Almost thirty years ago, residual neuromuscular blockade was documented in a surprisingly high proportion of patients (30%), despite an almost systematic use of anticholinesterase agents.1 Since then, even with the development of shorter-acting neuromuscular blockers, pharmacological reversal, and more widespread use of nerve stimulation, residual paralysis is still a problem that has been associated with episodes of hypoxia,2 respiratory distress,3 airway obstruction,4 and patient disquiet.5 Since the introduction of rocuronium and cisatracurium in the mid 1990s, no new blocking agents have been introduced into clinical practice. A new reversal drug, sugammadex, is available in certain countries, but not in the United States or Canada. With this background in mind, three questions should be asked. First, when are neuromuscular blocking agents indicated, and if they are indicated, how should they be used? Second, if neuromuscular blocking agents are used, how can we best avoid residual paralysis? Third, how can current and future reversal agents be used in anesthetic practice?

INDICATIONS FOR NEUROMUSCULAR BLOCKING AGENTS

Neuromuscular blocking agents are used to facilitate tracheal intubation, provide muscle relaxation and immobility during surgical procedures, and facilitate mechanical ventilation. In all instances, however, the need for unconsciousness and analgesia is present. With the availability of short acting analgesic drugs such as remifentanil and new airway devices, such as the laryngeal mask airway (LMA), the need for neuromuscular blocking agents has been reexamined. Many studies showed that intubating conditions improved when propofol was given with increasing doses of remifentanil. Still, intubating conditions are better with neuromuscular blocking agents, even when compared with remifentanil doses as high as 4 µg/kg.6 Insertion of LMAs requires less relaxation than endotracheal intubation. There are few studies that correlated surgical conditions with the degree of neuromuscular blockade, but improvement in the quality of the surgical field has been obtained with neuromuscular blocking agents.7 Some studies have identified neuromuscular blocking agents as a risk factor of awareness.8 Although an association can be found in clinical studies, the underlying problem is not the presence of neuromuscular blocking agents in these cases, but the lack of anesthetic and analgesic drugs. The problem of awareness is addressed by administration of more anesthesia, not less neuromuscular blocking agents.

PHYSIOLOGICAL CONSEQUENCES OF NEUROMUSCULAR BLOCKADE

Clinically the most important targets of neuromuscular blocking agents are muscles of the respiratory system, those of the upper airway, and those that protect the lungs against aspiration. However, most studies on the effects of neuromuscular blocking agents involved measurement of the force of contraction of the adductor pollicis in response to electrical stimulation of the ulnar nerve, most often using the train-of-four (TOF) mode, ie, four stimuli separated by a 0.5-sec interval, because monitoring at the thumb is convenient. To get clinically meaningful information, it is important to be aware of the correlations between the TOF recordings obtained at the thumb and the respiratory effects of neuromuscular blocking agents. The TOF response is generally expressed as the fourth to first twitch ratio (TOF ratio).

Respiratory system.

Patients can maintain a normal tidal and minute ventilation in spite of profound muscle paralysis characterized by the complete lack of TOF response,9 because the diaphragm is particularly resistant to the effects of neuromuscular blockers. However, vital capacity, essential for coughing, is reduced at low levels of neuromuscular blockade, ie, at a TOF ratio ~ 0.5. Maximum expiratory and inspiratory pressures are reduced when the TOF ratio is <0.7.

Upper airway.

Upper airway patency is dependent upon the coordinated action of a several muscles, and it is difficult to consider them separately. Nevertheless, three muscles, the geniohyoid,10 the masseter10,11 and the genioglossus,9 have been found to be as sensitive, and possibly more sensitive to neuromuscular blocking agents than the adductor pollicis when stimulated with the TOF mode. It is quite possible that other muscles ensuring upper airway patency are as sensitive, since the airway size is greatly reduced when TOF ratio ~ 0.7. In volunteers, it was also noted that a TOF ratio >0.86 was required for a subject to hold a tongue depressor between his/her teeth against attempts by another person to remove it.12
Protection against aspiration.

Swallowing is a very efficient mechanism protecting the tracheobronchial tree from aspiration of fluids or solids. Upper esophageal sphincter tone measured by manometry has been found to be reduced by more than 50% when the TOF ratio = 0.7. Following the administration of neuromuscular blocking agents, these values go back to normal only at a TOF ratio >0.9. Moreover, an increased incidence of laryngeal aspiration was noted when the TOF ratio went under the 0.9 threshold.

