Recent advances in pharmacological knowledge and pharmaceutical techniques have produced a large series of new drugs of low toxicity and few side effects. These advantages together with more specific properties allow their continued use over long periods in the management of chronic disease. At first sight few of these drugs are of direct interest to anaesthetists and consequently tend to be largely ignored in the specialty. Experience has shown, however, that a number, unconnected with anaesthesia, are capable of modifying profoundly the normal response to anaesthesia should surgery have to be undertaken during their administration. In particular, the dangers associated with the cortisone group of drugs are sufficiently serious to justify the warning given (Wood-Smith and Payne, 1955) that all patients about to undergo surgery should be specifically questioned about treatment with cortisone. Shortly after cortisone was introduced into clinical practice it could be assumed with a fair degree of certainty that any patient suffering from chronic inflammatory disease was likely to have had one or more courses of cortisone therapy so that anaesthetists were forced to modify their techniques accordingly.

The use of mecamylamine in the treatment of hypertension (Freis, 1955) has brought further problems. Chemically, 3-methyl-aminoisocamphane hydrochloride (Stone et al., 1956), this drug is a ganglion blocking agent which is stored in the tissues (Milne et al., 1957) and not readily excreted. In addition, it is rapidly and apparently completely absorbed from the alimentary canal and therefore can be conveniently given by mouth. For these reasons it is very suitable for the long term management of the hypertensive patient. Mecamylamine, however, is not without side effects; constipation and gastrointestinal atony have been reported (Freis, 1955) and experimental work has indicated that in the cat the action of mecamylamine is potentiated by the accumulation of carbon dioxide (Payne and Rowe, 1957). The experiments to be described emphasize a further difficulty; if hexamethonium is given to a cat previously treated with mecamylamine, neuromuscular block results. It remains to be shown that these observations apply to man, but it would be foolish to ignore them in the absence of that proof.

Method

Five healthy cats were used for the experiments. After induction with ethyl chloride and ether, anaesthesia was established with intravenous chloralose (80 mg/kg). A tracheal cannula was inserted and artificial respiration established by means of an ‘Ideal’ respiration pump. The right external jugular vein was cannulated for the purpose of intravenous injections and the blood pressure was recorded directly from the left carotid artery using a mercury manometer. The tendon of the right tibialis anterior muscle with its nerve supply was isolated after the manner described by Brown (1938). The tendon was attached to a flat steel spring myograph recording on a smoked drum and the nerve was stimulated through shielded platinum electrodes. A supramaximal square wave pulse of 0.5 m.sec duration was used with a strength of 1–3 volts at 10-second intervals. At varying periods of time after the administration of intravenous mecamylamine, hexamethonium was given and the effects on the muscle twitch and blood pressure recorded. In one instance trimetaphan camphorsulphonate (Arfonad) was substituted for hexamethonium.
RESULTS
In five cats previously given mecamylamine the intravenous injection of hexamethonium was followed by neuromuscular block. The quantitative relationships between the factors involved are set out in table I. Normally the dose of hexamethonium employed in these experiments has no effect on the muscle twitch, as shown in figure 1A.

In four of the five cats mecamylamine block was preceded by potentiation of the twitch (fig. 2A) which persisted for several minutes before signs of neuromuscular block ultimately became apparent. In the fifth cat the absence of potentiation (fig. 1B) may have been due to the earlier administration of hexamethonium.

The competitive nature of hexamethonium block after mecamylamine is shown in figures 1, 2 and 3. Initial potentiation is absent and there is no evidence of muscle fasciculation nor spontaneous contractions. The rate of onset and duration

<table>
<thead>
<tr>
<th>Weight of cat (kg)</th>
<th>Dose of mecamylamine (mg/kg)</th>
<th>Time between drugs (min)</th>
<th>Dose of hexamethonium (mg/kg)</th>
<th>Depression of twitch (%)</th>
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<td>2.7</td>
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<td>50</td>
<td>4</td>
<td>80</td>
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</tbody>
</table>

Fig. 1
Records of tibialis anterior contraction and blood pressure in a cat.
Time interval 30 sec.
Hypotension without neuromuscular block after intravenous hexamethonium (A). 250 minutes later, marked hypotension and slight neuromuscular block after 10 mg/kg mecamylamine (B). 90 minutes later nearly complete muscular block without further hypotensive effect after 10 mg/kg hexamethonium (C).
Records of tibialis anterior contraction and blood pressure in a cat.
Time interval 30 sec.

Potentiation of neuromuscular twitch and hypotension after 10 mg/kg mecamylamine (A). 30 minutes later, neuromuscular block without further hypotension after trimetaphan (B). First injection of trimetaphan (not shown) lowered blood pressure from 80 mm Hg to 45 mm Hg. Finally, after a further 20 minutes, neuromuscular block without further hypotension after nexamethonium (C).

The neuromuscular block produced by trimetaphan camphorsulphonate closely resembles that of hexamethonium but is much weaker (fig. 2b).

The influence of carbon dioxide on the combined effects of hexamethonium and mecamylamine is obvious from figure 3. The neuromuscular block was potentiated and the blood pressure further reduced when the animal was ventilated with 10 per cent carbon dioxide.

