Rajinder K Mirakhur

MD PhD FRCA

R K Mirakhur worked with Professor John Dundee and Dr RS Clarke (Reader in Anaesthetics) in Belfast. He was appointed senior lecturer in 1990 and to a personal chair in 1996. He is well known for his work on drugs that work at the neuromuscular junction. The neuromuscular junction is the point at which the South American ‘arrow poison’ curare works, and changed anaesthetic practice for ever. Curare competes with acetyl choline (ACh) at the junction between the motor nerve and the muscle. ACh facilitates the electrical impulse from the nerve to the muscle that causes a muscle to contract – curare blocks this and causes paralysis which makes surgery easier and means that anaesthesia can be ‘lighter’.

The following drugs cause paralysis – suxamethonium (depolariser) and the rest (non-depolarisers) pancuronium, vecuronium, atracurium, doxacurium, mivacurium, pipecuronium, rapacuronium and rocuronium.

The following are antidotes to non-depolarisers – neostigmine and edrophonium (the author has never seen this used in clinical practice, nor pyridostigmine), and now sugammadex. Atropine and glycopyrrolate prevent bradycardia and salivation secondary to neostigmine.

Mirakhur studied all these drugs, and more, and the technique used for studying the degree of neuromuscular blockade is the electrical stimulation of the nerve and the assessment of either the electrical effect on the muscle (EMG) or the physical movement of the muscle. The most commonly used patterns of electrical stimulation are the ‘so-called’ Train-Of-Four (TOF) or a tetanic stimulus. The former is a series of four electrical shocks which

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1 J F Nunn. British Journal of Anaesthesia. 1999; 83(6): 916
produces different patterns of muscle contraction, the greater the degree of paralysis the larger the difference between the 1\textsuperscript{st} and the 4\textsuperscript{th} muscle twitch, the T1-T4 ratio. A tetanic stimulus is a continuous series of electrical shock that cause a continuous muscle contraction.

This represents the number of papers published each year for the five different categories. 1987, 1993 and 1995 were the busiest years with 10, 10 and 14 paper respectively – an extraordinary rate of publication.

**Monitoring the Neuromuscular Junction**

Mirakhur’s first publication was in 1972; his first publication about neuromuscular blockade was in 1977, and the first specifically on the TOF ten years later in 1987. We will address the monitoring of the neuro-muscular junction first as it will create a foundation for the understanding of the other work.

**The ‘Train-of-Four’ (TOF)**

“Four consecutive stimuli are delivered along the path of a nerve, and the four responses of the muscle (T1, T2, T3 and T4) is measured in order to evaluate stimuli that are blocked versus those that are delivered” \textsuperscript{ii}

The first in 1987 [74] was to determine the TOF value that might indicate that another dose of muscle relaxant was necessary. The TOF

\textsuperscript{ii} http://medical-dictionary.thefreedictionary.com/train-of-four
responses were measured during recovery of neuromuscular block (paralysis) from atracurium, vecuronium, pancuronium and tubocurarine in order to quantify the height of T1 at which T2, T3 and T4 reappear. The 4th response (T4) appeared at approximately 30% height of T1 (previously thought to occur at 25%). It was recommended that the appearance of T3 (at about 25% of T1) be used as the trigger for a further dose of muscle relaxant.

In 1989 [90] fade in the TOF responses during onset of neuromuscular block was studied following administration of atracurium, vecuronium, pancuronium and tubocurarine. TOF ratios (T1:T4, fade) were measured at heights of T1 of 75, 50 and 25%. Fade increased as the height of T1 decreased; maximum fade at T1 of 25%. Vecuronium showed the least fade and pancuronium, atracurium and tubocurarine showed increasing fade. I'm unsure of the significance of these results.

Again in 1989, the fade in response to tetanic stimulation was studied [89]. Patients received atracurium, vecuronium, pancuronium and tubocurarine and tetanic fade was measured either at maximum block or at 10% recovery depending on the dose given. They stated that “If fade in response to tetanic stimulation represents a prejunctional effect ... that neuromuscular blocking drugs cannot be differentiated with respect to their relative prejunctional effects by measurement of tetanic fade...”

