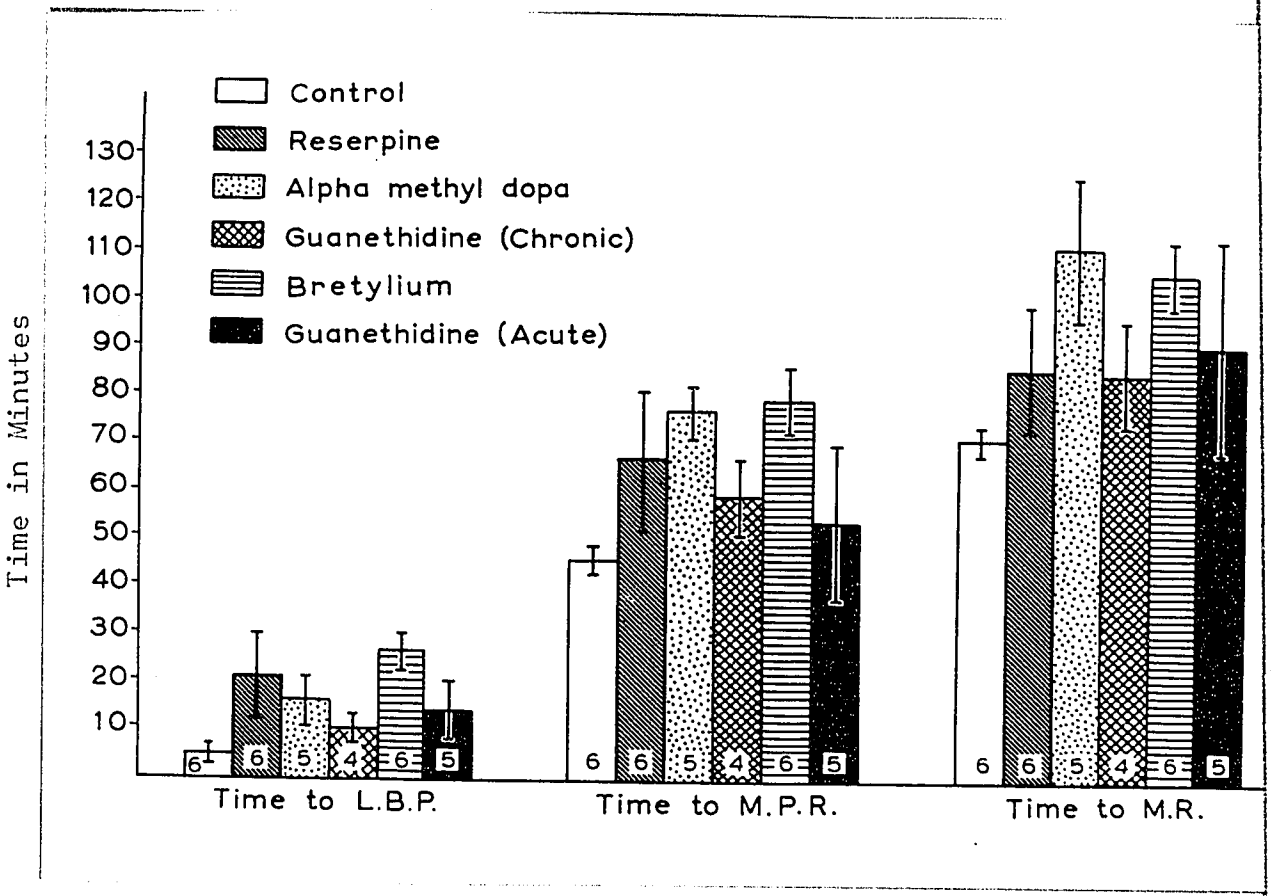

Figure 23

Combined results from Groups V, VI, VII, VIII, IX and X. Single noradrenaline infusion (8 μg/kg/minute for 5 minutes) was administered to cats under pentobarbitone anaesthesia, to control cats, and to cats pretreated with reserpine, alpha methyldopa, guanethidine (chronic pretreatment), bretylium and guanethidine (acute administration), respectively.
Time to L.B.P., M.P.R. and M.R. calculated in minutes. Mean $\pm$ S.E.M. are represented. Number of experiments is shown on the histogram.

induced by reserpine, alpha methyldopa, guanethidine (chronic treatment) and bretylium was statistically significant (t test) from the control cats. Time to L.B.P. after guanethidine (acute pretreatment) was increased, but the difference was not statistically significant from the control value.

Time to reach M.P.R. of blood pressure level was 45 ± 3 minutes in control cats, 66 ± 15 minutes in reserpinized cats, 76 ± 6 minutes in alpha methyldopa experiments, 58 ± 8 minutes in guanethidine pretreated (chronic pretreatment) cats. In bretylium and guanethidine (acute administration) treated cats, time to M.P.R. was 78 ± 7 minutes and 53 ± 16 minutes, respectively. Statistical analysis (t test) showed that increase in time to reach M.P.R. was significantly longer after pretreatment with reserpine, alpha methyldopa, guanethidine (chronic treatment) and bretylium as compared to controls; however there was no significant difference in time to reach M.P.R. of blood pressure level between guanethidine (acute administration) treated cats and control cats.

Time to reach M.R. of blood pressure level was 70 ± 3 minutes in control cats, and 85 ± 13 minutes, 110 ± 15 minutes, 84 ± 11 minutes in reserpinized, alpha methyldopa and guanethidine (chronic pretreatment) treated cats respectively. In bretylium and guanethidine pretreated cats (acute administration), time to reach M.R. of blood

pressure level was 105 ± 7 minutes and 90 ± 22 minutes respectively. This increase in time to reach M.R. of blood pressure was found to be statistically significant from the control value after pretreatment with alpha methyldopa, guanethidine (chronic treatment) and bretylium. The difference in time to reach M.R. of blood pressure between guanethidine (acute administration) and reserpinized cats was not statistically significant from the control cats.

The times to reach L.B.P., M.P.R. and M.R. of blood pressure level were all increased after catecholamine depletion and after peripheral adrenergic blockade. These results seem to indicate that the recovery from N.P.H. is significantly prolonged when the sympathetic tone of blood vessels is decreased either by depletion of catecholamine stores, or by peripheral adrenergic blockade.

RESULTS - PART IV

EFFECT OF QUINDONIUM BROMIDE ON N.P.H.

Quindonium Bromide

Melville et al (1964) reported that quindonium bromide, an isoquinolinium derivative, exerted a protective action against haemorrhagic shock in dogs. Prophylactic administration of quindonium (10 mg/kg) 15 minutes before induction of haemorrhage, produced a significant increase in the survival rate. The effect of this drug on N.P.H. was investigated. In 6 cats, 10 mg/kg of quindonium bromide was administered intravenously 30 minutes previous to noradrenaline infusion (Group X).

A summary of the results obtained is represented in Figure 24.

Changes in Blood Pressure

Quindonium pretreated cats showed a lower pre-infusional blood pressure level than control animals (116 ± 8 mm Hg as compared to 142 ± 5 mm Hg in controls). The peak of blood pressure rise induced by noradrenaline infusion was 196 ± 8 mm Hg in treated as compared to 232 ± 4 mm Hg seen in the control animals. The difference between control blood pressure and the peak of blood pressure rise was 80 ± 3 in the treated animals as compared

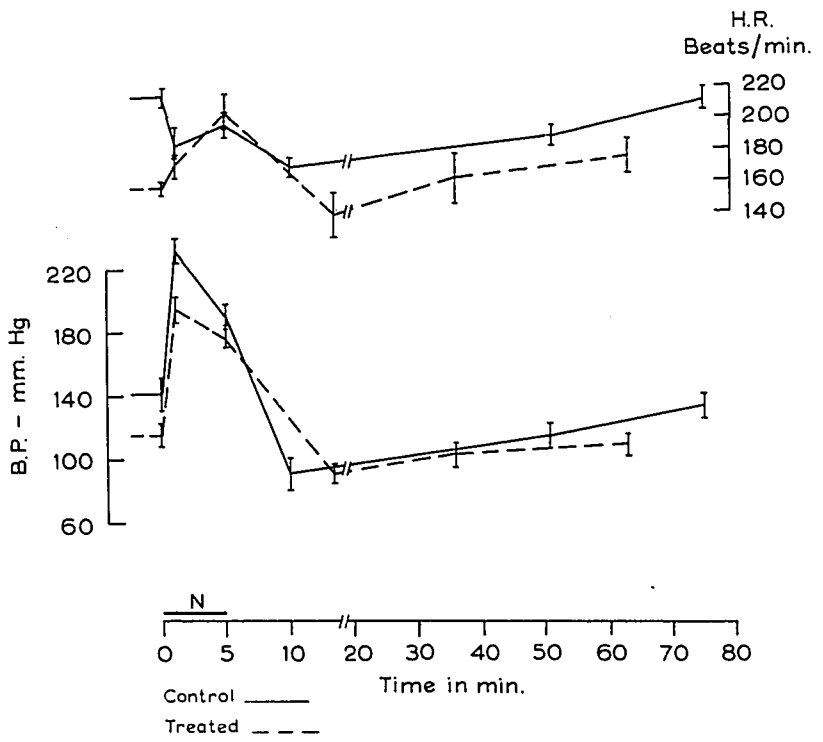

Figure 24

Changes in the heart rate and blood pressure (Mean ± S.E.M. of 6 experiments) induced by noradrenaline infusion (8 µg/kg/minute for 5 minutes) in cats pretreated with quindonium bromide (10 mg/kg i.v.) 30 minutes before noradrenaline infusion.
N indicates time of noradrenaline infusion.

to 90 ± 5 mm Hg in the control animals. In both the pre-treated and non-treated cats, tolerance development to the pressor response was observed during continuous administration of noradrenaline infusion. The blood pressure declined from 196 ± 8 mm Hg to 177 ± 8 mm Hg at the end of infusion; in quindonium treated cats this tolerance was less than in the control experiments where a decline from 232 ± 4 mm Hg to 191 ± 4 mm Hg was seen.

After the infusion was discontinued, quindonium treated cats showed a more gradual fall in blood pressure than that observed in control experiments. Table I shows that the time to reach L.B.P. was 12 ± 3 minutes in the experimental animals, while in the control experiments L.B.P. was reached in 5 ± 2 minutes; the difference was statistically significant. The time to reach M.P.R. of blood pressure level was 31 ± 10 minutes; the difference from the control value was not statistically significant. Time to reach M.R. of blood pressure level was 58 ± 6 minutes; this time was significantly shorter than in the control experiments. The decrease in the times to reach M.P.R. and M.R. of blood pressure level indicated a faster recovery of blood pressure from the hypotensive phase towards the preinfusional level in quindonium pre-treated cats.

Changes in Heart Rate

Preinfusional heart rates were slower in the quindonium pretreated cats (153 ± 7 beats/minute) as compared to the controls (210 ± 6 beats/minute). During noradrenaline infusion, instead of the usually seen bradycardia, a marked tachycardia ensued. At the last minute of the infusion the heart rate increased to 201 ± 11 beats/minute. After the arrest of the infusion the heart rate gradually declined towards preinfusional values. At L.B.P. heart rate was well below the preinfusional value (average of 136 ± 15 beats/minute). With the recovery of blood pressure from the hypotensive phase, heart rate gradually increased. At M.P.R. of blood pressure level it was 160 ± 17 beats/minute. Heart rate was 175 ± 11 beats/minute when M.R. of blood pressure level was reached, i.e., above the preinfusional value.

Changes in E.C.G.

Figure 25 represents an example of changes in E.C.G. induced by noradrenaline infusion in control cats (upper tracing) and in cats pretreated with quindonium bromide (lower tracing). Preinfusional heart rate in this cat pretreated with quindonium was almost the same as in control animal, however as shown in Figure 24 the average preinfusional heart rate in treated animals was slower than

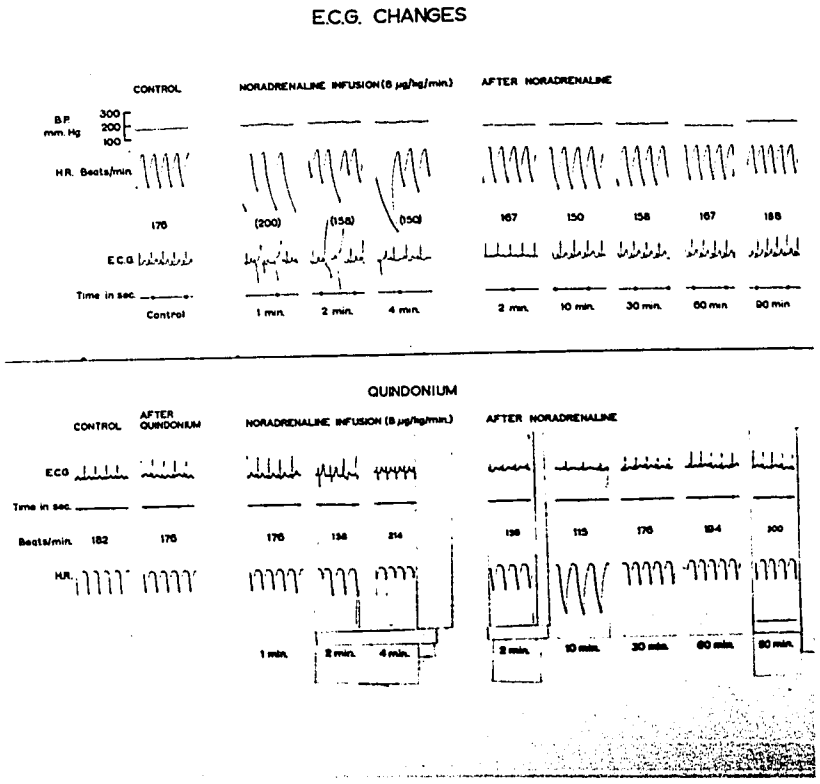

Figure 25

Upper record. Cat (3 kg male). In descending order are represented changes in blood pressure, heart rate and electrocardiogram induced by noradrenaline infusion (8 µg/kg/minute for 5 minutes) in control animal.

