and its metabolites by column chromatography (Graefe, Stefano & Langer, 1973).

AH 5158 ($10^{-7}-3\times10^{-4}$ M) produced a dose dependent increase in the overflow of [^{3}H] following nerve stimulation ($r=0.83$; $P<0.02$; $n=8$). The dose required to produce a 50% increase in overflow was 2.3×10^{-5}M. These results are similar to those obtained by measurement of the overflow of endogenous noradrenaline (Blakeley & Summers, 1976).

AH 5158 had no apparent effect on the production of [^{3}H]-DOMA [3,4-dihydroxy mandelic acid] or the 0-methylated deaminated metabolites, [^{3}H]-MOPEG [3-methoxy 4-hydroxy phenyl glycol and [^{3}H]-VMA [3-methoxy 4-hydroxy mandelic acid], indicating that the drug does not directly inhibit MAO, COMT or extraneuronal uptake. [^{3}H]-DOPEG (3:4 dihydroxy phenyl ethylene glycol) production was inhibited, particularly during the last 3 min of collection when, under normal conditions, a high proportion of [^{3}H] overflowed as metabolites. The inhibition was dose-dependent and the doses required to reduce [^{3}H]-DOPEG production by 50% in the last 3 min of collection were 1.2×10^{-5} M, 2.3×10^{-5} M and 2.4×10^{-5} M. There was a significant ($r>0.885$, $P<0.001$, $n>6$) inverse relationship between the change in proportion of [^{3}H]-(−)-noradrenaline and [^{3}H]-DOPEG recovered for each of the last three 1 min collection periods. DOPEG is thought to be derived from the fraction of transmitter taken back into the nerves which is metabolized by MAO and aldehyde reductase (Kopin, 1972), and the amount formed has been taken as an index of neuronal uptake (Cubeddu, Barnes, Langer & Weiner, 1974). Since both the neuronal uptake inhibitor cocaine (Cubeddu *et al.*, 1974) and AH 5158 inhibit the production of [^{3}H]-DOPEG following nerve stimulation it is likely that the site of uptake inhibition by AH 5158 is neuronal.

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The receptors involved in catecholamine mediated growth and secretion in rat parotid gland

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Catecholamines increase the rate of growth and produce a protein-rich secretion in rat salivary glands (Schneyer, 1974; Muir, Pollock & Turner, 1975). These effects are inhibited by propranolol and are presumably mediated via β-adrenoceptors. The increase in growth may arise from a depletion of secretory material (especially amylase) following catecholamine stimulation (Schneyer, 1974). This hypothesis was investigated by comparing the ability of sympathetic nerve stimulation and several adrenergic agonists to enhance growth and deplete amylase and total protein stores. A classification of the β-adrenoceptor involved in terms of β_1 or β_2 activity (Lands, Arnold, McAuliff, Luduena & Brown, 1967) was also made.

In anaesthetized (halothane 3%, N_2O/O_2 2:1) rats the cervical sympathetic trunk or the parasympathetic nerves to the parotid were stimulated (20 Hz, 1 ms, 30 s/min supramaximal for up to 90 min) unilaterally or drugs given i.p. and saliva collected from the cannulated duct. Pieces of gland (10–20 mg) were removed before and again after (90 min) treatment and the total protein (Lowry, Rosebrough, Farr & Randall, 1951) and amylase levels (Phadebas commercial kit) compared. Saliva was also assayed for total protein and amylase content. Total protein and amylase content of unstimulated contralateral glands measured before and after nerve stimulation were not significantly different. Increased growth was measured, as an increased DNA synthesis by the uptake of [^{3}H]-thymidine and as an increase in the

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.