This was followed six years later by “Nondepolarizing neuro-muscular blocking drugs and train-of-four fade” [144]. Again, the aim was to assess differences in prejunctional effects of different relaxants but this time by measuring the TOF fade. It was concluded that the relative prejunctional effects of the relaxants were similar.

In the same year they assessed a new TOF monitor [141]. The TOF-Guard (it incorporated an accelerometer) was compared to a standard mechanomyographic (Myograph 2000). When the data were analysed using the Bland and Altman technique the 95% limits of agreement were not so close. They recommend that results from the TOF-Guard and the Myograph 2000 should not be considered equivalent but that the TOF-Guard was an improvement on tactile evaluation of the TOF.

Once again, in 1998, fade associated with TOF stimulation was examined [167]. The fade, which was thought to be due to a prejunctional
effect\textsuperscript{ii}, was assessed after doses of cisatracurium, atracurium, vecuronium, mivacurium or rocuronium. The TOF fade (during onset and offset of the block) was greater with a low dose of cisatracurium compared with all other relaxants. Cisatracurium, a stereoisomer of atracurium, had a slower onset of action than all the others but the duration of action was similar.

In 2001 Mirakhur wrote an editorial in the European Journal of Anaesthesiology on "Current developments in anaesthesia and neuromuscular transmission" [190].

We will now examine some of the muscle relaxants, many occur in various combinations in the same study.

**Curare** was first prepared in 1832
**Suxamethonium** was discovered in 1906 but the neuromuscular blocking properties were not described until 1949
**Pancuronium** was synthesised in 1964
**Vecuronium** was synthesised in 1973
**Atracurium** was synthesised in 1974
**Rocuronium** was introduced to clinical practice in 1994

The 1970s and 80s were a great time for NMB investigations.

**Suxamethonium**
The aspects of this depolarising agent that were investigated were its duration of action, the muscle pain that followed its use and associated biochemical changes, the pretreatments aimed at reducing this side effect, the management of associated bradycardia and the speed of onset compared with other agents. The latter is described in the following section on nondepolarisers.

Bradycardia occurs subsequent to administering a second dose and the effect is minimised by the use of antimuscarinic agents. In 1979 they wished to determine the efficacy of a new agent, glycopyrrolate, and compared it with the standard drug atropine, and so they studied patients who received intermittent doses of suxamethonium [16]. There were 28 patients in each group. "Although no statistically significant differences were seen, clinically,

\textsuperscript{ii} Bowman WC. Anesthesia and Analgesia 1980; 59: 935–43.
glycopyrrolate seems to afford better protection against the cardiac changes resulting from intermittently administered suxamethonium.” Considering the lack of statistical significance the following statement of efficacy seems unsupported.

Another early paper, in 1984, [49] was a report of the investigation of how long suxamethonium’s effect lasted in children, and the plasma cholinesterase activity. There was no difference in cholinesterase activity between children and adults but the apnoea was of shorter duration in children; it was suggested that this might have been due to their larger volume of extracellular fluid.

Suxamethonium is well recognised clinically by the muscle fasciculations that occur before paralysis, by the cellular release of creatine kinase (CK) and by the subsequent muscle pains, myalgia. Myalgia, although an unwanted, unpleasant side effect, was never considered a contraindication to the use of suxamethonium in clinical situations where its use was considered necessary. However a variety of measures were tried to reduce its severity: In 1983 pretreatment with vecuronium and neuromuscular blocking agents [42], in 1985 pretreatment with benzodiazepines [52] and in 1992/93 there were two papers on the biochemical changes associated with myalgia with various pretreatments [113, 119].

Pretreatment with nondepolarisers [42]: Patients were assessed for muscle pain on the 1st and 2nd postoperative days. Vecuronium, gallamine, tubocurarine or pancuronium were given one or two minutes before the suxamethonium. The incidence of pain was halved with pretreatment (from 40% to 20%).

Pretreatment with benzodiazepines: Several studies investigated these phenomena. Diazepam and midazolam failed to reduce the myalgia but tubocurarine was effective as a pretreatment; it virtually abolished fasciculation but it also reduced the intensity and duration of the neuromuscular block [52]. Changes in serum potassium, creatinine phosphokinase and aldolase were clinically insignificant...”.... although 5 out of 47 showed an atypical rise in creatinine phosphokinase.”

