than 0·04 pH units in 0·01M hydrochloric acid in the presence of a detergent would therefore barely be detectable, and would certainly be insignificant compared to the changes of up to 2 pH units observed with acids which are solubilised.

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The effect of monoamine oxidase inhibition on guanethidine-induced noradrenaline release and sympathetic blockade

SIR,—We have measured the noradrenaline content of the hearts of rats injected with iproniazid alone or followed by guanethidine and have related the noradrenaline depletion to the monoamine oxidase inhibition.

The noradrenaline in individual rat hearts was measured after butanol extraction by fluorimetry (Fielden & Green, 1965). Monoamine oxidase activity was assayed by the dinitrophenylhydrazine method (Green & Haughton, 1961). The hearts from groups of 4 rats were homogenised in 5 or 6 volumes of 0·1 M phosphate buffer (pH 7·4) and 3·2 ml samples of the homogenates were shaken in air at 25° with 0·125 M semicarbazide (0·4 ml) and 0·1 M tyramine (0·4 ml). After 30 min., the reaction was terminated with 0·5 N acetic acid (1 ml); the remaining steps in the assay were then as previously described.

Table 1 summarises the results of experiments in which various doses of iproniazid phosphate were injected subcutaneously into rats 20 hr before subcutaneous injection of guanethidine sulphate (10 mg/kg). The rats were killed after a further 4 hr for assay of the noradrenaline and monoamine oxidase in their hearts. Sympathetic blockade at this time was estimated from the extent of ptosis, which was recorded on a 0–8 scale (Rubin, Malone, Waugh & Burke, 1957). The 20 hr interval was chosen to minimise interference by shorter-lasting effects of iproniazid unconnected with monoamine oxidase inhibition, but very similar results were obtained in a few experiments in which the iproniazid was given only 2 hr instead of 20 hr before the guanethidine, as was done by Gessa, Cuenca & Costa (1963). It is clear from Table 1 that no significant protection would be afforded against guanethidine-induced noradrenaline

depletion by doses of iproniazid which did not inhibit monoamine oxidase, and that 50% or more inhibition is needed before protection becomes appreciable. This is in complete contrast to the results of Gessa & others (1963), who reported that iproniazid caused only 5% inhibition of monoamine oxidase at a dose (12·5 mg/kg), which reduced the extent of noradrenaline depletion due to guanethidine (10 mg/kg intraperitoneally) from 90% to 32%.

TABLE 1. MONOAMINE OXIDASE INHIBITION, HEART NORADRENALINE LEVELS AND PTOSIS IN RATS TREATED WITH IPRONIAZID AND GUANETHIDINE

The mean noradrenaline content is given, together with the range, in parentheses, and the number of rats, in brackets

Dose of iproniazid phosphate (mg/kg)	Monoamine oxidase inhibition (%)	Heart noradrenaline content (μg/g)		Ptosis iproniazid + guanethidine
		Iproniazid alone	Iproniazid + guanethidine	
0	0	0·97 (0·66–1·29) [18]	0·20 (0·14–0·31) [8]	5·8
10	35	—	0·21 [2]	6·0
20	55	1·01 (0·69–1·24) [4]	0·45 (0·34–0·60) [4]	4·6
40	75	0·95 (0·78–1·18) [4]	0·69 (0·60–0·85) [5]	5·2
80	90	1·11 (0·78–1·41) [4]	0·88 (0·75–1·02) [4]	3·6

Our results suggest that the protection afforded by iproniazid against guanethidine-induced noradrenaline depletion is related to the amount of monoamine oxidase inhibition, and that there may be no need to invoke a bretylium-like adrenergic neurone blocking effect (Gessa & others, 1963) to account for this protection. In addition, they lend further support to the conclusion reached by Kopin & Gordon (1963) from metabolic studies, that the bulk of the noradrenaline released from the tissue stores by guanethidine is metabolised intraneuronally by monoamine oxidase. It may also be noted from Table 1 that diminution by iproniazid of guanethidine-induced noradrenaline depletion is accompanied by no more than a slight lessening in the amount of ptosis. This may be contrasted with the well-known ability of iproniazid to prevent the ptosis caused by reserpine as well as reducing the extent of tissue depletion of noradrenaline (Carlsson, Rosengren, Bertler & Nilsson, 1957).

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