DESCENDANTS OF DECAMETHONIUM*

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With perhaps one exception, decamethonium has been the parent of the main neuromuscular blocking agents introduced, since its discovery, for clinical trial as muscle-relaxants. Its descendants (see fig. 1) include suxamethonium (succinylcholine), suxethonium (362 I.S.), Ro 3-0386 and Laudolissin. The exception (fig. 2) is benzoquinonium (Mytolon), which was derived from an experimental anti-bacterial substance by the chemical process of quaternization (Hoppe, 1951). Since benzoquinonium has the practical disadvantage of causing excessive salivation and bronchorrhea (Foldes, 1951; Robertazzi, 1951), the new relaxants at present in use appear all to be descendants of decamethonium.

Chemists have found decamethonium a useful starting point because it combines simplicity of structure with high potency. Its molecule not only represents one of the simplest forms imaginable to block the neuromuscular junction potently; but it is the most powerful relaxant yet used clinically, being two to three times as strong as d-dimethyl-tubocurarine and four to five times as d-tubocurarine itself. In developing new compounds, some of the simplicity and potency of decamethonium can be comfortably exchanged for other desirable features which this drug lacks.

That decamethonium does lack certain desirable features is evident from its comparative failure to win favour.

* Based on a paper read to the Yorkshire Society of Anesthetists, Leeds.
Descendants of Decamethonium

(a) Decamethonium iodide; (b) Suxamethonium chloride; (c) Suxethonium iodide; (d) Ro 3-0386; (e) Ro 2-4161; and (f) Laudolissin.
among anaesthetists, in spite of its freedom from unwanted side-effects. This is probably because, while being a comparatively long-acting compound, it yet has no satisfactory antagonist. The failure of decamethonium to win a place in everyday use, and the practical requirements outlined to me by some anaesthetists, led me to conclude (Collier, 1951) that clinical needs existed for new relaxant drugs of two types:

"(i) A really short-acting relaxant . . . preferably antagonized by neostigmine.

(ii) A relaxant acting for as long as or longer than d-tubocurarine, but without liability to its side-effects, and antagonized by neostigmine."
Descendants of Decamethonium

It is under these two heads that the newer muscle-relaxants may now conveniently be considered.

It has been found that drugs approaching both these types can be developed from the pattern of decamethonium by suitable changes in the molecule. In making changes, chemists can either alter the linking chain, or the end-groups, or both. Modification of the chain can produce ultra-short-acting compounds, of which suxamethonium is the most important. Such compounds, however, are not antagonized by neostigmine and they owe their convenience and safety to their shortness of action. Modification of the end-groups, on the other hand, can produce true curarizing drugs, antagonized by neostigmine, such as Laudolissin.

ULTRA-SHORT-ACTING RELAXANTS

Suxamethonium

Shortly after the discovery of decamethonium (Barlow and Ing, 1948; Paton and Zaimis, 1948), groups of workers in London (Buttle and Zaimis, 1949; Walker, 1950), in Rome (Bovet et al., 1949) and in Tuckahoe, New York (Phillips, 1949; Castillo and de Beer, 1950) showed independently that suxamethonium possessed high neuromuscular blocking activity. In spite of its relative high potency, suxamethonium was not developed for clinical purposes by any of these groups of investigators. Bovet preferred the corresponding bisethiodide (suxethonium iodide, 362 I.S.), which he considered might lack some minor side-effects anticipated from suxamethonium itself; and in London, and perhaps also in the United States, suxamethonium was not pursued further at the time, because it was thought to be too short-acting.

The need in anaesthesia for a really short-acting relaxant was too insistent, however, to allow suxamethonium to
remain long unused. The possibility of its employment was explored independently in Sweden (Thesleff, 1951; von Dardel and Thesleff, 1951), in Austria (Brücke et al., 1951) and in this country (Bourne et al., 1952). All these groups of workers found that the side-effects feared by Bovet were absent or negligible in man and that the effect of suxamethonium lasted for a much shorter time than the considerably more potent decamethonium. Here is a concrete example of the exchange of potency for the more desirable property of brief action.

