Beagle dogs of either sex were studied (10.5–16.0 kg) under sodium pentobarbitone anaesthesia (30 mg/kg i.v.). The animals were artificially respired and arterial PO_2, PCO_2 amd pH were checked repeatedly during the experiments and maintained within normal physiological limits. Both cervical vago-sympathetic nerve trunks were sectioned and the chest was opened in the mid-line. Left ventricular pressure, dp/dt max., aortic blood pressure and heart rate were obtained by use of Millar catheter tip pressure transducers, an appropriate differentiator and ratemeter and registered on a Devices M19 8-channel recorder.

Cocaine hydrochloride (5 mg/kg i.v., and 1 mg/kg every 45 min) was used to block uptake 1 (Trendelenburg, 1959), and (±)-metanephrine (40 μg kg^{-1} min^{-1} i.v.) to block uptake 2 (Burgen & Iversen, 1965). Dose-response curves to i.v. bolus injections of isoprenaline (50 ng/kg–1 μg/kg) and noradrenaline (100 ng/kg–2 μg/kg) and frequency-response curves (supramaximal voltage, 5 ms pulse width, 1.0–20 Hz) of electrical stimulation of the left ansa subclavia nerve established under control conditions were compared with those obtained during individual and combined administration of the uptake antagonists. Statistical testing was by analysis of variance.

Cocaine potentiated responses to noradrenaline or nerve stimulation, but did not affect those to isoprenaline. Metanephrine potentiated positive inotropic responses to all doses of isoprenaline ($P < 0.05$) and positive chronotropic responses were enhanced at doses ⩾100 ng/kg. Positive inotropic responses to noradrenaline were enhanced significantly at doses ⩾250 ng/kg, and chronotropic responses at doses ⩾1 μg/kg. Metanephrine did not affect positive inotropic responses to sympathetic nerve stimulation of any frequency and cardiac responses to noradrenaline or nerve stimulation obtained after administration of cocaine were not further modified by the concurrent administration of metanephrine. Similarly, responses to isoprenaline in the presence of both cocaine and metanephrine were similar to those obtained in the presence of metanephrine alone, but subsequent administration of cocaine to those preparations already receiving metanephrine still potentiated cardiac responses to noradrenaline or nerve stimulation.

Our results confirm the known effects of cocaine on cardiovascular responses to noradrenaline and sympathetic nerve stimulation and establish that metanephrine enhances cardiac responses to isoprenaline *in vivo*. However, plots of dp/dt max. against heart rate demonstrate that cocaine preferentially enhances chronotropic responses to noradrenaline, but that metanephrine does not discriminate between inotropic and chronotropic effects of isoprenaline.

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Studies on the rebound hypertension after clonidine withdrawal in conscious hypertensive cats, rats, and dogs

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Clonidine is a potent antihypertensive agent which is known to act on central cardiovascular sites and its effect on these centres is thought to be due to stimulation of central α-adrenoceptors (Schmitt, Schmitt & Fénard, 1973; Finch, 1974). The reports of a severe rebound rise in blood pressure if the drug is withdrawn abruptly remains a problem in the treatment of patients and also its mechanism is poorly understood (Hunyor, Hansson, Harrison & Hoobler, 1973).

In both spontaneous hypertensive and normotensive rats ($n = 8$), clonidine (2 × 0.2 mg/kg s.c. for 14 days) produced a marked fall in blood pressure measured by the indirect tail cuff method: on withdrawal of clonidine (15 days), the blood pressures returned to normal.

In conscious renal hypertensive cats ($n = 6$) with blood pressure recorded from cannulae chronically implanted into the thoracic aortae (Finch, 1974), treatment with clonidine (3 × 0.025 mg p.o. for 10 days) also produced a sustained fall in mean blood pressure (40 mmHg). However, after completion of the clonidine treatment (day 11), 4 cats exhibited a

rebound hypertension (20–30 mmHg) above pretreatment levels and also a marked tachycardia.

