vasoconstrictor responses elicited by sympathetic nerve stimulation, the impairing effect being more susceptible to blockade by atropine than the enhancing effect. The mechanism of the effects may involve an interaction between McN-A-343 and the sites at which acetylcholine may act in mediating noradrenaline release by sympathetic nerve impulses.

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The uptake of adrenergic neurone blocking drugs

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Boura & Green (1965) suggested that the concentrations of adrenergic neurone blocking drugs which accumulate in sympathetic nerves might be sufficient to block conduction in the nerve terminals. However, Rand & Wilson (1967) showed that, in a group of guanidine compounds, there was no direct relationship between the local anaesthetic activity of individual drugs and their potency as adrenergic neurone blocking drugs.

In the present experiments uptake of four compounds previously studied by Rand & Wilson (1967) has been measured in the rat's heart. These compounds have similar local anaesthetic activity but differ in their adrenergic neurone blocking activity. Thus, guanethidine and EM 311 (2-cyclohexylamino-2-methylethyl guanidine) are potent adrenergic neurone blocking drugs, while EM 97 (3-cyclohexylamino-*n*-propyl guanidine) and EM 336 (2-cyclohexylamino-2-ethylethyl guanidine) are virtually inactive in this respect. Figures for uptake are shown in Table 1. The reduction in uptake after pretreatment of the rats with dexamphetamine was taken as a measure of uptake into the sympathetic nerves. Uptake by the heart of

TABLE 1. *Uptake of guanidine derivatives into rat hearts and the effect of dexamphetamine (5 mg/kg intraperitoneally, 30 min before giving the guanidine derivative) on this uptake. Each figure is the mean result (±S.E.) obtained using twelve rats*

Drug	Concentration in heart (nmol/g)	Concentration in heart (nmol/g) after dexamphetamine pretreatment	Depression of uptake by dexamphetamine
Guanethidine 10 mg/kg	63·4±2·2	43·5±1·7	19·9
EM 311 10 mg/kg	60·4±2·8	44·9±2·2	15·4
EM 336 10 mg/kg	29·2±3·2	—	—
EM 336 20 mg/kg	52·1±1·8	56·0±2·0	0
EM 97 10 mg/kg	171·2±6·9	145·4±5·8	25·8

EM 336 was less than that of any of the other compounds and was not reduced by dexamphetamine. This therefore appears to be a non-specific uptake by tissues other than the sympathetic nerves. The inability of EM 336 to accumulate in sympathetic nerves would explain its lack of adrenergic neurone blocking activity. However, uptake of EM 97 into the sympathetic nerves was at least as great as that of guanethidine and EM 311. Thus if the concentrations of guanethidine and EM 311 taken up by the sympathetic nerves were sufficient to block conduction in the nerve endings, EM 97 would be expected to have the same action. The fact that EM 97 has very low adrenergic neurone blocking activity supports the suggestion by Rand & Wilson (1967) that the local anaesthetic activity of these compounds is not relevant to their actions at sympathetic nerve endings.

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The effects of α- and β-adrenoceptor blocking agents on the responses of the rat uterus to catecholamines throughout the oestrous cycle

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It is well known that in dioestrus adrenaline, noradrenaline and isoprenaline have solely an inhibitory effect on the uterus of the rat. Isoprenaline is the most active and noradrenaline the least active in this respect. Stimulation of the hypogastric nerve also has an inhibitory effect. In 1949 Mann showed excitatory responses to adrenaline, noradrenaline and stimulation of the hypogastric nerve when the rat was in oestrus. More recently other workers have contributed to this study with conflicting results (Rudzik & Miller, 1962; Levy & Tozzi, 1963; Diamond & Brody, 1966; Tothill, 1967).

A study has been made of both α- and β-adrenoceptor blocking agents on the effects of catecholamines on the uterus of the Wistar rat throughout the oestrous cycle. The stage of the cycle was determined by the vaginal smear. Contractions of the uterus *in vivo* were recorded by measuring the increase in the intraluminal pressure using a modification of the method of Bell & Robson (1937). Contractions of the uterus *in vitro* were recorded both isotonically and isometrically.

The results obtained from the *in vivo* studies were qualitatively the same as those obtained *in vitro*. The uterus from the animal in oestrus contracted when noradrenaline was given. Adrenaline in small doses caused an inhibition of the tissue and produced a biphasic effect of excitation followed by inhibition in larger doses. Electrical stimulation of the hypogastric nerve caused an excitatory response similar to that from noradrenaline. Throughout the cycle isoprenaline produced inhibitory responses and in no experiment was it possible to produce a contraction of the uterus with this catecholamine. Furthermore similar doses of isoprenaline were required to produce the inhibitory action at all stages of the cycle, whereas larger doses of adrenaline were needed to produce comparable inhibitory effects in oestrus to those in dioestrus.