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 We are using higher doses of practolol in hypotensive therapy (Prichard, Day & Boakes, unpublished) and we report the inhibitory effect of doses up to 160 mg intravenously.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.

Subjects again rested supine, and were given 5 mg practolol intravenously. The sequence of observations was repeated, and again following a further 15 mg practolol (incremental total 20 mg), again after another 60 mg (80 mg total), and again after 80 mg (160 mg total). Blood pressure was taken by the London School of Hygiene and Tropical Medicine sphygmomanometer (Rose, Holland & Crawley, 1964) and heart rate was recorded by an electrocardiogram.

Resting pulse was unchanged; there was progressive reduction in the tachycardia induced by isoprenaline and by endogenously induced sympathetic activity (see Table 1). Results have been expressed in terms of the final pulse rate reached from

TABLE 1

	Resting pulse	Tachycardia induced by isoprenaline 4 μg/min	Tachycardia end effort Valsalva (40 mm Hg for 20 s)	Tachycardia exercise 100 watts for 2 min
Control	73	104	105	120
$n=6$		N.S.	$P<0{\cdot}01$	N.S.
After practolol				
5 mg	72	103	99	116
$n=5$		$P<0{\cdot}05$	$P<0{\cdot}005$	$P<0{\cdot}05$
20 mg	72	97	89	111
$n=6$		$P<0{\cdot}005$	$P<0{\cdot}05$	$P<0{\cdot}01$
80 mg	72	88	84	105
$n=6$		N.S.	$P<0{\cdot}05$	N.S.
160 mg	75	87*	81	**105
$n=5$				

* Average pulse rate reduction between 80 mg and 160 mg=4·2 in five patients receiving both dose levels of practolol.

** Average pulse rate *reduction* between 80 mg and 160 mg=1·8 in five patients receiving both dose levels of practolol.

P values indicate the probability of a difference between the figures immediately above and below.

the stimulus concerned. Calculations based on the increment in pulse rate to each stimulus show a similar pattern. By extrapolation, the isoprenaline dose required to increase the pulse rate by 20 beats/min shows no change after 5 mg practolol but a dose dependent relationship is apparent at increasing doses of practolol. Log/dose response curves suggest competitive inhibition by practolol both in response to challenge by isoprenaline and endogenously liberated catecholamine. Assessment of the changes in blood pressure makes it appear unlikely that reflex vagal changes are responsible for the results.

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The fate of isoprenaline administered by pressurized aerosols

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The cardiac response to an inhaled dose of isoprenaline can be reproduced by administering approximately 2% of the same dose intravenously. It has not previously been determined whether this is because the major part of the isoprenaline inhalation is swallowed and inactivated or because it is inactivated in the bronchi.