local anaesthetics in blocking intramural nerves of isolated intestine may, however, be questioned because cocaine in doses which inhibited the response to nicotine had little effect on electrically stimulated contractions of guinea-pig ileum (Bennett, 1965). Although we favour the idea that prostaglandin E_1 acts partly by stimulating non-cholinergic excitatory nerves, the possibility that tetrodotoxin acts atypically, for example by interfering with the excitation of prostaglandin receptors on the muscle, cannot be excluded.

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The effect on intracellular atrial potentials of bretylium in relation to its local anaesthetic potency

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Bretylium has been reported to have anti-arrhythmic properties, (Leveque, 1965 ; Bacaner, 1968 ; Ellis, Barnes & Cozzi, 1968). Earlier studies revealed that several anti-arrhythmic compounds had some features in common. In the isolated rabbit auricle, they greatly reduced the rate of rise and the height of the intracellularly recorded action potential and decreased conduction velocity, but did not significantly affect either the resting potential or the duration of the action potential (Vaughan Williams, 1958, 1966 ; Szekeres & Vaughan Williams, 1962). In addition most of these compounds were shown to possess local anaesthetic activity. It was therefore of interest to compare the cardiac and local anaesthetic actions of bretylium with those of other anti-arrhythmic agents.

In isolated rabbit atria, electrically driven at a rate of 180/min, therapeutic concentrations of bretylium (5–20 mg/l.) did not significantly affect the transmembrane potentials. A marked decrease in the rate of rise was only observed at a concentration as high as 1,200 mg/l. The latter effect was associated with some reduction in the height of the action potential, but the resting potential was not significantly altered. Similar changes can be produced by procaine at 7.5 mg/l. or propranolol at 0.3 mg/l. In some experiments, bretylium induced a small transient increase in the height and rate of rise of the action potential and a small initial increase in atrial rate, contractility, conduction velocity, and maximum driving frequency, as well as a short-lasting reduction in the electrical threshold. Bretylium (1,200 mg/l.) after 60–180 min exposure, slightly reduced the atrial rate, conduction velocity, maximum driving frequency and increased the electrical threshold, but did not reduce the contractility.

On the desheathed sciatic nerve of the frog bretylium proved to be about 90 times less potent than procaine as a local anaesthetic, and was approximately 300 times less active than propranolol.

On the basis of these results it might be suggested that the mode of action of therapeutic concentrations of bretylium in cardiac arrhythmias is different from that of the well known quinidine-like compounds.

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The action of procaine on transmission at the mammalian neuromuscular junction

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Procaine is able to produce neuromuscular paralysis both *in vivo* and *in vitro*, (Jaco & Wood, 1944 ; Straughan, 1961) but the mechanism of this paralysis is not fully understood. Evidence has been presented (Straughan, 1961) suggesting that in mammals the failure of normal neuromuscular transmission may have arisen from anaesthesia of the motor nerve terminals. Electrophysiological investigations in frog indicated that the paralysis arose from changes in the postjunctional membrane (Maeno, 1966 ; Furukawa, 1957). The present study was undertaken to obtain further information on the paralysis in rat phrenic nerve-diaphragm preparations.

Using intracellular recording electrodes, end-plate regions were identified in non-curarized tissue as the sites of spontaneous miniature end-plate potentials (m.e.p.p.s) of maximum amplitude (Liley, 1956). In curarized preparations end-plate regions were identified as those from which end-plate potentials (e.p.p.s) with a short rise time (<2 msec) were recorded after supra-maximal stimulation of the phrenic nerve.

Low concentrations of procaine hydrochloride (0.05 to 0.2 mM) rapidly reduced the mean size of the m.e.p.p.s without altering their frequency. Increasing concentrations resulted in an increased reduction in the mean size of the m.e.p.p.s. The rise times of the m.e.p.p.s were not altered by procaine but the decay of potential was greatly slowed. All effects were readily reversed by washing the preparations with drug-free Krebs solution.

End-plate potentials recorded from nerve-diaphragms in which transmission had been blocked by either (+)-tubocurarine hydrochloride (0.0015 mM) or magnesium chloride in high concentrations (12 to 14 mM) were reduced in amplitude by the addition of procaine (0.1 to 0.4 mM) to the perfusion fluid. In preparations paralysed by high Mg^{++} concentrations procaine did not change the mean quantal content of e.p.p.s per nerve impulse. In addition, the rate of decay of the end-plate potential was reduced, as had been shown for m.e.p.p.s with lower procaine concentrations.