Gastroesophageal Reflux and Aspiration of Gastric Contents in Anesthetic Practice

Alexander Ng, FRCA, and Graham Smith, MD, FRCA

University Department of Anaesthesia, Critical Care and Pain Management, Leicester Royal Infirmary, Leicester LE1 5WW, England

General anesthesia may predispose patients to aspiration of gastroesophageal contents because of depression of protective reflexes during loss of consciousness. In addition, some patients may be at increased risk of pulmonary aspiration because of retention of gastric contents caused by pain, inadequate starvation, or gastrointestinal pathology resulting in reduced gastric emptying and gastroesophageal reflux. Despite increasing knowledge of the problems associated with aspiration, the relatively small incidence and associated mortality rates in the perioperative period do not appear to have changed markedly over the last few decades. In this review article, the physiological factors associated with an increased risk of gastroesophageal reflux and aspiration are considered together with some of the methods that are used to prevent aspiration. In particular, preoperative starvation, the use of drugs designed to increase gastric pH, recent developments in airway devices, and appropriate application of cricoid pressure are critically appraised.

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Examination of the literature suggests that the incidence of pulmonary aspiration in the perioperative period is relatively infrequent and that there has been little change in the last few years. In 1986, a study of Scandinavian Teaching Hospitals suggested that the incidence of aspiration varied between 0.7 and 4.7 per 10,000 general anesthetics (1). A report published one decade later suggested that the incidence was 2.9 per 10,000 at a Norwegian hospital (2).

Studies from the Mayo Clinic indicated that the incidence of aspiration is similar in adults (3.1 per 10,000) (3) and children (3.8 per 10,000) (4) although another study from the United States suggested that the incidence of aspiration in children was more frequent (10.2 per 10,000) (5).

It is generally held that obstetric anesthetic practice is a high-risk area for aspiration and also that the mortality rate is likely to be more frequent during obstetric aspiration than during general surgery. However, a recent study examining obstetric procedures (excluding cesarean delivery) between 1979 and 1993 demonstrated only one case of aspiration in 1870 general anesthetics, an incidence of 5.3 per 10,000. Of particular interest in this study sent from Israel is the

fact that despite the universal recommendation for tracheal intubation, general anesthesia was administered via a face mask (6).

In low-risk cases, where the standard contraindications to the use of the laryngeal mask airway (LMA) were followed (e.g., absence of gastrointestinal pathology, obesity, history of reflux, or emergency surgery), the use of the LMA from the time of its introduction into clinical practice in 1988 until 1993 was examined by using a metaanalysis. There were only three reported cases of aspiration in 12,901 anesthetics, an incidence of 2.3 per 10,000 (7).

There is little doubt that the incidence of aspiration after trauma is markedly increased owing to the risk of both recent ingestion of food, depression of consciousness and airway reflexes, and gastric stasis induced by raised sympathoadrenal tone. A study confirming these views was undertaken recently and showed that in 53 adults with a Glasgow Coma Scale score ≤ 8 and whose tracheae were intubated by members of the London Helicopter Emergency Medical Service, the incidence of gross aspiration was 38% (8).

Studies on the incidence of aspiration in the perioperative period are summarized in Table 1. It may be seen that, over the last few decades, there is no evidence to suggest that the incidence of this important anesthetic complication has changed. Although they have not been subjected to formal evaluation, it is

Table 1. Incidence of Aspiration

Publication	Period of Assessment	Method of Assessment	Patient Group	Number of Anesthetics	Number of Aspirations	Incidence of Aspiration Per 10000	Factors Thought to Contribute to the Risk of Aspiration
Olsson, 1986 (1)	1967–1970 1975–1985	Retrospective study from database at Karolinska Hospital, Sweden	Children and adults	185,358	87	4.7	Emergency; abdominal surgery; history of delayed gastric emptying; pregnancy; obesity; pain; stress; raised intracranial pressure
Warner, 1993 (3)	1985–1991	Retrospective study from database at Mayo Clinic, Rochester, New York	Adults	215,488	67	3.1	Emergency; lack of coordination of swallowing; depressed conscious level; previous esophageal surgery; recent meal; laryngoscopy; tracheal extubation
Brimacombe, 1995 (7)	1988–1993	Meta-analysis of 101 publication on the Laryngeal Mask Airway	Children and adults	12,901	3	2.3	Emergency; Trendelenberg position; bronchospasm and light anesthesia
Mellin-Olsen, 1996 (2)	1989–1993	Prospective study from database at Trondheim University Hospital, Norway	Children and adults	85,594	25	2.9	Emergency; general anesthesia
Borland, 1998 (5)	1988–1993	Retrospective study from database at Children's Hospital of Pittsburgh, Pennsylvania	Children	50,880	52	10.2	Increased severity of illness; intravenous induction; ages 6 to 11; emergency
Ezri, 2000 (6)	1979–1993	Retrospective study from a hospital database	Adult females Peripartum period, except Cesarean Sections	1870	1	5.3	—
Warner, 1999 (4)	1985–1997	Prospective study from database at Mayo Clinic, Rochester, New York	Children	63,180	24	3.8	Emergency; depressed conscious level; gastrointestinal problems such as gastroesophageal reflux, ileus, bowel obstruction, hemoperitoneum, recent meal; sepsis; shock
Lockey, 1999 (8)	1999	Prospective study of the London Helicopter Emergency Medical Service	Adults Severe trauma from road traffic accidents and falls from heights	53	18	3396.2	Emergency

suggested that the factors that contribute to the likelihood of aspiration include the urgency of surgery, airway problems, inadequate depth of anesthesia, use of the lithotomy position, gastrointestinal problems, depressed consciousness, increased severity of illness, and obesity.

Although the incidence of aspiration has remained infrequent and relatively constant, many anesthesiologists would opine that there has been a marked increase in the extent of surgery undertaken in the sick, more elderly population. In such a population, the incidence of regurgitation and aspiration would be expected to increase and the failure to demonstrate any change in the incidence of aspiration possibly results from improvements in clinical management.

Morbidity and Mortality Attributable to Aspiration

The morbidity attributable to aspiration has been assessed by examination of the presence of pulmonary infiltrates on chest radiography, the necessity for use of antibiotics or bronchodilators, and the duration of respiratory support required after aspiration. In many of the studies described in Table 1, there were no deaths from aspiration. For example, in the meta-analysis on aspiration in the presence of the LMA there were no deaths, but four patients required pulmonary ventilation for up to 7 days (7). In addition, there were no deaths from aspiration in the 25 patients in the Norwegian University Hospital study (2), in the children at the Mayo Clinic from 1985–1991 (4), and in the retrospective study at the Children's Hospital of Pittsburgh between 1981 and 1993 (5).

In the Australian Incident Monitoring Study, the death rate in patients who aspirated was 3.8% (9); whereas at the Mayo Clinic from 1985 to 1991, the death rate in adults was 4.5% (3). This value compares well with the death rate of 4.6% in Sweden from 1967 to 1970 and 1975–1985 (1).

In obstetric practice in the United Kingdom, more accurate data on mortality after aspiration are available as a result of the careful audit by the Confidential Enquiry into Maternal Deaths (10). In this particular branch of anesthesia, it is clear that the number of maternal deaths arising from anesthesia and specifically caused by aspiration has decreased over the last four decades. Despite an increase in the total number of anesthetics administered over this period, the number of deaths associated with anesthesia has declined markedly because of an increasing instrumental rate and delivery rate by cesarean delivery. Of the causes of death attributable to anesthesia, the proportion resulting from aspiration has also declined progressively, from 52%–65% 50 yr ago to 0%–12% in the last 10 yr. In the last two decades in the UK, the decrease in the proportion of anesthetic deaths is undoubtedly

a result of the shift that has occurred from general anesthesia toward spinal and epidural anesthesia.

Factors Predisposing to Aspiration Pneumonitis

The physiological mechanisms that prevent regurgitation and aspiration include the lower esophageal sphincter (LES), the upper esophageal sphincter (UES), and the laryngeal reflexes. It is important to appreciate how these mechanisms may be impaired so that the risk of aspiration pneumonitis can be minimized.

Gastric Contents.   By extrapolation from early studies in the rhesus monkey on direct administration of aspirate into the lungs, it is commonly held that patients are at risk of aspiration pneumonitis if there is a minimum gastric volume of 0.4 mL/kg and the pH of the gastric contents is <2.5. However, the volume of fluid aspirated into the lungs does not necessarily relate to the volume within the stomach, and the validity of extrapolating from one volume to the other needs to be clarified in studies demonstrating a temporal relationship with the development of aspiration pneumonitis (11). In a cat model, the gastric volume that appeared to produce spontaneous gastric regurgitation, and hence a potential for pulmonary aspiration, was 20.8 mL/kg (12). In addition, many adequately starved patients found to have gastric volumes exceeding 0.4 mL/kg were anesthetized without any evidence of aspiration (13,14).

However, there is some evidence to support a dose-response relationship for both the gastric volume instilled directly into the lung and gastric acidity. Aspiration of 0.8 mL/kg and 1.0 mL/kg at pH 1 were associated with increasingly severe pneumonitis in monkeys compared with 0.4 mL/kg and 0.6 mL/kg (15). In another study (16), hydrochloric acid was injected into the tracheae of 336 rats. Extreme acidity was associated with a much higher mortality. The late mortality rates were 90% with a volume of 0.3 mL/kg at pH 1 and 14% with a volume of 1–2 mL/kg at pH ≥1.8.

The effect of milky products on the lung has been studied in animals (17). The severity of lung injury after administration of milk was assessed in rabbits by measuring alveolar-arterial oxygen tension gradient and pulmonary compliance (18). Human breast milk acidified to pH 1.8 with hydrochloric acid increased the severity of aspiration pneumonitis compared with 5% dextrose, acidified to a pH of 1.8 with hydrochloric acid (19). Acidification of human breast milk with gastric juice instead of hydrochloric acid did not increase the severity of lung injury. In addition, less acidic human breast milk (at pH values of 3.0 and 7.0) caused a similar severity of injury. It was shown in rabbits that the type of milk had an effect on the severity of lung injury. Consequently, it appears that human milk is particularly noxious although other

types of milk are <u>less so.</u> Direct instillation of a soya-based formula, for example, caused a less severe form of acute lung injury than human breast milk or a dairy milk formula (20).