In conscious renal hypertensive dogs ($n=5$) with blood pressure recorded from chronically implanted arterial cannulae, clonidine pretreatments (3 x 0.15 mg p.o. for 4 or 10 day periods) produced sustained falls in blood pressure and marked bradycardia. In the 3 mongrel dogs a rebound hypertension (40–80 mmHg) and tachycardia was observed after completion of either treatment (day 5 or 11) but rebound hypertension was not observed in beagle dogs ($n=2$). The mechanism of this rebound hypertension on clonidine withdrawal remains to be investigated but it would seem that two experimental models are available for this study.

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The effects of β-adrenoceptor blockade on the development of deoxycorticosterone acetate (DOCA) hypertension in the dog

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Salt-loading in dogs with partial nephrectomy has been shown to produce hypertension which is dependent upon an elevation of cardiac output (Coleman & Guyton, 1969; Cowley & Guyton, 1975) followed by autoregulation and an increase in vascular resistance. It seemed possible therefore to examine this process during the development of DOCA hypertension. We have produced a model of DOCA hypertension in the dog in which it was possible to evaluate the effects of β-adrenoceptor blockade during the developmental stages to determine the role of changes in cardiac output.

Male beagle dogs (13.0–15.5 kg) were chronically implanted with carotid artery and jugular vein vinyl catheters from which blood pressure (BP) and cardiac output (CO dye-dilution) measurements were made. Plasma volume (PV) was measured by the Evans Blue method and extracellular fluid volume (ECFV) by determination of the thiocyanate space. Several weeks after unilateral nephrectomy, DOCA (1.0 g) was implanted subcutaneously in 5 dogs, and 3 days later they were given a drinking solution containing 1.0% NaCl, 0.25% KCl and 0.25% sugar *ad libitum* for a further 15 days. At the end of this period, drinking water containing 0.25% KCl and 0.25% sugar was provided. A group of 4 dogs similarly treated were given atenolol 150 mg twice daily during the saline drinking period to investigate the effect of β-blockade on the development of the hypertension.

In dogs receiving DOCA and saline alone there was an increase over 7 days in systolic BP 149 ± 3.3 to 182 ± 9.0 mmHg ($P<0.01$) and in diastolic BP 86 ± 1.9 to 111 ± 4.6 mmHg ($P<0.01$). These changes were sustained and were accompanied by an initial reduction in heart rate (HR) from 81 ± 4.3 to 60 ± 4.2 bts/min which gradually returned to control values. There was a small increase in CO of approximately 0.48 l/min after 7 days and total peripheral resistance (TPR) increased by 30% after 3 days but these changes were not statistically significant. PV increased from 917 ± 26 to 1116 ± 57 ml and ECFV 4.98 ± 0.20 to 5.94 ± 0.581 ($P<0.05$) at day 7 but returned to control values at day 14.

In the group receiving atenolol along with DOCA and saline, the BP rose as it did in the last group from 138 ± 4.8 to 189 ± 3.8 mmHg systolic ($P<0.01$) and 85 ± 4.5 to 113 ± 4.3 mmHg diastolic ($P<0.01$). HR fell from 90 ± 8.9 to 50 ± 11.6 bts/min (day 14), CO was reduced during the first 7 days from 2.30 ± 0.17 to 1.91 ± 0.29 l/min ($P<0.05$). This effect was more pronounced by day 14 when CO was 1.63 ± 0.07 l/min ($P<0.01$, TPR increased progressively over 14 days from 3696 ± 242 to 6289 ± 356 dynes sec cm^{-1} ($P<0.002$). The changes in PV and ECFV showed a small upward trend which was not statistically significant.

In control experiments in 4 normotensive dogs, atenolol 150 mg p.o. twice daily produced a small fall in BP from 145 ± 7.0 to 130 ± 5.0 mmHg systolic and 80 ± 7.0 to 58 ± 4.0 mmHg diastotic ($P<0.01$) over a period of 24 days.