The release of creatine kinase was increased if suxamethonium and halothane were used together in chicks [100], this did not occur to a significant degree when the drugs were used individually. The release of CK was thought to be due to muscle damage, possibly by the involvement of phospholipases because it was prevented by chloropromazine. In a clinical study [113] myalgia
was reduced by tubocurarine, chlorpromazine and alphatocopherol but only those who received tubocurarine and chlorpromazine had reduced CK efflux. As expected intubation conditions were not as good with the pretreatment with tubocurarine. A further study examined the effect of hypnotic induction agents [119], propofol or thiopentone. It was concluded that they had no effect on myalgia or CK release.

How did the pretreatments affect the neuromuscular blockade produced by suxamethonium [124]? Those pretreated with chlorpromazine, alphatocopherol or aspirin had no significant difference in time to maximum block or time to recovery of twitch response compared with those receiving no pretreatment. Those pretreated with d-tubocurarine took longer to achieve maximum block and the duration was shorter compared with those receiving no pretreatment. It was considered that chlorpromazine was the better drug in the prevention of the side effects of succinylcholine.

A relatively uncommon clinical scenario with suxamethonium is where it is necessary to re-intubate a patient after a non-depolarising agent has been 'reversed' with an anticholinesterase. The speed of onset of and duration of action of suxamethonium was assessed after the use of edrophonium or neostigmine (both anticholinesterases)[145]. Both the onset and duration were prolonged and plasma cholinesterase activity was reduced after neostigmine.

Non-depolarising muscle relaxants

Combinations:

Some of the earlier Mirakhur studies compared all three commonly used agents – pancuronium, vecuronium and atracurium [57, 66, 81, 86]. It was a great time for NMB investigations. Many other drugs were studied but few survived – rocuronium was a survivor. (see below)

Quickness of onset and duration of action of muscle relaxants are of clinical significance. In 1985, in a group of patients over 65 years of age, pancuronium, vecuronium and atracurium were assessed. The intubating conditions were similar but the time to complete block was shortest with vecuronium at 4.3 minutes, the differences were not significant. Atracurium and vecuronium, however, lasted a significantly shorter time, 35 vs. 99 minutes.

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*iv ‘Reversed’: a colloquial term for the administration of an antidote for the termination of the action of a non-depolarising muscle relaxant.*
Other clinically significant factors were the effects on the cardiovascular system. In 1986 the heart rate, rhythm and systolic, diastolic and mean arterial pressures were measured after giving atracurium, vecuronium or pancuronium in the presence of a standard anaesthetic. Pancuronium caused an increase in blood pressure and heart rate (and a junctional rhythm). Vecuronium caused a fall in diastolic blood pressure and some patients had signs of histamine release after atracurium.

To try and reduce the time from the patient going to sleep and the time to intubation the idea of a small ‘starter’ dose followed by a later dose was considered. In 1988 this was studied with the three agents. Ten percent of the total dose was given four minutes before the second dose. There were no significant differences between the single and divided dose groups.

Dose-response curves are a mainstay of pharmacokinetics and in 1989 were constructed for atracurium, vecuronium and pancuronium in another set of elderly patients. There appeared no significant differences between elderly and young adult subjects.

From the table below it can be seen that the main interests were vecuronium, atracurium and rocuronium with mivacurium a runner up.

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The comparison studies will be left for the reader to examine but some of the more interesting studies will be described.
Plasma cholinesterase [45]

Plasmacholinesterase (aka pseudocholinesterase) is produced in the liver and found in the plasma. Levels may be reduced in advanced liver disease but only a reduction to <25% of normal will result in significant prolongation of neuromuscular blockade with suxamethonium. Levels can be affected by various anaesthetic agents and so plasma cholinesterase levels were measured following pancuronium and vecuronium. Pancuronium produced a significant reduction in the enzyme levels but vecuronium was without any significant effect. Vecuronium was always considered a ‘clean’ drug.

**Drug interactions:** these are always important. The following were studied: doxapram, H2 receptor blockers, beta-blockers, calcium channel antagonists and anticonvulsants.