DEFINING THE RESIDUAL PARALYSIS THRESHOLD

For many years, residual paralysis was defined by the presence of a TOF ratio <0.7. This threshold was determined in the 1970s based on respiratory data obtained from a limited number of healthy volunteers. No significant decrease in inspiratory and expiratory pressures were noted at a TOF ratio = 0.7, but the effects of neuromuscular blockade on the maintenance of upper airway patency and swallowing were not considered. In the 1990s, a TOF ratio of 0.9 was suggested as a requirement to eliminate the possibility of the residual neuromuscular blocking effects. This new threshold is now widely accepted in the definition of residual paralysis, and it emphasizes the significance of neuromuscular blockade effects on all components of the respiratory system, including the upper airway.

INCIDENCE OF RESIDUAL PARALYSIS

In 1979, a Danish group found a 30% incidence of residual paralysis, based on the measurement of a TOF ratio <0.7 in the postanesthetic recovery unit (PACU). The majority of patients had received neostigmine, but neuromuscular monitoring was not a widespread practice. It should be noted that only a limited number of long-acting nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, gallamine) were available at that time. Further, if the current definition of residual paralysis ie, a TOF ratio = 0.9, had been applied to those results, the incidence of residual paralysis would have reached 72%! Using the threshold of 0.9, subsequent studies found incidences ranging from 0% to 95%, and close examination of these studies can identify some risk factors associated with residual paralysis.

Duration of action of neuromuscular blocking agents.

Unquestionably, the use of an intermediate-acting (atracurium, vecuronium, cisatracurium, rocuronium) instead of long-acting agents reduces the incidence of residual paralysis, no matter what TOF threshold is chosen as a definition of residual paralysis. However, even with intermediate-acting agents, the incidence of residual paralysis remains high: using the 0.9 threshold, an overall 41% incidence has been reported, and even with the conservative threshold of 0.7, the incidence still reached 12%! Long-acting agents are associated with incidences of 72% and 35%, depending on the threshold selected. Therefore, switching to shorter acting neuromuscular blocking drugs does not eliminate the problem completely.

Monitoring

A distinction must be made between devices that only stimulate and those equipped with a sensor that makes measurements and records the response. When the device includes a stimulator only, the anesthesiologist must assess the magnitude of the elicited movement by visual or tactile means. Over a TOF ratio value range between 0.4 and 0.9, it is difficult, if not impossible, to detect whether the fourth twitch is less than the first. The use of this so-called “subjective” evaluation can explain, in part, the high incidence of residual paralysis reported in the literature and the persistence of the problem in spite of monitoring. With devices equipped with accelerometry or displacement sensors that can measure accurately the TOF ratio, the incidence of residual paralysis should equal zero if anesthesiologists keep patients intubated until a 0.9 threshold is reached or exceeded. Studies show that in practice, anesthesiologists sometimes extubate patients early, but overall, the incidence of residual paralysis (defined as a T4/T1 ratio <0.9) is reduced if accelerometers are used.

Anticholinesterase agents.

When neuromuscular blocking drugs with intermediate duration of action became available, some anesthesiologists thought they could omit anticholinesterase agents to reverse neuromuscular blockade at the end of a procedure. In fact, in some countries and some hospitals, the use of anticholinesterase agents is not common. However, without the administration of anticholinesterase agents, the incidence of residual paralysis is high. For example, a 62% incidence, as defined by a 0.9 threshold, was reported with intermediate-acting neuromuscular blockers. In the same facility, over several years, a follow-up of strict practices produced an impressive reduction in the incidence of residual paralysis from 62% in 1995 to 3.5% in 2004, as defined by a TOF ratio <0.9. Over the same period, the proportion of patients receiving anticholinesterase agents increased from 6% to 42%.

Other factors.

Residual paralysis appears to be more common in the elderly, and older patients are also more subject to complications arising from residual paralysis. The administration of neuromuscular blocking agents as an infusion rather than intermittent boluses increases the risk of residual paralysis. It is conceivable that administration of halogenated agents would lead to more residual paralysis than intravenous anesthesia, because halogenated agents...
potentiate neuromuscular blockade, but there are no studies to corroborate such a hypothesis.

**CLINICAL EFFECTS OF RESIDUAL PARALYSIS**

Neuromuscular blocking agents are not the only drugs likely to produce respiratory depression in a clinical setting, but large-scale studies have indicated that residual paralysis increases the number of respiratory complications.

**Respiratory complications.**

Recently, a group of patients with complications such as hypoxia, upper airway obstruction and the need for an intervention to ensure adequate breathing was compared with a control group with no such complications. The mean TOF ratio was only 0.62 in the complications group, compared with 0.98 in the control group. In a study involving 49 patients who received pancuronium, the incidence of hypoxemia (saturation reduced by >5% compared with baseline values) reached 60% in patients with a TOF ratio < 0.7 and only 10% in the other patients. In another study, patients managed with an accelerometer during anesthesia had a higher TOF ratio in the recovery room. They also had fewer episodes of hypoxemia and required interventions to improve oxygenation less frequently than those with no monitoring and a lower TOF ratio.

