THE DEVELOPMENT AND USE OF MUSCLE RELAXANTS
IN THE UNITED KINGDOM

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British anaesthetists were introduced to the use of curare in anaesthetic practice by Gray and Halton in 1946, when they described a series of over a thousand patients anaesthetised with the assistance of d-tubocurarine chloride. This pure crystalline alkaloid (synthesised in London by Harold King in 1935) was used because Intocstrin, the curare preparation originally used by Griffiths and Johnson was difficult to obtain. Shortly after this, Prescott, Organe and Rowbotham reported on the use of Intocstrin in 180 cases and described their observations of the effect of this substance on human volunteers. A later report by Gray surveyed over 8,000 cases of the administration of d-tubocurarine and in this it was stated that "Griffiths ... revolutionised our specialty by removing for all time the need for deep anaesthesia." It has been emphasis on the use of light anaesthesia that has really influenced the development of their clinical application by anaesthetists in Britain. The recognition of the muscle relaxing properties of mephanesin (Myanesin) led Mallinson in 1947 to attempt introduction of this substance into clinical practice as a synthetic substitute for the naturally occurring curare alkaloid. Unfortunately, subsequent work showed that mephanesin was not satisfactory because of a high incidence of venous thrombosis and haemolysis probably due to the irritant propylene glycol in which mephanesin was dissolved. A further disadvantage was that relaxation produced by this compound was not as profound or controllable as that with d-tubocurarine so that a rather deeper plane of anaesthesia was necessary. The search for other synthetic relaxants was, however, continued by both pharmacologists and clinicians. By 1949 decamethonium and gallamine triethiodide (Flaxedil) had been submitted to clinical trials.

The latter had been synthesised as early as 1947 in France. Also in 1949, Collier and Taylor synthesised and described the paralytic action of a new nondepolarising drug laudexium (Laudolissin). However, it was not until 1952 that the detailed pharmacology of this substance was worked out and the preliminary clinical trials reported by Bodman and others. It was Italian workers who in the International Congress held in London in 1951 introduced the revolutionary, short acting relaxant, succinylcholine (suxamethonium). The conception that esters of choline, especially the succinyl derivatives, might be useful as neuromuscular blocking agents had been proposed and confirmed simultaneously on the continent and, independently, in Britain.

Since the introduction of these drugs, the research of British anaesthetists has been chiefly directed towards three aspects of their activity: (1) variations in the sensitivity of patients to them, (2) the so-called "dual effect" of the depolarising agents, and (3) the reversal of the nondepolarising anticholines.

HYPERSENSITIVITY AND TOLERANCE

Considerable interest has been taken by British clinicians in factors which influence the sensitivity of patients to relaxants. Several workers have described an "idiosyncrasy" to nondepolarising agents exhibited by a small number of patients. These isolated instances are sufficiently well documented to be convincing and the sensitivity appears to be unrelated to disease. 'Idiosyncrasy' is recognised as a term indicating that the cause is unknown. Because of this, one of us (T.C.C.) has always advocated the use of a small test dose equivalent to 0.5 mg. per 7 kg. to a maximum of 5 mg. of d-tubocurarine when nondepolarising relaxants are being used. This test dose serves also to uncover latent
myasthenic tendency \textsuperscript{26} and sensitivity due to factors such as electrolyte imbalance in cases of gastric and intestinal obstruction.

In 1950 Rees \textsuperscript{27} stated that he considered \textit{d}-tubocurarine chloride contraindicated in the new born infant. Stead,\textsuperscript{28} who recorded the respiration of these infants, demonstrated a myasthenic type of reaction to relaxants in that the neonate is hypersensitive to nondepolarisers and tolerant to the depolarising drugs.

More doubtful is the sensitivity reported in cases of carcinoma of the bronchus associated with neuropathy.\textsuperscript{29} Tolerance to nondepolarising relaxants on the other hand has been demonstrated to occur after prolonged dosage with powerful analgesic agents and in the presence of severe liver damage.\textsuperscript{25, 30}

The fact that “long reactors” to succinylcholine may occur was first established by Evans\textsuperscript{31} and his colleagues and by Bourne\textsuperscript{32} and his co-workers in 1952.

