oxyphenylbutazone levels were also lowered by pretreatment with desipramine from a control value of 22 ± 5 μg/ml to 2 ± 1·5 μg/ml at a dose of desipramine of 15 mg/kg indicating a possible effect of desipramine on phenylbutazone metabolism. This inhibitory effect on metabolism was also noticed after 6 hr when phenylbutazone was given intraperitoneally (Table 1).

These findings suggest desipramine interferes with the intestinal absorption of phenylbutazone. The effect of desipramine on the metabolism of phenylbutazone appears to be important in the light of the high doses required and the minor influence on the phenylbutazone and oxyphenylbutazone blood levels.

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Guanethidine and carbachol on the isolated frog rectus: a non-competitive interaction

SIR,—Guanethidine has been found to inhibit contractions caused by direct nerve and by direct muscle stimulation (Dixit, Gulati & Gokhale, 1961; Kroneberg & Stoepel, 1962; Green & Hughes, 1966; Chang, Chen & Cheng, 1967). Its main effect appeared to be on muscle fibres (Chang & others, 1967). On the other hand, in experiments in which avian and frog muscle were used, Rand & Wilson (1967b) concluded that guanethidine was a competitive antagonist of acetylcholine in these preparations. Gokhale, Gulati & others (1963), Chang & others (1967) and Rand & Wilson (1967b) attempted to modify the responses of the frog rectus to single doses of acetylcholine, but failed to analyse the dose-response curves before and after exposure to guanethidine. In recent work, Feinstein & Paimre (1967) used the same preparation to compare the effects which the competitive antagonist (+)-tubocurarine and the non-competitive antagonist tetracaine exerted on contractions elicited by carbachol, and found that while the first drug produced a parallel shift to the right of the dose-response curves, the second mainly reduced maximum contractility.

The object of the present work was to find out whether guanethidine was a competitive or non-competitive inhibitor of carbachol.

In Ringer solution, with oxygen bubbled through it, contractions of isolated rectus abdominis muscle of *Rana esculenta* were elicited by carbachol, of which the end-concentrations were $0{\cdot}2 \times 10^{-6}$ g/ml and the 2, 4, 8, 16-fold of it. The carbachol concentration was always doubled, without washing, when the effect of the preceding concentration had fully developed, and the dosing was continued until the maximum contraction developed. Five and 10 min after addition of the antagonists tubocurarine and guanethidine, respectively, the above procedure was repeated.