**Duration of action**

In the vast majority of patients a completely effective dose of suxamethonium lasts between 2 and 4 min. (see Bourne et al., 1952, fig. 2). In a few individuals, however, as might be expected, the effect of suxamethonium lasts longer. Thus in 5 of 546 patients reported by Bourne et al. (1952) apnoea lasted between 8 and 15 min. Evans et al. (1952) found 2 long reactors (20 and 21 min.) in more than 400 patients. Richards and Youngman (1952) noted no prolonged apnoea in 250 patients and Foldes (1952) saw none in 400. Butt (1952) noted apnoea exceeding 6 min. in only one patient (21 min.) among 1,000. Of an aggregate therefore of 2,600 patients, apnoea exceeded 7 min. in only 8 and 21 min. in none. Apart from these series, however, isolated instances of more prolonged apnoea after suxamethonium have been reported (e.g. Gould, 1952; Love, 1952; Harper, 1952; Hewer, 1952; Grant, 1952; MacKay, 1952; Reid and Neill, 1952; Mayrhofer, 1952, and Wolfers, 1952). So far, in all reported instances of prolonged apnoea after suxamethonium, eventual recovery has been completely satisfactory.
Descendants of Decamethonium

Cause of prolonged action

Several possibilities, which have not always been excluded, should be considered in examining the cause of prolonged action. It is possible that manual ventilation helps to prolong apnoea through (i) acapnia (Richards and Youngman, 1952); (ii) the Hering-Breuer reflex (Gray and Rees, 1952) and (iii) potentiation of other drugs used in anaesthesia, such as thiopentone (Dundee, 1952). The associated possibility that drugs other than suxamethonium may cause the prolonged apnoea has been discussed by Durrans (1952) who gives reasons suggesting that the effect is due to depression of the respiratory centre. His view is supported by the finding of Barron (1952) that high doses of nikethamide terminated some prolonged apnceas after suxamethonium, since nikethamide is well known to antagonize central respiratory depressants. It is of interest that Ellis et al. (1952) find that suxamethonium, in common with other neuromuscular blocking agents, when given in large doses depresses the respiratory centre of the cat.

A third possibility is that other drugs used in anaesthesia may prolong the action of suxamethonium. We are exploring this by experiments in mice which have so far shown that drugs such as morphine, papaveretum, thiopentone and hexamethonium do not prolong the action of suxamethonium when their dose bears the same approximate relation to suxamethonium as it does in man. Doses either of papaveretum or of hexamethonium that are relatively very high in comparison with that of suxamethonium (25 to 1) do prolong paralysis in mice. Likewise, in a similar high ratio of doses, Xylocaine and, to a lesser extent, procaine prolong suxamethonium paralysis in mice.

After exclusion of doubtful instances, it seems certain that suxamethonium does occasionally have prolonged
action, but this is rare and is generally slight. The explanation appears to lie in the level of "pseudo"-cholinesterase in the patients' plasma, since both Bourne et al. (1952) and Evans et al. (1952) independently found that patients who recovered slowly from suxamethonium had abnormally low cholinesterase in their plasma, while patients recovering at the usual rate were normal in this respect. Evans et al. (1953) have provided further evidence in support of this view and answered objections to it.

The products of hydrolysis of suxamethonium in the body are of interest in connection with the problem of long reactors. Whittaker and Wijesundera (1952) find that the cholinesterase of horse-serum hydrolyses suxamethonium to choline and succinic acid via the succinylmonocholine.

**Practical approach to long reactors**

The questions naturally arise, since rare individuals show prolonged apnoea after suxamethonium, as to how this long reaction can be foreseen and dealt with. The following suggestions have been made.

1. Reduction of the doses of drugs liable to depress the respiratory centre and avoidance of hyperventilation.

2. Reduction to a minimum of the dose of suxamethonium used (Foldes, 1952).

3. Observation of special caution in patients likely to have (a) low plasma-cholinesterase—e.g. those suffering from starvation, liver disease or exposure to certain insecticides (Bourne et al., 1952); (b) spasms of skeletal muscle (Mayrhofer, 1952).


5. A preliminary test dose of suxamethonium.
6. A preliminary test dose of acetylcholine.

7. Use of an antagonist.

These suggestions may be considered in the order in which they have been given.

1. The evidence of Durrans (1952) and of Barron (1952) implicates central respiratory depression as the cause of the prolonged apnoeas seen after suxamethonium. It is therefore logical to reduce the doses of drugs such as papaveretum and thiopentone, as a means of preventing these occurrences.

2. Other things being equal, it is evident from the data published by Thesleff (1952) and by Day (1952) that in normal patients the larger the dose of suxamethonium the longer it lasts. Hence it is desirable to use the least dose of suxamethonium that will give the relaxation needed. This dose cannot be foretold in advance; but Bourne (1952) has agreed that lower doses than those he initially used are generally adequate.

3. Special caution should be observed when administering suxamethonium to sufferers from starvation, liver disease or insecticide poisoning; or possibly hypocalcaemia.

4. Routine measurement of plasma-cholinesterase might become a possibility, but at present it appears to be impracticable.