Lower record. Changes in electrocardiogram and heart rate induced by the same noradrenaline infusion in quindonium pretreated cat (3.4 kg male). Quindonium bromide 10 mg/kg was administered 30 minutes before noradrenaline infusion.

in controls (Mean ± S.E.M. of 6 cats). In the treated cat only cardiac irregularities developed during noradrenaline infusion and disappeared after the infusion was arrested. Out of 6 experiments performed in this group, cardiac arrhythmias were seen in 5 cats. Cardiac irregularities, however, developed at a later stage after initiation of noradrenaline infusion. Development of bradycardia during noradrenaline infusion was not seen in most of the quindonium pretreated cats, heart rate increased instead; however, in this cat a short period of decrease in heart rate was evident 2 minutes after the start of the infusion. After the termination of infusion during the hypotensive phase, heart rate decreased below preinfusional value, but recovered 30 minutes after arrest of infusion. At 90 minutes after the arrest of noradrenaline infusion, heart rate was far above the preinfusional value.

TABLE I

The Influence of Quindonium Bromide* on N.P.H.

Number of Experiments	Pretreatment	Dose of Noradrenaline Infused	Time to L.B.P. in min.	Time to M.P.R. in min.	Time to M.R. in min.
6		8 μg/kg/minute for 5 minutes	5 ± 2	45 ± 3	70 ± 3
6	Quindonium bromide	8 μg/kg/minute for 5 minutes	12 ± 3**	31 ± 10	58 ± 6**

*Quindonium bromide 10 mg/kg was administered i.v. 30 minutes before an infusion of noradrenaline was started.

**Statistically significant.

DISCUSSION

Under these experimental conditions outlined in this investigation, infusion of a "control dose" of noradrenaline (8 μg/kg/minute for 5 minutes), induced an intense secondary postinfusional hypotension after the infusion was arrested (Group I). A gradual recovery towards the preinfusional blood pressure level was observed within the experimental time period but full recovery was not reached. During infusion of noradrenaline reflex vagal bradycardia ensued and cardiac arrhythmias were observed. After the arrest of infusion the slow heart rate observed during the secondary hypotensive phase gradually recovered after the blood pressure reached midpoint of recovery. Full recovery of the heart rate was seen within the experimental time period but it was not associated with a full recovery of blood pressure.

Repeated Infusions of Noradrenaline (Group I)

1) Repetition of the same "control" infusion of noradrenaline at suitable intervals in the same animal did not influence the development of tolerance to the pressor effect of noradrenaline during the infusion.

2) Reflex vagal bradycardia which ensued during the first infusion of noradrenaline did not develop during the second and third infusions of noradrenaline; tachycardia was seen instead.

3) Repetition of infusion did not seem to influence the development of cardiac arrhythmias during the infusion.

4) Time to reach lowest blood pressure level, i.e., onset

on N.P.H. was unchanged, while time to reach midpoint of recovery of blood pressure was shorter after successive infusions although the decrease was not statistically significant. Time to reach maximum recovery was significantly longer after the first infusion as compared to the third, and shorter after the third as compared to the second; however, the values for maximum recovery of blood pressure reached were lower after each consecutive infusion. 5) Within the experimental time period heart rate returned gradually to the preinfusional rate. However, full recovery of blood pressure from the secondary hypotensive phase to the preinfusional level was not seen within the experimental time period. Although the blood pressure stabilized more rapidly after each consecutive infusion the blood pressure attained was lower each time; this was the reason why in the next groups of comparative experiments, the effects of variation in dose, time and dose and time of infused noradrenaline were studied by administration of single infusion of noradrenaline to each animal.

I. <u>The Effects of Variation in Dose and Time of Infused Noradrenaline on N.P.H. (Group II-IV)</u>

The results obtained in Group II of experiments indicated that:

1) An increase in the dose of a single infusion of noradrenaline (while the duration of infusion was kept constant)

did not influence tolerance development to the pressor effect of noradrenaline during the infusion.

2) Reflex vagal bradycardia was seen only during infusion of the "control" dose of noradrenaline, but tachycardia ensued during the infusion of a double or four-fold dose of noradrenaline.

3) Under these experimental conditions, surprisingly, cardiac arrhythmias were less frequent during an infusion of double dose of noradrenaline than during a "control" dose, but they were present when a four-fold dose of noradrenaline was infused.

4) Time to reach L.B.P., i.e., the onset of N.P.H. was significantly delayed after a double dose as compared with the single "control" dose of noradrenaline, and after the four-fold dose as compared to the single dose.

5) The higher the dose of noradrenaline infused, the lower the blood pressure level reached at M.R. of blood pressure after the infusion was arrested.

6) Increase in the dose of noradrenaline infused resulted also in a significant increase in the time to reach M.P.R., and therefore recovery of blood pressure from the hypotensive phase after the arrest of infusion was more prolonged.

7) After the arrest of noradrenaline infusion a gradual recovery of heart rate towards the preinfusional rate ensued, which was not associated with the recovery of blood pressure.

In the following series of experiments (Group III) the time of noradrenaline infusion was increased while the dose was always identical (40 μg/kg).

The results indicated that:

1) Tolerance development to the pressor effect of noradrenaline during noradrenaline infusion was not influenced when the duration of infusion was increased, while the amount infused remained identical.

2) Reflex vagal bradycardia was of less intensity when noradrenaline infusion lasted for 10 minutes than when it was administered for 5 minutes. Heart rate was unchanged when the duration of infusion was 20 minutes. The recovery of heart rate during the postinfusional hypotensive phase was also speeded up when the time of noradrenaline infusion was increased.

3) Cardiac arrhythmias were less in intensity when the duration of infusion was increased, and were observed less frequently when the infusion of the same dose lasted for 10 minutes. They were absent during 20 minutes of infusion of noradrenaline.

4) Time to reach L.B.P., i.e., the onset of N.P.H. was unchanged, but the hypotension was less intense when the duration of infusion was increased. Time to reach M.P.R. was significantly decreased when the infusion lasted for 20 minutes as compared with 5 minutes infusion. Time to reach M.R. was also decreased although the change was not

statistically significant. Postinfusional blood pressure stabilized itself at a slightly lower level when the duration of infusion was increased.

In the next group of experiments (Group IV) the dose and time of noradrenaline was increased. The results indicated that:

1) Tolerance development to the pressor effect during noradrenaline infusion was potentiated to some degree.

2) An increase in the dose and time of infused noradrenaline resulted in a decrease in intensity and duration of reflex vagal bradycardia during the infusion of noradrenaline.

3) Cardiac arrhythmias were more intense during the infusion of noradrenaline when the dose and duration of infusion were doubled or increased fourfold.

4) Time to reach L.B.P., i.e., the onset of N.P.H. was delayed after an increase in the dose and time of infused noradrenaline, but the difference was not statistically significant. Despite the increase in dose and time of noradrenaline infused, the value obtained for L.B.P. did not change measurably from that due to "control" infusion.

5) Time to reach M.R. was significantly increased when the dose was 8 μg/kg/minute for 20 minutes; this indicates a slower recovery from the secondary postinfusional hypotensive phase when the dose and duration of infusion of noradrenaline are increased.

Tolerance development to the pressor response of noradrenaline during infusion of noradrenaline has been reported by several investigators.

Rosenthale and Dipalma (1962) showed that this tolerance was associated with a decrease in blood volume, haemoconcentration, and acidosis. Infusion of dextran caused a temporary reversal of tolerance. Coppola and Dipalma (1962) demonstrated that tolerance to noradrenaline was associated with an increase in the level of plasma histamine and that it was reduced when histamine stores were depleted.

Burn and Rand (1959) working with reserpinized cats, observed a striking decline in blood pressure from the peak pressor response in spite of the continuation of the infusion of noradrenaline. They suggested that low sensitivity to noradrenaline was due to the uptake of infused noradrenaline into the storage sites in blood vessel walls, from which it is slowly discharged. Due to this discharge receptors are occupied and therefore only a few are free on which the circulating noradrenaline can act. When the blood pressure fell to low levels after the termination of infusion of noradrenaline the workers showed that indirectly acting sympathomimetic amines were still effective in raising the blood pressure.

Perez-Reyes (1964) reported tachyphylaxis to noradrenaline and adrenaline in anaesthetized cats. The rate

of development of this tachyphylaxis was accelerated by cocaine which is known to block the uptake and storage of catecholamines.

Mulheims (1964) showed that in dogs, the pressor response to a single injection of noradrenaline (0.5 μg/kg) was markedly reduced if an infusion of noradrenaline (1 μg/kg/minute for 10 minutes) was administered prior to the injection. This development of tachyphylaxis to noradrenaline was not only prevented by an injection of guanethidine (1 mg), but the pressor response to noradrenaline was enhanced. The author suggested that a direct action of guanethidine on the adrenergic receptors in the blood vessel walls might account for the potentiation of catecholamines. Mulheims and co-workers (1965) further showed that guanethidine modified the development of tachyphylaxis to noradrenaline. In guanethidine pretreated dogs (15 mg/kg one day previously) the pressor response to repeated noradrenaline administration remained unaltered whereas it decreased markedly in the control group. This prevention of tachyphylaxis to noradrenaline by guanethidine was again suggested to be due to a direct action on the adrenergic receptors in blood vessel walls.

A number of investigators have suggested that peripheral vasodilatation is a factor responsible for development of N.P.H. after the arrest of infusion of noradrenaline, however a lot of controversy still exists

regarding the mechanisms involved in this vasodilator action. Lever and co-workers (1961) suggested that a vasodilator substance is liberated into the circulation during the infusion of noradrenaline.

Eakins and Lockett (1961) claimed to have detected an isoprenaline-like substance in circulating blood during pressor response to adrenaline, but failed to show the presence of such a substance after injection of noradrenaline. However, chromatographic studies of plasma samples withdrawn during N.P.H. showed no evidence for the presence of any vasodilator substance (Mazurkiewicz, personal communication). Until such a substance is isolated and identified the role of vasodilator substance in N.P.H. remains obscure.

Duner and von Euler (1957) suggested partial sympathetic ganglionic blockade to be a cause of N.P.H. However Mazurkiewicz and Murnaghan (1964) produced evidence against such a mechanism. They observed no change in ganglionic transmission during N.P.H. in anaesthetized cats. N.P.H. was absent not only in cats pretreated with hexamethonium, but also in normal cats when the preinfusional blood pressure was lowered by bleeding the animal. Despite ganglionic blockade with hexamethonium, N.P.H. was shown when the preinfusional blood pressure was raised by an infusion of angiotensin.

Many investigators observed a decreased blood volume after adrenaline infusion. (Bainbridge and Trevan,

1917; Erlanger and Gasser, 1919; Freedman, 1941.) Schmutzer and Ekhari (1961) showed a reduction in plasma volume in dogs given noradrenaline infusion.

Nickerson and Sutter (1964) observed a loss of relatively protein-poor fluid after equipressor doses of noradrenaline and angiotensin were infused in dogs. Rosenthale and Dipalma (1962) found that in dogs, tolerance to noradrenaline was associated with haemoconcentration, which was temporarily reversed with dextran. Haemoconcentration and decreased blood volume could be factors contributing to N.P.H., but others certainly must exist.

Gilbert and Hohf (1964) reported that after prolonged infusions of noradrenaline (8 µg/kg/minute for 120 minutes) in anaesthetized dogs, the cardiac output decreased, and central venous pressure was elevated. An increase in the blood volume induced by dextran administration did not elevate the reduced cardiac output. These investigators considered it possible that the decreased cardiac output resulted from deterioration of myocardial function. Similarly Page and Olmsted (1961) also reported a decrease in cardiac output after administration of noradrenaline infusion (4 µg/kg/minute for 1 hour) in dogs.

Under the present experimental conditions, reflex vagal bradycardia was consistently observed during an infusion of 8 µg/kg/minute for 5 minutes of noradrenaline. Subsequent infusion of the same dose of noradrenaline to

the same animal converted the bradycardia to a tachycardia. A double or a four-fold dose of noradrenaline administered over the same period of time as a single infusion to different animals resulted in tachycardia instead of bradycardia during the period of infusion, in spite of an intense rise in blood pressure. An increase in the time of noradrenaline infusion, while the dose was identical resulted in the absence of bradycardia. Under these conditions heart rate was almost unchanged although the blood pressure was elevated.

These results seem to indicate that in spite of a comparable rise in blood pressure induced by infusion of noradrenaline, reflex vagal bradycardia may be absent and tachycardia ensues instead. The mechanism of such an observation is unexplained at the present time.

Under these experimental conditions, N.P.H. was associated with bradycardia. As under normal physiological conditions hypotension is usually associated with reflex increase in the heart rate, our observations indicate some impairment of cardio-vascular reflexes during the secondary hypotensive phase.