Doxapram is a respiratory stimulant and it may be used at the end of anaesthesia to improve ventilation and therefore increase the elimination rate of volatile agents without affecting analgesia. There was some evidence that it enhanced neuromuscular block and so the rates of spontaneous and neostigmine-induced recovery were studied; the time from 25% recovery of T1 to 75% (RI). It was significantly longer after vecuronium in the presence of doxapram but there was no significant difference after atracurium or when neostigmine was administered. This suggested that only if neostigmine reversal was incomplete, a prolonged recovery might result [105].

H2 receptor blockers, cimetidine and ranitidine, are used to reduce gastric acid production. At the time there was “conflcting evidence about the occurrence of interactions between H2-receptor blocking agents and neuromuscular blocking drugs.” So a study of single oral doses of cimetidine or ranitidine on the neuromuscular blocking effects of vecuronium and atracurium was undertaken. With vecuronium the times following cimetidine were prolonged significantly but there were no significant differences in any of the variables following ranitidine pretreatment. Cimetidine pretreatment had no affect on atracurium [99].

Beta-blockers, calcium entry blocking drugs and anticonvulsants: The affects of these agents had been well studied on the neuromuscular junction and rocuronium at this time was a new drug and their effects with this agent needed to be assessed. Neuromuscular block was monitored during a fentanyl, propofol infusion and nitrous oxide anaesthetic. There were no differences in onset times. Apart from chronic therapy with anticonvulsant drugs, which
reduces the duration of action of rocuronium, there were no other significant changes [162].

**Intra-ocular pressure:** The effect on *intra-ocular pressure* was of importance as it is necessary to avoid excessive pressure if the globe is damaged or open during surgery. In all there were eight studies [64, 65, 79, 80, 84, 85, 91, 96].

The first, in 1985, was a comparison of the effects of Diprivan (propofol) and thiopentone. The next, in 1986. determined the effects of atracurium or succinylcholine during nitrous oxide-oxygen-fentanyl anaesthesia. Intra-ocular pressure was stable with atracurium but succinylcholine caused a significant increase. Thiopentone was associated with a decrease in pressure but it increased in both groups as a result of laryngoscopy and intubation [65].

In 1987 the effect of vecuronium was assessed during a normal induction of anaesthesia sequence (thiopentone + vecuronium) and during a rapid induction sequence (vecuronium + thiopentone). Vecuronium was associated with a decrease in intra-ocular pressure and even though tracheal intubation caused an increase it never exceeded pre-induction levels [80].

A year later a report was published in *Anaesthesia* where intra-ocular pressure was measured during induction of anaesthesia with propofol or thiopentone followed by vecuronium. The results were similar to previously [84] and in the same year in the *BJA* something similar again [85]. Post-intubation, intra-ocular pressure in the propofol group remained significantly less than the baseline value.

**Infusions:** Muscle relaxants are very suitable for use as infusions as their pharmacological effect is easily measured and therefore the dosage easily titrated.

In 1984 [50] it was shown that when vecuronium was given as a continuous intravenous infusion the dose required to maintain a steady state at 90% block was, on average, 0.083 mg kg⁻¹ h⁻¹ (5.8 mg h⁻¹ for a 70kg patient). Although there were large variations recovery was quick when the infusion was stopped. Five years later prolonged infusions (15-68h) in an intensive care unit were studied [88]. Recovery on cessation of the infusions took almost half an hour. No adverse affects were noted. A similar study was reported in 1991, this time in a paediatric intensive care unit [97]. Eleven infants and children and
four neonates received an infusion to maintain a 90% block for between 9.5 and 179 hr. The mean doses were in the region of 0.1 mg.kg\(^{-1}\).hr\(^{-1}\). The recovery times were in the region of 50 minutes. Again no adverse effects were noted.

Mivacurium and rocuronium were the subjects of subsequent infusion studies.

Thirty patients were infused with mivacurium during thiopentone, fentanyl and halothane anaesthesia [129]. Reversal was with either neostigmine or edrophonium, or spontaneous recovery was allowed. A significant negative correlation (r = -0.81, p < 0.001) was shown between time to recovery from the initial bolus dose.

