Acknowledgements. Paul Turner is in receipt of a Wellcome Senior Research Fellowship in Clinical Science. We thank the Board of Governors of St. Bartholomew's Hospital for a grant to J. H. Young. Professor Taylor and Drs. Linford Rees and C. M. B. Pare kindly allowed us access to their patients. Smith Kline and French Laboratories Ltd., provided tranylcypromine sulphate (Parnate). Dr. D. M. G. Armstrong, Mr. C. J. Thompson and Miss E. P. Saunders gave valuable assistance.

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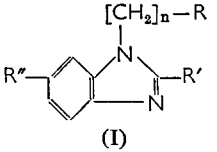
May 20, 1966

References

Maas, A. R. & Nimmo, M. J. (1959). *Nature, Lond.*, **184**, 547–548.
Udenfriend, S. (1962). *Fluorescence Assay in Biology and Medicine.* London: Academic Press.

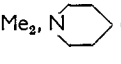
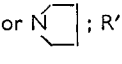
Inhibitory effect of 1-alkylbenzimidazoles on gastric secretion in the rat

SIR,—While examining the pharmacological effects of a new series of benzimidazole derivatives of general structure (I) we observed that they exerted an inhibitory effect on secretion of gastric acid and gastric juice.



(I)

The most active compounds are those in which

$n = 2$; $R = NMe_2$,  or  ; $R' = H$ or C_6H_5; $R'' = H$ or Cl.

With the most active derivatives, the dose causing a 50% inhibition of secretion of gastric acid and gastric juice in the rat is 5 to 10 mg/kg intramuscularly, while the intramuscular LD50 values are about 200 mg/kg.

Some effects of one of the compounds lying in the middle of the range of activity are now described. The compound is 1-(2-piperidinoethyl)benzimidazole (H-635). The inhibitory effect of this compound on gastric secretion in the rat is seen in Table 1.

TABLE 1. THE EFFECT OF 1-(2-PIPERIDINOETHYL)BENZIMIDAZOLE ON GASTRIC SECRETION IN THE RAT

No. of animals	Dose mg/kg i.m.	Inhibition (%) of secretion of:		
		Free acid	Total acid	Gastric juice
12	9·0	38·9	42·2	26·4
25	12·0	74·2	60·6	51·6
27	25·0	78·8	61·6	66·3
	ED50 mg/kg i.m.	10·0	11·2	16·4

The compound also increases gastric emptying time and inhibits intestinal motility when given intramuscularly or orally. These actions are shown in Table 2.

TABLE 2. THE EFFECT OF 1-(2-PIPERIDINOETHYL)BENZIMIDAZOLE ON GASTRIC EMPTYING TIME AND INTESTINAL MOTILITY IN THE RAT

No. of animals	Dose mg/kg	Increase (%) in gastric emptying time	Inhibition (%) of intestinal motility *in vivo*
12	12·5 i.m.	66	25
12	25·0 i.m.	166	not investigated
12	50·0 oral	131	not investigated
12	100·0 oral	322	45·0

This compound has no effect on either the acetylcholine-induced contraction of excised rat duodenum *in vitro* or acetylcholine-induced vasodepression in cats and dogs *in vivo*. We consider the compound to selectively block parasympathetic but not sympathetic transmission for the following reasons.

1. The vasodepression caused by cervical vagal stimulation in the cat is abolished in doses which do not influence the contraction of nictitating membrane induced by preganglionic electrical stimulation of the superior cervical ganglion. At the same time, the compound fails to alter the vasodepressive reaction to intravenously injected acetylcholine.

2. The bradycardia and vasodepression due to thoracic vagal stimulation are abolished by doses which do not affect the tachycardia and vasopressor effect induced by preganglionic electrical stimulation of the stellate ganglion.

3. The rise in blood pressure after intravenous injection of tetramethylammonium bromide is not affected by pretreatment with H-635; this rise is, however, completely blocked by tetraethylammonium bromide, a ganglion blocking drug also inhibiting sympathetic ganglia.

The effect of H-635 in blocking parasympathetic transmission seems also to occur in the central nervous system. The compound inhibits the rage reaction evoked in conscious cats by intrahypothalamic injection of carbachol, a reaction with a pathway which involves cholinergic transmission sites and which is not affected by either reserpine, chlorpromazine or phenobarbitone.

In addition, the compound exhibits a general sedative action and antagonises or reduces the increased motility of mice seen after desoxyephedrine. Similar effects were observed with other members of this chemical series.

The selective blockade of parasympathetic transmission and the sedative effect exerted on the central nervous system in general, and on the hypothalamus in particular both seem to be responsible for the inhibitory action of these compounds on gastric secretion.

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