During noradrenaline infusion electrocardiographic records showed development of cardiac arrhythmias (missed beats, inverted beats, ventricular tachycardia). Cardiac irregularities seen during the period of noradrenaline infusion disappeared after the infusion was arrested. Graham

and Jones (1964) showed that arrhythmias result from the administration of intravenous noradrenaline in rats; depression of conduction, blocked atrial conduction, and sometimes atrial fibrillation were seen. Atropinization or vagotomy converted bradycardia to tachycardia, but the arrhythmias were not abolished.

Similarly under the present experimental conditions cardiac arrhythmias were seen during infusion of noradrenaline whether reflex bradycardia or tachycardia ensued. It was previously observed in this laboratory that the primary hypertensive phase did not ensue when a mixture of isoprenaline with noradrenaline was infused. Prevention of the primary hypertensive phase induced by infusion of noradrenaline resulted in the absence of cardiac arrhythmias during the infusion (Mazurkiewicz, Arch. int. Pharmacodyn, in press). Under these experimental conditions N.P.H. did not ensue. It seems probable therefore that development of cardiac arrhythmias during infusion of noradrenaline is related to the primary hypertensive phase, and that cardiac arrhythmias may play some role in the secondary hypotensive phase. However, Kendrick (1959) showed in anaesthetized dogs the secondary depressor response of noradrenaline to persist even when the cardiac effects of the drug had been eliminated by replacing the heart with a "constant output pump." The pressure responses in these perfused animals reflected the changes in the resistance of the vascular system only.

On the other hand toxic effects of noradrenaline on the myocardium have been reported by Szackacs and Cannon (1958). Noradrenaline (0.8-0.9 µg/minute for 107-336 hours) caused focal myocarditis and necrotising arteriolitis in sedated dogs. Further, cardiac haemorrhage and pulmonary oedema as a result of noradrenaline administration were reported by Szackacs and Mehlman (1960). Szackacs, Dimmette and Cowart (1959) reported focal myocarditis, myocardial haemorrhage and medial necrosis with severe mechanical injuries to the mitral valve induced by previous noradrenaline administration. Fatty changes in the heart after a large dose of noradrenaline were also reported by Maling and Highman (1958) in dogs. Miller and co-workers (1955) as well as Littler and McKendrick (1957) reported development of cardiac arrhythmias in clinical cases treated with noradrenaline. The latter investigators showed also cardiac arrhythmias in monkeys and dogs induced by noradrenaline. Moss, Vittands and Schenk (1966) administered a sustained infusion of noradrenaline in graded doses of 1, 2 and 4 µg/kg/minute for 4 hours, to dogs. They observed that augmentation of cardiac function during the first 15 minutes of infusion was not maintained, the cardiac output declined and the peripheral resistance was increased. Electrocardiographic changes (elevation of ST segment, diminution of QRS amplitude, and abnormal Q wave) indicated a progressive deterioration of myocardial electrical activity.

Further Schenk and Moss (1966) showed that the major toxic effect of prolonged noradrenaline infusion in dogs, cats and rabbits in doses relatively comparable to those administered clinically was exerted on the myocardium. The cardiac lesions consisted of focal degeneration, necrosis of the myocardium and subendocardial haemorrhage.

II. The Effects of Catecholamine Depletion on the Response to Noradrenaline Infusions

Reserpine

Burn and Rand (1958) postulated that N.P.H. is a result of overfilling of catecholamine storage sites in the blood vessel walls during an infusion of noradrenaline. According to their theory secondary postinfusional hypotension is due to a leakage of noradrenaline from the overfilled stores on the receptors in the blood vessel walls, leaving a few receptors free for circulating noradrenaline to act upon. In order to investigate such a possibility, further studies were executed wherein noradrenaline was infused in reserpinized cats. Reserpine is known to deplete the peripheral tissue stores of the sympathetic transmitter (Burn and Rand, 1958; Carlsson and co-workers, 1957; Brodie and co-workers, 1960) and to prevent noradrenaline uptake at storage sites. One could therefore speculate that in reserpinized cats little noradrenaline will be taken up

by the storage sites and more noradrenaline will be available to act upon the receptors; therefore fewer receptors will remain free for the access of circulating noradrenaline. Under these conditions N.P.H. should be intensified. Hilton (1963) showed that catecholamine depletion by reserpine and guanethidine markedly increased the pressor response to adrenaline and it is known that the pressor response to noradrenaline is similarly increased (Burn and Rand, 1958). Previous investigations from this laboratory indicated that the primary pressor response induced by noradrenaline infusion may play a role in the development of N.P.H. (Mazurkiewicz, Arch. int. Pharmacodyn, in press).

If the initial pressor response induced by infusion of noradrenaline is a factor in development of N.P.H. reserpinization should accentuate N.P.H. also by the latter mechanism.

The results obtained in reserpinized animals (Group V) indicate that:

1) Preinfusional blood pressure level was lower and heart rate decreased in reserpinized animals as compared to controls.

2) Tolerance development to the pressor response to noradrenaline during infusion was not affected by reserpinization and was similar to that seen in the controls.

3) Although reserpinization increased the pressor response to noradrenaline, reflex vagal bradycardia during the in-

fusion was of less intensity and of shorter duration than in normal cats.

4) Cardiac arrhythmias were aggravated by reserpinization.

5) N.P.H. was delayed in onset, increased in intensity and increased in duration. In contrast to control preparation during the secondary hypotensive phase heart rate was not decreased but remained close to the preinfusional heart rate.

Several reports have appeared on the toxicity and deleterious effects of reserpine on the heart. Zaimis and Withrington (1961) showed that cats which were treated with reserpine (1 mg/kg 24 hours before) indicated signs of heart failure. Histological examination showed severe degenerative changes in the cardiac muscle. The dose of reserpine used by these investigators was, however, higher than the clinical dose.

Seifen and co-workers (1964) on the other hand showed that impairment or blockade of impulse transmission of the sympathetic system by reserpine did not impair the ability of the animal to compensate for a loss in blood volume.

Gaunt and co-workers (1954) reported that reserpine stimulates the production of anti-diuretic hormone in rats. This could account for the retention of water and salt.

Perera (1955) reported 5 cases with oedema after 0.4 mg of reserpine. Marley and Pare (1956) reported two cases of cardiac failure after reserpine treatment. Foote (1955) observed oedema of the face and ankle after reserpine treatment.

The British Medical Journal (1961) mentioned in its editorial, "A patient under reserpine treatment is a poor risk when cardio-vascular system has to cope with an increased load as in labour, under anaesthesia, or surgery."

Our results on cats seem to give some indication about the danger of infusion of noradrenaline in reserpinized cats.

Alpha Methyldopa

Alpha methyldopa, an inhibitor of the enzyme dopa decarboxylase, is known to deplete catecholamine stores, and interfere with tissue binding of noradrenaline (Dengler and Reichel, 1958; Dollery and Harrington, 1962). The action exerted by alpha methyldopa is based not only on its ability to inhibit synthesis of catecholamines but also by its ability to deplete their stores. The depletion of catecholamines by alpha methyldopa is presumed to be due to the action of its metabolites, alpha methylnorepinephrine, and alpha methyldopamine. Carlsson and Lindquist (1962) suggested that these metabolites might enter the noradrenaline and dopamine storage sites, and take over the function

of noradrenaline. These metabolites are weak pressor substances and are more potent in producing depletion of catecholamines than alpha methyldopa itself.

The experiments in Group VI were designed to investigate the effects of catecholamine depletion by alpha methyldopa on N.P.H.

1) Under the present experimental conditions, pretreatment with alpha methyldopa similar to pretreatment with reserpine decreased the preinfusional blood pressure level and heart rate. Pressor response to noradrenaline was potentiated.

2) Tolerance development to the pressor response to noradrenaline during the infusion was not affected by chronic administration of alpha methyldopa.

3) Reflex vagal bradycardia during noradrenaline infusion seemed to be more marked but of shorter duration than that seen in the control animals.

4) Cardiac arrhythmias ensued during noradrenaline infusion in alpha methyldopa treated cats similarly to those seen in the control experiments.

5) Development of the secondary postinfusional hypotensive phase was significantly slower; it was more intense and of longer duration in alpha methyldopa-pretreated than in normal cats.

6) In contrast to control experiments, in alpha methyldopa pretreated animals, similar to reserpinized animals, secondary postinfusional hypotensive phase was not

associated with a decrease in heart rate but rather a slight increase.

Guanethidine (chronic)

The effects of chronic guanethidine treatment on N.P.H. were studied in the next group of experiments (Group VII).

Mulheims and Walter (1964) showed in dogs that guanethidine delayed the tachyphylaxis to noradrenaline and suggested that guanethidine might exert a direct effect on the receptors. Similarly in hypovolaemic dogs, guanethidine was shown not only to restore but enhance the pressor effects of noradrenaline; again this may be due to a direct effect on the alpha-adrenergic receptors in the blood vessel walls (Mulheims, 1964).

The effects of guanethidine on the adrenergic system are exerted in two ways; by a peripheral adrenergic blockade (acute administration) and by depletion of catecholamine stores (chronic pretreatment) (Cass and co-workers, 1960).

Abboud and Eckstein (1962) reported in dogs a vasodilator action of guanethidine which was more pronounced when catecholamine stores were depleted either with reserpine or with repeated administration of guanethidine. They postulated that this vasodilator action of guanethidine was not mediated through either histamine or acetyl choline.

They further suggested that stimulation of beta adrenergic receptors may have in part been responsible for vasodilator effect, since this vasodilator effect was blocked by pre-treatment with dichloroisoproterenol (D.C.I.).

1) In our investigation, animals chronically pretreated with guanethidine showed a lower preinfusional blood pressure level and a slower heart rate as compared to the controls. The decrease in heart rate and blood pressure was similar to that seen after catecholamine depletion with reserpine and alpha methyldopa.

2) Tolerance development to the pressor response of noradrenaline during the infusion was not affected by chronic pretreatment with guanethidine.

3) Although the pressor response to noradrenaline was potentiated, reflex vagal bradycardia during noradrenaline infusion did not ensue and tachycardia was seen instead.

4) Cardiac arrhythmias occurred less frequently than in control cats (only in 50% of animals).

5) N.P.H. was delayed in onset but increased in intensity and significantly increased in duration. In contrast to controls, N.P.H. was not associated with a decrease in heart rate; heart rate remained rather close to the pre-infusional value.

III. The Effects of Peripheral Adrenergic Blockade on N.P.H.

Bretylium is known to induce a specific peripheral adrenergic blockade in cats, rabbits and guinea-pigs (Boura and Green, 1959). The effects of such a blockade induced by bretylium on N.P.H. were investigated in the next group of experiments (Group VIII).

1) Peripheral adrenergic blockade induced by bretylium resulted in a lower preinfusional blood pressure level and a slower heart rate as compared to the controls.

2) The tolerance development to the pressor effect of noradrenaline observed during the infusion was similar to that seen in the control experiments.

3) Although pressor response to noradrenaline was potentiated, reflex vagal bradycardia did not ensue during the infusion; instead marked tachycardia developed.

4) Cardiac arrhythmias during noradrenaline infusion were prevented in 6 out of 7 experiments.

5) N.P.H. was delayed in onset but increased in intensity and significantly increased in duration as compared to control experiments. Similar results were obtained in guanethidine and reserpine treated animals. In bretylium treated cats, N.P.H. was not associated with a decrease in heart rate but the heart rate remained close to the preinfusional heart rate.

The most striking feature of bretylium pretreatment was the protection against cardiac arrhythmias during noradrenaline infusion. Cardiac arrhythmias did not develop in 6 of 7 bretylium pretreated animals. These results are in agreement with the work of Bacaner (1966) which demonstrated the protective effect of bretylium tosylate on the canine heart against electrically induced ventricular fibrillation. A direct inotropic action of bretylium on heart was suggested by Gaffney (1961).

Guanethidine (acute)

The effects of peripheral adrenergic blockade induced by acute administration of guanethidine on N.P.H. were investigated in the next group of experiments (Group IX).

Adrenergic blockade induced by acute administration of guanethidine is independent of catecholamine depletion (Gaffney, Chidsey and Braunwald, 1963).

Abercrombie and Davies (1963) reported that the initial pressor action of guanethidine is the result of a direct sympathomimetic action and not due to a release of adrenaline or noradrenaline. McCubbin and co-workers (1960) demonstrated that the sustained rise of arterial pressure following intravenous injection of guanethidine was more prominent after section of the spinal cord at cervical 6, and accompanied by marked constriction of the denervated

hind limb; this would indicate that the rise in blood pressure is not dependent on central neurogenic mechanism. These workers assumed the sustained rise in blood pressure to be due to release of bound endogenous catecholamines, because this rise in pressure was prevented completely by phentolamine or by prior treatment with reserpine.

Under these experimental conditions, infusion of noradrenaline was administered after the primary hypertensive phase induced by guanethidine wore off. Peripheral adrenergic blockade was verified by the absence of the pressor response to the carotid occlusion test.

1) Peripheral adrenergic blockade induced by acute administration of guanethidine in cats, resulted in a lower preinfusional blood pressure level and a markedly slower heart rate than that seen in control animals.

2) Tolerance development to the pressor effect of noradrenaline during infusion was not affected, and was similar to that seen in the controls.

