insensitive to nicotinic stimulants. After post-ganglionic nerve section, injection of higher doses of AH 6405 (50 μg/kg intra-arterially) produced a contraction of the nictitating membrane which could be blocked by atropine but not by cocaine. This effect indicated that AH 6405 stimulated peripheral muscarinic sites as well as those in sympathetic ganglia. In anaesthetized and spinal cats the vasodepressor and pressor responses to intravenous AH 6405 were reduced or blocked by atropine (0·1 mg/kg) but not by pentolinium (1 mg/kg). Essentially similar results have been reported for the muscarinic ganglion stimulants McN-A343 and AHR-602 (see Roszkowski, 1961; Franko, 1963; Jones, 1963).

In vitro AH 6405 was about 1/300 as active as acetylcholine as a stimulant of gastrointestinal smooth muscle of the rabbit and guinea-pig. These responses were blocked by atropine (2 ng/ml), but not by mepyramine (1 μg/ml). Surprisingly AH 6405 had a transient stimulant effect on guinea-pig isolated atria and typical muscarinic effects on this preparation have not been seen. It was also inactive on toad rectus abdominal muscle in concentrations up to 350 μg/ml.

AH 6405 has muscarinic effects on smooth muscles and sympathetic ganglia but not on heart muscle. It has no obvious nicotinic action on ganglia or amphibian skeletal muscle. AH 6405 may be useful in the characterization of muscarinic receptors.

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Circadian rhythm in plasma corticosterone concentration and pituitary adrenocorticotrophic response to stress in the betamethasone treated rat

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Male rats were given betamethasone solution instead of drinking water over a 24 h period. The concentration of the solution (20 μg/ml) was adjusted on the basis of a series of preliminary experiments so that each rat received approximately 450 μg betamethasone/100 g. The circadian rhythm in plasma corticosterone concentration and the changes in the blood level of the steroid which occur in response to stress (exposure to ether vapour for 1 min) were studied at the end of betamethasone treatment and 1, 2 and 3 days afterwards. Both the circadian rhythm and the stress-induced rise in plasma corticosterone were abolished. Normal circadian rhythm returned within 1 day of withdrawal of the steroid, but the response to stress was not normal until 3 days after stopping the treatment. The effect on both the circadian and stress induced rise in plasma corticosterone was entirely due to the inhibition of corticotrophin release because the adrenal sensitivity to exogenous ACTH was unimpaired by the betamethasone treatment.

The final common pathway for ACTH release is known to be in the median eminence. Afferent nervous pathways to the hypothalamus control the circadian ACTH

rhythm, and these pathways differ from those regulating the release of the hormone in response to stress (Szentágothai, Flerko, Mess & Halasz, 1968). The difference in sensitivity of the two mechanisms to the inhibitory action of corticoids suggests that the corticosteroids do not act upon the final common pathway and provide further evidence for the existence of corticoid sensitive controllers in parts of the central nervous system other than the hypothalamus.

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Pituitary-adrenocortical activity in the ascorbic acid deficient guinea-pig

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Pituitary-adrenocortical activity was studied in young female guinea-pigs fed on a diet deficient in vitamin C. After 2 weeks on this diet, ascorbic acid had almost completely disappeared from the adrenal glands. However, there was no significant change in adrenal or plasma corticoid concentration and injected histamine or corticotrophin (ACTH) caused a rise in plasma corticoid concentration which did not differ from that in control animals. After three weeks, there was a tenfold increase in both plasma cortisol and corticosterone concentrations, and a significant fall in the concentration of these steroids in the adrenal glands. Neither histamine nor ACTH was capable of increasing the plasma corticoid concentration further.

The results suggest that ascorbic acid is not essential for the synthesis or release of corticosteroids. Scurvy appears to be a form of severe stress which results in such an increase in adrenocortical secretion that the synthesis rate of cortisol and corticosterone is incapable of matching the rate of release of these steroids.

The effect of graded doses of practolol on the tachycardia induced by isoprenaline, Valsalva's manœuvre and exercise

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Brick, Hutchinson, McDevitt, Roddie & Shanks (1968) showed that practolol in doses up to 20 mg intravenously reduced (but not to levels of statistical significance) the tachycardia induced by 3 μg/min isoprenaline. After atropine or hexamethonium there was also a significant inhibition of isoprenaline tachycardia. The inhibition of isoprenaline by practolol was thought to be non-competitive. We are using higher doses of practolol in hypotensive therapy (Prichard, Day & Boakes, unpublished) and we report the inhibitory effect of doses up to 160 mg intravenously.

Six volunteer mildly hypertensive patients stopped practolol 2 days before study. Subjects rested supine and received logarithmically graded isoprenaline (as hydrochloride) infusions (1 μg; 2 μg; 4 μg etc./min, dose expressed as salt), for 5 min at each dose level. After recovery patients were tilted 60° head up; 2 min later Valsalva's manœuvre was performed, followed by 2 min erect cycling at 100 watts.