M); and for leptazol approximately 1.5×10^{-3}M. While " circuiting " was never seen with strychnine, a brief episode of uncoordinated violent activity was a characteristic effect of this drug, and was used as the strychnine endpoint EC50 (approximately 2.5×10^{-6}M). Cunaniol was the most potent of these compounds, and it was also the most rapid in its onset of action. Only cunaniol acetate, with an EC50 of 4.5×10^{-7}M ($4.2–4.8 \times 10^{-7}$M) was potent, and acted with similar rapidity to cunaniol.

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Selection of two strains of rats with inherited hypertension. Preliminary studies with some hypotensive drugs

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The inability to reproduce essential hypertension in animals is one of the difficulties in searching for a rational therapeutic approach to this disease. Most investigators suggest that hereditary factors are involved in human essential hypertension, so an attempt has been made to use the hereditary hypertension of rats as an experimental model for pharmacological investigations. We have developed two strains of rats with inherited hypertension, by means of selective inbreeding from CF stock of Wistar rats, following suggestions by Smirk & Hall (1958) and Dahl & Schackow (1964). One strain was fed with a high salt diet (NaCl, 8%) and the other with a normal diet.

In the strain on a normal diet, the average blood pressure increased from 134 (± 1.4) mm Hg in the first generation to 162 (± 1.8) mm Hg in the fifth generation, and remained at this level until the eighth generation. In rats fed with high salt diet average blood pressure increased progressively from 145 (± 1.6) mm Hg in the first generation to 166 (± 1.5) mm Hg in the eighth generation.

The main difficulties encountered in the selection of these strains were reduction of body weight and decrease in fertility, both related to the inbreeding procedure. In rats with the high salt diet the rate of sterile matings increased after the seventh generation, because of sterility of the males, as demonstrated by cross breeding experiments. The hereditability coefficient of hypertension in both strains was high: 0.39 for rats fed with the normal diet and 0.64 for rats fed with the high salt diet.

Preliminary histological studies of kidneys and adrenals from rats of up to 8 months in age, did not show any significant differences from normal animals. The absence of renal or adrenal lesions and the involvement of hereditary factors, are two aspects of this experimental hypertension which are also shared by human essential hypertension. Several other aspects have to be investigated to demonstrate the suitability of this animal as an experimental model of the human disease.

The hypotensive effects of hydralazine (1, 2 and 4 mg/kg); methyldopa (50 mg/kg), morphine 0.5 and 3 mg/kg), papaverine (30 mg/kg), guanethidine (10 mg/kg), mecamylamine (2 and 8 mg/kg), reserpine (0.25 and 1 mg/kg), chlorothiazide (50 mg/kg) and phenoxybenzamine (1–3 mg/kg) have been studied on the rats belonging

to the seventh generations of the two strains. The results were compared with those obtained on renal hypertensive rats.

These substances had about the same effect in rats on normal diet and on high salt diet, but most of them appeared more active in renal hypertensive rats than in rats with hereditary hypertension.

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Cardiac effects of thyroxine

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Recent results suggested that the cardiovascular changes in thyroxine-treated animals may not be the result of an increased sensitivity of the cells to the catecholamines (Zaimis, Metaxas, Harvard & Campbell, 1965 ; Van der Schoot & Moran, 1965 ; Buccino, Spann, Pool, Sonnenblick & Braunwald, 1967). In the present study cats were treated with thyroxine, 0.3 mg/day for 12–16 weeks and guinea-pigs with 0.025 mg/day for 7–15 weeks. Guinea-pigs were more affected than cats. The myocardium of the thyroxine-treated animals showed an increase in excitability even before the appearance of tachycardia and an increased sensitivity to vagal stimulation.

Thyroxine treatment produced significant mitochondrial ultrastructural changes ; the most striking feature was a mitochondrial pleomorphism (Fig. 1). Many of the mitochondria were enlarged and assumed a variety of abnormal shapes. Measurements of mitochondrial areas showed that there was a 9-fold increase in enlarged mitochondria in the thyroxine-treated cats, and a 7-fold increase in the guinea-pigs.

In heart mitochondria isolated from thyroxine-treated animals, there was an apparent increase in the overall activity of the electron transport chain and the capacity of mitochondria for oxidative phosphorylation. For example, with succinate as substrate, there was an increase in basal rates of respiration as well as in respiration stimulated by adenosine diphosphate. Mitochondrial respiration was measured by means of an oxygen electrode.

It is suggested that in thyroxine-treated animals a cell membrane alteration has taken place, possibly as a result of inhibition of active transport.

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