3) Although pressor response to noradrenaline was potentiated, reflex vagal bradycardia did not ensue during noradrenaline infusion; instead marked tachycardia developed.

4) The cardiac arrhythmias that developed during noradrenaline infusion were not prevented and ensued in a manner similar to controls.

5) The onset of N.P.H. was significantly delayed but increased in intensity and duration.

6) N.P.H. was not associated with a decrease in heart rate and heart rate remained close to the preinfusional values. This is in contrast to controls in which N.P.H. was associated with a decrease in heart rate.

IV. The Effects of Quindonium Bromide on N.P.H.

Quindonium bromide, an isoquinolinium derivative, was synthesized by Meltzer and co-workers (1963). Osborne and co-workers (1964) reported that dogs given a prophylactic dose (10 mg/kg 15 minutes before) of quindonium bromide were protected from the stress resulting from acute experimental haemorrhage. This protection was exerted only when the drug was administered prophylactically. The mechanism of action of quindonium is obscure. Increased heart rate, increased myocardial contractile force, and vasoconstriction are early symptoms of marked sympathetic activity provoked by acute haemorrhage. According to these investigators quindonium appears to prevent haemostatic breakdown due to acute haemorrhage by altering the haemodynamic effects of prolonged sympathetic discharge. During critical phases of hypovolaemia, quindonium pretreated animals maintain myocardial integrity, show significantly lower heart rates and a reduced vasoconstriction as compared to control animals. They suggested that decrease in heart rate in the treated animal as compared to controls may aid in effecting a more efficient coronary perfusion during

hypovolaemia. The treated animals also showed vasodilatation and reinforcement of myocardial force of contraction during and after haemorrhage.

Since quindonium was shown to protect dogs against haemorrhagic shock, the role of this drug in protection against the postinfusional hypotension after the arrest of noradrenaline infusion was investigated.

Quindonium bromide (10 mg/kg) was administered intravenously 30 minutes before the infusion of noradrenaline was administered. Quindonium induced a fall in blood pressure, this might be due to the vasodilator action as suggested by Osborne and co-workers (1964). Infusion of noradrenaline was administered after the blood pressure was stabilized at a steady but lower level.

1) Pretreatment of animals with quindonium bromide resulted in a lower preinfusional blood pressure level, and a markedly slower heart rate.

2) Tolerance development to the pressor response of noradrenaline during the infusion was observed, however the decline in blood pressure was less intense than in any other group of experiments performed in this study.

3) Pressor response to noradrenaline was not markedly potentiated. Reflex vagal bradycardia during noradrenaline infusion did not ensue, but marked tachycardia developed instead.

4) Cardiac arrhythmias during noradrenaline infusion were not prevented by pretreatment with quindonium bromide.
5) The onset of N.P.H. was delayed, but L.B.P. reached was higher than in any other group of experiments performed. Recovery from the hypotensive phase was speeded up.

Although the present investigation did not elucidate the mechanism of N.P.H. some interesting results were obtained.

A. Tolerance Development to the Pressor Effect of Noradrenaline during an Infusion

It was observed that, "tolerance to the pressor effect of noradrenaline during the infusion," i.e., the decline in blood pressure, was less evident during repetition of the same dose of noradrenaline for a second and a third time at suitable intervals in the same animal. The peak blood pressure level reached during infusion was less after each consecutive infusion. An increase in the dose of infused noradrenaline (time constant) or in duration of infusion (dose constant) did not influence tolerance development. However, when both dose and time of infused noradrenaline was increased, it seemed that the decline in blood pressure during the infusion was accentuated.

A decline in blood pressure during noradrenaline infusion was demonstrated by Rosenthale and Dipalma (1962). In order to maintain the blood pressure in dogs (30-40 mm Hg above control levels) during a three hour noradrenaline infusion the rate of infusion had to be increased at least 5 times. The present results are different from those of Rosenthale and Dipalma (1962), as tolerance developed in spite of the increase in dose; however, in the experimental conditions outlined previously, the dose of noradrenaline was increased in each single infusion administered to a different animal and not during a constant infusion to the same animal. The explanation for these results cannot be offered at the present time.

If one assumes that insensitivity of the receptors is due to their being occupied by noradrenaline leaked from overfilled stores as postulated by Burn and Rand (1958), then after an increase in the dose and time of noradrenaline infused, the storage sites should be even more overfilled and tolerance to the pressor effect of noradrenaline during infusion as a result of leakage on receptors should be intensified and N.P.H. prolonged. The results obtained in this study seemed to support such a hypothesis. After an increase in the dose and time of noradrenaline infused, the decline in blood pressure during infusion was accentuated and N.P.H. prolonged. However, if the decline in blood pressure is due to an insensitivity of receptors as postu-

lated by Burn and Rand and if this is a prolonged phenomena as manifested by N.P.H., then after repetition of the same noradrenaline infusion in the same animal one would expect the decline in blood pressure during consecutive infusions to be intensified and N.P.H. prolonged, however this was not the case in these experiments; tolerance was of less intensity and N.P.H. of shorter duration after repeated noradrenaline infusions to the same animal.

Catecholamine depletion induced by reserpine did not influence tolerance development to the pressor effect of noradrenaline during the infusion, while depletion of catecholamine stores by alpha methyldopa or guanethidine slightly decreased the intensity of tolerance.

Tolerance development was also slightly attenuated but not prevented after peripheral adrenergic blockade was induced by acute administration of guanethidine. These results are in some agreement with those reported by Mulheims (1964) who observed that guanethidine elicited a marked pressor response, after tachyphylaxis to noradrenaline had developed and enhanced the pressor response to noradrenaline (Mulheims and co-workers, 1964). Moreover guanethidine administration maintained the pressor response to injected noradrenaline and delayed tachyphylaxis to noradrenaline (Mulheims, (1965)), in dogs.

Tolerance development was also attenuated after peripheral adrenergic blockade with bretylium. It is

possible that an increased sensitivity of adrenergic receptors to circulating noradrenaline after peripheral adrenergic blockade, may play a role in this slight decrease in tolerance development to the pressor effects of noradrenaline during the infusion; however pretreatment with quindonium bromide, which is not an adrenergic blocking agent, resulted in an even more marked attenuation of the decline in blood pressure, during noradrenaline infusion.

Under these experimental conditions, in spite of a slight attenuation by alpha methyldopa and guanethidine of tolerance development during noradrenaline infusion, N.P.H. was prolonged significantly in animals pretreated with these two drugs. These results seem to indicate that N.P.H. is perhaps not closely related to the tolerance development to pressor effects of noradrenaline during infusion.

B. Cardiac Arrhythmias during Noradrenaline Infusion

Cardiac arrhythmias during noradrenaline infusion were not influenced by repetition of the same infusion in the same animal. An increase in the time of noradrenaline infused, favourably influenced cardiac irregularities during the infusion; they were absent when a control dose of noradrenaline (40 μg/kg) was infused during a period of 20 minutes. It is possible that noradrenaline administered at a slower rate may be more rapidly metabolized and/or taken up into storage sites.

An increase in the dose and time of noradrenaline infused aggravated cardiac arrhythmias during infusion.

Depletion of catecholamines by reserpinization intensified cardiac arrhythmias during noradrenaline infusion; they were less frequent in animals chronically treated with guanethidine. Pretreatment with alpha methyldopa did not seem to have any effect. Peripheral adrenergic blockade induced by bretylium prevented cardiac arrhythmias during noradrenaline infusion in most experiments while adrenergic blockade induced by acute administration of guanethidine did not have any effect. It seems therefore that factors other than adrenergic blockade are involved in the beneficial action of bretylium seen under these experimental conditions.

C. Reflex Vagal Bradycardia

The maximum blood pressure increases during 3 consecutive identical noradrenaline infusions administered to the same animal were 240 ± 10, 225 ± 8 and 203 ± 7 mm Hg, respectively. Reflex vagal bradycardia ensued during the first infusion while tachycardia was seen during the second and third infusions.

A progressive increase in the dose of noradrenaline infused resulted in a greater peak in blood pressure rise attained during infusion; the consecutive values were 240 ± 10, 253 ± 8 and 251 ± 14 mm Hg. In spite of such an

increase in pressor response reflex vagal bradycardia was absent when the dose of noradrenaline was doubled or increased fourfold.

Increase in the duration of noradrenaline infused (dose constant) resulted in a less intense peak rise in blood pressure as the duration of infusion was increased from 5 to 10 to 20 minutes. The consecutive values were 240 ± 10, 207 ± 9 and 214 ± 12 mm Hg. During a 10 minute infusion, reflex vagal bradycardia was attenuated while no change in heart rate was seen during a 20 minute infusion.

Increase in dose and time of noradrenaline infused, resulted in a greater pressor response during consecutive infusions. The successive values reached for blood pressure were 240 ± 10, 237 ± 12 and 251 ± 13 mm Hg respectively. In spite of a greater pressor effect, reflex vagal bradycardia was decreased in intensity and duration after a progressive increase in dose and time of noradrenaline infused.

These results seem to demonstrate that under the present experimental conditions, reflex vagal bradycardia was not always dependent on the peak of blood pressure reached during the infusion of noradrenaline.

In control animals and animals treated with reserpine, alpha methyldopa, guanethidine (chronic), bretylium, guanethidine (acute) and quindonium, the corresponding peaks in blood pressure reached during noradrenaline infusion were

232 ± 4, 224 ± 5, 211 ± 8, 205 ± 10, 223 ± 10, 219 ± 11 and 196 ± 8 mm Hg, respectively. Reflex vagal bradycardia was present in reserpinized animals but it was of less intensity and duration than in controls; it was also present in alpha methyldopa pretreated cats. Reflex vagal bradycardia during infusion of noradrenaline did not ensue and tachycardia was seen instead, in cats treated with guanethidine either chronically or acutely and in bretylium and quindonium treated cats.

Since the peak blood pressure rise reached during infusion of noradrenaline in reserpinized and bretylium treated animals was almost identical and yet reflex vagal bradycardia occurred in the former and tachycardia in the latter, it seems possible that reflex vagal bradycardia is not always related to the peak blood pressure rise reached during noradrenaline infusion. Moreover animals pretreated with alpha methyldopa showed reflex vagal bradycardia during infusion of noradrenaline, while guanethidine (acute) treated animals showed tachycardia in spite of a similar rise in blood pressure during infusion of noradrenaline.

An interesting observation is that the occurrence of reflex vagal bradycardia during noradrenaline infusion did not seem to depend on the preinfusional heart rate.

The preinfusional heart rates were 210 ± 6, 132 ± 13, 173 ± 11, 178 ± 35, 173 ± 13, 137 ± 12 and 153 ± 7 beats/minute in control animals and those treated

with reserpine, alpha methyldopa, guanethidine (chronic), bretylium, guanethidine (acute) and quindonium, respectively.

Reflex vagal bradycardia ensued only in control, reserpinized and alpha methyldopa treated animals; tachycardia was seen in the other group of experiments. Due to a large standard error, the results obtained after chronic pretreatment with guanethidine (reflex vagal bradycardia absent) are not conclusive. It appears therefore that initiation of reflex bradycardia during administration of noradrenaline does not depend on the preinfusional heart rate.

D. Secondary Noradrenaline Postinfusional Hypotension

Under the present experimental conditions repetition of the same infusion of noradrenaline (identical dose and rate) to the same animal, resulted in secondary postinfusional drop in blood pressure, which was similar in intensity to the first fall in blood pressure; however the recovery seemed to be speeded up. An increase in the dose of noradrenaline (time constant) resulted in a slower decline in blood pressure below preinfusional blood pressure level and more prolonged recovery of blood pressure towards the preinfusional level. The recovery of blood pressure from the secondary postinfusional hypotension was more rapid when the time of infusion was increased (dose constant). An increase in the dose and duration of infusion of nor-

adrenaline resulted in a more prolonged recovery from N.P.H.

Full recovery of blood pressure towards the preinfusional level was never reached in any of the groups of experiments performed. At the time when the heart rates returned to the preinfusional rates, blood pressure remained below preinfusional level.

The onset of N.P.H. was significantly delayed after catecholamine depletion by reserpine, alpha methyldopa or guanethidine, and after peripheral adrenergic blockade by bretylium. It was also delayed after pretreatment with quindonium bromide.

The recovery of blood pressure towards the preinfusional blood pressure levels as judged by the time to reach M.P.R. was also significantly longer after depletion of catecholamines with reserpine, alpha methyldopa and guanethidine and after peripheral adrenergic blockade induced by bretylium. The increase in time to M.P.R. after guanethidine (acute) was not significant. Pretreatment with quindonium slightly speeded up the recovery of blood pressure from N.P.H.

It was observed routinely, that the recovery of heart rate to the preinfusional rates was reached at a time when blood pressure was still below preinfusional level. Full recovery of blood pressure to the preinfusional level was never reached in any of these experiments. (V - X).

The noradrenaline postinfusional hypotension which ensued after control noradrenaline infusion (8 µg/kg/minute for 5 minutes) was associated with bradycardia.

The recovery of heart rate towards preinfusional rate was seen within our experimental period of time. An increase in the duration of infusion of noradrenaline (dose constant) resulted in a more rapid recovery of heart rate toward control preinfusional rate.