In the same year rocuronium infusions were used [132]. Following a bolus dose of 0.45 mg kg\(^{-1}\) an infusion was adjusted manually to maintain T1 at 10%. Again neostigmine or edrophonium, or spontaneous recovery was allowed. Inter-patient dose requirements varied. Reversal with neostigmine and edrophonium was about four times quicker than spontaneous recovery which took about 36 minutes. Because of variable recovery rates neostigmine was considered a more reliable antagonist.

The final study was a pharmacokinetic study of rocuronium infusions [156]. The average rocuronium infusion rate for a steady state 90% block of T1 was about 0.5 mg kg\(^{-1}\) h\(^{-1}\). Spontaneous recovery time was about 30 minutes. Blood samples collected over six hours post infusion were analysed for concentrations of rocuronium and metabolites using HPLC. The pharmacokinetic data “were not significantly different from previously published data for a single bolus dose of rocuronium”.

**Reversal of neuromuscular blockade**

Reversal of neuromuscular blockade can be left to nature (spontaneous recovery) or can be stimulated by overcoming the existing competitive block between the neuromuscular blocking agent and acetyl choline (Ach). This is achieved by increasing the levels of ACh by decreasing its rate of breakdown by using an anticholinesterase. However an antidote is required for the antidote because anti-cholinesterases also have unwanted side effects: bradycardia and salivation. To oppose these effects atropine (old) and glycopyrrolate (relatively new, patented in 1960) are used. To complete the picture the newest, most expensive, and novel agent, sugammadex was also investigated.

The first four papers (1977-81) [10, 23, 24, 32] were comparative studies of atropine and glycopyrrolate. In the first a glycolpyrro-
late/neostigmine ratio of 0.2 mg/1.0 mg was thought safe and effective, heart rate was stable but the antiallogogue action of glycopyrrolate was superior. Arrhythmias were similar in both groups. The second paper was similar but they added another anticholinergic, antimuscarinic drug hyoscine. The third was a study in children (atropine vs. glycopyrrolate) and the fourth was a study where the effects were assessed if the neostigmine was given with, or after atropine and glycopyrrolate. If the drugs have different onset times then the overall effect could potentially be different. Given first, both anticholinergic agents produced an increase in heart rate which decreased after the administration of neostigmine. The bottom line was that anticholinergic drugs should be administered with neostigmine and that glycopyrrolate, 10 µg kg\(^{-1}\) produced a stable heart rate.

The second set of papers [37, 40] was about the effect of neostigmine and pyridostigmine on serum cholinesterase activity. Acetyl-cholinesterase is considered the target but there was evidence that they also inhibited serum cholinesterase (pseudocholinesterase). Serum cholinesterase activity was measured after reversal of pancuronium blockade and the enzyme activity was significantly depressed. The clinical importance is that a subsequent dose of suxamethonium could be prolonged; if a non-depolariser were to be given for further neuromuscular blockade an increased dose would be required. In 1986 [67] a similar study was done with edrophonium; this was after atracurium, there was no inhibition of enzyme activity. It was suggested that in previous studies the use of pancuronium may have been partially responsible for the depression of enzyme activity.

There were other comparative studies [56, 76, 77, 145]. However, one non-depolarising drug that is different to the others is mivacurium. It is metabolised by the action of plasma cholinesterase. In this study [160] it was given after the reversal, with neostigmine or edrophonium, of an atracurium induced block. As might be expected the action of mivacurium was prolonged by neostigmine but not by edrophonium.

We must now address the novel drug sugammadex [194, 198-200, 202, 204]. The action of this agent is akin to the way an antibody attaches itself to an antigen. The drug attaches itself to rocuronium (and less efficiently) to vecuronium and the pharmacological action is terminated, almost
immediately. Prior to this agent the early reversal of a non-depolarising neuromuscular blocking drug was virtually impossible. Attempting to reverse the block early caused problems and increasing the dose of the anticholinergic can cause an increase in the neuromuscular block!

2006: [194] Sugammadex, Org 25969, a cyclodextrin, was studied to determine its efficacy. After a profound block with rocuronium various doses of sugammadex were given. The time to achieve a TOF ratio to 0.9 was recorded and there was a dose-related decrease. It was determined that the fastest time possible to get to a TOF ratio of 0.9 to be 1:35 minutes and that a dose of 2-4 mg kg\(^{-1}\) would be effective.