\textbf{DUAL EFFECT}

The description and elucidation of the reaction which has been described as a “dual response” of the end-plate to depolarising drugs has exercised British pharmacologists and anaesthetists over the past seven years. Zaimis\textsuperscript{33} was the first to suggest that these drugs may affect the end-plate initially by producing depolarisation but later by an effect resembling that of the competitive inhibitors or nondepolarising drugs. She also stressed that drugs which caused depolarisation in man may have a different action in other species. For example, although decamethonium was a depolarising drug in man, it acted by competitive inhibition in monkeys, rabbits, hares and dogs. At the same time (1952) Churchill-Davidson and Richardson\textsuperscript{34, 35} showed by electromyography that whereas the myasthenic patient was resistant to the depolarising drug decamethonium, if the dosage was large or repeated these patients became sensitive and the prolonged paralysis which then resulted was reversible by neostigmine. Hunter\textsuperscript{36} and, in America, Harris and Dripps\textsuperscript{37} had already reported an increasing tolerance to decamethonium following repetition of its administration. They also reported that after repeated doses, the muscle paralysis persisted for longer than estimated and was reversible by neostigmine. Brennan\textsuperscript{38} demonstrated the same phenomenon following the administration of succinylcholine by the continuous drip method. Paton\textsuperscript{39} has recalled that a similar state of affairs has been demonstrated with acetylcholine and suggested that it should be regarded “not as a curarisation but as a developing refractoriness or accommodation of the receptors comparable perhaps to the process which leads to ‘inactivation’ of the sodium pump, if an excitable membrane is held in the depolarised state.” Observations on the action of neostigmine in myasthenic patients confirm this suggestion. Myasthenic patients treated with anticholinesterase drugs in excessive dosage or over a prolonged period may pass into myasthenic crises because the end-plate has become tolerant to the natural depolariser, acetylcholine. If such an end-plate were rested it might recover its normal sensitivity. This “rest” can be achieved by treatment with \textit{d}-tubocurarine. Churchill-Davidson and Richardson\textsuperscript{40} have described dramatic improvement in a patient treated for eight days by large doses of \textit{d}-tubocurarine, sedation and mechanical respiration.

Whatever may be the ultimate explanation of the phenomenon of “dual block” the fact that it occurs has influenced anaesthetists in Britain to avoid the use of depolarising agents for patients requiring muscular relaxation for more than the shortest period.

\textbf{USE OF ANTIDOTES}

Antidotes to \textit{d}-tubocurarine have been more widely used in England and Europe than in America. This is due to the fact that larger doses of the paralysant drugs are more generally used. It is surprising to find that one of the earliest British papers\textsuperscript{4} suggested that “if Prastigmine is to be effective, doses of the order of 5 mg, or more must be used” and advocated administering with the antidote 1.3 mg. of atropine to “balance” the marked parasympathomimetic effects of such large doses.

Until about 1951 it was common practice to administer atropine and neostigmine simultaneously mixed in the same syringe. However, in 1949 there were three reports of cardiac arrest, all associated with this practice and all occurring in patients in whom anaesthesia was maintained by cyclopropane. It was suggested, in light of work demonstrating the ini-
tial slowing effect of subcutaneous atropine on the heart, that even when given intravenously it might produce an initial slowing which would summate with the bradycardia caused by neostigmine and be conducive to cardiac arrest.\(^{41-45}\) However, Hunter\(^{46}\) showed that intravenous atropine did not cause an initial slowing but an immediate tachycardia and that the effect of 1.3 mg. of atropine with 2.5 mg. of neostigmine was to produce an initial tachycardia followed by bradycardia. He suggested that if the bradycardia decreased to less than 60 beats per minute a further dose of 0.65 mg. of atropine should be injected intravenously. His conclusion was that the combined injection of these two drugs was safe. More recently Morton and Thomas\(^{47}\) have shown that intravenous atropine may cause initially either a tachycardia or a bradycardia followed by an increase in the pulse rate, according to the dose and speed of injection of the drug. In view of this, the majority of clinicians would probably agree with the writers that it is safer to administer the atropine initially and only follow it with neostigmine when there is obvious cardiac acceleration. In view of the differences of opinion which exist regarding the administration of atropine and neostigmine, it is worthwhile emphasising that certain precautions are necessary. The writers believe that the amounts of atropine which are being given according to table 2 are inadequate. We would regard 0.02 mg./kg. up to a maximum of 1.3 mg. as a proper dose to be given before the injection of neostigmine. If a parasympathomimetic inhalation agent has been used to maintain anaesthesia, it should be eliminated before the neostigmine is given. The neostigmine should not be administered until the patient has developed a tachycardia following the injection of atropine. In cardiac surgery or in the very ill patient this increase in heart rate may give rise to concern. In these cases, therefore, vagolytic and vagotonic drugs may be "titrated" one against the other so that at no time does a detrimental degree of tachycardia or bradycardia arise. It is advisable not to inject neostigmine until spontaneous respiration has been established so that the effects of this drug may be observed.