In contrast to control experiments, N.P.H. was not associated with bradycardia, but the heart rate remained almost at preinfusional values in animals whose catecholamine stores were depleted with reserpine or guanethidine. Only a slight and short-lasting decrease in heart rate was seen in alpha methyldopa pretreated cats. After peripheral adrenergic blockade induced by bretylium or guanethidine, N.P.H. was not associated with any decrease in heart rate.

Pretreatment with quindonium bromide resulted in a lower preinfusional blood pressure level and a markedly slower heart rate. Tolerance development to the pressor effect of noradrenaline during the infusion was favourably influenced, i.e., tolerance was of less intensity. Reflex vagal bradycardia did not ensue during infusion but tachycardia was observed instead; cardiac arrhythmias during noradrenaline infusion were not prevented. The onset of N.P.H. was delayed but the time to reach M.P.R. was of shorter duration than in controls, although the change was not statistically significant.

As with control cats, noradrenaline postinfusional hypotension was associated with a decrease in heart rate in quindonium pretreated cats; however this decrease was of shorter duration when compared to control timings.

SUMMARY

I. The Development of Tolerance

(1) The development of tolerance, (i.e., the decline in blood pressure during the infusion) to the pressor effects of noradrenaline during the infusion of noradrenaline was slightly less evident during the second and third infusions of the same dose in the identical animal.

(2) Neither an increase in dose (time constant) nor an increase in the time of infusion (dose constant) seemed to influence significantly the decline in blood pressure seen during continuous infusions of noradrenaline.

(3) When both the dose and the time of infusion of noradrenaline were increased, the decline in blood pressure during the infusion was accentuated.

(4) The development of tolerance to the pressor effect of noradrenaline during the infusion was not influenced by reserpinization; catecholamine depletion induced by alpha methyldopa or chronic administration of guanethidine resulted in a slight attenuation of the decline in blood pressure during infusion of noradrenaline.

(5) Peripheral adrenergic blockade induced by bretylium or by the acute administration of guanethidine, attenuated slightly the decline in blood pressure during infusions of noradrenaline.

(6) Pretreatment with quindonium bromide attenuated the development of tolerance to the pressor effects of infused noradrenaline.

II. Cardiac Arrhythmias

(1) Cardiac arrhythmias during noradrenaline infusion were not influenced by a repetition of the same dose in the same animal. Under certain circumstances a marked increase in the time of infusion of the same dose of noradrenaline prevented cardiac arrhythmias. An increase in the dose and time of infusion aggravated cardiac irregularities.

(2) Catecholamine depletion by reserpine intensified cardiac arrhythmias during infusion of noradrenaline, while depletion of catecholamines by alpha methyldopa was without effect. Cardiac irregularities were less frequent in animals chronically pretreated with guanethidine.

(3) In most experiments peripheral adrenergic blockade induced by bretylium prevented cardiac arrhythmias during infusion of noradrenaline, while peripheral adrenergic blockade induced by acute administration of guanethidine was without effect.

(4) Pretreatment with quindonium bromide did not prevent cardiac arrhythmias during infusion of noradrenaline.

III. Reflex Vagal Bradycardia

(1) Under the present experimental conditions, reflex vagal bradycardia during infusion of noradrenaline was not always evident and it was not related to the peak rise in blood pressure attained during the infusion.

(2) Reflex vagal bradycardia did not ensue during noradrenaline infusion and instead tachycardia was seen in the following circumstances:

i) when the same dose of noradrenaline was infused several times in the same animal,

ii) when the dose of noradrenaline was increased as a single infusion of noradrenaline,

iii) when the dose of noradrenaline and time of noradrenaline infusion were increased,

iv) tachycardia occurred during infusion of noradrenaline in animals pretreated with guanethidine (acute and chronic), bretylium and quindonium bromide.

(3) Reflex vagal bradycardia was seen in control cats, reserpinized cats and in cats chronically treated with alpha methyldopa.

IV. Recovery of Blood Pressure from Noradrenaline Postinfusional Hypotension (N.P.H.)

(1) Recovery of blood pressure from N.P.H. towards preinfusional blood pressure levels was more rapid when

identical infusions were repeated in the same animal or when the "control" dose was infused more slowly. N.P.H. was more prolonged when the dose of infused noradrenaline was increased or when the dose and time of a "control" noradrenaline infusion was increased.

(2) Catecholamine depletion induced by reserpine, alpha methyldopa or guanethidine significantly increased the time of onset of N.P.H. and significantly prolonged the recovery of the blood pressure towards the pre-infusional value as judged by the time to reach M.P.R. Peripheral adrenergic blockade induced by bretylium and guanethidine also significantly delayed the onset of N.P.H., and prolonged the time to reach M.P.R.; the increase was statistically significant for bretylium but not for guanethidine.

(3) In cats pretreated with quindonium bromide, the onset of N.P.H. was delayed but the recovery from N.P.H. was more rapid as compared with nonpretreated cats; however, the change was not statistically significant.

(4) In contrast to controls, in animals whose catecholamine stores were depleted by reserpine and guanethidine, N.P.H. was not associated with bradycardia, but the heart rate remained close to the preinfusional value. Only a slight decrease in heart rate during N.P.H. was seen in alpha methyldopa pretreated cats.

(5) In contrast to controls, after peripheral adrenergic blockade induced by bretylium and guanethidine, N.P.H. was not associated with a decrease in heart rate.

(6) Similarly to control experiments, in quindonium pretreated animals, N.P.H. was associated with a decrease in the heart rate. However, this bradycardia was of shorter duration than that seen in controls.

Complete data of all mean arterial blood pressure and heart rate values in nontreated and treated animals is given in the appendices (pp.173-206).

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APPENDICES

APPENDIX I

Changes in Blood Pressure induced by Noradrenaline Infusion

8 µg/kg/minute for 5 minutes

First Infusion

Group No. Ii

Experiment Number	C.B.P.* (mm Hg)	M.B.P.** (mm Hg)	B.P. at*** end of infusion (mm Hg)	L.B.P.† (mm Hg)	Time to L.B.P. (min)	M.P.R.†† (mm Hg)	Time to M.P.R. (min)	M.R.††† (mm Hg)	Time to M.R. (min)
1	175	285	240	105	2	140	40	175	70
2	125	220	180	80	14	102	53	135	90
3	110	230	185	50	3	80	15	95	75
4	140	240	175	70	2	105	37	125	75
5	155	220	185	95	5	125	40	140	62
6	170	245	190	65	4	117	57	150	142
Mean±S.E.M.	146±10	240±10	192±10	77±8	5±2	111±8	40±6	136±11	86±12

* Control pre-infusional blood pressure level before administration of noradrenaline infusion.

** Maximum rise in blood pressure induced by noradrenaline infusion.

*** Blood pressure level immediately before the arrest of infusion.

† Lowest blood pressure reached following termination of infusion.

†† Midpoint of recovery representing the level of mean blood pressure when 50% recovery from the lowest blood level was attained.

††† Maximum recovery of blood pressure representing the maximum recovery of blood pressure from post-infusional hypotensive phase within experimental period of time (90-120 minutes).

APPENDIX II

Changes in Heart Rate induced by Noradrenaline Infusion

8 µg/kg/minute for 5 minutes

First Infusion

Group No. Ii

Experiment Number	C.Heart Rate* (beats/min)	Heart Rate** at M.B.P. (beats/min)	Heart Rate*** at end of infusion (beats/min)	Heart Rate† at L.B.P. (beats/min)	Heart Rate†† at M.P.R. (beats/min)	Heart Rate††† at M.R. (beats/min)
1	230	130	250	200	230	230
2	176	156	166	150	176	176
3	272	166	214	187	176	250
4	214	136	150	136	187	214
5	200	176	176	156	150	166
6	214	200	230	125	156	200
Mean±S.E.M.	218±13	161±11	198±16	159±12	179±12	206±13

* Control pre-infusional heart rate before administration of noradrenaline infusion.
** Heart rate at peak of blood pressure response induced by noradrenaline infusion.
*** Heart rate immediately before termination of noradrenaline infusion.
† Heart rate at lowest blood pressure level reached after termination of infusion.
†† Heart rate at midpoint of recovery, i.e., when a recovery of 50% from lowest blood pressure was attained.
††† Heart rate when maximum recovery of blood pressure from the post-infusional hypotensive phase was reached within the experimental period of time (90-120 minutes).

APPENDIX III

Changes in Blood Pressure induced by Noradrenaline Infusion

8 μg/kg/minute for 5 minutes

Second Infusion

Group No. Iii

Experiment Number	C.B.P.* (mm Hg)	M.B.P.** (mm Hg)	B.P. at*** end of infusion (mm Hg)	L.B.P.† (mm Hg)	Time to L.B.P. (min)	M.P.R.†† (mm Hg)	Time to M.P.R. (min)	M.R.††† (mm Hg)	Time to M.R. (min)
1	175	260	220	120	14	145	55	150	62
2	135	215	180	70	3	102	24	120	77
3	90	210	190	45	2	70	4	85	71
4	125	240	200	55	2	90	35	130	78
5	140	210	185	90	3	115	35	120	62
6	140	215	180	75	4	110	18	125	66
Mean±S.E.M.	134±11	225±8	192±6	76±11	3±2	105±10	28±7	122±9	68±3

* Control pre-infusional blood pressure level before administration of noradrenaline infusion.

** Maximum rise in blood pressure induced by noradrenaline infusion.

*** Blood pressure level immediately before the arrest of infusion.

† Lowest blood pressure reached following termination of infusion.

†† Midpoint of recovery representing the level of mean blood pressure when 50% recovery from the lowest blood level was attained.

††† Maximum recovery of blood pressure representing the maximum recovery of blood pressure from post-infusional hypotensive phase within experimental period of time (90-120 minutes).

APPENDIX IV

Changes in Heart Rate induced by Noradrenaline Infusion

8 μg/kg/minute for 5 minutes

Second Infusion

Group Iii

Experiment Number	C.Heart Rate* (beats/min)	Heart Rate** at M.B.P. (beats/min)	Heart Rate*** at end of infusion (beats/min)	Heart Rate† at L.B.P. (beats/min)	Heart Rate†† at M.P.R. (beats/min)	Heart Rate††† at M.R. (beats/min)
1	230	300	300	250	272	272
2	176	187	214	166	166	187
3	250	230	230	214	214	250
4	214	250	166	150	166	250
5	166	200	230	166	187	214
6	200	214	250	176	187	200
Mean±S.E.M.	206±13	230±17	232±18	187±15	199±16	229±14

* Control pre-infusional heart rate before administration of noradrenaline infusion.
** Heart rate at peak of blood pressure response induced by noradrenaline infusion.
*** Heart rate immediately before termination of noradrenaline infusion.
† Heart rate at lowest blood pressure level reached after termination of infusion.
†† Heart rate at midpoint of recovery, i.e., when a recovery of 50% from lowest blood pressure was attained.
††† Heart rate when maximum recovery of blood pressure from the post-infusional hypotensive phase was reached within the experimental period of time (90-120 minutes).

APPENDIX V

Changes in Blood Pressure induced by Noradrenaline Infusion

8 μg/kg/minute for 5 minutes

Third Infusion

Group Iiii

Experiment Number	C.B.P.* (mm Hg)	M.B.P.** (mm Hg)	B.P. at*** end of infusion (mm Hg)	L.B.P.† (mm Hg)	Time to L.B.P. (min)	M.P.R.†† (mm Hg)	Time to M.P.R. (min)	M.R.††† (mm Hg)	Time to M.R. (min)
1	150	210	195	105	16	‡	‡	125	38
2	110	200	170	55	3	82	58	90	63
3	85	210	195	35	1	60	2	75	46
4	130	230	210	75	1	‡	‡	95	15
5	120	180	165	80	3	100	8	110	52
6	125	190	180	75	3	100	8	120	42
Mean±S.E.M.	120±9	203±7	186±7	71±10	5±2	86±10	19±13	102±6	43±6

* Control pre-infusional blood pressure level before administration of noradrenaline infusion.

** Maximum rise in blood pressure induced by noradrenaline infusion.

*** Blood pressure level immediately before the arrest of infusion.

† Lowest blood pressure reached following termination of infusion.

†† Midpoint of recovery representing the level of mean blood pressure when 50% recovery from the lowest blood level was attained.

††† Maximum recovery of blood pressure representing the maximum recovery of blood pressure from post-infusional hypotensive phase within experimental period of time (90-120 minutes).

‡ Midpoint of recovery was not reached in 2 out of 6 experiments.

APPENDIX VI

Changes in Heart Rate induced by Noradrenaline Infusion

8 µg/kg/minute for 5 minutes

Third Infusion

Group Iiii

Experiment Number	C.Heart Rate* (beats/min)	Heart Rate at M.B.P.** (beats/min)	Heart Rate at end of infusion*** (beats/min)	Heart Rate† at L.B.P. (beats/min)	Heart Rate†† at M.P.R. (beats/min)	Heart Rate††† at M.R. (beats/min)
1	272	300	333	300	‡	300
2	187	187	200	166	176	176
3	250	214	230	214	214	272
4	250	300	214	230	‡	214
5	214	214	230	200	200	230
6	200	230	250	166	176	187
Mean±S.E.M.	229±13	241±19	243±19	213±20	192±9	230±20

* Control pre-infusional heart rate before administration of noradrenaline infusion.
** Heart rate at peak of blood pressure response induced by noradrenaline infusion.
*** Heart rate immediately before termination of noradrenaline infusion.
† Heart rate at lowest blood pressure level reached after termination of infusion.
†† Heart rate at midpoint of recovery, i.e., when a recovery of 50% from lowest blood pressure was attained.
††† Heart rate when maximum recovery of blood pressure from the post-infusional hypotensive phase was reached within the experimental period of time (90-120 minutes).
‡ Midpoint of recovery was not reached in 2 out of 6 experiments performed.