**Atelectasis.**

One of the few randomized trials investigating the consequences of residual paralysis involved patients given pancuronium, atracurium or vecuronium by neostigmine at the end of the procedure. As expected, a TOF ratio <0.7 was found more often in patients receiving pancuronium (30%), a long-acting neuromuscular blocker, than in those who received atracurium or vecuronium (5%), two intermediate-acting neuromuscular blockers. The incidence of atelectasis confirmed by chest X-ray two days after surgery was three times higher (17%) in patients who had residual paralysis (TOF ratio <0.7) in the recovery room than in the other patients (5%). This indicates that short-term residual paralysis can have long-term consequences.

**Mortality.**

A Dutch study examined mortality attributed to anesthesia in over 800 000 patients, and the authors attempted to identify the factors predicting coma and death. Among the possible pre- or intraoperative actions having a positive influence on outcome, management issues such as the availability of an anesthesiologist were found to be important factors. The only pharmacological treatment that correlated with improved patient outcome was the administration of a reversal agent for neuromuscular blockade, which was associated with a 10-fold reduction in the incidence of mortality and coma.

**PREVENTING RESIDUAL PARALYSIS**

It is essential to avoid residual paralysis in the PACU in extubated patients, and there is solid physiological and epidemiological evidence for this recommendation. Strategies to prevent residual paralysis are based on judicious use of anticholinesterase agents, and a strict practice guidelines based on adequate monitoring, whenever neuromuscular blocking drugs are administered (Table 1).

**Anticholinesterase agents.**

Neostigmine, edrophonium, and pyridostigmine are used to reverse neuromuscular blockade. Edrophonium has a rapid onset, but is not as effective as neostigmine for deep blocks. Pyridostigmine has a slow onset, which makes it ill-suited to the reversal of intermediate-acting neuromuscular agents. Discussion will therefore focus on neostigmine, which remains the most commonly used anticholinesterase agent, although many principles can also apply to edrophonium and pyridostigmine. The effectiveness of anticholinesterase agents is limited by a ceiling effect; for instance, neostigmine reduces the intensity of neuromuscular blockade in a dose-dependent manner up to 0.04 - 0.05 mg/kg, but higher doses have little if any additional benefit. In addition, the agent must be injected only when sufficient spontaneous recovery is observed. It is recommended to wait until there are four visible twitches following TOF stimulation before administering neostigmine.

If no fade is visible, significant residual blockade is possible, but adequate reversal requires only 0.02-0.03 mg/kg of neostigmine. If three or fewer twitches are visible, it is preferable to maintain anesthesia until there are four visible twitches and then give neostigmine at the usual 0.04-0.05 mg/kg doses. When the reversal agent is administered too early, recovery might be incomplete, and residual paralysis difficult to diagnose, as human senses cannot detect fade when the TOF ratio is 0.4 or greater.

**Choice of neuromuscular blocking agent.**

Long-acting neuromuscular blocking agents should be avoided in patients for whom extubation is planned at the end of the procedure. None of the intermediate-acting neuromuscular blockers (rocuronium, cisatracurium, vecuronium or atracurium) produce significantly less residual paralysis than the others. Nevertheless, they should be administered in doses such that, at the end of the surgery, spontaneous recovery is sufficient for the anticholinesterase agent to be effective.

**Monitoring.**

The limitations encountered with traditional monitoring, namely the visual or tactile evaluation of a patient’s responses to TOF stimulation, have led some authors to recommend the compulsory use of so-called “objective” monitoring, which involves a
display of TOF ratio measurements. Unfortunately, currently available devices such as accelerometers and displacement sensors are often fragile and prone to breakage in everyday clinical practice.

FUTURE DIRECTIONS
Residual paralysis is the result of limitations in the pharmacology of the currently available neuromuscular blocking agents and their antagonists. Efforts have been made to develop short-acting neuromuscular blockers such as gantacurium, with a fast recovery profile that would, in practice, eliminate the possibility of residual paralysis. Currently, none of these products is available. An alternative approach has been to develop products that accelerate neuromuscular recovery. Sugammadex is the result of these efforts, but despite its availability in Europe and elsewhere, it is not yet available in North America.