We consider it safer to use neostigmine always when nondepolarising relaxants have been administered. In the experience of one of us (T. C. G.) extending over fourteen years during which nondepolarising relaxants have been used for all abdominal and thoracic operations and reversed in every case, there have only been two seriously disturbing incidents. One patient had a transient cardiac arrest and the other developed status asthmaticus. Both of these incidents occurred when the neostigmine and atropine were given as a single injection.

Attempts to find satisfactory substitutes for neostigmine have so far failed, and the clinical trials of edrophonium (Tensilon) by Doughty and Wylie\(^{48}\) and Hunter\(^{49}\) did not provide an answer. The duration of its action may be shorter than the duration of the paralysis caused by the relaxant drug and a patient in whom the curarisation has appeared to be reversed by edrophonium may, after 15 minutes or so, relapse into a partially paralysed condition. The use of this drug is now largely confined to diagnosis in conditions of prolonged apnoea or in myasthenic crisis, when its short action may be advantageous and when it may elucidate the nature of the paralysis which exists.

For some time there has been a recognition that all patients did not respond equally well to the antagonistic drug, but more often than not this was attributed to the poor condition of the patient rather than to any specific sensitivity to the relaxants. Hunter\(^{50}\) in 1956 drew attention to this when he reported on 6 patients who had shown continued respiratory depression despite the administration of neostigmine and, since this publication, so-called "neostigmine resistant curarisation" has been a term increasingly used and abused. Hunter described his patients as "elderly and dilapidated," and further factors in common were that five out of the six were anaesthetised by junior personnel and all six received both depolarising and anti-depolarising drugs. Moreover, in all the patients, electrolyte imbalance was either demonstrated or suggested. In some of these patients the paralysis was diminished by the administration of potassium. Following on this report Foster\(^{51}\) proposed the hypothesis that in hypokalaemia there might be not only sensitisation of the myoneural junction to the non-depolarising relaxants but also a breakdown of
the barrier between the central synapses and the extracellular fluid—blood-brain barrier. This might result, he suggested, in the penetration of large molecules, such as the relaxants, into the central synapses with consequent depression of the central nervous system. His observation was that such patients not only remained paralysed but also asleep when the sole anesthetic, nitrous oxide, was withdrawn. In such cases neostigmine was of no benefit.

There is, however, no doubt that many of the cases of respiratory depression or apnoea attributed to the relaxants have in fact a much simpler aetiology, and the depression can be accounted for by mechanical factors such as disorders of pulmonary ventilation, producing carbon dioxide lack or excess, or by errors in the administration of drugs.\textsuperscript{25}