The <u>LES</u>. The LES forms the border between the stomach and the esophagus. At this point, the left margin of the lower esophagus makes an <u>acute angle</u> with the gastric fundus and contraction of the right crus of the diaphragm forms a sling around the abdominal esophagus (21). A <mark>reduction in LES pressure is the major physiological derangement in patients with gastroesophageal reflux during anesthesia and in disease states.</mark> Manometry and pH monitoring have been the major tools used to evaluate patients with gastroesophageal reflux (22) and in patients with reflux esophagitis. Multivariate logistic regression analysis identified <u>three</u> pathophysiological <u>factors</u> (23): basal LES <u>pressure</u>, <u>peak acid output</u>, and the number of <u>refluxes</u> lasting <u>>5 min</u> (reflecting acid clearance). It should be noted that the <u>tendency to regurgitation</u> is <u>not dependent</u> on the <u>LES pressure</u> itself, but on the <u>difference</u> between the LES pressure and gastric pressure; this difference is termed the <mark>"barrier pressure."</mark>

The LES possesses variable features, including its basal pressure, axial length, asymmetry, and the location of the high-pressure zone relative to the diaphragmatic hiatus. In a study of <u>seven</u> patients with a hiatus hernia, the <u>maximum</u> pressure at the gastroesophageal junction was <u>lower</u> in patients with <u>hiatus hernia</u> than it was in seven <u>healthy</u> volunteers (Fig. 1) (24). In the volunteers, the mean (sem) maximal pressure was <u>28 (1.2) mm Hg</u> and was 34% asymmetric at the level of the diaphragm. The squamocolumnar junction was 0.5 (0.1) cm below the diaphragmatic hiatus and the axial length of the high-pressure zone was 4 cm. In patients with <u>hiatus hernia</u> there were two areas of high pressure. The proximal zone was above the squamocolumnar junction and the distal zone was at the level of the diaphragmatic hiatus below the squamocolumnar junction. The mean ($\pm$ sem) pressure and axial length ($\pm$ sem) were 17.1 ± 1.0 mm Hg and 2.8 ± 0.2 cm in the proximal zone and 13 ± 2.0 mm Hg and 2.7 ± 0.3 cm in the distal zone. The pressure in the proximal zone above the diaphragm was symmetrical, whereas the pressure in the distal zone was asymmetrical. These asymmetric spatial results at the distal level suggest that the diaphragm contributes to the asymmetric component of the high-pressure zone. The symmetry at the proximal zone above the level of the diaphragm demonstrates the symmetrical characteristics of the muscle wall of the lower esophagus.

Patients who present for anesthesia may have coexisting <u>gastroesophageal pathology</u> that <u>predisposes</u> to <u>reflux.</u> In most instances, the prevailing mechanism for reflux is <u>transient relaxation</u> of the <u>LES</u> (25,26). In addition, <u>anesthetics</u> and techniques may <u>reduce LES</u>
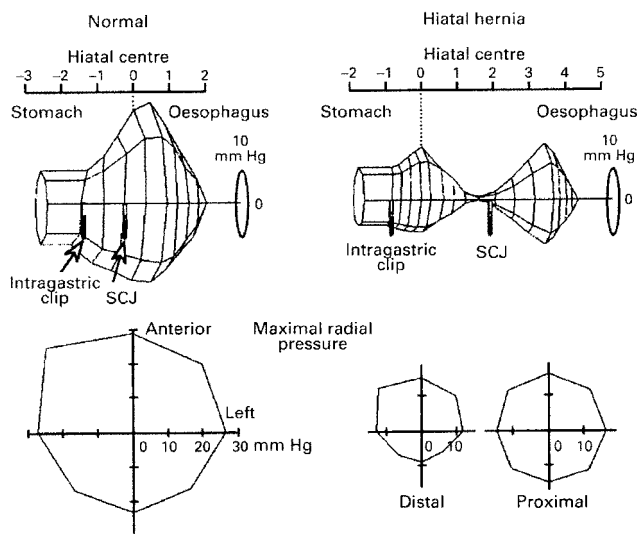

Figure 1. Axial (top) and radial (bottom) pressure topography of the gastroesophageal junction of normal subjects and patients with a hiatus hernia. Position zero on the axial scale is the midpoint of the diaphragmatic hiatus. The proximal clip indicates the median position of the squamocolumnar junction (SCJ) and the distal clip marks the median position of the intragastric aspect of the gastroesophageal junction as imaged endoscopically. With permission (24).

pressure and therefore <u>promote</u> gastroesophageal reflux because of a reduction of barrier pressure (27). In general antiemetics, cholinergic drugs, succinylcholine, and antacids increase LES pressure. LES pressure is <u>reduced</u> by <u>anticholinergics, thiopental, opioids,</u> and <u>inhaled</u> drugs; whereas atracurium, vecuronium, ranitidine, and cimetidine have <u>no effect</u> on LES pressure (27). A study of <u>propofol</u> in 8 healthy volunteers breathing air and oxygen in the supine position with the head covered by a canopy demonstrated that a dose of 2 mg/kg had <u>no effect</u> of barrier pressure at 1, 3, 5, 10, and 20 min. Both LES pressure and gastric pressure <u>decreased</u> at 1 min and then returned to their basal values (28).

<u>Table 2</u> summarizes the effect of anesthetic drugs and techniques on barrier pressure. It may be seen that a typical anesthetic in which a patient is given opioids, modern muscle relaxant drugs, nitrous oxide, and inhaled drugs is likely to be associated with a <u>reduction</u> in <u>barrier pressure</u> and therefore an <u>increased tendency</u> to <u>regurgitation</u> that is greater with increasing concentrations of inhaled drugs. Although LES tone and barrier pressure change concomitantly, it is noteworthy that <u>barrier pressure</u> can be <u>maintained</u> in <u>cirrhotic</u> patients with <u>ascites.</u> In this study, LES tone showed adaptive changes, increasing with abdominal compression and decreasing with diuresis (29).

The <u>UES</u>

The <u>cricopharyngeus</u> muscle acts as the functional UES. It is one of the two inferior constrictor muscles of

Table 2. Effect of Drugs Used in Anesthesia on Lower Esophageal Sphincter Tone

Increase	Decrease	No change
Metoclopramide	Atropine	Propranolol
Domperidone	Glycopyrrolate	Oxprenolol
Prochlorperazine	Dopamine	Cimetidine
Cyclizine	Sodium nitroprusside	Ranitidine
Edrophonium	Ganglion blockers	Atracurium
Neostigmine	Thiopental	?Nitrous oxide
Succinylcholine	Tricyclic antidepressants	
Pancuronium	β adrenergic stimulants	
Metoprolol	Halothane	
α adrenergic stimulants	Enflurane	
Antacids	Opioids	
	?Nitrous oxide	
	Propofol	

With permission (27, 28).

the pharynx. It extends around the pharynx from one side of the cricoid arch to the other and is continuous with the circular muscular coat of the esophagus (30). In conscious healthy patients, the UES helps to prevent aspiration by sealing off the upper esophagus from the hypopharynx. There is evidence to indicate that its function is impaired during anesthesia and during normal sleep (31).

UES tone alters during the induction of anesthesia. Thiopental 4 mg/kg and midazolam 0.05 mg/kg (32) cause a significant reduction in upper esophageal tone. With thiopental, mean ($\pm$ SD) sphincter pressure decreased from 43 $\pm$ 19 to 9 $\pm$ 7 mm Hg, and with midazolam it decreased from 38 $\pm$ 2 to 7 $\pm$ 3 mm Hg. There was some reduction in tone from 31 $\pm$ 15 to 24 $\pm$ 13 mm Hg with 1% end-tidal halothane (33), whereas there was no change in tone with ketamine 2 mg/kg. Administration of succinylcholine 1 mg/kg caused a reduction in UES tone to 7 $\pm$ 4 mm Hg after the induction of anesthesia with halothane (33).

Nondepolarizing muscle relaxants were studied in 102 healthy patients undergoing general anesthesia for varicose vein surgery (34). UES tone was measured using a 6-cm oil-filled sphinctometer and the presence of reflux was assessed by using pH electrodes at the level of the lower esophagus and the hypopharynx. In patients who received atracurium there was a significantly lower UES tone compared with patients who did not receive a nondepolarizing relaxant. Despite this difference, the incidence of reflux into the lower esophagus (19% vs 13%) and the hypopharynx (6% vs 8%) was similar in both groups. Furthermore, during anesthesia, there was no reflex change in UES pressure when reflux occurred into either the lower esophagus or hypopharynx.

Another issue that has been investigated in awake volunteers aged 22 to 49 concerns the effect of residual neuromuscular blockade on the risk of aspiration. Using manometry and fluoroscopy, the behavior of the UES and pharyngeal constrictor muscles above were studied at train-of-four ratios (TOF) of 0.6, 0.7, 0.8, and 0.9 with the patients lying in the right lateral position. In the trial involving vecuronium (35), resting UES tone decreased significantly at TOF of 0.8 and below, whereas in the trial involving atracurium (36), resting UES tone decreased significantly from control at any level of neuromuscular blockade. By assessing the relationship of pharyngeal muscle function to UES function, these investigations were able to demonstrate abnormalities in swallowing, including impaired coordination of pharyngeal and upper esophageal muscles. In the clinical setting, it was shown in 693 patients (37) that the incidence of postoperative residual neuromuscular blockade, defined as a TOF <0.7, was significantly more frequent in patients who had pancuronium (1.5 $\times$ 95% effective dose [ED$_{95}$]) compared with those who had vecuronium (1.5–2 $\times$ ED$_{95}$) or atracurium (1.5–2 $\times$ ED$_{95}$). There was no significant difference in the incidence of pulmonary complications among the three groups. However, by multiple regression analysis, increasing age, anesthetics longer than 200 min, and abdominal surgery were associated with increased risk of postoperative pulmonary complications.

Therefore, with the exception of ketamine, most anesthetic techniques are likely to reduce UES tone and increase the likelihood of regurgitation of material from esophagus into the hypopharynx. In addition, patients who have received neuromuscular blocking drugs may be at risk of aspiration, even with a TOF of 0.7, because of reduction in UES tone and impaired swallowing. Other factors such as duration of anesthetic, type of surgery, and patient age may also influence the risk of postoperative pulmonary complications.

Protective Airway Reflexes. Airway reflexes protect the lungs from aspiration; therefore, it is important to identify situations in which they are impaired. Four well-defined reflexes have been described in the upper airway.

- Apnea with laryngospasm. During this reflex, there is closure of both the false and true cords. If laryngospasm is prolonged, the false cords relax while the true cords remain constricted.
- Coughing. This reflex is a forceful expiratory effort preceded by a brief period of inspiration. The false cords open wider during expiration than inspiration.
- Expiration. This reflex is a forceful expiratory effort without a preceding inspiration. Sudden opening of the glottis follows closure of the false cords.
- Spasmodic panting. This reflex involves shallow breathing at a frequency of 60 breaths per minute for <10 s. The glottis opens and closes rapidly.

These protective airway reflexes have been studied in 22 healthy patients anesthetized with propofol (38) by instilling 0.2 mL of distilled water onto the laryngeal mucosa around the vocal cords. It was found that the expiration reflex was the most common protective reflex elicited. Incremental doses of fentanyl progressively reduced the incidence of the expiration reflex, spasmodic panting, and cough reflex, but laryngospasm was not abolished with the larger doses of fentanyl that tended to induce apnea.