Pharmacology of sugammadex
Sugammadex is a gamma-cyclodextrin, a ring-shaped molecule made up of eight sugars with the addition of negatively-charged side chains. The vecuronium molecule, which is charged positively, has a size that fits well into the hole of sugammadex molecule and is bound by the adjoining negative charges. As a result, sugammadex inactivates rocuronium molecules and indirectly decreases the intensity of neuromuscular blockade. Once bound, the kidney excretes the sugammadex- rocuronium complex. To a lesser extent, sugammadex also shows an affinity for vecuronium and pancuronium; however, it has no affinity for other neuromuscular blockers such as suxamethonium, atracurium, cisatracurium, and doxacurium.

Dosage
In clinical trials, the effectiveness of sugammadex has been studied in three typical situations:
- moderate blockade, ie, only two twitches are visible following TOF stimulation;
- deep blockade, defined as no twitches seen after TOF stimulation and only 1-2 responses after post-tetanic count (PTC);
- 3-5 minutes after rocuronium administration, ie, when the failure of direct laryngoscopy and tracheal intubation is noted.

The dose of sugammadex required depends on the depth of blockade and optimal results are obtained with 2,4, and 16 mg/kg for moderate blockade, 27 deep blockade, 28 and failure to intubate, 29 respectively. These dosages are valid for both rocuronium and vecuronium (Table 1). The recovery time following sugammadex administration is exceptionally fast, ie, approximately 2 minutes.

Role of sugammadex in clinical practice.
At the time of writing (early 2010), sugammadex had been available for clinical use in a number of countries, including those of the European Union, for over one year. Unfortunately, it is not available in the USA or Canada. The Food and Drug Administration (FDA) raised concerns over possible allergic reactions in volunteers receiving large doses. In countries where the drug is available, use is generally restricted because of its high cost (approximately $100 for a standard 200 mg dose). The advantage of this drug is that it is effective at every level of blockade, which is not the case with neostigmine; however, the situations where sugammadex would be particularly useful are those requiring relatively high doses, and thus greater expense. Actually, neostigmine is reasonably effective when it is administered at two visible twitches in response to TOF stimulation, and even more so if there are four. In the case of deep blockade, neostigmine is not very effective, but the sugammadex dose required at that point is ≥ 4 mg/kg. As a result, it is still too early to recommend the administration of large rocuronium doses during surgery while depending on a sugammadex safety net to reverse neuromuscular blockade. Furthermore, the potential for rapid antagonism by sugammadex should not lead the frivolous use of neuromuscular blocking agents in the management of a difficult airway.

CONCLUSION
Residual paralysis undoubtedly contributes to a large proportion of postoperative respiratory complications such as hypoxia, hypoventilation, airway obstruction, atelectasis, and even death. Adequate monitoring, preferably based on the objective assessment of neuromuscular blockade, is required for a reliable diagnosis. However, monitoring cannot replace rigorous practices. A reversal strategy must be planned from the initial administration of a neuromuscular blocking agent, which should have intermediate duration of action and be given in a dose that is appropriate for the planned duration of the surgical procedure. Neuromuscular blockade should be monitored throughout the anesthetic to ensure sufficient recovery in order for neostigmine to have an optimal effect. Sugammadex could increase flexibility, but it will not eliminate the need for appropriate clinical choices regarding dosage of neuromuscular blocking agents. Irrespective of the approach, the goal should be to bring the TOF ratio to ≥ 0.9 before emergence from anesthesia and extubation.
Table 1: Strategy for neuromuscular blockade reversal at the end of the intervention

<table>
<thead>
<tr>
<th>Number of TOF twitches at the adductor pollicis</th>
<th>Other data</th>
<th>If atracurium, cisatracurium, rocuronium or vecuronium used</th>
<th>If rocuronium or vecuronium used and if sugammadex available</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>PTC = 0</td>
<td>Fentanyl patient, wait for 4 twitches</td>
<td>Sugammadex, 8-16 mg/kg</td>
</tr>
<tr>
<td>0</td>
<td>PTC &gt; 1</td>
<td>Ventilate patient, wait for 4 twitches</td>
<td>Aufmmswz, 4 mg/kg</td>
</tr>
<tr>
<td>1-3</td>
<td></td>
<td>Ventilate patient, wait for 4 twitches</td>
<td>Sugammadex, 2 mg/kg</td>
</tr>
<tr>
<td>4</td>
<td>TOF fade present</td>
<td>Neostigmine, 0.04-0.05 mg/kg</td>
<td>Sugammadex, 2 mg/kg</td>
</tr>
<tr>
<td>4</td>
<td>TOF fade not detected by sight or touch</td>
<td>Neostigmine, 0.02-0.03 mg/kg or edrophonium, 0.2-0.3 mg/kg</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Documented</td>
<td>Reversal not required</td>
<td>Reversal not required</td>
</tr>
</tbody>
</table>

REFERENCES