APPENDIX VII

Changes in Blood Pressure induced by Noradrenaline Infusion

16 µg/kg/minute for 5 minutes

Group IIb

Experiment Number	C.B.P.* (mm Hg)	M.B.P.** (mm Hg)	B.P. at*** end of infusion (mm Hg)	L.B.P.† (mm Hg)	Time to L.B.P. (min)	M.P.R.†† (mm Hg)	Time to M.P.R. (min)	M.R.††† (mm Hg)	Time to M.R. (min)
1	160	250	235	115	16	140	80	160	120
2	180	265	210	110	5	145	40	155	62
3	160	285	235	85	20	120	82	125	96
4	140	230	175	75	24	105	125	110	128
5	140	250	200	75	11	110	95	115	136
6	150	240	185	75	18	110	114	110	114
Mean±S.E.M.	155±6	253±8	206±10	89±9	16±3	122±7	89±12	129±9	109±11

* Control pre-infusional blood pressure level before administration of noradrenaline infusion.

** Maximum rise in blood pressure induced by noradrenaline infusion.

*** Blood pressure level immediately before the arrest of infusion.

† Lowest blood pressure reached following termination of infusion.

†† Midpoint of recovery representing the level of mean blood pressure when 50% recovery from the lowest blood level was attained.

††† Maximum recovery of blood pressure representing the maximum recovery of blood pressure from post-infusional hypotensive phase within experimental period of time (90-120 minutes).

APPENDIX VIII

Changes in Heart Rate induced by Noradrenaline Infusion

16 µg/kg/minute for 5 minutes

Group IIb

Experiment Number	C.Heart Rate* (beats/min)	Heart Rate** at M.B.P. (beats/min)	Heart Rate*** at end of infusion (beats/min)	Heart Rate† at L.B.P. (beats/min)	Heart Rate†† at M.P.R. (beats/min)	Heart Rate††† at M.R. (beats/min)
1	200	250	230	214	230	250
2	176	200	176	156	187	214
3	142	214	200	125	166	156
4	136	176	230	176	230	250
5	136	156	200	83	176	176
6	230	214	230	187	230	230
Mean±S.E.M.	170±16	202±13	211±9	157±19	203±12	213±16

* Control pre-infusional heart rate before administration of noradrenaline infusion.
** Heart rate at peak of blood pressure response induced by noradrenaline infusion.
*** Heart rate immediately before termination of noradrenaline infusion.
† Heart rate at lowest blood pressure level reached after termination of infusion.
†† Heart rate at midpoint of recovery, i.e., when a recovery of 50% from lowest blood pressure was attained.
††† Heart rate when maximum recovery of blood pressure from the post-infusional hypotensive phase was reached within the experimental period of time (90-120 minutes).

APPENDIX IX

Changes in Blood Pressure induced by Noradrenaline Infusion

32 µg/kg/minute for 5 minutes

Group IIc

Experiment Number	C.B.P.* (mm Hg)	M.B.P.** (mm Hg)	B.P. at*** end of infusion (mm Hg)	L.B.P.† (mm Hg)	Time to L.B.P. (min)	M.P.R.†† (mm Hg)	Time to M.P.R. (min)	M.R.††† (mm Hg)	Time to M.R. (min)
1	160	320	210	50	34	105	80	90	112
2	155	250	170	80	16	115	42	105	90
3	135	235	200	75	16	105	72	120	72
4	125	240	195	85	22	105	50	95	156
5	115	240	230	85	12	100	75	115	112
6	135	220	200	95	48	115	114	115	150
Mean±S.E.M.	137±7	251±14	201±8	78±6	25±6	108±2	72±16	107±5	115±13

* Control pre-infusional blood pressure level before administration of noradrenaline infusion.

** Maximum rise in blood pressure induced by noradrenaline infusion.

*** Blood pressure level immediately before the arrest of infusion.

† Lowest blood pressure reached following termination of infusion.

†† Midpoint of recovery representing the level of mean blood pressure when 50% recovery from the lowest blood level was attained.

††† Maximum recovery of blood pressure representing the maximum recovery of blood pressure from post-infusional hypotensive phase within experimental period of time (90-120 minutes).

APPENDIX X

Changes in Heart Rate induced by Noradrenaline Infusion

32 μg/kg/minute for 5 minutes

Group IIc

Experiment Number	C.Heart Rate* (beats/min)	Heart Rate** at M.B.P. (beats/min)	Heart Rate*** at end of infusion (beats/min)	Heart Rate† at L.B.P. (beats/min)	Heart Rate†† at M.P.R. (beats/min)	Heart Rate††† at M.R. (beats/min)
1	142	156	156	120	142	156
2	200	250	230	176	200	214
3	176	176	214	176	200	200
4	230	250	300	142	187	200
5	156	150	214	176	166	166
6	187	230	214	156	200	200
Mean±S.E.M.	182±13	202±9	221±19	158±9	183±10	189±9

* Control pre-infusional heart rate before administration of noradrenaline infusion.
** Heart rate at peak of blood pressure response induced by noradrenaline infusion.
*** Heart rate immediately before termination of noradrenaline infusion.
† Heart rate at lowest blood pressure level reached after termination of infusion.
†† Heart rate at midpoint of recovery, i.e., when a recovery of 50% from lowest blood pressure was attained.
††† Heart rate when maximum recovery of blood pressure from the post-infusional hypotensive phase was reached within the experimental period of time (90-120 minutes).

APPENDIX XI

Changes in Blood Pressure induced by Noradrenaline Infusion

4 μg/kg/minute for 10 minutes

Group IIIb

Experiment Number	C.B.P.* (mm Hg)	M.B.P.** (mm Hg)	B.P. at*** end of infusion (mm Hg)	L.B.P.† (mm Hg)	Time to L.B.P. (min)	M.P.R.†† (mm Hg)	Time to M.P.R. (min)	M.R.††† (mm Hg)	Time to M.R. (min)
1	160	210	170	110	3	135	6	160	18
2	120	215	185	70	3	95	7	120	32
3	135	190	175	105	4	120	48	125	66
4	115	175	150	75	2	95	7	115	88
5	155	215	165	35	2	95	56	120	118
6	155	235	195	115	3	135	7	150	72
Mean±S.E.M.	140±8	207±9	173±7	85±13	3±2	113±8	22±10	132±8	66±15

* Control pre-infusional blood pressure level before administration of noradrenaline infusion.
** Maximum rise in blood pressure induced by noradrenaline infusion.
*** Blood pressure level immediately before the arrest of infusion.
† Lowest blood pressure reached following termination of infusion.
†† Midpoint of recovery representing the level of mean blood pressure when 50% recovery from the lowest blood level was attained.
††† Maximum recovery of blood pressure representing the maximum recovery of blood pressure from post-infusional hypotensive phase within experimental period of time (90-120 minutes).

APPENDIX XII

Changes in Heart Rate induced by Noradrenaline Infusion

4 µg/kg/minute for 10 minutes

Group IIIb

Experiment Number	C.Heart Rate* (beats/min)	Heart Rate** at M.B.P. (beats/min)	Heart Rate*** at end of infusion (beats/min)	Heart Rate† at L.B.P. (beats/min)	Heart Rate†† at M.P.R. (beats/min)	Heart Rate††† at M.R. (beats/min)
1	214	200	200	200	214	230
2	214	176	214	200	214	214
3	187	176	200	187	214	214
4	214	166	176	176	200	200
5	187	166	214	136	156	187
6	200	156	176	176	200	272
Mean±S.E.M.	203±5	173±6	197±7	179±10	200±9	219±12

* Control pre-infusional heart rate before administration of noradrenaline infusion.
** Heart rate at peak of blood pressure response induced by noradrenaline infusion.
*** Heart rate immediately before termination of noradrenaline infusion.
† Heart rate at lowest blood pressure level reached after termination of infusion.
†† Heart rate at midpoint of recovery, i.e., when a recovery of 50% from lowest blood pressure was attained.
††† Heart rate when maximum recovery of blood pressure from the post-infusional hypotensive phase was reached within the experimental period of time (90-120 minutes).

APPENDIX XIII

Changes in Blood Pressure induced by Noradrenaline Infusion

2 µg/kg/minute for 20 minutes

Group IIIc

Experiment Number	C.B.P.* (mm Hg)	M.B.P.** (mm Hg)	B.P. at*** end of infusion (mm Hg)	L.B.P.† (mm Hg)	Time to L.B.P. (min)	M.P.R.†† (mm Hg)	Time to M.P.R. (min)	M.R.††† (mm Hg)	Time to M.R. (min)
1	110	210	150	55	1	85	5	110	14
2	150	260	175	85	13	110	32	150	48
3	140	230	180	125	1	135	4	140	30
4	120	170	150	70	2	95	3	120	6
5	140	200	170	95	2	120	12	140	130
6	110	215	170	80	1	95	22	110	52
Mean±S.E.M.	128±7	214±12	166±5	85±10	3±2	107±8	13±5	128±7	48±18

* Control pre-infusional blood pressure level before administration of noradrenaline infusion.

** Maximum rise in blood pressure induced by noradrenaline infusion.

*** Blood pressure level immediately before the arrest of infusion.

† Lowest blood pressure reached following termination of infusion.

†† Midpoint of recovery representing the level of mean blood pressure when 50% recovery from the lowest blood level was attained.

††† Maximum recovery of blood pressure representing the maximum recovery of blood pressure from post-infusional hypotensive phase within experimental period of time (90-120 minutes).

APPENDIX XIV

Changes in Heart Rate induced by Noradrenaline Infusion

2 µg/kg/minute for 20 minutes

Group IIIc

Experiment Number	C.Heart Rate* (beats/min)	Heart Rate** at M.B.P. (beats/min)	Heart Rate*** at end of infusion (beats/min)	Heart Rate† at L.B.P. (beats/min)	Heart Rate†† at M.P.R. (beats/min)	Heart Rate††† at M.R. (beats/min)
1	166	187	187	156	176	176
2	214	187	187	166	200	250
3	214	200	187	200	200	214
4	187	187	200	166	176	187
5	187	214	214	187	187	200
6	176	142	176	150	156	176
Mean±S.E.M.	191±8	186±10	192±5	171±8	183±7	200±11

* Control pre-infusional heart rate before administration of noradrenaline infusion.
** Heart rate at peak of blood pressure response induced by noradrenaline infusion.
*** Heart rate immediately before termination of noradrenaline infusion.
† Heart rate at lowest blood pressure level reached after termination of infusion.
†† Heart rate at midpoint of recovery, i.e., when a recovery of 50% from lowest blood pressure was attained.
††† Heart rate when maximum recovery of blood pressure from the post-infusional hypotensive phase was reached within the experimental period of time (90-120 minutes).

APPENDIX XV

Changes in Blood Pressure induced by Noradrenaline Infusion

8 µg/kg/minute for 10 minutes

Group IVb

Experiment Number	C.B.P.* (mm Hg)	M.B.P.** (mm Hg)	B.P. at*** end of infusion (mm Hg)	L.B.P.† (mm Hg)	Time to L.B.P. (min)	M.P.R.†† (mm Hg)	Time to M.P.R. (min)	M.R.††† (mm Hg)	Time to M.R. (min)
1	135	205	155	95	3	115	45	125	96
2	150	255	180	65	7	110	120	125	135
3	125	275	195	75	20	100	48	110	64
4	145	245	160	80	22	110	75	120	80
5	135	240	175	75	14	105	100	115	110
6	140	200	160	80	22	110	60	120	86
Mean±S.E.M.	138±4	237±12	171±6	78±4	15±4	108±2	74±12	119±2	95±10

* Control pre-infusional blood pressure level before administration of noradrenaline infusion.

** Maximum rise in blood pressure induced by noradrenaline infusion.

*** Blood pressure level immediately before the arrest of infusion.

† Lowest blood pressure reached following termination of infusion.

†† Midpoint of recovery representing the level of mean blood pressure when 50% recovery from the lowest blood level was attained.

††† Maximum recovery of blood pressure representing the maximum recovery of blood pressure from post-infusional hypotensive phase within experimental period of time (90-120 minutes).

APPENDIX XVI

Changes in Heart Rate induced by Noradrenaline Infusion

8 µg/kg/minute for 10 minutes

Group IVb

Experiment Number	C.Heart Rate* (beats/min)	Heart Rate** at M.B.P. (beats/min)	Heart Rate*** at end of infusion (beats/min)	Heart Rate† at L.B.P. (beats/min)	Heart Rate†† at M.P.R. (beats/min)	Heart Rate††† at M.R. (beats/min)
1	200	166	166	187	200	200
2	176	142	214	142	156	176
3	200	156	214	150	230	250
4	250	156	200	200	300	300
5	214	300	333	214	250	300
6	214	125	187	125	166	187
Mean±S.E.M.	209±10	174±26	219±24	170±14	217±22	235±23

* Control pre-infusional heart rate before administration of noradrenaline infusion.
** Heart rate at peak of blood pressure response induced by noradrenaline infusion.
*** Heart rate immediately before termination of noradrenaline infusion.
† Heart rate at lowest blood pressure level reached after termination of infusion.
†† Heart rate at midpoint of recovery, i.e., when a recovery of 50% from lowest blood pressure was attained.
††† Heart rate when maximum recovery of blood pressure from the post-infusional hypotensive phase was reached within the experimental period of time (90-120 minutes).