Influence of Relaxants on Anaesthetic Technique

With the exception of nitrous oxide and ethylene the general anaesthetic drugs are potent depressants affecting the central nervous system, the cardiovascular system, both directly and indirectly, and the parenchymatous organs. After the work of Griffith and Johnson\textsuperscript{3} the vista of a selective depression of the nervous system was opened, for d-tubocurarine chloride was a drug affecting to all intents and purposes one group of synapses, the myoneural junction. Nitrous oxide, an anaesthetic producing essentially one effect—narcosis—was already available. Some anaesthetists in Britain began to think in terms of the components of anaesthesia each of which might be produced as and when required and in just the intensity required. Thus was put forward the “triad” concept in which anaesthesia was looked upon as consisting of three desirable effects, narcosis, relaxation and analgesia, each of which might be produced in varying intensity by the exhibition of the suitable agent.\textsuperscript{5} The first two components of the “triad” can be produced with single agents and are clearly understood, but the latter, analgesia, has given rise to some anxiety and speculation. The fear that lightly anaesthetised patients, in whom the central nervous system and autonomic activity were not sufficiently depressed might respond to surgical stimuli is in line with the thought of Crile.\textsuperscript{8} In the United States, Neff, Mayer and Perales\textsuperscript{4} suggested that light anaesthesia might usefully be supplemented by analgesic agents such as meperidine. This suggestion has been popular in Britain since its introduction by Mushin and Rendell-Baker.\textsuperscript{55} It has seemed to the writers, however, that this concept has very little reasonable basis and probably no experimental foundation. “Analgesia” signifies freedom from pain. Pain implies a conscious appreciation of an unpleasant sensation. Clearly the patient who is asleep, that is narcotic, cannot experience pain and in this sense is analgesic. If “analgesia” is intended to signify a freedom from reflex responses to stimuli, then the matter requires further consideration. The reflex responses presumably may be both in the autonomic and central nervous systems. There is no evidence that meperidine or other analgesics have any selective effect on the autonomic responses in which anaesthetists are interested, as for example, traction on the mesentery during abdominal surgery or vagal reflexes during mediastinal dissection. In fact, during deep ether anaesthesia, traction reflexes may be demonstrated and it seems likely that they may be elicited in every operation. Their intensity will vary with the depth of anaesthesia, and the administration of analgesics is merely one way of deepening anaesthesia.

The central nervous reflexes under anaesthesia may be divided into two groups: firstly, active movement in response to a stimulus. This reflex will clearly be damped by a dose of relaxant. The paralysis alone, however, is unlikely to be sufficient so to paralyse the patient as to make him unable to move. It has been suggested that a dose of d-tubocurarine of from 200 to 400 mg. would be required for this.\textsuperscript{56} The paresis caused by a much more moderate dose of relaxant added to the analgesic effects of nitrous oxide will, however, achieve immobility. The second central nervous responses are those which are less easily definable and observed. Loder\textsuperscript{57} described three reactions which may be exhibited by patients who are inadequately anaesthetised; namely, sudden hypotension with pallor and bradycardia following visceral traction, pallor and sweating with an unchanged blood pressure, and, postoperatively, mental exhaustion and slowed cerebration. Others do not consider these effects to be any more common under
light anaesthesia. A recent study has suggested that patients can be adequately anaesthetised for extensive abdominal surgery with nitrous oxide and oxygen only, combined with a relaxant, provided that pulmonary ventilation is increased sufficiently to produce a respiratory alkalosis. The hypothesis was suggested, and supported by reference to the work of several neurophysiological authorities, that the hypocarbia produced by pulmonary hyperventilation depressed the reticular activating system of the midbrain and thereby had the effect of deepening the narcosis and increasing the protection from undesirable reflexes.

The over-all effect of the introduction of relaxants in Britain has been to encourage the use of much lighter anaesthesia and the practice of anaesthetists varies from those who not uncommonly use nitrous oxide only, with full relaxation, to those who use moderately deep anaesthesia with smaller doses of relaxant.

THERAPEUTIC USES

The use of d-tubocurarine in cases of poliomyelitis and tetanus is well known. More recently, however, this drug has proved to be of value in children suffering from convulsions associated with hyperpyrexia. Rees has noted a fall in body temperature in children who are anaesthetised by a technique which includes the use of relaxants and control of the respiration. In Britain this finding has been applied in the treatment of salicylate poisoning, status epilepticus and convulsions associated with oliguria.

Succinylcholine is commonly used in electroconvulsive therapy and tetanus. In 1958 its use was described in the treatment of acute respiratory infections of the older infant when tracheo-bronchial aspiration of secretions through an endotracheal tube played an important part in re-establishing the airway and full ventilation.