5. A preliminary test injection of suxamethonium would be difficult, especially as the drug should not be given to the conscious subject. Where, however, it is intended to give suxamethonium repeatedly or by intravenous drip, the first dose (for intubation) can be regarded as a test dose (Bourne, 1952).
6. A test dose of acetylcholine would be of little value, because it would be destroyed by the cell, or "true", cholinesterase, which has no appreciable effect on suxamethonium.

7. Although we found in mouse experiments that a relatively very high dose of aneurine antagonizes suxamethonium, it was not possible to show antagonism clinically with this compound. Theoretically the obvious antagonist is plasma-cholinesterase itself; and Evans et al. (1953) report its effectiveness in a few individuals. As Lehmann (1952) points out, fresh plasma or whole blood, which contains active plasma-cholinesterase, might be useful. A large transfusion would be needed, however, to raise appreciably the enzyme concentration of the recipient's plasma.

**Mode of action**

There seems no doubt that suxamethonium blocks the neuromuscular junction of man and of the cat by "depolarizing" the motor end-plate. That is to say, it induces a state of excitation that prevents further impulses being transmitted. Two views as to how this excitation arises have been suggested. One is that suxamethonium acts, like decamethonium, directly on the end-plate by mimicking the action of acetylcholine. This view rests on measurement by Paton and Vianna Dias (1949) of the electrical potential of the motor end-plate in relation to that of the rest of the muscle. Such measurement, as yet unpublished, shows that very small quantities of suxamethonium excite the end-plate, although relatively enormous quantities of neostigmine fail to do so. Another view, that suxamethonium acts indirectly, by inhibiting the destruction of acetylcholine, has been put forward by Evans et al. (1952); and Hall et
al. (1953) advance further experimental support, which is however based on work in dogs. Several difficulties arise in accepting this: (i) it is not easily reconciled with the unpublished observation of Paton and Vianna Dias; (ii) it seems unlikely from the figures of Evans et al. and from other evidence that the concentrations of suxamethonium effective in paralysing the human body are sufficient appreciably to inhibit cholinesterase; and (iii) twitches due to intravenous injection of suxamethonium in man appear without any latency, other than the circulation time, even in resting muscles.

**Stability**

The idea that suxamethonium is a very unstable compound perhaps arises through its rapid disappearance in the body and also its rapid destruction when mixed with thiopentone solution, which is alkaline. Suxamethonium chloride, on the contrary, forms a reasonably stable solution in saline, as the experiment illustrated in Table I shows.

<table>
<thead>
<tr>
<th>I.V. dose in μg. per kg.</th>
<th>Fresh solution</th>
<th>1 day</th>
<th>Solution stood 3 days</th>
<th>21 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>5/20</td>
<td>4/20</td>
<td>4/20</td>
<td>3/10</td>
</tr>
<tr>
<td>200</td>
<td>16/20</td>
<td>17/20</td>
<td>17/20</td>
<td>9/10</td>
</tr>
</tbody>
</table>

In this experiment the potency of the same 5 per cent solution of suxamethonium chloride was examined in mice immediately after it was made up and again after it had stood at room temperature on a windowsill for 1, 3 and 21 days. It will be seen from the table that after standing in these conditions the potency of the solution was not detectably altered.
Malone and Blayney (1952) find suxethonium to be rather less potent than suxamethonium and even briefer in action. It was first prepared (as 362 I.S.) by Bovet et al. (1949) at the Institute Superiore di Sanita in Rome and tried clinically by Valdoni (1949). Bovet initially preferred this compound to suxamethonium because he thought the latter might have certain unwanted side-effects, such as salivation and rise in blood pressure. Experience has failed to show that suxamethonium causes any salivation in man and, though rises in blood pressure have been observed (Bourne et al., 1952; Franks, 1952), very high doses are required to bring them about in anaesthetized patients.

Ro 3–0386

R. B. Taylor (1952) has reported the use of a heteropoly-methylene-bis-trimethylammonium di-iodide (Ro 3–0386) for softening electroconvulsions in man. This compound, which is derived from decamethonium by the replacement of two adjacent methyl groups of the linking chain by two sulphur atoms (Morrison, 1952), appears to be of higher potency but of slightly longer duration than suxamethonium. It would thus seem to be intermediate in potency and duration between decamethonium and suxamethonium. Another dithio compound, similar to Ro 3–0386 in structure and activity, was prepared and examined in Ware some years ago (E. P. Taylor, 1952b).

