mitotic index determined 32 h after commencing treatment and 8 h after colchicine (1 mg/kg i.p.). Controls were contralateral unstimulated glands or glands from saline treated animals (Drug experiments).

Isoprenaline (100 n mol/g) and sympathetic nerve stimulation 90 min but not salbutamol (100 n mol/g) or oxymetazoline (50 n mol/g) significantly increased growth. Isoprenaline, salbutamol and both sympathetic and parasympathetic nerve stimulation for 90 min evoked secretion. Parasympathetic nerve stimulation produced the highest volume (190 ± 34 µl $n=3$), salbutamol the lowest (15 ± 1 µl $n=3$) over 90 minutes. Isoprenaline, sympathetic nerve stimulation and salbutamol, unlike parasympathetic nerve stimulation produced an amylase-rich secretion. Isoprenaline and sympathetic nerve stimulation, but neither salbutamol nor parasympathetic nerve stimulation depleted protein and amylase levels by approximately 80% and 50% respectively after 90 minutes.

Only treatments which activate β_1-adrenoceptors (isoprenaline and sympathetic nerve stimulation) enhanced growth. Salbutamol mainly a β_2 agonist, oxymetazoline, an α agonist and parasympathetic nerve stimulation were ineffective. A similar picture emerges when the ability to deplete protein and amylase is considered. These results suggest that, (a) the mechanism responsible for catecholamine induced growth operates via a β_1-adrenoceptor and (b) only those treatments depleting residual secretory material cause a significant increase in the rate of gland growth.

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Studies on the marked antihypertensive properties of indapamide (SE 1520) in rats and cats

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SE 1520 (Indapamide, N-3-sulphamoyl-4-chlorobenzamide)-2-methyl-indoline) has been reported to be active in the treatment of mild to moderate hypertension (Seedat & Reddy, 1974; Whately & Heraty, 1976). The mode of action of SE 1520 as an antihypertensive agent was, therefore, studied in experimental hypertensive cats and rats.

In conscious renal hypertensive cats (Finch, 1975), SE 1520 (2×10 mg orally) produced a moderate fall in blood pressure without any accompanying change in the resting heart rate. In conscious DOCA/NaCl hypertensive rats ($n=4$), SE 1520 (2×10 mg/kg orally) produced a marked fall in the mean blood pressure for a period of 24 h when measured from cannulae implanted directly in the aortic arch (Finch, Hersom & Hicks, 1975). SE 1520 (10 mg/kg orally for 10 days) and hydrochlorothiazide (5 mg/kg i.p. for 10 days) also produced a marked hypotensive effect in the DOCA/NaCl hypertensive rats, when measured by the tail/cuff method.

In pithed rat preparations ($n=8$) pretreatment with SE 1520 (10×10 mg/kg orally) markedly reduced the pressor responses to noradrenaline, tyramine and stimulation of the entire sympathetic outflow (Gillespie & Muir, 1967), whilst pretreatment with hydrochlorothiazide (10×5 mg/kg i.p.) did not alter the cardiovascular reactivity of the pithed rat preparation. However, in both the isolated portal vein preparation and the Krebs perfused mesenteric artery preparation from rats pretreated with SE 1520 (10×10 mg/kg orally) the responses to noradrenaline were similar to those obtained using untreated rats.

In conclusion, SE 1520 exerts an antihypertensive action in experimental hypertensive animals and after a 10 day pretreatment also markedly reduced the cardiovascular reactivity to various pressor agents. Since no changes in cardiovascular reactivity could be observed after similar pretreatment with hydrochlorothiazide, SE 1520 may have a novel mode of action as an antihypertensive agent.

SE 1520 (Natrilix®) was donated by Servier Laboratories, Greenford, Middlesex.

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Effect of endogenous metabolites on the binding of *o*-methyl red to human serum albumin

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The binding of several acidic drugs and dyes to the plasma proteins of patients with renal insufficiency is decreased (Reidenberg & Affrime, 1973), and the dye *o*-methyl red, for example, shows a typical decrease (Breyer & Radcliff, 1954; Campion, 1973). Campion (1973) investigated the effect of adding some hydrophilic metabolites known to accumulate in uraemia on the binding of *o*-methyl red to normal serum and found a slight but non-significant decrease in binding. However, Odar-Cederlöf (1975) found evidence that retained uraemic metabolites may be responsible for the inhibition of binding of warfarin. We have therefore used equilibrium dialysis to investigate the effect of some endogenous metabolites, which accumulate in uraemia, on the binding of *o*-methyl red to human serum albumin (HSA) *in vitro*.

Hydrophilic metabolites were added to the albumin-dye solution 20 min prior to dialysis and fatty acids were added by the method of Spector & Hoak (1969).

Table 1 Effect of endogenous metabolites on the binding of *o*-methyl red to human serum albumin. Equilibrium dialysis at 37°C was carried out with *o*-methyl red (1.33×10^{-4} M) and HSA (1.45×10^{-4} M) in 0.1 M phosphate buffer pH 7.4

Metabolite	*Total concentration (mM)*	*Unbound dye (D) (%)*	*Percentage increase in D relative to control*
Indoxyl sulphate	0	15.2 (±1.2)†	
	0.1 – 1.0	*17.7 (±0.8)–31.5 (±1.5)	16–107
Uric acid	0	15.8 (±0.2)	
	0.18 – 0.54	16.1 (±0.5)–15.8 (±0.1)	—
Phenol	0	15.6 (±0.3)	
	0.053– 0.27	15.6 (±0.3)–16.0 (±0.5)	—
Urea	0	15.4 (±0.3)	
	4.2 –16.7	15.0 (±0.2)–15.6 (±0.5)	—
Creatinine	0	15.0 (±0.4)	
	0.18 – 1.1	14.9 (±0.7)–14.5 (±0.3)	—
Lauric acid	0	15.6 (±0.5)	
	0.12 – 0.64	*18.6 (±0.4)–54.8 (±0.7)	19–251
Myristic acid	0	15.4 (±0.6)	
	0.07 – 0.39	*16.0 (±0.3)–37.9 (±0.6)	4–146

* $P < 0.005$

† Each result is the mean (± s.d.) of five or more experiments