The larynx and trachea are more sensitive than the bronchus in eliciting these protective airway reflexes. In 11 female adults anesthetized with sevoflurane, the airway reflexes were lessened when distilled water was administered into the bronchus compared with both larynx and trachea (39). The expiratory reflex, the cough reflex, and spasmodic panting were not observed after bronchial stimulation. Furthermore, the occurrence of apnea after laryngeal and tracheal stimulation was significantly more frequent than after bronchial stimulation.

In addition to the bronchus, trachea, and larynx, the esophagus is also thought to be a sensory site for the initiation of coughing. By using 24-h ambulatory monitoring of esophageal pH and gastroesophageal reflux, it was shown that coughing was initiated by episodes of reflux (40,41).

The type of airway reflex induced by physiological stimuli changes over time. After a period of 2 to 7 h of anesthesia with sevoflurane, it was shown in 14 intubated patients that although apnea and forceful expiratory efforts were more prominent at the beginning of anesthesia, the swallowing reflex predominated at the end (42).

Unconscious patients are at risk of aspiration because of impaired airway reflexes, but the relationship between a reduced conscious level and these reflexes is not straightforward. The cough reflex was examined in 47 patients with a reduced Glasgow Coma Scale score of ≤8 as a result of head injury, seizure, drug overdose, and alcohol intoxication. The presence of a normal cough reflex did not correlate with the depth of unconsciousness as quantified by the Glasgow Coma Scale score. Normal cough reflexes existed in patients within the range of scores from 3–8. However there were other patients with attenuated or absent cough reflexes when the score was ≤6 (43).

Protective airway reflexes may be impaired at any stage in the perioperative period. The sensitivity of these reflexes has been studied using inhaled ammonia (44). Using this technique, oral diazepam 10 mg in 10 healthy male volunteers reduced upper airway reflex sensitivity 30 to 150 min after administration (45). In another study of 102 healthy nonsmoking volunteers aged 17 to 96, there was a progressive decrease in upper airway reflex sensitivity with increasing age (46). Two hours after recovery from general anesthesia for day case surgery, upper airway reflex sensitivity had not returned to baseline values. However, the auditory reaction time, a measure of recovery from general anesthesia, had returned to normal at this time and the patients were allowed to go home (47). It seems therefore that patients may have reduced airway reflex sensitivity, not only in the intraoperative but also in the preoperative period if premedicated, and also after recovery from anesthesia, perhaps for longer than may be estimated from objective tests of recovery. Furthermore, the elderly have less active airway reflexes and should be considered at increased risk of aspirating pharyngeal material.

Methods to Minimize Regurgitation and Aspiration

Methods used to minimize aspiration and its morbidity involve control of gastric contents, reduction in gastroesophageal reflux, prevention of pulmonary aspiration, and attenuation of the effects of aspiration (48). The former two involve preoperative starvation, a decrease in gastric acidity, facilitation of gastric drainage, and maintenance of a competent LES, although the latter two factors may require tracheal intubation or the use of other airway devices and application of cricoid pressure. In the reports of the National Confidential Enquiry into Perioperative Deaths, attention was drawn to prevention of pulmonary aspiration of stomach contents at the induction of anesthesia by application of cricoid pressure, the use of postural changes, preoxygenation without lung inflation, and aspiration via a nasogastric tube (49).

Control of Gastric Contents

Preoperative Starvation. The aim of preoperative starvation is to minimize the risk and degree of regurgitation and possible pulmonary aspiration during anesthesia. This issue has been highlighted in the National Confidential Enquiry into Perioperative Deaths (50).

Methods of Assessment of Gastric Emptying of Clear Fluids, Milk and Solids.   The methods used to assess gastric emptying have been summarized in Table 3. In comparison with the other techniques, paracetamol absorption is particularly useful owing to its simplicity. It is noninvasive, avoiding the use of nasogastric intubation and gastroscopy. It does not involve radiation or expensive equipment, such as ultrasonography or electrical impedance tomography, and hence it is particularly suitable during pregnancy (51,52). Paracetamol absorption is a technique that has been widely used (53–56) and compares well with scintigraphic and polyethylene glycol dilution techniques (57).

The relative risk of regurgitation and possible aspiration in more recent studies on preoperative starvation have involved a comparison of the volume of aspirated gastric contents after a shorter fasting period after clear fluids, milk, or solids with the traditional fasting period of ≥6 h.

Clear Fluids

Children.   In healthy children given clear fluids up to 2 h preoperatively, gastric volumes and pH do not differ significantly from the control values of patients starved for longer periods (72–74). The volume of clear fluid was 9.9 ± 0.3 mL/kg (mean $\pm$ SD) in one trial (72) and unrestricted in two other studies (73,74).

It has also been observed that a large proportion of patients given fluids up to 2 h preoperatively and those starved for longer periods had a pH <2.5 and a gastric volume >0.4 mL/kg (73,74). Thus there seems to be little difference between the gastric contents of those starved of clear fluids for up to 2 h and those who had undergone longer periods of starvation. Such studies were the basis of the statement in the guidelines of the ASA (75) that it is appropriate for clear fluids to be allowed up to 2 h preoperatively. Clear fluids include water, fruit juices without pulp, carbonated beverages, clear tea, and black coffee. In a survey of members of the Association of Pediatric Anaesthetists in the UK (76), there seems to be agreement on a 2-h fasting time for clear fluids in neonates and children.

Adolescents and Adults.   In two clinical trials, one involving 152 adolescents aged 13–19 yr (69) and another involving 199 healthy adults (70) aged 18 to 70, the risk of aspiration was assessed after allowing unrestricted clear fluids up to 3 h preoperatively. It was observed that the residual gastric volumes and pH in patients allowed unrestricted clear fluids up to 3 h preoperatively did not differ statistically from the data in those who fasted for longer. There is evidence therefore that healthy adults are not at an increased risk of regurgitation and aspiration if they are allowed to consume clear fluids until approximately 3 h preoperatively.

Table 3. Methods of Assessment of Gastric Emptying

Method	Reference
Paracetamol absorption	51–57
Electrical impedance tomography	58, 59
Radiolabelled diet	57, 60–64
Ultrasonography	65–68
Aspiration of gastric contents under direct vision with a gastroscope	13, 14
Polyethylene glycol dilution	57
Blind aspiration of gastric contents	69–71

Milk

Gastric handling of milk differs from that of clear fluids. In a study using the technique of ultrasonography (validated by Hveem et al. (77) and Marzio et al. (78)) to compare gastric emptying of milk and glucose in children, it was found that the maximum gastric emptying times of low-fat milk and human breast milk were 2.75 h compared with 1.75 h for glucose (65).

Different types of milk vary considerably in their constituents. Milk may be casein or whey based. Whey-based milk is emptied more quickly from the stomach. Casein is insoluble and is formed from caseinogen under the influence of rennin. Whey is the liquid that separates from the clot in cheese making and it contains lactalbumin but almost no casein or fat. Whey proteins are eliminated quickly from the stomach but casein forms curds that are digested more slowly. Thus, there are two phases to the elimination of milk: an initial rapid liquid phase followed by a constant zero-order solid phase (79).

The three main types of milk available for babies are human breast milk, cow's milk, and a variety of formula milk for infants. Formula milk may be either whey-predominant or casein-predominant; the former mimics human breast milk and the latter conforms more closely to cow's milk. In a study of 201 infants using sulfur-colloid Tc and cinegastroscintigraphy, the rate of emptying was faster with human milk and slower with cow's milk. One-hundred-twenty minutes after ingestion, the percentage gastric residual activity was $19 \pm 16\%$ (mean $\pm$ SD) for human milk, $25 \pm 18\%$ for the whey-predominant formula, 38 ± 21 for the casein-predominant formula, and $48 \pm 19\%$ for cow's milk (60).

Another study using a different technique to assess gastric emptying in 29 infants supports previous observations that breast milk empties quickly (61). Using 13C-octanoic acid breath tests it was found that gastric emptying was significantly faster after human milk than formula milk. The half-emptying time (range) was 65 (27–98) min for the formula-fed infants and 47 (16–86) min for the breast-fed infants.

Fortification of human breast milk increases its energy, protein, carbohydrate, vitamin, and mineral content, and it is becoming more common for infants of low birth weight. To evaluate if this practice induces a delay in gastric emptying, a blinded cross-over study of 22 low-birth-weight infants was undertaken using ultrasonography to measure gastric antral cross-sectional area. There was no significant difference in gastric emptying; thus it seems that the fortifier used in this study had no effect on gastric emptying of human breast milk (66).

Solids

In assessing gastric emptying of solids, it is important to differentiate between different types of food. For example, although cow's milk is a liquid, it separates into liquid and solid phases (curd) in the stomach. In contrast, gelatin is a solid that liquefies rapidly in the stomach (80).

Gastric emptying of solids depends on type and quantity. In a study of 50 healthy volunteers, gastric emptying was assessed by scintigraphic techniques after ingestion of digestible and indigestible material (62). The digestible and indigestible materials were two eggs and ten polyvinyl capsules respectively. The mean (SD) half-life of gastric emptying was 59.4 (7.7) min for the eggs. Assuming that five half-lives are required, it can be expected that up to 5 h are required for the stomach to empty after a light digestible meal. In the case of the indigestible material, 4 h elapsed before the capsules were emptied. These results concur with those from a study of healthy female volunteers who had a light breakfast comprising a slice of buttered toast with jam, one cup of coffee without milk or sugar, and one glass of pulp-free orange juice (67). Ultrasonography showed that 4 h elapsed before the stomach was considered to be clear of solid particles. This period cannot be applied to a heavy meal, which takes more than 9 h to empty from the stomach (81).

Altered Physiological States. Altered physiological states such as pregnancy, gastrointestinal disorders, and diabetes mellitus are associated with alterations in the rate of gastric emptying. The effect of labor on gastric emptying has been studied in a randomized controlled trial of 94 patients who were either allowed to eat or allowed to have water only (68). The eating group was allowed semisweet biscuits, bread, butter, jam, low fat cheese, cereal, milk, coffee, tea, hot chocolate, fruit juice, squash, and water. The proportion of patients who vomited and the volume expelled were significantly more in the patients who were allowed to eat compared with those who were allowed water only. Although the pH of the contents vomited was not measured, the presence of solid particles in the vomit from the eating group was of concern. In this study, the gastric antral cross-sectional area was measured within an hour of delivery using real-time ultrasonography. The eating group had a significantly larger gastric antral cross-sectional area compared with those who ingested water. This study supports the view that eating should not be allowed during labor, especially when there is a chance that epidural or general anesthesia may be required.

The other issue in labor is that of mobile epidural infusions, which are currently in vogue. In the maintenance phase, these epidurals are administered by a continuous infusion of a small dose of local anesthetic with an opioid. The important clinical question is how much epidural opioid needs to be administered before there is delayed gastric emptying and hence an increase risk of aspiration. This issue has been made clearer using the paracetamol absorption technique in a randomized controlled study of 55 women who were given either a small-dose bupivacaine infusion without fentanyl or a dose with fentanyl (52). In comparison with the control group, gastric emptying was significantly delayed in the patients who had fentanyl after it had been infused epidurally for a mean time of 4.5 h when approximately 113 ± 8.5 μg of fentanyl (± SD) had been given. The time (SD) to maximum plasma concentration of paracetamol was significantly increased in this group: 76.1 (23.9) min compared with 54.2 (27.8) min in the control group.