In contrast to its action at the motor endplate hexamethonium had no further effect on blood pressure after a fall had been achieved with mecamylamine. Trimetaphan camphorsulphonate, however, lowered the blood pressure from 80 mm Hg to 45 mm Hg in the only experiment in which the drug was used, but additional doses had no further effect.

One of the features of the methonium compounds is the manner in which their pharmacological properties are altered by the reduction in length of the carbon chain connecting the quaternary nitrogen atoms. In particular, the neuromuscular blocking action which is marked with decamethonium is almost negligible if hexamethonium is substituted; with this drug the head-drop test in rabbits is positive only when large doses are employed (Paton and Zaimis, 1952). There is no evidence that with the doses used in this series hexamethonium will produce neuromuscular block either in the cat (fig. 1A) or in man in normal circumstances. The present study shows, however, that if such doses are preceded by intravenous mecamylamine a considerable degree of neuromuscular block will result.

Mecamylamine itself possesses a weak neuro-
MECAMYLAMINE AND OTHER GANGLIONIC BLOCKING AGENTS

Records of tibialis anterior contraction and blood pressure in a cat previously given 40 mg/kg mecamylamine. Time interval 30 sec.

After 320 minutes, neuromuscular block produced by two injections of hexamethonium without further hypotension (A); potentiation of neuromuscular block and hypotension by inhalation of 10 per cent carbon dioxide (B).

Muscular blocking action (Stone et al., 1956) and it may be that hexamethonium merely potentiates this effect. Such potentiation is known to occur when cats previously given mecamylamine are exposed to carbon dioxide (Payne and Rowe, 1957). It was also shown that the increase in neuromuscular block was associated with a raised plasma level of the drug and it was suggested that carbon dioxide acts by mobilizing mecamylamine from the tissues. It seems unlikely that hexamethonium can act in this way as it can neither readily penetrate the cell membrane, nor has it any demonstrable ability to alter the plasma pH.

The evidence in favour of a direct action by hexamethonium is more convincing. The neuromuscular block observed in the present study is competitive in nature and similar to that reported by Paton and Zaimis (1952) in their detailed account of the properties of hexamethonium. It differs from mecamylamine block in several respects; there is no initial increase in the amplitude of the muscle twitch, the block develops faster and recovery is more rapid. In one respect, however, it resembles that of mecamylamine. Both blocks respond to carbon dioxide by further depression of neuromuscular activity. The significance of this observation is difficult to assess because carbon dioxide antagonizes the blocking action of certain other members of the methonium series, decamethonium and suxamethonium, as well as that of gallamine (Payne, 1957), and it might be expected that hexamethonium would react in the same way.

Acetylcholine is essential for the normal transmission of impulses at the motor endplate and if its release is impeded it is possible that the weak block produced by hexamethonium may be potentiated. According to Crawford (personal communication), there is some evidence to suggest that mecamylamine does inhibit the normal synthesis of acetylcholine. If this is so the block obtained could be explained by the relative increase in the amount of hexamethonium available to compete with acetylcholine.

Even if it is accepted that mecamylamine is not directly responsible for the neuromuscular block it must be agreed that the block is influenced by the drug. Mecamylamine may modify the motor endplate in such a way that the receptor sites can accommodate hexamethonium to the exclusion of acetylcholine. Evidence that mecamylamine can disturb the normal process at the motor endplate is forthcoming from the work of Zaimis and her colleagues (personal communication), who have shown that when suxamethonium is given to fowls previously treated with mecamylamine the normal response of neck retraction is changed to head-drop and the rigid extension of the limbs is replaced by flaccid paralysis. There is in fact a shift from depolarization block to competition block.

Personal experience, both clinical and experimental, suggested that trimetaphan camphorsulphonate extended the duration of the neuromuscular block produced by gallamine. This was attributed to the lowered renal blood flow and the subsequent reduction in the excretion rate of gallamine. A weak curare-like action has previously been reported in dogs given trimetaphan (Randall...
et al., 1949). This was interpreted as evidence of a reduced blood flow through the limb muscles subsequent to a fall in arterial pressure rather than to a direct action at the motor endplate. It is apparent, however, that in certain circumstances trimetaphan camphorsulphonate is capable of a weak neuromuscular blocking action (fig. 2B) which is independent of the state of the blood pressure.

Whatever the mechanisms involved it is certain that if similar changes can be demonstrated in man the potential hazards of anaesthesia will be increased. Admittedly, the factor of species difference introduces an element of doubt, but until definite evidence is forthcoming, it is surely wise to avoid the use of such combinations of drugs except under strictly controlled conditions where the risk to the patient is minimized and where the results can be carefully assessed.

**SUMMARY**

Hexamethonium is shown to produce neuromuscular block in cats previously given mecamylamine.

Trimetaphan camphorsulphonate is shown to have a similar but less marked action at the motor endplate under the same conditions.

The mechanism by which mecamylamine modifies the action of these ganglion blocking agents is discussed.

Attention is drawn to the potential risk if similar influences prevail in man.

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