APPENDIX XVII

Changes in Blood Pressure induced by Noradrenaline Infusion

8 µg/kg/minute for 20 minutes

Group IVc

Experiment Number	C.B.P.* (mm Hg)	M.B.P.** (mm Hg)	B.P. at*** end of infusion (mm Hg)	L.B.P.† (mm Hg)	Time to L.B.P. (min)	M.P.R.†† (mm Hg)	Time to M.P.R. (min)	M.R.††† (mm Hg)	Time to M.R. (min)
1	110	185	140	90	14	100	19	110	58
2	175	255	185	90	3	130	90	140	134
3	160	265	180	45	6	100	72	130	150
4	115	265	185	95	18	105	70	115	96
5	170	270	210	110	3	140	77	155	148
6	170	265	195	75	17	115	52	140	132
Mean±S.E.M.	150±12	251±13	183±10	84±9	10±3	115±7	63±10	132±7	120±15

* Control pre-infusional blood pressure level before administration of noradrenaline infusion.
** Maximum rise in blood pressure induced by noradrenaline infusion.
*** Blood pressure level immediately before the arrest of infusion.
† Lowest blood pressure reached following termination of infusion.
†† Midpoint of recovery representing the level of mean blood pressure when 50% recovery from the lowest blood level was attained.
††† Maximum recovery of blood pressure representing the maximum recovery of blood pressure from post-infusional hypotensive phase within experimental period of time (90-120 minutes).

APPENDIX XVIII

Changes in Heart Rate induced by Noradrenaline Infusion

8 μg/kg/minute for 20 minutes

Group IVc

Experiment Number	C.Heart Rate* (beats/min)	Heart Rate at M.B.P.** (beats/min)	Heart Rate at end of infusion*** (beats/min)	Heart Rate at L.B.P.† (beats/min)	Heart Rate at M.P.R.†† (beats/min)	Heart Rate at M.R.††† (beats/min)
1	187	142	200	156	156	166
2	200	214	214	166	214	214
3	200	166	272	230	230	230
4	214	156	250	187	187	200
5	214	200	230	166	250	272
6	166	187	250	142	200	230
Mean±S.E.M.	197±7	178±11	236±11	175±12	206±14	219±14

* Control pre-infusional heart rate before administration of noradrenaline infusion.
** Heart rate at peak of blood pressure response induced by noradrenaline infusion.
*** Heart rate immediately before termination of noradrenaline infusion.
† Heart rate at lowest blood pressure level reached after termination of infusion.
†† Heart rate at midpoint of recovery, i.e., when a recovery of 50% from lowest blood pressure was attained.
††† Heart rate when maximum recovery of blood pressure from the post-infusional hypotensive phase was reached within the experimental period of time (90-120 minutes).

APPENDIX XIX

Changes in Blood Pressure induced by Noradrenaline Infusion

8 µg/kg/minute for 5 minutes

Control Group

Experiment Number	C.B.P.* (mm Hg)	M.B.P.** (mm Hg)	B.P. at*** end of infusion (mm Hg)	L.B.P.† (mm Hg)	Time to L.B.P. (min)	M.P.R.†† (mm Hg)	Time to M.P.R. (min)	M.R.††† (mm Hg)	Time to M.R. (min)
1	135	215	190	85	5	110	51	125	64
2	140	220	205	120	11	132	43	145	70
3	135	250	220	80	3	107	47	125	74
4	135	245	165	105	5	120	39	125	80
5	130	230	170	95	3	112	33	130	80
6	115	250	185	75	4	95	30	125	75
7	175	285	240	105	2	140	40	175	70
8	125	220	180	80	14	102	53	135	90
9	110	230	185	50	3	80	15	95	75
10	140	240	175	70	2	105	37	125	75
11	155	220	185	95	5	125	40	140	62
12	170	245	190	65	4	117	57	150	142
13	85	195	170	65	6	75	30	90	66
14	145	210	175	70	6	107	48	135	68
15	150	210	185	80	5	115	93	120	96
16	120	195	170	85	3	103	48	120	80
17	160	230	200	125	7	142	40	150	64
18	150	230	190	90	3	120	115	115	120
19	150	230	170	65	5	95	55	115	85
20	145	200	160	100	2	122	75	125	80

continued on p.192

Appendix XIX (Continued)

Experiment Number	C.B.P.* (mm Hg)	M.B.P.** (mm Hg)	B.P. at end of infusion*** (mm Hg)	L.B.P.† (mm Hg)	Time to L.B.P. (min)	M.P.R.†† (mm Hg)	Time to M.P.R. (min)	M.R.††† (mm Hg)	Time to M.R. (min)
21	115	220	190	75	12	95	32	120	60
22	160	210	190	115	2	140	33	150	85
23	200	230	220	165	2	180	38	195	55
24	200	230	230	105	2	160	50	180	55
25	140	70	240	125	5	130	15	135	30
26	105	235	170	65	6	85	58	90	70
27	120	240	220	95	7	110	33	115	60
28	120	240	170	80	5	100	33	125	51
29	175	250	190	80	5	125	24	165	58
30	160	270	190	115	6	135	40	150	60
Mean±S.E.M.	142±5	232±4	191±4	92±4	5±1	117±4	41±3	132±4	70±3

* Control pre-infusional blood pressure level before administration of noradrenaline infusion.

** Maximum rise in blood pressure induced by noradrenaline infusion.

*** Blood pressure level immediately before the arrest of infusion.

† Lowest blood pressure reached following termination of infusion.

†† Midpoint of recovery representing the level of mean blood pressure when 50% recovery from the lowest blood level was attained.

††† Maximum recovery of blood pressure representing the maximum recovery of blood pressure from post-infusional hypotensive phase within experimental period of time (90-120 minutes).

APPENDIX XX

Changes in Heart Rate induced by Noradrenaline Infusion

8 µg/kg/minute for 5 minutes

Control Group

Experiment Number	C.Heart Rate* (beats/min)	Heart Rate** at M.B.P. (beats/min)	Heart Rate*** at end of infusion (beats/min)	Heart Rate† at L.B.P. (beats/min)	Heart Rate†† at M.P.R. (beats/min)	Heart Rate††† at M.R. (beats/min)
1	214	214	177	158	188	188
2	214	231	180	143	167	188
3	200	125	167	158	131	200
4	250	214	250	188	188	250
5	158	104	214	123	150	150
6	150	131	150	131	136	136
7	250	250	250	136	150	167
8	200	200	150	158	167	167
9	214	158	167	188	214	214
10	214	131	158	158	188	250
11	272	150	167	188	214	214
12	190	220	240	240	240	240
13	225	240	240	240	240	240
14	240	225	210	240	240	300
15	210	270	240	150	210	200
16	170	125	170	120	150	180
17	187	200	176	156	187	200
18	230	250	214	187	230	250

continued on p.194

Appendix XX (continued)

Experiment Number	C. Heart Rate* (beats/min)	Heart Rate** at M.B.P. (beats/min)	Heart Rate*** at end of infusion (beats/min)	Heart Rate† at L.B.P (beats/min)	Heart Rate†† at M.P.R. (beats/min)	Heart Rate††† at M.R. (beats/min)
19	230	176	187	156	200	230
20	166	142	136	187	176	176
21	166	120	166	115	136	156
22	200	214	230	150	166	200
23	214	130	166	156	230	230
24	230	150	214	176	214	207
25	230	130	250	200	230	230
26	176	156	166	150	176	176
27	272	166	214	187	176	250
28	214	136	150	136	187	214
29	200	176	176	156	150	166
30	214	200	230	125	156	200
Mean±S.E.M.	210±6	178±9	192±8	165±6	186±6	206±7

* Control pre-infusional heart rate before administration of noradrenaline infusion.
** Heart rate at peak of blood pressure response induced by noradrenaline infusion.
*** Heart rate immediately before termination of noradrenaline infusion.
† Heart rate at lowest blood pressure level reached after termination of infusion.
†† Heart rate at midpoint of recovery, i.e., when a recovery of 50% from lowest blood pressure was attained.
††† Heart rate when maximum recovery of blood pressure from the post-infusional hypotensive phase was reached within the experimental period of time (90-120 minutes).

PART II

APPENDIX XXI

Changes in Blood Pressure induced by Noradrenaline Infusion

8 μg/kg/minute for 5 minutes in Reserpinized‡ cats

Group V

Experiment Number	C.B.P.* (mm Hg)	M.B.P.** (mm Hg)	B.P. at*** end of infusion (mm Hg)	L.B.P.† (mm Hg)	Time to L.B.P. (min)	M.P.R.†† (mm Hg)	Time to M.P.R. (min)	M.R.††† (mm Hg)	Time to M.R. (min)
1	85	210	175	60	52	‡‡	‡‡	70	
2	110	245	150	75	8	95	32	100	35
3	90	195	170	80	24	85	58	90	90
4	95	215	170	65	38	‡‡	‡‡	70	
5	115	245	190	80	4	100	80	110	115
6	100	210	150	75	75	‡‡	‡‡	70	
7	95	215	170	80	5	90	23	95	65
8	100	250	200	85	14	‡‡	‡‡	85	
9	95	215	180	75	56	85	80	90	85
10	100	225	170	75	72	‡‡	‡‡	75	
11	110	230	200	80	65	‡‡	‡‡	85	
12	115	230	195	90	30	105	122	105	122
Mean±S.E.M.	101±3	224±5	177±5	77±2	37±8	93±3	66±15	87±4	85±13

* Control pre-infusional blood pressure level before administration of noradrenaline infusion.

** Maximum rise in blood pressure induced by noradrenaline infusion.

*** Blood pressure level immediately before the arrest of infusion.

† Lowest blood pressure reached following termination of infusion.

†† Midpoint of recovery representing the level of mean blood pressure when 50% recovery from the lowest blood level was attained.

††† Maximum recovery of blood pressure representing the maximum recovery of blood pressure from post-infusional hypotensive phase within experimental period of time (90-120 minutes).

‡ Reserpine 5 mg/kg i.p. was administered 24-48 hours before the experimental procedure.

‡‡ Midpoint of recovery was reached in 6 out of 12 experiments.

APPENDIX XXII

Changes in Heart Rate induced by Noradrenaline Infusion

8 µg/kg/minute for 5 minutes in Reserpinized‡ cats

Group V

Experiment Number	C.Heart Rate* (beats/min)	Heart Rate** at M.B.P. (beats/min)	Heart Rate*** at end of infusion (beats/min)	Heart Rate† at L.B.P. (beats/min)	Heart Rate†† at M.P.R. (beats/min)	Heart Rate††† at M.R. (beats/min)
1	142	136	156	115	‡‡	142
2	150	142	200	142	166	176
3	150	88	150	136	166	176
4	125	125	130	125	‡‡	130
5	136	111	176	130	160	166
6	107	107	130	107	‡‡	115
7	125	100	150	130	130	130
8	142	120	187	156	‡‡	156
9	125	100	136	120	125	125
10	125	90	115	130	‡‡	136
11	125	130	200	120	‡‡	142
12	130	142	150	111	125	130
Mean±S.E.M.	132±3	116±6	157±8	127±4	145±8	144±6

* Control pre-infusional heart rate before administration of noradrenaline infusion.
** Heart rate at peak of blood pressure response induced by noradrenaline infusion.
*** Heart rate immediately before termination of noradrenaline infusion.
† Heart rate at lowest blood pressure level reached after termination of infusion.
†† Heart rate at midpoint of recovery, i.e., when a recovery of 50% from lowest blood pressure was attained.
††† Heart rate when maximum recovery of blood pressure from the post-infusional hypotensive phase was reached within the experimental period of time (90-120 minutes).
‡ Reserpine 5 mg/kg i.p. was administered 24-48 hours before the experimental procedure.
‡‡ Midpoint of recovery was reached in 6 out of 12 experiments.

APPENDIX XXIII

Changes in Blood Pressure induced by Noradrenaline Infusion

8 μg/kg/minute for 5 minutes

in Alpha Methyldopa‡ pretreated cats

Group VI

Experiment Number	C.B.P.* (mm Hg)	M.B.P.** (mm Hg)	B.P. at end of infusion*** (mm Hg)	L.B.P.† (mm Hg)	Time to L.B.P. (min)	M.P.R.†† (mm Hg)	Time to M.P.R. (min)	M.R.††† (mm Hg)	Time to M.R. (min)
1	110	185	140	60	6	85	67	90	87
2	115	210	185	70	32	95	95	115	152
3	115	215	180	80	28	100	68	115	82
4	115	235	195	65	3	90	72	115	138
5	95	210	195	70	12	85	78	90	90
Mean±S.E.M.	110±4	211±8	179±10	69±3	16±6	91±3	76±5	105±6	110±15

* Control pre-infusional blood pressure level before administration of noradrenaline infusion.

** Maximum rise in blood pressure induced by noradrenaline infusion.

*** Blood pressure level immediately before the arrest of infusion.

† Lowest blood pressure reached following termination of infusion.

†† Midpoint of recovery representing the level of mean blood pressure when 50% recovery from the lowest blood level was attained.