In obstetric practice, anesthesia may also be required for a postpartum patient. After delivery, the time at which the risk of aspiration returns to normal is an important clinical consideration. Gastric emptying was studied by using electrical impedance tomography in the postpartum period in 14 healthy mothers. The gastric emptying of 400 mL of distilled water was assessed at 37 to 40 wk of pregnancy, 2–3 days postpartum, and 6 wk postdelivery (58). The respective mean gastric emptying times (SD) were 15 (6.05), 11 (5.9), and 15 (5.5) min. It would appear therefore that there is no impairment of gastric emptying of clear fluids 3 days after delivery. However, there is insufficient evidence to clarify changes in risk in the first 24 h of the postpartum period, when operative procedures are common. During this period, the anesthesiologist would need to take into account several factors, such as feeding practice during labor, analgesia used, case mix, and surgical factors, in the clinical decision-making process.

Caution is required when assessing gastric emptying in patients with gastrointestinal pathology. Clearly, there is a very high risk of aspiration in patients with bowel obstruction or peritonitis, but in the absence of a definitive diagnosis, anesthesiologists may encounter patients with less definitive symptoms of abdominal pain, vomiting, or reflux.

Schwartz et al. (14) observed that children with abdominal pain had significantly larger gastric volumes than those whose primary problems were vomiting or reflux. In this study, gastric contents were obtained from 155 of 248 children presenting for upper gastrointestinal endoscopy. All patients were starved for 8 h except infants <6 mo of age who were starved for 6 h. However, larger gastric volumes in this study were comparable with the volumes observed in healthy patients in other studies. Despite these recent published observations, it would still seem prudent to manage patients with abdominal symptoms as if they were at high risk of aspiration.

In Type I diabetic patients, gastric emptying is delayed as assessed by radioisotopic techniques and electrical impedance tomography. Digestible material consisting of two eggs emptied from the stomach with a half-life (SD) of 88.1 (8.9) min in Type I diabetic patients compared with 59.4 (7.7) min in healthy volunteers (62). The indigestible material of 10 capsules was emptied in 82% of diabetic patients after 6 h whereas they were emptied in all the healthy volunteers at 4 h. In another study, the residual radioactivity 50 min after a semisolid meal was 71.3 ± 15% (mean ± SD) in 83 Type I diabetic patients compared with 53.5 ± 13% in 48 healthy volunteers (63). In this latter study, the delay in gastric emptying correlated with the presence of autonomic neuropathy but not with the degree of peripheral neuropathy, preprandial blood glucose HbA_{1C}, duration of diabetes, or age. In another study, gastric emptying measured by electrical impedance tomography was also delayed in Type I diabetic patients (59). After ingestion of a semisolid meal, the mean half-time of gastric emptying was 54.8 ± 26.6 min in diabetic patients compared with 40.4 ± 8.6 min in healthy volunteers. Thus there is considerable evidence to suggest that these diabetic patients require a longer fasting period than healthy patients do.

Guidelines and Clinical Practice. The objectives of all concerned are to avoid regurgitation and aspiration. However, a long fasting time leads to thirst and general discomfort with associated dehydration and possible hypoglycemia. With respect to ward practices, alterations in fasting times from the traditional nil by mouth routine may cause confusion, especially if different regimens are prescribed for age variations and different disease processes. There is still limited evidence for patients with different disease states, and in such complex clinical situations where evidence is incomplete, application of a decision analysis model would provide a structured approach. The model would be helpful, as it would incorporate the current evidence base and allow the assessment of the risk-benefit ratio of shorter and longer fasting times under

a variety of situations. Whatever they may be, preoperative guidelines on starvation should be unequivocal and should include a margin of safety. For example, in patients who have ingested milk with morning coffee, it would be judicious to increase the preoperative starvation period from that for clear fluids to that for cow's milk.

There is now good evidence that for clear fluids the period of preoperative starvation may be reduced from that traditionally recommended. After a Norwegian National consensus on fasting times in 1993, 69% of hospitals were shown to have changed their local guidelines by 1996. Ninety-three percent and 79% of hospitals allowed <6 h of preoperative fasting for clear fluids in children and adults respectively in 1996, compared with 71% and 63% respectively in 1993 (82). Surveys have shown that US and UK pediatric anesthesiologists are becoming more relaxed in their fasting policy on clear fluids (76,83).

On the issue of milk, the American Society of Anesthesiologists (ASA) supports a fasting period of four hours for breast milk, and six hours for infant formula and nonhuman milk (75). These recommendations for formula milk have erred on the side of caution, treating all types of formula milk in the same way as cow's milk. In a survey in the US of pediatric preoperative fasting practices (84), there is general agreement with a 4-h fasting time for breast milk in the majority of hospitals despite a wide range of two to eight hours. For formula milk, there is agreement with a ≥4-h fasting time, and most hospitals recommend a period of 6 h. A survey of members of the Association of Pediatric Anaesthetists in the UK has shown that acceptable fasting times are 4 h for breast milk and 6h for formula milk in neonates, and 6 h for milk in children (76).

Solids take longer than fluids to empty from the stomach. The current ASA recommendation for solids for adults is 6 h of fasting after a light meal (75). Further guidance is required for the starvation time after a heavy meal.

Reducing Gastric Acidity. The two main issues on gastric acidity in the preoperative period are the type and timing of drugs that would be effective in increasing gastric pH and the situations in which these drugs should be used. H_2 antagonists and proton pump inhibitors (PPIs) are two commonly used groups of drugs.

H_2 antagonists are histamine analogues that bind competitively to receptors on the parietal cell basal membrane (85). Important pharmacological features concerning this class of drug are the considerable interindividual variation of acid inhibition with the same plasma concentration, the reversible development of tolerance within a few days of therapy, and the lack of a direct temporal relationship between the

peak plasma concentration of drug and maximum inhibition of acid secretion (86).

PPIs are pyridyl methylsulfinyl benzamidazoles, which are converted to sulfenamides on the acidic luminal side of the gastric parietal cell. They form disulphide covalent bonds with cysteine residues of the α domain of the H^+/K^+ ATPase pump (87). Important pharmacological features include marked interindividual variation in first-pass metabolism and hence variable acid suppression for a given dosage, absence of a temporal relationship between the peak plasma concentration of drug and maximum inhibition of acid secretion, and continued suppression of acid secretion in the absence of detectable plasma drug concentrations (86).

In anesthetic practice, there have been many double-blinded randomized controlled clinical trials of H_2 antagonists and the PPIs in healthy patients to assess their effect on gastric pH and volume. The methods used in these studies have usually been blind aspiration via a nasogastric tube with the patients in various positions (88). Alternative methods are more complex, involving dye dilution and also aspiration under direct vision with a gastroscope. The former is time consuming and provides results similar to those of the blind aspiration technique although the latter method may stimulate gastric secretion.

Administration of a single dose of ranitidine 150 mg a few hours before the induction of anesthesia significantly increases gastric pH and reduces gastric volume (88–90). Ranitidine has been compared with famotidine in a double-blinded randomized control study of children aged 2–8 yr (91). It was observed that gastric pH and gastric volume were significantly increased and reduced respectively with famotidine 0.5 mg/kg compared with ranitidine 2 mg/kg.

Prescription of PPIs, however, requires knowledge of their pharmacodynamic effects in the preoperative setting. Clinical trials have shown that rabeprazole, lansoprazole, and omeprazole (88–90) are most effective when given in two successive doses, the evening before and on the morning of anesthesia. When a single dose of rabeprazole or lansoprazole was given to patients on the evening before anesthesia, the gastric volumes and pH measured during anesthesia on the next morning were 0.22 $\pm$ 0.20 mL at pH 3.8 $\pm$ 2.2 and 0.31 $\pm$ 0.28 mL at pH 2.7 $\pm$ 1.3 respectively, compared with 0.18 $\pm$ 0.21 mL at pH 4.2 $\pm$ 2.4 and 0.21 $\pm$ 0.18 mL at pH 4.5 $\pm$ 1.8 respectively when given on the morning of anesthesia. Different results were obtained with a single dosing of omeprazole. The gastric volume and pH measured during anesthesia were 0.31 $\pm$ 0.21 mL at pH 3.7 $\pm$ 2.1 when omeprazole was administered on the evening before anesthesia, compared with 0.43 $\pm$ 0.20 mL at pH 2.9 $\pm$ 1.5 when it was given on the morning of anesthesia. It is suggested from these clinical studies that PPIs should

be used in two successive doses. If, however, they are used as a single dose, then rabeprazole and lansoprazole should be given on the morning of anesthesia, as they are not sufficiently effective when given the night before. Omeprazole as a single dose, however, is not effective if it is given on the morning of anesthesia; it should be given on the previous night. However, it should be noted that a single dose of ranitidine is just as effective as two doses of any of the PPIs in the preoperative setting in healthy patients.

Although H_2 antagonists are effective in healthy patients in the preoperative setting, their use in patients with peptic ulcers and reflux esophagitis needs further clarification. In many double-blinded randomized control trials symptomatic relief, healing rates, and recurrence rates are significantly better with PPIs than with H_2 antagonists (92,93). In the preoperative setting, when there is time to optimize significant coexisting disease, the evidence is clearly in favor of the PPIs rather than the H_2 antagonists.

The effectiveness of ranitidine and omeprazole has been studied in obstetric practice. In 384 patients (94) undergoing emergency cesarean deliveries, different combinations of sodium citrate, metoclopramide, ranitidine, and omeprazole were used. The proportion of patients with a gastric pH <3.5 and volume >25 mL was significantly larger in patients who had a combination with either ranitidine or omeprazole. This proportion was 43/185 in patients who had citrate and citrate-metoclopramide compared with 18/199 in patients who had combinations of omeprazole-citrate, raniditine-citrate, omeprazole-citrate-metoclopramide, and ranitidine-citrate-metoclopramide.

Although it is possible to show that these drugs increase gastric pH and reduce gastric volumes, there is no evidence to support their routine use because of the infrequent incidence of aspiration and the multiplicity of factors that are associated with this complication. If it were possible to demonstrate a significant reduction in morbidity and mortality from increasing the pH of gastric contents, the number of patients who would have to be treated to obtain benefit in one patient would be enormous. Indeed, the routine prescription of these drugs has not been recommended in the ASA guidelines (75). The level of evidence for the use of these drugs in a clinical situation is largely opinion-based. In addition, clinical trials have been conducted mostly in healthy patients and not in those patients who would be likely to regurgitate and aspirate.

Reducing Gastric Volume

Nasogastric Tubes.   It is common to insert a nasogastric tube into patients at risk of aspiration. Current issues with nasogastric tubes include whether they should be inserted and then removed before induction

of anesthesia in the emergency situation, whether they should be inserted during elective abdominal surgery, the effect of size on gastroesophageal reflux and aspiration in mechanically ventilated patients, and the inclusion of an occlusive balloon to prevent gastroesophageal reflux.