SAMPLE SURVEY OF USE OF RELAXANTS FOR ANAESTHESIA IN THE UNITED KINGDOM

Impressions are notoriously fallacious, and while it may be one individual's belief that a particular method of using the relaxants is that followed by his colleagues, factual information may give a different picture. There is certainly the impression that practice in Britain varies from that in the United States in two particulars, namely, that British anaesthetists use larger doses of relaxants and a lighter plane of anaesthesia. Information regarding dosage received from the teaching centres in the United Kingdom indicates that when d-tubocurarine is used in adults for abdominal surgery, the dose is never less than 15 mg.; it is most usually between 30–45 mg. and not infrequently up to 70 mg. or more. An attempt has been made to acquire more definite information as to the usual way in which British clinicians use these drugs and on such factors as the administration of neostigmine and the use of controlled or assisted pulmonary ventilation. Questionnaires were sent by the writers to a random selection of anaesthetists throughout Britain. Randomisation was achieved by selection of every third anaesthetist appearing in the list of Fellows of the Association of Anaesthetists of Great Britain and Ireland. The following are the questions asked and the answers received.

Questionnaire

What percentage of your patients undergoing general anaesthesia receive relaxants.—(a) For abdominal surgery? (b) For thoracic operations? (c) For body wall surgery including herniae and haemorrhoids? (d) For other operations? (Please specify)

The answers to this question are detailed in table 1.

Ninety-two of 104 anaesthetists answering administered relaxants for over 90 per cent of their abdominal surgery, 92 out of 97 for over 90 per cent of their thoracic surgery and a somewhat small number (46 of 95 answering) for over 90 per cent of minor operations on the body wall.

Do you use short acting relaxants for intubation when muscle paralysis is otherwise not required? Always?

One hundred and nine satisfactory replies were received, 100 of these indicating that relaxants were used for tracheal intubation. Forty-six of them used relaxants in all cases requiring intubation whereas the other 54 anaesthetists used them, but not invariably. It was clear from the replies that those answering did not include anaesthetics for children.
TABLE 1

Results of Questionnaire Sent to Anaesthetists Throughout Britain Concerning Use of Relaxants

<table>
<thead>
<tr>
<th>What Percentage of Your Patients Undergoing General Anaesthesia Receive Relaxants for:</th>
<th>Satisfactory Answers</th>
<th>100%</th>
<th>90-100%</th>
<th>More Than 80%</th>
<th>More Than 50%</th>
<th>Less Than 50%</th>
<th>Nil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal surgery</td>
<td>104</td>
<td>67</td>
<td>25</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Thoracic surgery</td>
<td>97</td>
<td>84</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Body wall surgery, including herniae and haemorrhoids</td>
<td>95</td>
<td>28</td>
<td>18</td>
<td>11</td>
<td>19</td>
<td>14</td>
<td>5</td>
</tr>
</tbody>
</table>

What relaxant is most commonly used for long cases in your hospital?

One hundred and three satisfactory answers were received. Ninety-six of the 103 anaesthetists reported the use of nondepolarising agents as the most common and only 7 the depolarisers. This is confirmation of the impression that succinylcholine or other depolarising agents are not used extensively in Britain for this purpose.

When relaxants are used, do you favour:—(a) The lightest plane of "unawareness" (unconsciousness) plus full dosage of relaxant? (b) Moderate depth of anaesthesia with smaller doses of relaxant? (c) Routine use of neostigmine and atropine? (d) Occasional use of neostigmine and atropine?

One hundred and one satisfactory answers to questions (a) and (b) were received. It was clear that 55 of these anaesthetists used the lightest plane of anaesthesia, whereas 51 preferred moderate anaesthesia. Of the 51 who used moderate anaesthesia, 20 used the lightest plane of anaesthesia if it seemed indicated. This gave an interesting and probably accurate picture of the practice in this country. It can be seen that 75 per cent of those answering considered the very lightest plane of "unawareness" a reasonable technique and approximately 55 per cent aim to use it always.

One hundred and seven satisfactory answers were received concerning the use of neostigmine. Thirty-two of those replying used this antidote routinely after nondepolarising agents (3 of these routinely only when d-tubocurarine was being used). A further 15 used it almost always, making a total of 47 using neostigmine routinely or very frequently. Fifty-seven used the antidote occasionally, 2 almost never and 1 never.

Very nearly 50 per cent therefore almost always reversed d-tubocurarine chloride or gallamine.