TRUE CURARIZING RELAXANTS

Molecular Form and Neuro-muscular Block

It is common to distinguish between relaxants of the decamethonium and of the curare type; but Bovet (1951)
has suggested that the distinction is one of degree. There are several reasons for agreement with this point of view. One is that decamethonium itself in some animals appears to have a dual action, one part of which resembles curare (Zaimis, 1952). Again d-tubocurarine has effects on denervated muscle like those of acetylcholine (McIntyre et al., 1945). In fact, since both decamethonium and d-tubocurarine affect the transmission of the nervous message by acetylcholine at the nerve-muscle junction, it is simplest to suppose that all three substances are absorbed initially on the same chemoreceptors of the motor end-plate (Bovet et al., 1951; Collier, 1951). The difference between decamethonium and d-tubocurarine may lie in the former compound carrying the process of mimicking acetylcholine a stage further than the latter. The view that the two types of relaxant are absorbed initially on the same receptors is strengthened by the finding that the peak length of the polyethylene chain for curarizing activity is about the same as that in the decamethonium series (Collier, 1952).

There are other reasons to suggest that the difference in mode of action between decamethonium and d-tubocurarine is one of degree. One reason is the existence of compounds intermediate between these two relaxants, such as benzoquinonium. Hoppe (1951) found that benzoquinonium was weakly antagonized by neostigmine, and Randall (1951) that it was weakly potentiated by Tensilon, which is an antagonist of d-tubocurarine. This property, however, may be associated with the anticholinesterase activity of benzoquinonium. Another reason is provided by several instances of chemical modification that produce a change from decamethonium to curare type of action. This change can be brought about, for example, by replacing a pair of methyl groups at each end of the decamethonium molecule by a tetrahydroquinolinium (Collier and Taylor, 1949), or
by a tetrahydroisoquinolinium ring (Taylor and Collier, 1950, 1951), as in Laudolissin (fig. 1). Randall (1951, 1952) provides further instances. For example, replacing one methyl group at each end of decamethonium by a nitrobenzyl group produces the true curarizing substance Ro 2–4161 (fig. 1). Likewise, replacing each of the terminal benzyl groups of benzoquinonium by a nitrobenzyl group, as in Ro 2–4395 accentuates the curarizing activity (see fig. 2). Again, Zaimis (1952) finds that the tridecamethylene homologue of decamethonium exhibits curarizing properties in the cat and chick.

**Laudolissin**

Laudolissin is a long-acting curarizing agent. It appears to be the first of the descendants of decamethonium to combine these properties with high potency and lack of side-effects. Bodman (1952) reported that a group of volunteers found it indistinguishable, subjectively and objectively, from d-tubocurarine when given in equipotent dose, except that Laudolissin lasted slightly longer. In animal experiments, also, Laudolissin closely resembles d-tubocurarine, but it exhibits considerably less hypotensive and ganglion-blocking activity (Collier and Macauley, 1952).

In 236 major surgical operations Bodman, Morton and Wylie (1952) found that Laudolissin gave adequate relaxation without side reactions, such as changes in pulse rate, blood pressure or electrocardiogram, salivation, bronchoconstriction or haemolysis. Clinically, it was clearly antagonized by neostigmine, as might have been expected from experiments in animals and in volunteers.

These authors also noted certain differences from d-tubocurarine. Laudolissin was somewhat slower in onset and longer in duration of action. Because of its slow onset and because the vocal cords were not thoroughly relaxed, Bod-
Descendants of Decamethonium

man and his colleagues used suxamethonium for intubation. Suxamethonium was also sometimes used to procure additional brief relaxation at the end of a long operation. Used in this way suxamethonium did not retard subsequent recovery from Laudolissin.

The experience of these anaesthetists shows that Laudolissin can be used successfully as a long-acting curarizing agent in major surgical operations. A wider trial is yet needed before its value can be fully assessed in relation to other drugs.

SUMMARY AND CONCLUSION

Consideration of the new muscle-relaxant drugs shows that much of recent work stems from the discovery of decamethonium. Progress from decamethonium has been made by exchanging some of its simplicity and potency for more desirable properties, such as brevity of action, as in suxamethonium, and capacity to be antagonized by neostigmine, as in Laudolissin.

ACKNOWLEDGEMENTS

I should like to thank Miss M. P. Hatton for technical assistance in the experiments described. Dr. R. I. Bodman, Dr. J. G. Bourne, Dr. H. J. V. Morton, and Dr. E. P. Taylor have kindly read the typescript and Dr. H. Lehmann and Dr. W. D. M. Paton discussed certain points. I am indebted to the Directors of Messrs. Allen and Hanburys Ltd., for permission to publish this paper.

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Descendants of Decamethonium