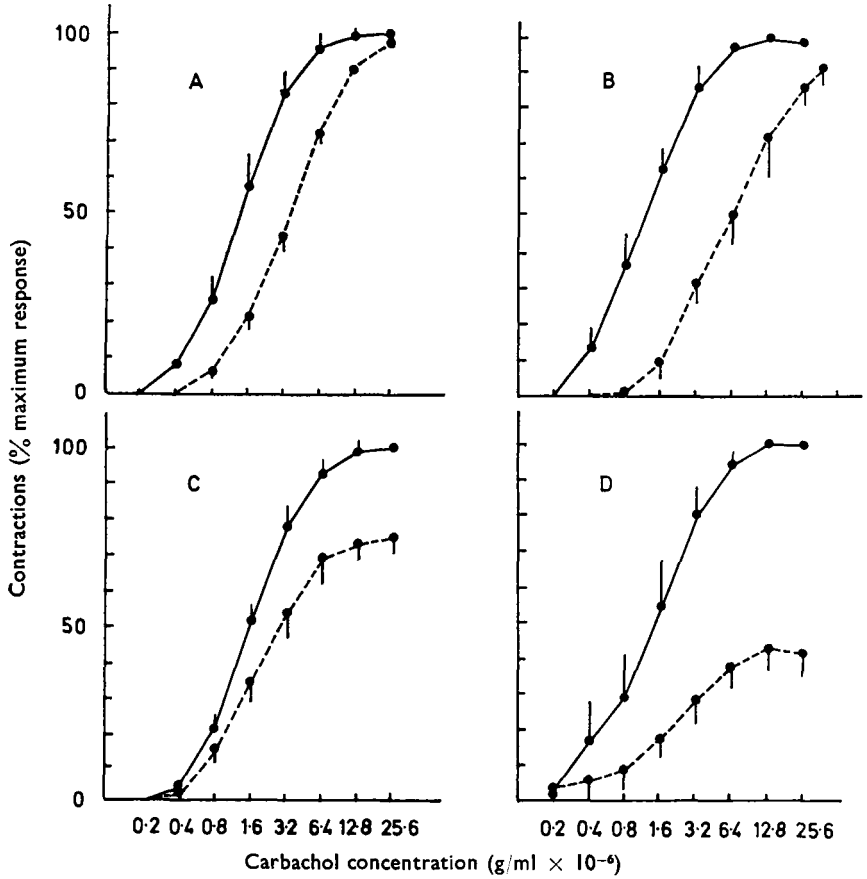

FIG. 1. Carbachol dose-response curves before and after the antagonists on frog isolated rectus. Each point is the mean ± the standard error. A. 2×10^{-7} g/ml tubocurarine, mean values of 6 experiments. pA_2 6·72 ± 0·26. B. 5×10^{-7} g/ml tubocurarine, mean values of 5 experiments. pA_2 6·79 ± 0·36. C. 5×10^{-6} g/ml guanethidine, mean values of 7 experiments. pD_2 4·19 ± 0·32. D. 10^{-5} g/ml guanethidine, mean values of 6 experiments. pD_2 4·55 ± 0·28. (± values: probability interval, P_{95}, for the mean values, Ariëns & Simonis, 1961).

In our experiments the two antagonists could be washed out; on the same preparation the carbachol effect could be inhibited and restored 3 or 4 times.

The results illustrated in Fig. 1 show that guanethidine produces no parallel shift to the right of the dose-response curves for carbachol, but depresses the maximum; it acts in the way of tetracaine and, therefore, cannot be considered a competitive antagonist.

It is not impossible that the non-competitive antagonistic effect of guanethidine on carbachol stems from its local anaesthetic property. Adrenergic neuron blocking agents and classical local anaesthetics differ essentially in their activities, for example, the latter drugs act quickly and can be readily washed out (Rand & Wilson, 1967a), but this is not evidence for a difference in the mechanism of action. The classical local anaesthetics are lipophilic and the

adrenergic blocking agents lipophobic. Both the quaternary local anaesthetics (Herr, Nádor & others, 1953) and the adrenergic neuron blocking agents are characterized by their slow but persistent action. The relation between local anaesthetic and adrenergic neuron blocking activity was first observed by Hey & Willey (1954). The present work seems to confirm the statement of Boura & Green (1965): "the possibility remains that the depressant action of the adrenergic fibre terminals is analogous to the impairment of nerve conduction in nerve trunks caused by local anaesthetics".

Our results show that on the rectus abdominis muscle of the frog, guanethidine like the local anaesthetics, is a non-competitive antagonist to carbachol.

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The effect of diethyldithiocarbamate on brain amine levels in the rabbit

SIR,—Sodium diethyldithiocarbamate or its oxidation product disulfiram inhibit both dopamine β-hydroxylase and monoamine oxidase in the brains of rats or guinea-pigs (Yamada & Yasunobu, 1962; Goldstein & Contrera, 1961; Musacchio, Kopin & Snyder, 1964; Collins, 1965; Carlsson, Lindquist & others, 1966). While investigating the neurotoxic action of sodium diethyldithiocarbamate in the rabbit (Edington, 1967), I have found differences in the level of central nervous system amines in this animal.

Twelve adult male or female Dutch rabbits 1·8–2·4 kg, were paired in similar weights and given sodium diethyldithiocarbamate as a buffered isotonic solution (Sunderman, White & others, 1963) at 750 mg/kg or saline intravenously. Two hr after the injection the rabbits were killed in a cold room, the brain removed, sectioned sagitally, and one half placed in a preweighed homogenized tube containing 10·0 ml of ice cold acid butanol. This tissue was homogenized and subsequently diluted to 30·0 ml. Fluorimetric estimations of 5-hydroxytryptamine (5-HT) and noradrenaline were made on the homogenized sample. The treated animals (6) had an estimated 5-HT brain content of $0{\cdot}67 \pm 0{\cdot}08$ μg/g brain while the controls (6) had $0{\cdot}45 \pm 0{\cdot}07$ μg/g wet weight. Noradrenaline