without affecting the muscle contractions at the slow rate of stimulation. The duration of neuromuscular block was 50 min. At the time of maximum block the responses of the muscle to close intra-arterial injections of acetylcholine were decreased to a similar extent as the twitch response; a tetanus was poorly sustained and transiently antagonized the block. The response to direct stimulation of the muscle was unaffected. Neostigmine (0·1 mg/kg intravenously) only partially reversed the neuromuscular block induced by AH 5183 as also did choline. In conscious chicks AH 5183 (10 mg/kg intravenously) caused a flaccid paralysis which lasted 10–20 min. These results indicated that AH 5183 has a blocking action at the neuromuscular junction resembling that of (+)-tubocurarine. However, the high selectivity of action of AH 5183 on the tibialis anterior muscle stimulated at high rates indicated that the drug might also possess a prejunctional action in inhibiting either the uptake of choline or the synthesis of acetylcholine. The latter properties might be expected to be common to all cholinergic nerves. Accordingly, the effects of AH 5183 on the guinea-pig isolated ileum coaxially stimulated (Paton, 1957) were next investigated. At a concentration of 1 μg/ml. AH 5183 caused a 50–80% reduction in the responses to electrical stimulation without affecting the acetylcholine-induced responses of the preparation. The action of AH 5183 was very quick in onset and, after the drug was washed out of the bath, the responses of the preparation returned quickly to normal. These effects contrasted markedly with those of (+)-tubocurarine (10 μg/ml.), which had little or no effect on the responses of the ileum to acetylcholine or coaxial stimulation.

AH 5183 has a blocking action at the neuromuscular junction resembling that of (+)-tubocurarine, and also a pre-junctional inhibitory action on post-ganglionic parasympathetic nerves and perhaps at motor nerves. The nature of these actions is being further investigated.

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Effects of catecholamine beta-receptor blocking agents on striated muscle

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The depressant effects of propranolol on neuromuscular transmission and on the response of electrically stimulated muscle was thought to be due to the local anaesthetic action of the drug (Wislicki & Rosenblum, 1967). Two recently described compounds which in doses of a few micrograms block cardiac beta-adrenoceptors have a weak local anaesthetic effect or are apparently devoid of it: 4-(2-hydroxy-3-isopropylaminopropoxy)acetanilide (I.C.I. 50,172), in a concentration of 400 μg/ml., reduced the action potential only slightly (Dunlop & Shanks, 1968), and up to 6·4% of (±)-erythro-4-(2-methylamino-1-hydroxypropyl)methanesulphoanilide (MJ 1998) did not produce local anaesthesia (Lish, Weikel & Duncan, 1965).

In the sciatic nerve–gastrocnemius preparation of the frog (*Rana ridibunda* (L.)) I.C.I. 50,172 (900 μg/ml.) abolished the response to indirect and reduced the effect

of direct stimulation while concentrations of MJ 1998 of 5 and 60 mg/ml. were required to obtain similar results.

Both substances reduced the acetylcholine (ACh)-induced contraction in the frog rectus abdominis muscle but while with I.C.I. 50,172 the response to ACh (0·5 μg/ml.) was reduced by 1 μg/ml. and reversibly abolished by 5 μg/ml. (Fig. 1), similar effects appeared with MJ 1998 only with concentrations of 5–10 mg/ml. Larger doses of I.C.I. 50,172 (750 μg/ml.) and of MJ 1998 (50 mg/ml.) caused marked and prolonged contractions.

These apparently contradictory effects may be due to multiple sites of action of beta-receptor blocking agents when applied in various concentrations, for it has been shown that propranolol has both pre- and post-synaptic effects (Werman & Wislicki, unpublished). These experiments of Werman and Wislicki indicate that the drug depolarized the nerve membrane and increased the function of the nerve terminal as shown by an increase in facilitation; however, a curariform effect was apparent at lower concentrations and masked the neural effects: with higher concentrations depolarization and increased conductance in the endplate region were seen.

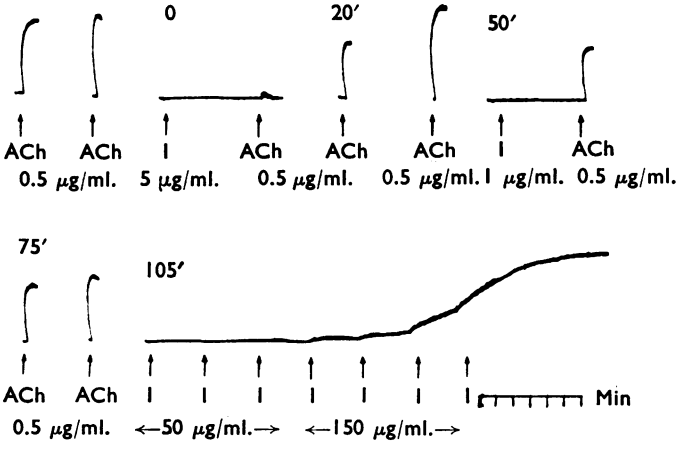

FIG. 1. Effects of I.C.I. 50,172 on the frog rectus abdominis muscle. Contraction produced by acetylcholine (ACh) (0·5 μg/ml.) was reversibly abolished by I.C.I. 50,172 (I) (5 μg/ml.) and reduced by I (1 μg/ml.); after recovery, I itself, given in three doses of 50 μg/ml. followed by four doses of 150 μg/ml. (total 750 μg/ml.), induced a prolonged contraction.

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