In the emergency situation, it has become standard practice to apply cricoid pressure during a rapid sequence induction. Although the nasogastric tube is inserted to empty the stomach before anesthesia and may impair UES and LES function (95), there is evidence from two cadaver studies (96,97) to show that the efficacy of cricoid pressure is not diminished by its presence. In addition, the lumen of the nasogastric tube is thought to provide a passageway for the drainage of gastroesophageal contents when effective cricoid pressure is applied. On the basis of this evidence, it would be our recommendation that the nasogastric tube be left *in situ* during a rapid sequence induction.

There is some evidence to suggest that a nasogastric tube may facilitate regurgitation. In a study of 15 patients undergoing elective abdominal surgery, the number of episodes of reflux defined as a lower esophageal pH of <4 was significantly greater in patients with a nasogastric tube *in situ*. In addition, the mean LES pressure was lower in these patients compared with those who were without a nasogastric tube (98). As this clinical trial was published in abstract form, further operative and patient details were unavailable for review.

In a cross-over study involving 17 intubated patients in the intensive care unit (99), the incidences of gastroesophageal reflux and aspiration were assessed using two sizes of nasogastric tube, 2.85 mm and 6.0 mm. Using a radioactive technetium technique, it was found that there was no significant difference in the incidence of gastroesophageal reflux (67% vs 81%) and aspiration (20% vs 31%) between the small- and large-gauge tubes respectively. It seems therefore that in this clinical situation, reducing the size of the nasogastric tube does not reduce the risk of aspiration.

To reduce regurgitation in the presence of a nasogastric tube, a device has been designed to occlude the gastric cardia with an inflatable balloon (Fig. 2) (100). Using this nasogastric tube with a gastric balloon, it was shown in 12 pigs that were provoked to regurgitate by gastric filling, head-down positioning, external gastric compression, drug-induced vomiting, and pyloric ligation that gastroesophageal reflux did not occur. This finding has been confirmed in 26 healthy volunteers who ingested 1 L of mineral water (100). In addition, gastroesophageal reflux did not occur in 42 surgical patients who were considered to be at risk of aspiration and in whom a rapid sequence induction was not performed (100).

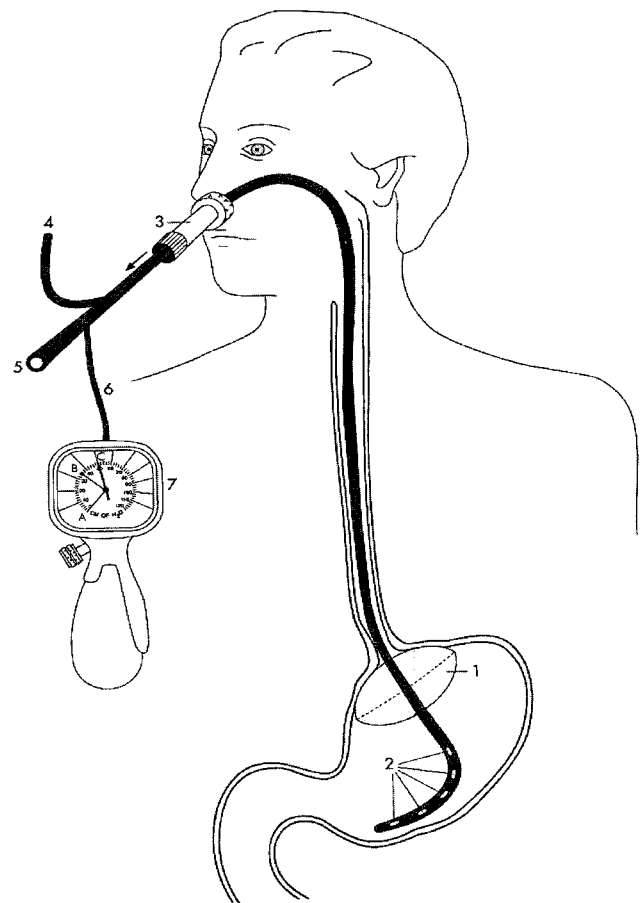Using dye indicator as evidence of gastroesophageal reflux into the oropharyngeal space, the gastric

Figure 2. Nasogastric tube with a balloon. 1, inflatable balloon; 2, lateral openings to aspirate the stomach contents and equilibrate pressure between the stomach and the outside air; 3, pliable nose stopper with foam ring and locking device (over dimensional drawing for purpose of illustration); 4, separate lumen; 5, main lumen with aspiration of connection; 6, branch tube with subsidiary lumen leading into inside of the balloon; 7, pressure monitoring device. With permission (100).

balloon tube has also been studied in conjunction with the LMA. It was found that the tube did not interfere with insertion of the LMA in one group and that the LMA did not impede insertion of the tube in the other group (101). In addition, by inspection of the LMA and oropharynx, it was observed that gastroesophageal reflux did not occur. The implication from these findings is that the nasogastric balloon tube may reduce the risk of aspiration when a LMA has to be used to manage a difficult airway in a patient who is likely to have gastroesophageal reflux.

Cricoid Pressure

Cricoid pressure has become standard practice during the induction of anesthesia in patients with a potentially full stomach (102). The evidence in support of its efficacy includes prevention of gastric insufflation in children (103) and adults (104,105), an increase in UES

pressure (106), and occurrence of reflux in 3 of 26 patients at risk when cricoid pressure was released (95). There is no convincing evidence to suggest that cricoid pressure has reduced the incidence of aspiration or mortality. Although studies have raised concerns about its harmful effects and misapplication (107), it is likely that cricoid pressure will remain as a standard maneuver in clinical practice, especially in emergency anesthesia.

Effect of Cricoid Pressure on the LES.   Application of cricoid pressure decreases LES tone (108) with restoration to baseline values after release. This suggests that there may be mechanoreceptors in the pharynx that mediate reflex relaxation of the LES. However, this effect does not seem to promote gastroesophageal reflux in healthy, conscious volunteers (109).

Magnitude of Cricoid Pressure.   There is evidence to show that cricoid pressure may be misapplied with implications for oxygenation, ventilation, and protection of the airway. In an endoscopic study of 30 patients, it was shown that cricoid pressure might cause cricoid deformation, vocal cord closure, and difficult ventilation, especially in females (110). One of the current issues therefore concerns the magnitude of force that should be applied to the cricoid cartilage. This force should be sufficient to prevent aspiration but not so great as to cause airway obstruction or allow the possibility of esophageal rupture in the event of vomiting.

The force traditionally suggested is 44N, but cricoid occlusion and vocal cord closure may occur at pressures <30N (110). Furthermore, cricoid pressure is effective in preventing regurgitation at forces <44N. In a study using the double-lumen Salem sump tube in 20 females undergoing emergency cesarean delivery under general anesthesia (111), the mean gastric pressure was 11 (range, 4–19) mm Hg. It was predicted that 99% of women undergoing emergency cesarean delivery are likely to have a gastric pressure of <25 mm Hg. Evidence from a study of 10 cadavers (96) suggests that a force of 20N is likely to prevent regurgitation of esophageal fluid at 25 mm Hg.

In view of the possible occlusive effects of cricoid pressure, the next clinical question is this: what force would be appropriate for children of different age groups? There are no data available to clarify this issue. However, a bench-top model has been designed to investigate the force that would be applied to a 5-yr-old child in clinical practice (112). This observational study showed that the mean (sd) force applied would be 25.1 (2.7) N and 22.4 (1.7) N by anesthesiologists of all grades and anesthetic assistants respectively.

Timing of Cricoid Pressure

Forty years ago, Sellick (95) made a recommendation that although moderate pressure is appropriate in a conscious patient, firm pressure is applied as soon as consciousness is lost. This issue concerning the time at which cricoid pressure should be applied has been reexamined by Hartsilver and Vanner (113). In conscious individuals, the full force of 44N on the cricoid cartilage is uncomfortable and has been associated with retching (114). Therefore, it has been suggested that the force applied initially should be low and that it should be increased only when the patient becomes unconscious (113).

Direction of Cricoid Pressure.   The direction of the force applied on the cricoid cartilage has been questioned. It appears that the application of cricoid pressure should be in an upward and backward direction to improve the view at laryngoscopy (115). However, if manual ventilation becomes necessary, then the direction should be changed to a backward direction. Hartsilver and Vanner (113) observed that the tidal volumes delivered were reduced if the direction of cricoid pressure at 30N was backward and upward, as opposed to directly backward.

Cricoid Pressure in Clinical Practice

The next consideration with cricoid pressure is whether a predetermined force can be applied and whether this force can be sustained in clinical practice. In a study of 135 anesthetic assistants, the application of the correct force was highly subjective and ranged from <10N to >90N (116). However the extent of this variation may be reduced with training. In a study of six anesthetic assistants (117) it was observed that the application of cricoid pressure with a flexed arm could be sustained only for a mean time of 3.7 min at 40N, with the onset of considerable pain after a mean time of 2.3 min. This suggests that cricoid pressure cannot be sustained reliably for more than a few minutes. Extending the arm position allows an increase in the duration of effective cricoid pressure but, in practice, this position obstructs the laryngoscope handle and therefore it should be used only if attempts at intubation have terminated.

An important clinical scenario to consider is the situation of failed intubation with cricoid pressure in the presence of a full stomach. In these circumstances, a LMA might facilitate oxygenation and ventilation, but the key clinical question is whether cricoid pressure obstructs the correct placement of the LMA and therefore impedes ventilation and tracheal intubation through the LMA. In clinical trials, cricoid pressure significantly impeded the correct placement of the LMA (118,119) and decreased mean expiratory tidal volume (105,119). Fiberoptic tracheal intubation through the LMA with cricoid pressure applied is significantly more difficult (120), even if cricoid pressure is applied only after correct placement of the LMA (121). It has been clearly demonstrated in a study

of 50 patients that cricoid pressure may impair successful tracheal intubations through the intubating LMA (ILMA) (122). If the decision is made to use a LMA during a failed intubation, it may be necessary to release cricoid pressure temporarily to facilitate oxygenation, ventilation, and tracheal intubation through the LMA. This release would seem reasonable in view of the evidence demonstrating that cricoid pressure may become ineffective after a few minutes of application.

The Effect of Method of Airway Control on the Risk of Aspiration

Intubation. Tracheal intubation is the gold standard in protecting the airway from aspiration in anesthetized patients. However, evidence has suggested that evaluation of the seal provided by the cuff is necessary. In a bench top model (123) and subsequently by using intubated patients (124,125) in the intensive care unit, the high-volume, low-pressure cuff allowed methylene blue dye to leak from the subglottis via the longitudinal folds of the cuff into the trachea. A new cuff under evaluation, termed the pressure-limited tracheal tube cuff does not have these folds, and no leak was detectable in any of the patients tested. In addition, lubrication of the high-volume, low-pressure cuffs prevented leakage past the cuff *in vitro* (126).