Have you seen any serious or disturbing effects after giving neostigmine if it has been preceded by atropine?

One hundred and two answered this question satisfactorily, of whom 58 had not seen serious sequelae and 44 had; 20 of the latter

TABLE 2

Results of Questionnaire Concerning Doses of Atropine and Neostigmine Used

<table>
<thead>
<tr>
<th>What dose of atropine do you usually use?</th>
<th>Gr. 1/200</th>
<th>Gr. 1/100</th>
<th>Gr. 1/75</th>
<th>Gr. 1/50</th>
<th>Gr. 1/25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of satisfactory answers</td>
<td>1</td>
<td>37</td>
<td>25</td>
<td>25</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What dose of neostigmine do you usually use?</th>
<th>0.5-1.25 mg.</th>
<th>1.25 mg.</th>
<th>1.25-2.5 mg.</th>
<th>2.5-5 mg.</th>
<th>5 mg.</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of satisfactory answers</td>
<td>12</td>
<td>32</td>
<td>23</td>
<td>10</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>
TABLE 3
THE FOLLOWING QUESTIONNAIRE WAS CIRCULATED TO THOSE ANAESTHETISTS WHO HAD REPORTED CASES OF CARDIAC ARREST FOLLOWING THE INJECTION OF ATROPINE AND NEOSTIGMINE

<table>
<thead>
<tr>
<th>Case</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of atropine</td>
<td>0.65 mg.</td>
<td>0.65 mg.</td>
<td>0.65 mg.</td>
<td>0.65 mg.</td>
<td>0.65 mg.</td>
</tr>
<tr>
<td>When it was given relative to dose of neostigmine</td>
<td>Same time</td>
<td>5 minutes before</td>
<td>After pulse had risen to 100</td>
<td>4 minutes before</td>
<td>4 minutes before</td>
</tr>
<tr>
<td>How much neostigmine was given?</td>
<td>2.5 mg.</td>
<td>2.5 mg.</td>
<td>2.5 mg.</td>
<td>1.5 mg.</td>
<td>2.5 mg.</td>
</tr>
<tr>
<td>How long after injection of neostigmine did cardiac arrest occur?</td>
<td>1-2 minutes</td>
<td>Within 2 minutes</td>
<td>2 minutes</td>
<td>Immediately</td>
<td>Within 1 minute</td>
</tr>
<tr>
<td>Were the doses divided?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>What was the general anaesthetic used?</td>
<td>Cyclo.</td>
<td>N₂O + meperidine</td>
<td>N₂O + largactil</td>
<td>N₂O + meperidine</td>
<td>N₂O + trichloroethylene</td>
</tr>
<tr>
<td>Was cardiac massage done?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No (only by external means)</td>
</tr>
<tr>
<td>Did the patient recover?</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Age in years</td>
<td>38</td>
<td>78</td>
<td>39</td>
<td>72</td>
<td>Middle aged</td>
</tr>
</tbody>
</table>

had seen bradycardia, 21 profuse salivation and 5 reported cardiac arrest.

An attempt was made to clarify the relationship between the administration of neostigmine and the occurrence of cardiac arrest by means of a second questionnaire, which will be discussed later (table 3).

Table 2 gives some idea of the range of doses of atropine and neostigmine used.

When relaxants are used, do you favour:—(a) Controlled respiration? (b) Assisted respiration?

One hundred and three satisfactory answers were received. Fifty-five used controlled respiration, 18 favoured assisted respiration and 30 used both types as seemed to be indicated.

What drugs or agents do you prefer for maintenance of anaesthesia when relaxants are used?

One hundred and seven satisfactory answers to this question were received. Only 10 claimed to use nitrous oxide alone and 2 used nitrous oxide supplemented by a local analgesic block. Nitrous oxide in addition to supplementary meperidine was favoured by 33, supplementary meperidine or phenothiazine derivatives by 13, meperidine or inhalation agents by 30. Nineteen gave nitrous oxide and inhalation agents only and of these 19, 6 used halothane only. It was interesting to find that of the 110 anaesthetists replying to this questionnaire halothane was used by 27 at some time or other and one used halothane without relaxants for all cases.

