hydrochloride (15 mg/kg I.V.). The pressor responses to propranolol and tyramine hydrochloride (100 μg) were not seen when the animals had been pretreated with reserpine, 10 mg/kg I.P., 48 hr and 24 hr before the experiment. A slow intravenous infusion of noradrenaline (10–15 μg in 20–30 min) in the presence of bretylium tosylate (1 mg/kg I.V.) as suggested by Clark & Leach (1968), restored the response to tyramine but not to propranolol. The response due to propranolol was also lost by pithing the rat by the method of Shipley & Tilden (1947).

It may therefore be concluded that the pressor response due to small doses of propranolol is mediated partly through a peripheral β-receptor stimulating action on the heart but also via a central mechanism, since pithing or reserpinization prevents the response. The failure of α-receptor blockade to prevent the pressor response to propranolol may reflect the ability of this drug to restore the response to noradrenaline after α-receptor blockade. The persistence of the pressor response despite ganglion blockade by hexamethonium is rather difficult to explain.

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Adrenergic mechanisms in hypertension

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The effectiveness of anti-adrenergic drugs in hypertensive animals and man has focused a great deal of attention on the role of adrenergic mechanisms such as increased activity of vasoconstrictor neurones, supersensitivity of vascular smooth muscle (Doyle & Frazer, 1961), increased cardiovascular reactivity (McCubbin & Page, 1963), decreased uptake or increased elimination rate of noradrenaline (Champlain, Krakoff & Axelrod, 1966), at reduced tissue noradrenaline content (Gitlow, Wilk, Wolf & Nafthi, 1964).

We have studied some aspects of the role of adrenergic mechanisms in experimental hypertension. In conscious dogs with nephrogenic or neurogenic hypertension, the pressor responses to tyramine and angiotensin are significantly greater than in normal dogs. Angiotensin appears not to release catecholamines from the adrenal to any great extent under these conditions because the dimethylphenylpiperazinium (DMPP) and noradrenaline pressor responses remain unchanged. The enhancement of tyramine and angiotensin but not of noradrenaline shows that supersensitivity of vascular smooth muscle to noradrenaline is not the cause of the tyramine and angiotensin potentiation.

The supersensitivity may be due to changes in vessel wall characteristics. In rats with nephrogenic hypertension the non-inulin space, Na^+, K^+ and water content of the hypertensive vessel is increased. Furthermore the membrane potential of the vascular smooth muscle cell is raised. This suggests a shift of Na^+, K^+ and water to the paracellular ground substance and not to the smooth muscle cell. There would then be an increased wall volume, decreased elasticity and reduced vessel diameter as suggested by Jones,

Peterson & Feigel (1967). These changes could also be responsible for the decreased sensitivity of the carotid baroreceptors to stretch which we observed in cats with nephrogenic hypertension in agreement with McCubbin, Green & Page (1956) and Kezdi's (1967) observations in renal hypertensive dogs.

An increase of the catecholamine content of the brain and adrenals and a slight decrease in heart noradrenaline content can be demonstrated in rats with renal hypertension. This change could reflect reduced neuronal activity and transmitter pile-up, or enhanced rate of transmitter formation. The evidence, however, that transmitter content can increase during neuronal rest or during chronic hyperactivity makes it difficult to relate these changes to the functional state of adrenergic neurones.

Adrenergic mechanisms appear not to contribute to hypertension beyond their physiological role. The dilatation of arterioles by antiadrenergic drugs in a vascular system with a reduced diameter would produce greater decrease in resistance and fall in systemic pressure than is possible in normotension with vessels of normal diameter and low resistance.

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The state of shock induced by cystamine and cysteamine

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We believe that the pharmacological actions of sulphur-containing radioprotecting substances (cysteamine=MEA; cystamine; AET or mercaptoethylguanidine, etc.) play a decisive part in the mechanisms of the protection of mammals against ionizing radiation (Bacq, 1965). The following facts have been established mainly in the rat but also in other animal species. The effects of cystamine (S–S) are usually more marked than those of cysteamine (SH).

1. There is cardiovascular shock and hypotension which is long lasting after large radioprotective doses (150 mg/kg, I.P. or I.V.) (Lecomte, Cession-Fossion, Libon & Bacq, 1964; Lecomte & Bacq, 1965; Beaumariage, Van Caneghem & Bacq, 1966).

2. There is haemoconcentration, hypoproteinemia without decrease of the albumin/globulin ratio and a marked decrease (30–40%) of sialic acid in the plasma (Van Caneghem & Stein, 1967).

3. There is considerable leakage into the plasma of five intracellular enzymes (Plomteux, Beaumariage, Bacq & Heusghem, 1967).

4. There are early (10–20 min) and rapidly repaired (1–2 hr) lesions of the mitochondria and endoplasmic reticulum (Hugon, Maisin & Borgers, 1966; Firket & Lelievre, 1966).