However, despite possible improvements in cuff design, lung infection continues to be a problem in patients undergoing mechanical ventilation. It is believed that one mechanism involves microaspiration of secretions passing below the glottis through small channels between the cuff and tracheal mucosa. To test this hypothesis, a tracheal tube with a separate dorsal lumen ending proximal to the cuff has been compared with a standard tracheal tube in 190 patients undergoing ventilation (127). This new tube was designed to allow continuous aspiration of subglottic secretions. The incidence of ventilator-associated pneumonia was reduced significantly (19.9 episodes per 1000 ventilator days compared with 39.9 per 1000 ventilator days) in the patients who had their subglottic secretions aspirated continuously.

The cuffed tracheal tube is currently the standard device used for airway protection during mechanical ventilation. However, conventional tracheal tubes cause epithelial inflammation when *in situ* for several days. A new cuffless tube (Fig. 3), which has a low pressure sealing system consisting of 12–20 toroidal layers of a thin polyurethane film termed gills, has been designed to obviate tracheal damage. This tube is oval-shaped at the level of the gills and its contour provides a matching fit for the pentagonal-shaped glottic opening. In a study in sheep comparing this cuffless tube with a standard cuffed tracheal tube
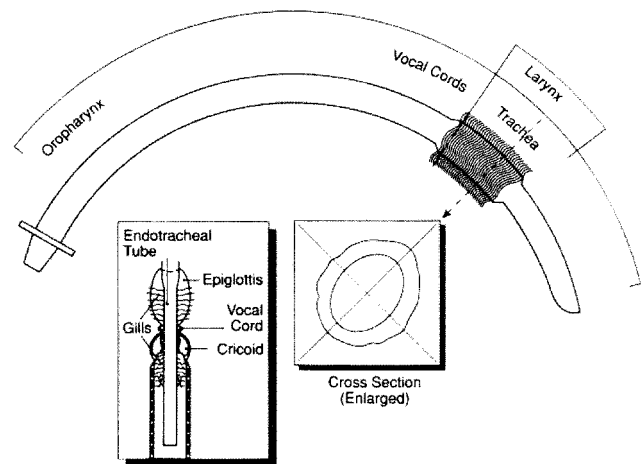

Figure 3. The ultra thin-walled two stage endotracheal tube. The approximate midsection of the endotracheal tube labeled "larynx" is positioned at the level of the glottic opening. Some of the "gills" will be above and some will be below the level of the vocal cords. The optimal position is midway. Gills that pass across the glottic opening are folded. With permission (128).

(128), methylene blue was used to detect aspiration. The dye was observed in the tracheae of 2 of 11 sheep intubated with a standard cuffed tube but was not found when the tracheal tube with gills was used. In addition, histology showed that epithelial injury was increased in tracheae intubated with a cuffed tube rather than in those in which the tube with gills was used. If this new tube is to be adopted, extensive clinical trials will be required to assess its safety and its role in anesthetic and intensive care practice.

In obstetric practice, where difficulty with intubation may be encountered, regional anesthesia is the technique of choice for operative procedures. In a 6-yr prospective review from 1993 to 1998 in the South Thames region in the UK, the percentage of cesarean deliveries performed under general anesthesia has been declining while cesarean deliveries as a proportion of the total number of deliveries have been increasing. There were 36 cases of failed intubation, giving an incidence of 1/249 (95% confidence interval, 1/370 to 1/187). No cases of aspiration or other adverse outcome were reported after these incidents (129).

A similar clinical scenario is the situation in which some anesthesiologists elect to avoid tracheal intubation in patients who may be at risk of aspiration. Obstetric patients in the peripartum period are an important population that has been reviewed retrospectively (6). There was one mild case of aspiration of 1870 patients who underwent general anesthesia for obstetric procedures except cesarean delivery. No precautions were made in terms of cricoid pressure and tracheal intubation. Although these patients were potentially at risk of aspiration, it is surprising that the incidence of aspiration was not more frequent.

In the emergency situation, there may be occurrences when a difficult airway is encountered and awake fiberoptic intubation is performed. From the foregoing, it is clear that the risk of regurgitation and aspiration is increased with sedation and local anesthesia of the respiratory tract. The clinical decision-making process is influenced by many factors, not only the risk of aspiration but also the presence of a difficult airway, patient cooperation, and the experience of the anesthesiologist. The evidence available in this situation is insufficient for any definitive recommendations to be made.

Airway Devices

There have been considerable technical advances in the last two decades in the development of new airway devices. These include the LMA, the cuffed oropharyngeal airway (COPA), the esophageal-tracheal Combitube (ETC), and the laryngeal tube. Studies on regurgitation and aspiration with these new devices have tended to concentrate on the LMA.

Laryngeal Mask Airway.   The use of the LMA is associated with a reduction in barrier pressure at the LES (130). In a study of 40 spontaneously breathing patients, there was a reduction in barrier pressure of 3.6 cm H_2O in the LMA group, and an increase in barrier pressure of 2.2 cm H_2O in a group anesthetized by using a face mask. To evaluate if this decrease in lower esophageal barrier pressure has clinical implications, a pH electrode may be placed in the midesophageal zone to detect gastric fluid. In a study of 20 patients comparing the cuffed tracheal tube with the LMA during general anesthesia with positive pressure ventilation, Valentine et al. (131) found that there were significantly more episodes of reflux in the LMA group. Although reflux was defined as a change of pH of ≥1 or an absolute decrease in pH to <5, in no patient did the pH decrease to a value <2.5. However, in another study involving 82 patients undergoing elective orthopedic surgery (132), there were no episodes of reflux at any time. In this study the pH electrode was positioned in the lower esophagus and in no patient did the lower esophageal pH decrease to <4.

In slightly more complex studies, measurements of pH were performed simultaneously at two esophageal levels. In 55 patients (133), it was found that the proportion of patients with reflux at the lower esophageal level was significantly more in a LMA group (53.5%) than in a Face Mask group (22.2%). In addition, in a study by Roux et al (134) who measured lower esophageal pH, the incidence of gastroesophageal reflux was 50% and 65% in females and males respectively anesthetized using a LMA, compared with 15% in the patients in whom a face mask and oropharyngeal airway were used. At the midesophageal level, the incidence of gastroesophageal reflux was much less in both studies and there was no significant difference in the incidence of reflux between the LMA and Face Mask groups. The reason for the association between gastroesophageal reflux with the LMA is unclear. There is insufficient direct evidence to support the hypothesis that the reduction in lower esophageal pH is influenced directly by either the pressure or the volume in the cuff of the LMA (134). However, because application of cricoid pressure causes a reduction in LES pressure (108), a similar reflex caused by increased pharyngeal pressure may also be induced by the LMA.

Bapat and Verghese (135) studied pH at the level of the larynx in 100 patients undergoing anesthesia with a LMA and positive pressure ventilation for gynecological laparoscopy. Methylene blue and fiberoptic laryngoscopy were used in addition to the pH electrode to assess regurgitation. There was no evidence of regurgitation in 99 of 100 patients. There was one case of regurgitation but not aspiration, as demonstrated by the presence of methylene blue in the laryngopharynx. This study supports the findings of Joshi et al. (136) who placed a pH electrode in the hypopharynx of spontaneously breathing patients in whom a LMA or tracheal tube was present. The hypopharyngeal pH did not decrease to below four in either group.

The infrequent incidence of gastroesophageal reflux in these two studies conflicts with observations in 20 healthy patients undergoing general anesthesia with the LMA (137). In this study in which the patients were breathing spontaneously, the incidence of gastroesophageal reflux was 60% and 20% at the lower esophageal level and at the bars of the LMA respectively. The reduction in pH at the level of the LMA occurred only in patients who were in the lithotomy position. It would seem, therefore, that although the LMA may reduce barrier pressure and pH at the lower esophageal level during general anesthesia, the upper esophagus and larynx are spared, provided that the patient is supine and not in the lithotomy position.

Other authors have suggested that the use of the LMA during either spontaneous ventilation (133) or positive pressure ventilation (138) may promote gastroesophageal reflux. It has been suggested that during spontaneous ventilation, a high negative intrathoracic pressure may be generated during inspiration and that during positive pressure ventilation, gastric insufflation may occur and cause increased intragastric pressures. In a study by Skinner et al. (139) using esophageal pH electrodes to compare reflux in 40 patients undergoing gynecological laparoscopies, there was no significant difference in the incidence in regurgitation between a group breathing spontaneously and one undergoing intermittent positive pressure ventilation. In a study by Akhtar and Street (138) involving 50 patients undergoing a variety of surgical procedures, methylene blue was used to assess regurgitation. During both spontaneous ventilation and intermittent positive pressure ventilation there was an

incidence of regurgitation of 1:25. From these studies, it may be deduced that the mode of ventilation does not appear to unduly influence the small risk of pharyngeal regurgitation in patients undergoing anesthesia with the LMA.

The timing of the removal of the LMA at the end of general anesthesia has been studied in a prospective, randomized controlled trial of 63 healthy patients (140). Lower esophageal pH was measured to assess the incidence of gastroesophageal reflux. The pH was significantly increased in patients in whom the LMA remained *in situ* until mouth opening occurred to command, compared with those in whom the LMA was removed when signs of rejection, such as restlessness, swallowing, and struggling, were observed. It is suggested therefore that the LMA should be removed when patients are able to open the mouth to command.

The distal end of the LMA sits in the hypopharynx at the junction with the esophagus and it has been suggested that it may inhibit regurgitation of material from esophagus into pharynx. This question has been examined in a study of 25 female and 25 male cadavers (141). Flexible and standard LMA 4 and LMA 5 were evaluated in a supine position with the head and neck in the neutral position. The regurgitation pressure, defined as the esophageal pressure at which fluid was first seen above the cuff or within the bowl of the LMA, was 19 cm H_2O at 0 mL of cuff volume, 47 cm H_2O at 10 cuff volume, and 51 cm H_2O at 20 mL cuff volume. In the control group without a LMA, the regurgitation pressure when fluid was noted in the hypopharynx was 7 cm H_2O. The position of the LMAs was checked with the fiberoptic laryngoscope at various airway sealing pressures and cuff volumes, and it was demonstrated that displacement of the LMA did not occur. Therefore, it may be concluded that LMAs that are placed correctly and that remain undisplaced attenuate liquid flow between the esophagus and pharynx of cadavers. However, the application of these results to clinical practice requires caution, as cadavers do not mimic the same conditions present in anesthetized patients. Indeed there have been reports of pulmonary aspiration after the use of the LMA (7,142,143).