Do you mix relaxants (e.g., suxamethonium [succinylcholine] for intubation followed by d-tubocurarine)?

Fifty-five of those asked this question mixed relaxants but of these, 25 only occasionally. Forty-eight never mixed relaxants.
Do you see transient hypotension after:
(a) d-Tubocurarine chloride? (b) Gallamine triethiodide? (c) Suxamethonium [succinylcholine]?

Sixty-two claimed to have seen hypotension following the administration of d-tubocurarine chloride, 77 following gallamine and 81 following succinylcholine. Many, however, remarked that they could not be sure that the hypotension was attributable to the relaxant and indicated that there were other factors, as for example, the previous administration of thiopentone or the initiation of artificial pulmonary ventilation.

A further 63 reported that they had seen a definite slowing of the heart beat after succinylcholine, and 42 that they had not.

This question was asked having in mind the similarity of succinylcholine to acetylcholine and the possibility of it exerting cholinergic effects. The writers know of two instances where the attempt to hasten induction with an irritant volatile agent (ether) by inflating the lungs with a high concentration of the anaesthetic during the apnoea following succinylcholine has resulted in cardiac arrest. The answer to this question would seem to confirm that it is a definite possibility that the slight cholinergic activity of succinylcholine might sensitize the pulmo-cardiac reflex.

In intestinal obstruction, do you use:—(a) Non-depolarising agents? (b) Depolarising agents? (c) Both in same patient?

One hundred and three satisfactory answers were received. Nondepolarising agents alone were used by 30, depolarising agents alone by 12, of whom 2 used a suxamethonium drip. Twenty-one of those who replied reported that they used either but did not mix the relaxants; 38 used both in the same patient. Of these 38, 3 used the relaxants rarely in such cases and 14 used them only for intubation. Three of those replying never used relaxants in cases of intestinal obstruction.

The fact that 100 of the 103 consultants still used relaxant agents seemed to indicate that with care the danger of 'neostigmine resistant curarisation' in these patients was not excessive and that the advantages of relaxants were judged to outweigh the disadvantages.

The second questionnaire provided information regarding the five cases of cardiac arrest which were reported following the administration of neostigmine and it is proposed to discuss them in more detail.

Case 1. This patient, who has been reported on before, was aged 38 and was gravely ill with an acute abdominal condition and chest signs suggestive of bilateral basal collapse or consolidation. At operation a perforated gangrenous appendix was removed and four pints of purulent fluid were aspirated from the peritoneal cavity.

Anaesthesia was maintained with nitrous oxide and cyclopropane. Relaxation was inadequate and serial doses of d-tubocurarine were required to provide satisfactory operating conditions. At the end of the operation the pulse rate was 100 per minute, but the tidal volume was inadequate. Atropine, 0.65 mg., and 2.5 mg. neostigmine were injected together, and 1–2 minutes later the pulse could not be palpated. Adrenaline, 0.5 ml., was given into the intravenous drip and cardiac massage started, with no effect.

Postmortem examination showed collapse of the lower lobes of both lungs, dilatation of the right side of the heart and widespread peritonitis. Cardiac arrest probably resulted from the combined vagomimetic effects of cyclopropane and neostigmine.

Case 2. The patient, aged 78, had had repeated haematemesis and during his first three days in hospital he was transfused with six pints of blood. Following a haemorrhagic episode during the ensuing emergency gastrectomy, his blood pressure fell to 80 mm. of mercury systolic. The infusion of four pints of blood restored this reading to 110 mm. of mercury.

Anaesthesia was maintained with nitrous oxide and meperidine and as the peritoneum was being closed, 0.65 mg. atropine was followed by the injection of 2.5 mg. of neostigmine. Within two minutes, the pulse could not be palpated and the patient died.

Postmortem examination demonstrated the coronary vessels to be atheromatous but there was no evidence of coronary thrombosis or pulmonary embolism. This patient suffered from asthma and therefore might have had a vagotonic diathesis. In view of the hypotension, a cerebral accident cannot be absolutely excluded.

