Waterfield, 1970; Lees, Kosterlitz & Waterfield, 1972). If calcium ions play an important role in the morphine-sensitive mechanism of ACh release, variations in calcium concentration should have different effects on evoked ACh release from the myenteric plexus of the guinea-pig and rabbit. Myenteric plexus-longitudinal muscle preparations of the two species were immersed in Krebs solution containing physostigmine (7·7 μM) and choline (20 μM). ACh release was evoked by supramaximal field stimulation with a fixed number of pulses (1–540) at 1 and 10 Hz. $CaCl_2$ concentrations were 2·54, 1·27, 0·64 and 0·32 mM. In the guinea-pig, single pulses induced a large release which was depressed by a reduction in calcium concentration from 2·54 to 0·64 mM; in the rabbit, the amount of ACh which was released by single pulses was below the sensitivity of the bioassay. The ACh release evoked by trains of 20 to 540 pulses at 1 and 10 Hz was depressed by lowering of the calcium concentration; this effect was more marked in the guinea-pig than in the rabbit.

$MnCl_2$ (1mM) depressed ACh output from the guinea-pig myenteric plexus, the reduction being greater at low than at high frequencies of stimulation. A depressant effect on the evoked release of ACh at the neuromuscular junction of the frog was demonstrated recently (Kajimoto & Kirpekar, 1972).

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AH 8165: A new short-acting, competitive neuromuscular blocking drug

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In the conscious mouse and chick 1,1′-azobis[3-methyl-2-phenyl-1H-imidazo(1,2-a) pyridinium]dibromide (AH 8165), 0·05–0·2 mg/kg i.v., caused a short lasting flaccid paralysis without sign of muscle fasciculations. These results indicated that AH 8165 could be a short lasting competitive neuromuscular blocking agent and further experiments were carried out, primarily in the anaesthetized cat, dog and monkey, to investigate the mechanism of action of this compound in more detail.

In the chloralose anaesthetized cat maintained on artificial ventilation AH 8165, 0·2 mg/kg i.v., caused a $74·0 \pm 8·3\%$ depression of maximal twitches of the tibialis anterior muscle elicited indirectly at 1 Hz. The blockade occurred within 10 s, it was not preceded by potentiation of the twitch response or accompanied by muscle fasciculations and recovery took 2–4 min. The degree of blockade was related to the frequency of nerve stimulation, at high rates (5 Hz) the blockade was more effective. In all subsequent experiments muscle twitches were elicited at a frequency of 1 Hz. AH 8165, 0·4 mg/kg i.v., caused almost complete neuromuscular blockade and during the recovery period responses of the muscle to indirect tetanic stimulation

were poorly sustained and a transient post-tetanic facilitation of the twitch response was observed. As with other competitive neuromuscular blocking agents the blockade induced by AH 8165 was reversed by neostigmine, 0·1 mg/kg i.v. In further experiments in which the tibialis muscle was stimulated directly, AH 8165 had no effect on these responses at doses far in excess of those which caused neuromuscular blockade.

Fully effective neuromuscular blocking doses of AH 8165 did not affect the blood pressure, heart rate or the E.C.G. However, at very high doses, 2–5 mg/kg, falls in blood pressure (5–50 mmHg) occurred sometimes accompanied by slight increases in heart rate (5–25 beats/min). Further analysis of these blood pressure effects showed that they were not due to histamine release but resulted from ganglion blocking activity.

In the anaesthetized dog and monkey AH 8165, 0·05–0·4 mg/kg i.v., caused short lasting, competitive neuromuscular blockade but the duration of action in the monkey was slightly longer (1·5 ×) than that seen in the cat or dog. In all the species examined AH 8165 possessed competitive neuromuscular blocking activity, and the compound had a quicker onset and a shorter duration of action than (+)-tubocurarine, gallamine or pancuronium. AH 8165 has potential as a muscle relaxant in surgery and, perhaps, in electroconvulsive therapy; clinical trials are in progress.

The effects of procaine, amylobarbitone on drug induced changes in the surface potentials of an isolated sympathetic ganglion

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Procaine and amylobarbitone are examples of drugs which have moderately selective depressant actions on autonomic ganglia and on nerve-skeletal muscle preparations. Because of technical difficulties it has not been possible to define their mode of action on the ganglion cells as thoroughly as has been achieved for these and other compounds on the skeletal muscle receptors.

In the present study a number of drugs have been studied for their effects on dose-response curves of depolarization to carbachol on the isolated superior cervical ganglion of the rat; the method being similar to that employed for an isolated skeletal muscle preparation by Nicholls & Quilliam (1956) and Payton (1966). The drugs were also compared for their effect on the rate of recovery of the ganglion from nicotine evoked depolarization, following the removal of nicotine from the bath.

Isolated de-sheathed superior cervical ganglia were obtained from Wistar strain rats (ca.200 g) anaesthetized with 25% urethane I.P. The ganglia were suspended in Krebs solution at room temperature (19·0–24·5° C) and changes in the surface potentials were measured by means of the moving-fluid-electrode technique as described by Brown (1966).

The ganglion blocking agents hexamethonium ($4{\cdot}5\times^{-4}$M), tetra-ethylammonium ($1{\cdot}5\times10^{-3}$M), and pempidine ($5{\cdot}3\times10^{-5}$M) in concentrations which just abolished transmission, caused a parallel shift to the right of the dose response curves of depolarization for carbachol, with some variable degree of depression of the maximum depolarization.