If a standard LMA is not thought to protect the airway from aspiration in the event of regurgitation of gastric contents, would a redesigned LMA with an esophageal vent be useful? Such a device has recently been developed and is termed the ProSeal LMA (PLMA) (Laryngeal Mask Company, Henley-on-Thames, UK); this has an esophageal vent that allows the passage of a small orogastric tube, as shown in Figure 4 (144). The cuff of the PLMA has a flat dorsal component that has been manufactured to allow the ventral elliptical part to reside firmly in the periglottic tissues. In a study of 32 healthy patients, the PLMA provided a better seal than the LMA, with lower oropharyngeal leak pressures measured at zero cuff volume (145). Although the role of the PLMA
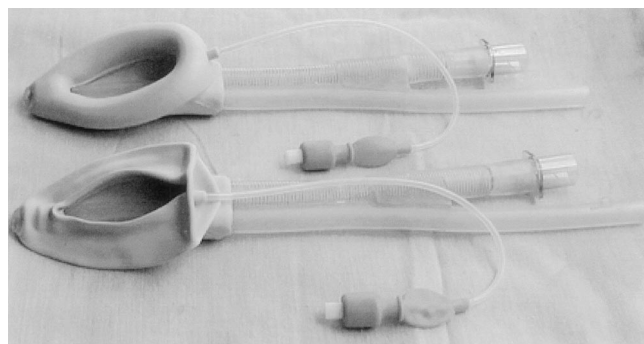

Figure 4. ProSeal Laryngeal Mask Airway. With permission (144).

in clinical practice has not yet been evaluated, it is possible to predict that the PLMA may be useful in a patient with a potentially full stomach when attempts to intubate the trachea have failed. The drainage tube may allow controlled drainage of gastric contents, and the more effective oropharyngeal seal of the airway would minimize the possibility of gastric insufflation during positive pressure ventilation.

In the Australian Incident Monitoring Study (9), the presence of a difficult airway and inadequate anesthesia have been included within the list of factors predisposing to regurgitation, vomiting, and aspiration. The importance of an unobstructed airway and adequate anesthesia cannot be overstated. To facilitate these objectives when other simple measures to obtain an airway have been unsuccessful, the ILMA, the COPA, the ETC, and the laryngeal tube may be useful.

The ILMA does not protect the airway from aspiration, but it allows airway maintenance and facilitates tracheal intubation (146) with a cuffed tube, as shown in Figure 5. In two studies (146,147) of 100 and of 60 blind intubations through the ILMA in patients without a difficult airway, the success rate was 93%. In a multicenter clinical study (148) of 500 patients, the success rate of blind intubations was 96.2%. In other studies of 12 patients (149) and 6 patients (150) who were suspected of having a difficult airway, all underwent successful intubation via the ILMA. In each Mallampati grade, from 1 to 4, there were intubation failures of 3.2%, 4.9%, 3.8%, and 0.0% respectively, in the multicenter clinical trial of 500 patients (148). Another study has shown that the use of a lightwand-guide improves the success rate of intubation via the ILMA and so minimizes the possibility of esophageal intubation (150). In a clinical trial in which healthy patients without neck abnormalities simulated a trauma scenario by wearing a semirigid neck collar, the ILMA was difficult to insert. Ventilation was difficult and tracheal intubation was successful in only 2 of the 10 patients. Fifty patients were planned for this trial but only ten were enrolled owing to the difficulties experienced (151).
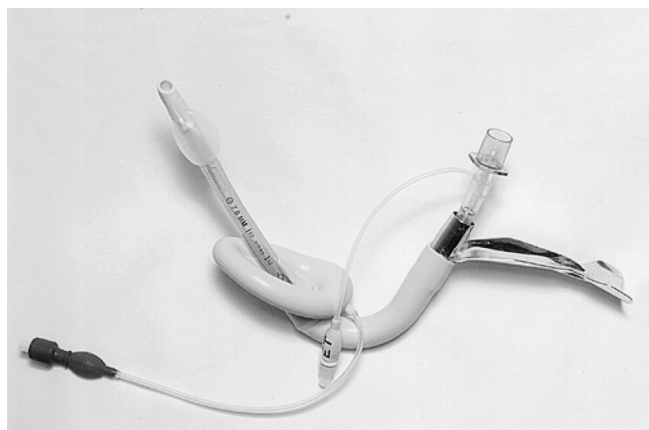
Figure 5. Intubating Larygeal Mask Airway (size 3) with a cuffed silicone tracheal tube of internal diameter 7.0 mm.

One case report cited a death attributable to the ILMA and several attempts at intubation. This patient was involved in a clinical trial and had an esophageal rupture (152). Other reported complications with the ILMA have not been life threatening. The most common airway complication was mucosal injury

COPA.   The COPA is an airway device that was not designed to protect the airway from aspiration. However, in a manner similar to that of the standard Guedel airway, it assists in the maintenance of an unobstructed airway and may reduce one of the predisposing factors to regurgitation and aspiration of gastric contents. One of the proposed benefits of the COPA is the presence of an inflatable cuff, which is said to form a seal in the proximal laryngopharynx, with the pointed anterior cuff elevating the epiglottis from the posterior pharyngeal wall. However, a fiberoptic assessment in 20 anesthetized patients did not show that the epiglottis was elevated from the posterior pharyngeal wall (153). In addition, the use of the COPA frequently requires airway adjustment maneuvers such as jaw lift, head rotation, neck extension, and adjustments (154–157).

The COPA has often been compared with the LMA and not the standard Guedel airway (155,157). In a randomized cross-over study of the COPA and the LMA, the LMA performed better than the COPA. The oropharyngeal leak pressure was higher for the LMA than the COPA, demonstrating that the LMA provided a better seal than the COPA (153). The implication of this difference with the COPA is that in the presence of ventilation with positive pressure, the possibility of gastric insufflation and hence gastric aspiration may be increased.

ETC.   Another airway device that is not commonly used but is given a role in the ASA practice guidelines for the management of the difficult airway (158) is the ETC. This is a double lumen tube with a high volume low-pressure tracheoesophageal distal cuff and a

proximal pharyngeal balloon. In a study of 23 patients (159), the performance of the distal cuff placed in the esophagus under direct laryngoscopy was assessed. All patients were paralyzed and their lungs were ventilated via the pharyngeal perforations with the proximal pharyngeal balloon inflated to sufficient pressure to just prevent an air leak. Regurgitation was assessed using methylene blue, which was not detected in the hypopharynx before insertion of the ETC, during laryngoscopy, or after removal.

Although this device may protect against regurgitation and allows drainage of gastric contents, if required, its use requires sufficient training and it is associated with some complications. In a prospective, randomized controlled study of 75 patients who were within 20% of their ideal body weight and who did not have a history of difficult intubation (160), complications were assessed after the use of the ETC, tracheal tube, and LMA. The four participating anesthesiologists were thoroughly familiar with all three devices. Despite this experience, the incidence of complications associated with the ETC, such as sore throat, dysphagia, and hematoma, was significantly more than that associated with tracheal intubation or LMA insertion. The main exception was the significantly frequent incidence of hoarseness associated with tracheal intubation.

Another more serious complication has been reported in a series of 1139 patients resuscitated with the ETC by basic emergency technicians (161). Autopsies were performed in four of the eight patients who had subcutaneous emphysema. In three of the four autopsies, esophageal lacerations were found. It has been suggested that these lacerations may be the pathway for the development of the subcutaneous emphysema. In addition, a case report of a midesophageal perforation and subcutaneous emphysema has been described during a clinical trial involving the ETC (162). Despite these complications produced by blind insertion, one study of 10 emergency patients did not report any significant problems caused by the ETC (163).

In other studies in which the ETC was inserted under direct vision, not blindly, major complications were avoided (159,164). In view of the seriousness of esophageal lacerations and the frequent incidence of sore throat, dysphagia, and hematoma, the ETC is not recommended for routine use unless it is inserted under direct vision. In the emergency situation when airway protection is required, the potential function of the ETC needs to be balanced against the problems that it might create.

Laryngeal Tube.   An airway device termed the "laryngeal tube" has recently been evaluated. In common with the ETC, the laryngeal tube has a proximal pharyngeal cuff and a distal esophageal cuff. In contrast with the ETC, this tube is shorter and has a single lumen allowing ventilation through the port between the two

cuffs. Owing to the single lumen, free gastric drainage is not possible with an inflated esophageal cuff. However, the marketed advantage of the laryngeal tube is its ease of blind placement compared with the ETC. In a recent study of 30 patients (165), all laryngeal tubes were inserted successfully on the first attempt. Fiberoptic laryngoscopy confirmed correct placement. In all cases, the tip of the tube was in the esophageal inlet and the epiglottis and/or the posterior pharyngeal wall were seen. Ease of handling has been cited in another study of 20 patients undergoing urological procedures (166). The ability of this tube to prevent regurgitation and aspiration remains to be evaluated.

To conclude, relevant past and present trials on the methods to minimize the risk of regurgitation and pulmonary aspiration have been presented. In particular, control of gastric contents, use of cricoid pressure, and methods of airway control have been discussed in detail. It is envisaged that the available evidence will help the anesthesiologist in clinical decision-making and hence lead to improvements in anesthetic management (64,71).