Case 3. This patient, aged 39, had a perforated duodenal ulcer complicated by a moderate haematemesis. He had a history of alcoholism and his liver was enlarged three fingerbreadths below the costal margin. An emergency partial gastrectomy was performed without difficulty and anaesthesia was maintained with nitrous oxide and 12.5 mg. chlorpromazine and a relaxant. At the time of suturing the anterior rectus sheath, 0.65 mg. atropine was given and after the pulse rate had risen
to 100 beats per minute, 2.5 mg. neostigmine was injected. This was followed two minutes later by disappearance of the radial pulse. Cardiac massage through the abdominal wound was ineffective, but the heart beat was restored after the intracardiac injection of 5 ml., 1 in 1,000 solution of adrenaline.

The blood pressure, state of electrolyte balance, and time interval between the injections of atropine and neostigmine were not recorded in the case history and the actual cause of the cardiac arrest is not clear.

Case 4. This obese patient, aged 72, had a polyp removed from the colon through an abdominal incision.

Anaesthesia was maintained with nitrous oxide, a relaxant and a total of 75 mg. of meperidine. During the operation the pulse and blood pressure were 80 beats per minute and 100/80 mm. of mercury, respectively. Atropine, 0.65 mg., was given at the end of the operation and after a period of four minutes, during which the pulse was not observed, 1.5 mg. neostigmine was injected by a separate venipuncture. Immediately after this injection the radial pulse disappeared but after a short pause, a slow pulsation of about 10 beats per minute was observed in the neck, although the radial pulse remained impalpable. Atropine, 1.30 mg., was given intravenously and the radial pulse soon was detectable and increased to a rate of 40 beats per minute. Within the next half hour it had reached 52 beats per minute and then suddenly doubled to 104 beats per minute. This was followed by a period of auricular fibrillation which later reverted to normal rhythm.

According to the anaesthetist, the cardiac arrest in this patient was probably due to the atropine being inadvertently injected into the tissues and not exerting its full effect.

There was a complete heart block following the neostigmine which was not entirely relieved by 1.2 mg. of atropine. The auricular rate may, however, have been high from the time of the administration of the atropine—yet it was at least half an hour before all beats got through to the ventricle. Perhaps this condition of affairs in the elderly patient was exacerbated by cardiac ischaemia.

Case 5. The patient was middle aged and underwent a hysterectomy.

Anaesthesia was maintained with nitrous oxide, a relaxant and trichloroethylene. At the end of the operation the pulse rate and volume were satisfactory and 0.65 mg. atropine was given intravenously. Four minutes later, during which time the pulse was not observed, 2.5 mg. neostigmine was injected and followed within one minute by cardiac arrest. Cardiac massage was attempted by intermittent pressure in an upward direction on the abdominal musculature, with the abdomen closed. Eighteen minutes after cardiac arrest had occurred, procaine was injected into the heart and was followed within a few seconds by restoration of the beat to 40 per minute.

Anaesthesia in this patient was maintained with trichloroethylene and the effects following the neostigmine may have an aetiology similar to Case 1. It is fairly clear that this heart was never in a state of arrest.

Summary

The development of muscle relaxants is reviewed and their use in clinical medicine is described. Abnormal reactions such as hypersensitivity and tolerance, the dual effects of depolarising agents and the reversal of non-depolarising agents are briefly discussed.

Questionnaires, which were circulated to anaesthetists in the United Kingdom suggested that the usual technique was a full dose of relaxant agent with light anaesthesia. Relaxants were used in the great majority of patients undergoing abdominal or thoracic surgery and almost invariably for endotracheal intubation in other cases.

Seventy-five per cent of those answering found the very lightest plane of unawareness (unconsciousness) to be a useful technique and approximately 55 per cent used it always.

The serious or disturbing effects following injection of neostigmine as an antidote to relaxants is recorded. Five cases of cardiac arrest are detailed and an explanation offered as to their aetiology. Precautions are described which have been found necessary to avoid this complication when neostigmine is administered.

Fifty per cent of British anaesthetists always reversed the nondepolarisers and 100 of 103 answering used them in cases of intestinal obstruction in spite of the dangers of neostigmine resistant curarisation. This probably signifies that the danger is not excessive and the advantages of using relaxants in this condition are judged to outweigh the disadvantages.

References

44. Harris, I.: Action of digitalis and atropine on the peripheral blood pressure, Lancet 1: 1072, 1921.