2008: [198] This study compared the reversal of rocuronium-induced neuromuscular block with sugammadex with that of neostigmine for reversal of cisatracurium. The reversal agent was administered when \(T_2\) appeared and it was shown that recovery to a TOF ratio of 0.9 was 4.7 times faster with sugammadex than with neostigmine. [The author would like to ask: Why not compare rocuronium reversal with neostigmine with rocuronium reversal with sugammadex?]

2009: [200] This was a review article. It described how the neuromuscular block of both rocuronium and vecuronium can be reversed by sugammadex; for a shallow block 2mg kg\(^{-1}\), for a deep block 4mg kg\(^{-1}\), for a really deep block (16 mg kg\(^{-1}\)). Using 1-1.2 mg kg\(^{-1}\) of rocuronium produces a rapid block which raised *the possibility of using rocuronium as a replacement for suxamethonium*. Sugammadex was said to have an *acceptable safety profile*.

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v The author was fortunate in being the recipient of both the first box of rocuronium in New Zealand, and the first box of sugammadex. Sugammadex is, simultaneously, both an exciting and boring drug. It works extraordinarily well and has virtually no side effects (apart from a few drug interactions). The first time he used it the rapidity and completeness of recovery appeared almost miraculous. A reflection, perhaps, of 30 year's experience of slow and less than 100% recovery; the cognitive recovery of the patient also seemed enhanced (an impression and, of course, anecdotal).
2009: [202] This was a phase IIIA study to explore the efficacy and safety of sugammadex in infants, children, adolescents and adults. All was well, it rapidly, effectively and safely reversed rocuronium neuromuscular blockade in all patients.

2011: [204] Rescue reversal refers to the situation where a neuromuscular blocking drug has been and the airway cannot be secured. The quick return of spontaneous breathing is required. This letter pointed out some facts in previously reported studies including that by Hogg et al. Journal of Anaesthesia 2010; 105: 726–727P. Return of diaphragmatic movement was recorded about 40 seconds after a 16 mg kg\(^{-1}\) dose of sugammadex. With pre-oxygenation this should maintain oxygen saturation. It was pointed out in the letter that the storage place for the sugammadex should be widely known so that it should be available within one minute, and the dose should be known: 3 vials of 500 mg\(^{vi}\).

**Anticholinergics**

There are 25 papers involving atropine, or glycopyrrolate or hyoscine [10-12, 14, 16, 20, 23-26, 28-33, 35, 38, 39, 43, 58-60, 78, 135]. Excluding those already mentioned which ones are of particular interest?

**Hypersensitivity to atropine** [11]

This is a 10 line letter – “...We were interested in the case report of hypersensitivity to atropine by Giala and Tzovairi-Tsakona (1978). A safer and appropriate alternative to atropine is glycopyrronium.”

**Gastric acidity and glycopyrrolate premedication** [20]

This letter was making comment about a paper by Baraka et al (Anesth Analg 1977; 56:642-645). They make the point that the doses of the two anticholinergics studied were not comparable. Their observations showed that 0.2 mg of glycopyrrolate and 1.0 mg of atropine were indistinguishable regarding the effects on pH of gastric contents. They also criticised the statistical tests used and the data presented. They said that anticholinergic

\(^{vi}\) At this time (2011) the cost of sugammadex in New Zealand was about 1$ / mg. This was not a cheap exercise.
agents reduced the opening pressure of the cardio-oesophageal sphincter and in addition they reduce the motility and “perhaps” delay gastric emptying. They believed that obstetric anaesthesia would be safer with cimetidine and metoclopramide. Glycopyrrolate they considered better than “the dubious and unproven attribute of raising the pH of gastric contents.”

**Atropine premedication and respiratory complications** [29]  
This was a letter in response to an article by Jones and Drummond who showed that atropine did not change the frequency of postoperative respiratory complications. Mirakhur and Clarke were questioning why atropine was used routinely for premedication when it had no obvious benefit [19, 21] and left the patient with a dry mouth. Routine anti-cholinergic medication has not been used in routine anaesthetic practice for several decades; coinciding with a move against intramuscular premedication.

