INTRODUCTION

Quaternary ammonium type and amine type of ganglionic blocking agents prevent the depolarization of the postganglionic neurone by acetylcholine. The agents do not depress the release of acetylcholine transmitter and unlike nicotine do not cause an initial excitation of the ganglion. Tetraethylammonium was the first of the competitive ganglion blocking agents (Burn & Dale, 1915). Its action is brief. Paton & Zaimis (1949, 1951) worked with the methonium drugs of which hexamethonium and pentamethonium were successfully used in antihypertensive therapy for some years. Pentolinium has greater potency and longer duration of action (Mason & Wein, 1955). Stone et al, (1956) suggested that mecamylamine, a secondary amine, acts similarly to the quaternary ammonium ion, hexamethonium. This was questioned by Bennet et al, (1957) who proposed that mecamylamine acts at some site other than that where competitive and depolarising drugs normally act. This hypothesis was based on evidence that during partial block of ganglionic transmission with mecamylamine fatigue did not occur and that in the presence of mecamylamine drugs which usually produce depolarizing neuromuscular block became competitive inhibitors of neurotransmission. Corne & Edge (1958) failed to confirm a major difference between mecamylamine and quaternary ammonium salts on preganglionic nerve stimulation of the nictitating membrane.

The degree of block of ganglia would be expected to be dependent upon the amount of acetylcholine released at the synapse. This amount would decline during continuous stimulation, so that after threshold doses of the ganglionic blockers the ganglion may be able to transmit a brief burst of stimuli but would fail to transmit during continuous stimulation. Characteristic of this, the nictitating membrane of the cat gives a spike contraction followed by a decline during continuous stimulation of its preganglionic nerve. The rate of decline of contraction seems to be greater after some compounds, for example, hexamethonium than after others, for example, mecamylamine. This would be in keeping with hexamethonium behaving as a competitive antagonist and mecamylamine behaving mainly as a noncompetitive antagonist on acetylcholine receptors of rectus abdominis muscle of frog (van Rossum & Ariens, 1959). However, this is a different tissue and the evidence for ganglion is conflicting. Mecamylamine antagonizes noncompetitively the effects of the ganglionic stimulant dimethylphenylpiperazinium (DMPP) on isolated guinea pig ileum (Trendelenburg, 1961 c). van Rossum (1962 a, b) reported that tetraethylammonium, pentamethonium and hexamethonium act as competitive ganglionic blocking agents of nicotine. Mecamylamine and pempidine were thought to have a dual mode of action while Presidal and Ecolid acted as noncompetitive antagonists of nicotine on guinea pig jejunum. Melsaac & Millekschoen (1963) found that mecamylamine acts similarly to hexamethonium as a competitive antagonist of acetylcholine during blockade of nerve transmission on the superior cervical ganglion of the cat. The

characteristics of ganglionic blockade with mecamylamine and hexamethonium were similar with respect to (i) the influence of frequency of stimulation on intensity of block (ii) the maximum block obtained (iii) the development of fatigue in ganglionic transmission and (iv) the effect on dose-response curve of intra-arterial acetylcholine. Finally, the interaction between mecamylamine and other blocking agents can be best explained in terms of a competition for the same receptor. Recently, Barnett & Benforado (1966) reported that hexamethonium produced a combination of surmountable and non-surmountable inhibition of the nicotinic effects of nicotine while mecamylamine produced purely non-surmountable block on isolated guinea pig atria.

In view of the controversial literature reports on the nature of antagonism exhibited by the nicotinic ganglion blockers and the interest envinced in the muscarine receptors from time to time (Corne & Edge, 1958; Salerno & Coon, 1949; Holmstedt, 1951; Root, 1951; Spinks et al, 1958; Franko et al, 1963), it was decided to investigate the mode of action of several nicotinic ganglion blockers and also of atropine (muscarinic ganglion blocker) in great detail employing a variety of test objects.