††† Maximum recovery of blood pressure representing the maximum recovery of blood pressure from post-infusional hypotensive phase within experimental period of time (90-120 minutes).

‡ Alpha methyldopa 100 mg/kg i.p. was administered daily for 3 days before the experimental procedure.

APPENDIX XXIV

Changes in Heart Rate induced by Noradrenaline Infusion

8 µg/kg/minute for 5 minutes

in Alpha Methyldopa‡ pretreated cats

Group VI

Experiment Number	C.Heart Rate* (beats/min)	Heart Rate** at M.B.P. (beats/min)	Heart Rate*** at end of infusion (beats/min)	Heart Rate† at L.B.P. (beats/min)	Heart Rate†† at M.P.R. (beats/min)	Heart Rate††† at M.R. (beats/min)
1	136	75	166	125	176	200
2	166	166	230	136	176	176
3	187	125	166	166	200	200
4	176	156	176	166	187	187
5	200	130	166	166	214	214
Mean±S.E.M.	173±11	130±16	180±12	152±9	191±7	195±6

* Control pre-infusional heart rate before administration of noradrenaline infusion.
** Heart rate at peak of blood pressure response induced by noradrenaline infusion.
*** Heart rate immediately before termination of noradrenaline infusion.
† Heart rate at lowest blood pressure level reached after termination of infusion.
†† Heart rate at midpoint of recovery, i.e., when a recovery of 50% from lowest blood pressure was attained.
††† Heart rate when maximum recovery of blood pressure from the post-infusional hypotensive phase was reached within the experimental period of time (90-120 minutes).
‡ Alpha methyldopa 100 mg/kg i.p. was administered daily for 3 days before the experimental procedure.

APPENDIX XXV

Changes in Blood Pressure induced by Noradrenaline Infusion

8 μg/kg/minute for 5 minutes

in cats pretreated chronically with Guanethidine‡

Group VII

Experiment Number	C.B.P.* (mm Hg)	M.B.P.** (mm Hg)	B.P. at end of infusion*** (mm Hg)	L.B.P.† (mm Hg)	Time to L.B.P. (min)	M.P.R.†† (mm Hg)	Time to M.P.R. (min)	M.R.††† (mm Hg)	Time to M.R. (min)
1	100	185	165	80	14	90	44	100	56
2	105	195	170	45	5	75	75	95	107
3	110	230	190	50	7	80	44	110	82
4	105	210	185	75	15	90	70	100	90
Mean±S.E.M.	105±2	205±10	178±6	63±9	10±3	84±4	58±8	101±3	84±11

* Control pre-infusional blood pressure level before administration of noradrenaline infusion.

** Maximum rise in blood pressure induced by noradrenaline infusion.

*** Blood pressure level immediately before the arrest of infusion.

† Lowest blood pressure reached following termination of infusion.

†† Midpoint of recovery representing the level of mean blood pressure when 50% recovery from the lowest blood level was attained.

††† Maximum recovery of blood pressure representing the maximum recovery of blood pressure from post-infusional hypotensive phase within experimental period of time (90-120 minutes).

‡ Guanethidine 5 mg/kg i.p. was administered daily for 7 days before the experimental procedure.

APPENDIX XXVI

Changes in Heart Rate induced by Noradrenaline Infusion

8 μg/kg/minute for 5 minutes

in cats pretreated chronically with Guanethidine ‡

Group VII

Experiment Number	C.Heart Rate* (beats/min)	Heart Rate** at M.B.P. (beats/min)	Heart Rate*** at end of infusion (beats/min)	Heart Rate† at L.B.P. (beats/min)	Heart Rate†† at M.P.R. (beats/min)	Heart Rate††† at M.R. (beats/min)
1	158	187	230	150	150	150
2	176	200	214	176	166	187
3	272	300	333	272	300	300
4	107	200	250	136	136	158
Mean±S.E.M.	178±35	222±26	257±27	184±31	188±38	199±35

* Control pre-infusional heart rate before administration of noradrenaline infusion.
** Heart rate at peak of blood pressure response induced by noradrenaline infusion.
*** Heart rate immediately before termination of noradrenaline infusion.
† Heart rate at lowest blood pressure level reached after termination of infusion.
†† Heart rate at midpoint of recovery, i.e., when a recovery of 50% from lowest blood pressure was attained.
††† Heart rate when maximum recovery of blood pressure from the post-infusional hypotensive phase was reached within the experimental period of time (90-120 minutes).
‡ Guanethidine 5 mg/kg i.p. was administered daily for 7 days before the experimental procedure.

PART III

APPENDIX XXVII

Changes in Blood Pressure induced by Noradrenaline Infusion

8 µg/kg/minute for 5 minutes

in Bretylium‡ pretreated cats

Group VIII

Experiment Number	C.B.P.* (mm Hg)	M.B.P.** (mm Hg)	B.P. at*** end of infusion (mm Hg)	L.B.P.† (mm Hg)	Time to L.B.P. (min)	M.P.R.†† (mm Hg)	Time to M.P.R. (min)	M.R.††† (mm Hg)	Time to M.R. (min)
1	105	195	190	70	18	90	86	105	104
2	90	190	165	60	25	75	67	90	118
3	90	225	190	70	45	80	90	90	92
4	155	255	185	80	20	120	105	130	120
5	110	230	180	70	20	90	64	110	115
6	110	240	215	85	30	100	58	110	78
Mean±S.E.M.	110±10	223±10	188±7	73±4	26±4	93±7	78±7	106±6	105±7

* Control pre-infusional blood pressure level before administration of noradrenaline infusion.

** Maximum rise in blood pressure induced by noradrenaline infusion.

*** Blood pressure level immediately before the arrest of infusion.

† Lowest blood pressure reached following termination of infusion.

†† Midpoint of recovery representing the level of mean blood pressure when 50% recovery from the lowest blood level was attained.

††† Maximum recovery of blood pressure representing the maximum recovery of blood pressure from post-infusional hypotensive phase within experimental period of time (90-120 minutes).

‡ Bretylium 5 mg/kg i.v. was administered 15-30 minutes before the infusion of noradrenaline was commenced.

APPENDIX XXVIII

Changes in Heart Rate induced by Noradrenaline Infusion

8 μg/kg/minute for 5 minutes

in Bretylium‡ pretreated cats

Group VIII

Experiment Number	C.Heart Rate* (beats/min)	Heart Rate at M.B.P.** (beats/min)	Heart Rate at end of infusion*** (beats/min)	Heart Rate at L.B.P.† (beats/min)	Heart Rate at M.P.R.†† (beats/min)	Heart Rate at M.R.††† (beats/min)
1	150	187	200	115	125	142
2	156	166	200	166	176	176
3	230	272	300	230	230	230
4	187	214	230	176	187	230
5	166	230	214	166	176	187
6	150	156	200	156	156	150
Mean±S.E.M.	173±13	204±18	224±16	168±15	175±14	186±16

* Control pre-infusional heart rate before administration of noradrenaline infusion.
** Heart rate at peak of blood pressure response induced by noradrenaline infusion.
*** Heart rate immediately before termination of noradrenaline infusion.
† Heart rate at lowest blood pressure level reached after termination of infusion.
†† Heart rate at midpoint of recovery, i.e., when a recovery of 50% from lowest blood pressure was attained.
††† Heart rate when maximum recovery of blood pressure from the post-infusional hypotensive phase was reached within the experimental period of time (90-120 minutes).
‡ Bretylium 5 mg/kg i.v. was administered 15-30 minutes before the infusion of noradrenaline was commenced.

APPENDIX XXIX

Changes in Blood Pressure induced by Noradrenaline Infusion

8 µg/kg/minute for 5 minutes

in cats treated with Guanethidine‡ (acute pretreatment)

Group IX

Experiment Number	C.B.P.* (mm Hg)	M.B.P.** (mm Hg)	B.P. at end of infusion*** (mm Hg)	L.B.P.† (mm Hg)	Time to L.B.P. (min)	M.P.R.†† (mm Hg)	Time to M.P.R. (min)	M.R.††† (mm Hg)	Time to M.R. (min)
1	85	190	150	45	5	65	72	75	125
2	105	225	205	80	38	95	95	105	128
3	110	250	210	90	6	100	9	110	15
4	120	230	200	75	12	100	70	120	120
5	85	200	190	65	8	75	20	85	60
Mean±S.E.M.	101±7	219±11	191±11	71±8	14±6	87±7	53±16	99±8	90±22

* Control pre-infusional blood pressure level before administration of noradrenaline infusion.

** Maximum rise in blood pressure induced by noradrenaline infusion.

*** Blood pressure level immediately before the arrest of infusion.

† Lowest blood pressure reached following termination of infusion.

†† Midpoint of recovery representing the level of mean blood pressure when 50% recovery from the lowest blood level was attained.

††† Maximum recovery of blood pressure representing the maximum recovery of blood pressure from post-infusional hypotensive phase within experimental period of time (90-120 minutes).

‡ Guanethidine 1 mg/kg i.v. was administered 30-50 minutes before noradrenaline infusion was started.

APPENDIX XXX

Changes in Heart Rate induced by Noradrenaline Infusion

8 µg/kg/minute for 5 minutes

in cats treated with Guanethidine‡ (acute pretreatment)

Group IX

Experiment Number	C.Heart Rate* (beats/min)	Heart Rate at M.B.P.** (beats/min)	Heart Rate at end of infusion*** (beats/min)	Heart Rate at L.B.P.† (beats/min)	Heart Rate at M.P.R.†† (beats/min)	Heart Rate at M.R.††† (beats/min)
1	158	150	166	158	158	166
2	150	214	166	136	136	136
3	107	136	176	136	125	130
4	150	156	214	115	130	136
5	125	107	230	125	120	136
Mean±S.E.M.	138±10	153±18	190±13	134±7	134±7	147±6

* Control pre-infusional heart rate before administration of noradrenaline infusion.
** Heart rate at peak of blood pressure response induced by noradrenaline infusion.
*** Heart rate immediately before termination of noradrenaline infusion.
† Heart rate at lowest blood pressure level reached after termination of infusion.
†† Heart rate at midpoint of recovery, i.e., when a recovery of 50% from lowest blood pressure was attained.
††† Heart rate when maximum recovery of blood pressure from the post-infusional hypotensive phase was reached within the experimental period of time (90-120 minutes).
‡ Guanethidine 1 mg/kg i.v. was administered 30-50 minutes before the infusion of noradrenaline was started.

PART IV

APPENDIX XXXI

Changes in Blood Pressure induced by Noradrenaline Infusion

8 μg/kg/minute for 5 minutes

in Quindonium‡ pretreated cats

Group X

Experiment Number	C.B.P.* (mm Hg)	M.B.P.** (mm Hg)	B.P. at end of infusion*** (mm Hg)	L.B.P.† (mm Hg)	Time to L.B.P. (min)	M.P.R.†† (mm Hg)	Time to M.P.R. (min)	M.R.††† (mm Hg)	Time to M.R. (min)
1	80	170	150	70	10	75	12	80	44
2	135	220	190	105	25	120	75	120	75
3	115	180	170	95	7	105	8	105	65
4	120	200	160	95	12	110	38	120	65
5	115	195	190	80	6	100	20	115	35
6	130	210	200	110	11	120	30	130	64
Mean±S.E.M.	116±8	196±8	177±8	93±6	12±3	105±9	31±10	112±7	58±6

* Control pre-infusional blood pressure level before administration of noradrenaline infusion.

** Maximum rise in blood pressure induced by noradrenaline infusion.

*** Blood pressure level immediately before the arrest of infusion.

† Lowest blood pressure reached following termination of infusion.

†† Midpoint of recovery representing the level of mean blood pressure when 50% recovery from the lowest blood level was attained.

††† Maximum recovery of blood pressure representing the maximum recovery of blood pressure from post-infusional hypotensive phase within experimental period of time (90-120 minutes).

‡ Quindonium Bromide 10 mg/kg i.v. was administered 30 minutes before the infusion of noradrenaline was commenced.

APPENDIX XXXII

Changes in Heart Rate induced by Noradrenaline Infusion

8 µg/kg/minute for 5 minutes

in Quindonium‡ pretreated cats

Group X

Experiment Number	C.Heart Rate* (beats/min)	Heart Rate at M.B.P.** (beats/min)	Heart Rate at end of infusion*** (beats/min)	Heart Rate at L.B.P.† (beats/min)	Heart Rate at M.P.R.†† (beats/min)	Heart Rate at M.R.††† (beats/min)
1	125	136	166	90	93	125
2	142	156	200	176	200	200
3	150	187	200	120	166	176
4	176	166	250	120	166	187
5	156	156	187	125	136	187
6	166	200	200	187	200	176
Mean±S.E.M.	153±7	167±9	201±11	136±15	160±17	175±11

* Control pre-infusional heart rate before administration of noradrenaline infusion.
** Heart rate at peak of blood pressure response induced by noradrenaline infusion.
*** Heart rate immediately before termination of noradrenaline infusion.
† Heart rate at lowest blood pressure level reached after termination of infusion.
†† Heart rate at midpoint of recovery, i.e., when a recovery of 50% from lowest blood pressure was attained.
††† Heart rate when maximum recovery of blood pressure from the post-infusional hypotensive phase was reached within the experimental period of time (90-120 minutes).
‡ Quindonium Bromide 10 mg/kg i.v. was administered 30 minutes before infusion of noradrenaline was commenced.