**Antiemetic effects** [31, 135]  
This [31] was also a letter but a very detailed one – a mini-paper! The message from this was that glycopyrrolate does not have an anti-emetic action and this was thought to be due to its inability to cross the blood-brain barrier.  
This was revisited in 1995 [135]. Children having squint surgery, who are prone to vomiting, were studied to assess the effectiveness of anticholinergics as antiemetics. The incidence of the intra-operative oculocardiac reflex was also recorded. Glycopyrrolate and atropine reduced the incidence of the oculocardiac reflex by over 90%. There was no significant difference in emesis between the placebo group and the anticholinergics.

**Now for the non-neuromuscular studies:**

**Propofol**  
Propofol was studied with regard to intraocular pressure [64, 79, 84, 85], propofol-opiate anaesthesia [126, 134, 158, 188, 193] and propofol and cellular function [138, 197]. The last two are of interest.

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Delayed hypersensitivity reactions and T lymphocyte proliferation were studied. Thiopentone and propofol were given to volunteers as an infusion on two occasions. Skin antigen tests were carried out before and after administration. The results showed that the reactions were depressed but there was no effect on T lymphocyte proliferation [138].

The second study was about the protective effect of propofol on myocardial contractility during ischaemia. Rat ventricular cardiomyocytes were made ischaemic for two hours. Under normal conditions, propofol decreased the contraction of cardiomyocytes by approximately 37%. However, during ischemia, propofol was associated with responses where ischaemic values were equal to normal values. This showed that propofol can offset the effects of free radical compounds on cardiomyocytes undergoing oxidant stress and actually improve contractility [197].

Remifentanil
Remifentanil was studied with regard to cardiovascular effects [177, 180, 183], recovery from anaesthesia [184, 188] and case reports of three adrenalectomies [191].

Remifentanil can suppress the cardiovascular effect of laryngoscopy/intubation [177] and so its use for adrenalectomies seemed appropriate. There were no adverse events during resection of an adrenal cortical tumour but there was hypotension and bradycardia. It did not prevent increases in blood pressure or plasma catecholamine levels during excision of the two phaeochromocytoma, even with alpha and beta blockade [191].

The elderly
The elderly were also studied – seven related to neuromuscular blockade but another two were about pre- and post-anaesthesia oxygenation.

In brief - [98] It was decided that, in those over 65 years of age, at least two minutes preoxygenation was necessary to give the maximum apnoea time before oxygen saturation dropped to 93%.

[111] This study was in patients over 70 years of age having eye surgery. Oxygen saturation was recorded on the pre-operative night, immediately postoperative, within the first 60 minutes, and then on the first postoperative night. The percentage of time during which the patients had an oxygen saturation of less than 90% was less than 0.15%. There were no
differences between general and local anaesthesia for this minimally invasive surgery.

**Laryngoscopes**

Finally, a series of five studies about a new laryngoscope [123, 143, 147, 157, 192].

The first four are about the McCoy designed laryngoscope – McCoy is a co-author in each paper. The McCoy laryngoscope had a modified Macintosh blade; it had a hinged tip that was activated by a lever on the handle. It enhanced the ability to elevate the epiglottis and it was claimed to reduce the difficulty of larynx visualisation associated with an anterior larynx [123]. The second [143] was a technical paper on measuring the forces exerted at laryngoscopy which was then used to compare laryngoscopy with the Macintosh and McCoy blades [157]. The year before a comparison was also made by assessing the cardiovascular changes, at laryngoscopy, with the two blades.

The final one in the series [192] was a modification of the modification – an adjustable mirror was added to the blade. Using in-line neck stabilisation to simulate difficult intubation, the mirrored laryngoscope out performed both the McCoy and the Macintosh. It was concluded this new laryngoscope offered "considerable advantages over the Macintosh and the McCoy laryngoscopes"; McCoy was not involved in this study.

Mirakhur was the first author in 79 of these studies. He had many co-authors. A number were RS Clarke, involved in 32 publications, Elliott P 21, Gibson FM 21, McCoy EP 20, Maddineni VR 17, Lavery GG 16, McCarthy GJ 15, Cooper RA 13, Ferres CJ 10 and Reid J 10.

After 34 years studying neuromuscular blockade I think I might have become a bit jaded with train-of-four ratios. However, it all ended with sugammadex, a very interesting exciting and stimulating endgame.
References


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