References

1. Olsson GL, Hallen B, Hambraeus-Jonzon K. Aspiration during anaesthesia: a computer-aided study of 185 358 anaesthetics. Acta Anaesthesiol Scand 1986;30:84–92.
2. Mellin-Olsen J, Fastin S, Gisvold SE. Routine preoperative gastric emptying is seldom indicated: a study of 85 594 anaesthetics with special focus on aspiration pneumonia. Acta Anaesthesiol Scand 1996;40:1184–8.
3. Warner MA, Warner ME, Weber JG. Clinical significance of pulmonary aspiration during the perioperative period. Anesthesiology 1993;78:56–62.
4. Warner MA, Warner ME, Warner DO, et al. Perioperative pulmonary aspiration in infants and children. Anesthesiology 1999;90:66–71.
5. Borland LM, Sereika SM, Woelfel SK, et al. Pulmonary aspiration in pediatric patients during general anesthesia: incidence and outcome. J Clin Anesth 1998;10:95–102.
6. Ezri T, Szmuk P, Stein A, et al. Peripartum general anaesthesia without tracheal intubation: incidence of aspiration pneumonia. Anaesthesia 2000;55:421–6.
7. Brimacombe JR, Berry A. The incidence of aspiration associated with the laryngeal mask airway: a meta-analysis of published literature. J Clin Anesth 1995;7:297–305.
8. Lockey DJ, Coats T, Parr MJA. Aspiration in severe trauma: a prospective study. Anaesthesia 1999;54:1097–109.
9. Kluger MT, Short TG. Aspiration during anaesthesia: a review of 133 cases from the Australian Anaesthetic Incident Monitoring Study (AIMS). Anaesthesia 1999;54:19–26.
10. Department of Health and Social Security. Deaths due to complications of anaesthesia. In: Report on confidential enquiries into maternal deaths in England and Wales. London: Her Majesty's Stationary Office; 1957–98.
11. Schreiner MS. Gastric fluid volume: is it really a risk factor for pulmonary aspiration? Anesth Analg 1998;87:754–6.
12. Plourde G, Hardy JF. Aspiration pneumonia: assessing the risk of regurgitation in the cat. Can Anaesth Soc J 1986;33:345–8.
13. Ingebo KR, Rayhorn NJ, Roxanne M, et al. Sedation in children: adequacy of two-hour fasting. J Pediatr 1997;131:155–8.
14. Schwartz DA, Connelly NR, Theroux CA, et al. Gastric contents in children presenting for upper endoscopy. Anesth Analg 1998;87:757–60.
15. Raidoo DM, Rocke DA, Brock-Utne JG, et al. Critical volume for pulmonary acid aspiration: reappraisal in a primate. Br J Anaesth 1990;65:248–50.
16. James CF, Modell JH, Gibbs CP, et al. Pulmonary aspiration: effects of volume and pH in the rat. Anesth Analg 1984;63:665–8.
17. Brodsky JB, Brock-Utne AJ, Levi DC, et al. Pulmonary aspiration of a milk/cream mixture. Anesthesiology 1999;91:1533.
18. O'Hare B, Lerman J, Endo J, Cutz E. Acute lung injury after instillation of human breast milk or infant formula into rabbits' lungs. Anesthesiology 1996;84:1386–91.
19. O'Hare B, Chin C, Lerman J, Endo J. Acute lung injury after instillation of human breast milk into rabbits' lungs. Anesthesiology 1999;90:1112–8.
20. Chin C, Lerman J, Endo J. Acute lung injury after tracheal instillation of acidified soya-based or Enfalac formula or human breast milk in rabbits. Can J Anaesth 1999;46:282–6.
21. Sinnatamby CS. Abdomen. In: Sinnatamby CS, ed. Last's anatomy regional and applied. Edinburgh: Churchill Livingstone, 1999:215–320.
22. McLauchlan G. Oesophageal function testing and antireflux surgery. Br J Surg 1996;83:1684–8.
23. Cadiot G, Bruhat A, Rigaud D, et al. Multivariate analysis of pathophysiological factors in reflux oesophagitis. Gut 1997;40:167–74.
24. Kahrilas PJ, Lin S, Chen J, Manka M. The effect of hiatus hernia on gastroesophageal junction pressure. Gut 1999;44:476–82.
25. Dent J, Holloway RH, Toouli J, Dodds WJ. Mechanisms of lower oesophageal sphincter incompetence in patients with symptomatic gastrooesophageal reflux. Gut 1998;29:1020–8.
26. Schoeman MN, Tippett MD, Akkermans LM, et al. Mechanisms of gastroesophageal reflux in ambulant healthy human subjects. Gastroenterology 1995;108:289–91.
27. Cotton BR, Smith G. The lower oesophageal sphincter and anaesthesia. Br J Anaesth 1984;56:37–57.
28. Gardaz JP, Theumann N, Guyot J, et al. Effects of propofol on lower oesophageal sphincter pressure and barrier pressure. Eur J Anaesthesiol 1996;13:203.
29. Van Thiel DH, Stremple JF. Lower esophageal sphincter pressure in cirrhotic men with ascites: before and after diuresis. Gastroenterology 1977;72:842–4.
30. Sinnatamby CS. Head and neck and spine. In: Sinnatamby CS, ed. Last's anatomy regional and applied. Edinburgh: Churchill Livingstone, 1999:321–447.
31. Kahrilas PJ, Dodds WJ, Dent J, et al. Effect of sleep, spontaneous gastroesophageal reflux, and a meal on upper oesophageal sphincter pressure in normal human volunteers. Gastroenterology 1987;92:466–71.
32. Vanner RG, Pryle BJ, O'Dwyer JP, Reynolds F. Upper oesophageal sphincter pressure and the intravenous induction of anaesthesia. Anaesthesia 1992;47:371–5.
33. Vanner RG, Pryle BJ, O'Dwyer JP, Reynolds F. Upper oesophageal sphincter pressure during inhalational anaesthesia. Anaesthesia 1992;47:950–4.
34. McGrath JP, McCaul C, Byrne PJ, et al. Upper oesophageal sphincter function during general anaesthesia. Br J Surg 1996;83:1276–8.
35. Eriksson LI, Sundman E, Olsson R, et al. Functional assessment of the pharynx at rest and during swallowing in partially paralysed humans. Anesthesiology 1997;87:1035–43.
36. Sundman E, Witt H, Olsson R, et al. The incidence and mechanisms of pharyngeal and upper esophageal dysfunction in partially paralysed humans. Anesthesiology 2000;92:977–84.
37. Berg H. Is residual neuromuscular block following pancuronium a risk factor for postoperative pulmonary complications? Acta Anaesth Scand 1997;110:156–8.
38. Tagaito Y, Isono S, Nishino T. Upper airway reflexes during a combination of propofol and fentanyl anesthesia. Anesthesiology 1998;88:1459–66.
39. Nishino T, Kochi T, Ishii M. Differences in respiratory reflex responses from the larynx, trachea and bronchi in anesthetized female subjects. Anesthesiology 1996;84:70–4.

40. Ing AJ, Ngu MC, Breslin ABX. Pathogenesis of chronic persistent cough associated with gastroesophageal reflux. Am J Respir Crit Care Med 1994;149:160–7.

41. Irwin RS, Madison JM, Fraire AE. The cough reflex and its relation to gastroeosphageal reflux. Am J Med 2000;108:73S–8S.

42. Hasegawa R, Nishino T. Temporal changes in airway protective reflexes elicited by an endotracheal tube in surgical patients anaesthetized with sevoflurane. Eur J Anaesthesiol 1999;16:98–102.

43. Moulton C, Pennycook AG. Relation between Glasgow coma score and cough reflex. Lancet 1994;343:1261–2.

44. Langton JA, Murphy PJ, Barker P, et al. Measurement of the sensitivity of upper airway reflexes. Br J Anaesth 1993;70:126–30.

45. Murphy PJ, Langton JA, Barker P, Smith G. Effect of oral diazepam on the sensitivity of upper airway reflexes. Br J Anaesth 1993;70:131.

46. Erskine RJ, Murphy PJ, Langton JA, Smith G. Effect of age on the sensitivity of upper airway reflexes. Br J Anaesth 1993;70:574–5.

47. Caranza R, Nandwani N, Tring JP, et al. Upper airway reflex sensitivity following general anaesthesia for day-case surgery. Anaesthesia 2000;55:367–70.

48. McIntyre JWR. Evolution of 20th century attitudes to prophylaxis of pulmonary aspiration during anaesthesia. Can J Anaesth 1998;45:1024–30.

49. Gallimore SC, Hoile RW, Ingram GS, Sherry KM. Questionnaire in the report of the national confidential enquiry into perioperative deaths 1994–5. London: NCEPOD; 1997.

50. Strunin L. In the report of the national confidential enquiry into perioperative deaths. London: NCEPOD; 1995;6:76–8.

51. Nimmo WS, Wilson J, Prescott LF. Narcotic analgesics and delayed gastric emptying during labour. Lancet 1975;1:890–3.

52. Porter JS, Bonello E, Reynolds F. The influence of epidural administration of fentanyl infusion on gastric emptying in labour. Anaesthesia 1997;52:1151–6.

53. Marsh RH, Spencer R, Nimmo WS. Gastric emptying and drug absorption before surgery. Br J Anaesth 1984;56:161–4.

54. Tarling MM, Toner CC, Withington PS, et al. A model of gastric emptying using paracetamol absorption in intensive care patients. Intensive Care Med 1997;23:256–60.

55. Lydon A, McGinley J, Cooke T, et al. Effect of anxiety on the rate of gastric emptying of liquids. Br J Anaesth 1998;81:522–5.

56. Hammas B, Hyarfner A, Thorn SE, Wattwil M. Propofol sedation and gastric emptying in volunteers. Acta Anaesthesiol Scand 1998;42:102–5.

57. Naslund E, Bogefors J, Gryback H, et al. Gastric emptying: comparison of scintigraphic, polyethylene glycol dilution and paracetamol tracer techniques. Scand J Gastroenterol 2000;35:375–9.

58. Sandhar BK, Elliot RH, Windram I, Rowbotham DJ. Peripartum changes in gastric emptying. Anaesthesia 1992;47:196–8.

59. Vaisman N, Weintrob N, Blumental A, et al. Gastric emptying in patients with Type I diabetes mellitus. Ann N Y Acad Sci 1999;873:506–11.

60. Billeaud C, Guillet J, Sandler B. Gastric emptying in infants with or without gastroesophageal reflux according to the type of milk. Eur J Clin Nutr 1990;44:577–83.

61. Van Den Driessche M, Peeters K, Marien P, et al. Gastric emptying in formula-fed and breast-fed infants measured with the 13C-Octanoic Acid Breath Test. J Pediatr Gastroenterol Nutr 1999;29:46–51.

62. Caballero-Plasencia AM, Muros-Navarro MC, Martin-Ruiz JL, et al. Gastroparesis of digestible and indigestible solids in patients with insulin-dependent diabetes mellitus or functional dyspepsia. Dig Dis Sci 1994;39:1409–15.

63. Merio R, Festa A, Bergmann H, et al. Slow gastric emptying in Type I diabetes: relation to autonomic and peripheral neuropathy, blood glucose, and glycaemic control. Diabetes Care 1997;20:419–23.

64. Villanueva-Meyer J, Swischuk LE, Cesani F, et al. Pediatric gastric emptying: value of right lateral and upright positioning. J Nucl Med 1996;37:1356–8.

65. Sethi AK, Chatterji C, Bhargava SK, et al. Safe pre-operative fasting times after milk or clear fluid in children. Anaesthesia 1999;54:51–85.

66. McClure RJ, Newell SJ. Effect of fortifying breast milk on gastric emptying. Arch Dis Child Fetal Neonatal Ed 1996;74:60F–2F.

67. Soreide E, Hausken T, Soreide JA, Steen PA. Gastric emptying of a light hospital breakfast: a study using real time ultrasonography. Acta Anaesthesiol Scand 1996;40:549–53.

68. Scrutton MJL, Metcalfe GA, Lowy C, et al. Eating in labour. Anaesthesia 1999;54:329–34.

69. Splinter WM, Schaefer JD. Ingestion of clear fluid safe for adolescent up to 3H before anaesthesia. Br J Anaesth 1991;66:48–52.

70. Maltby JR, Lewis P, Martin A, Sutherland LR. Gastric fluid volume and pH in elective patients following unrestricted oral fluid until three hours before surgery. Can J Anaesth 1991;38:425–9.

71. Litman RS, Wu CL, Quinlivan JK. Gastric volume and pH in infants fed clear liquids and breast milk prior to surgery. Anesth Analg 1994;79:482–5.

72. Maekawa N, Mikawa K, Yaku H, et al. Effects of 2, 4 and 12 hour fasting intervals on preoperative gastric fluid pH and volume, and plasma glucose and lipid homeostasis in children. Acta Anaesthesiol Scand 1993;37:783–7.

73. Splinter WM, Schaefer JD. Unlimited clear fluid ingestion two hours before surgery in children does not affect volume or pH or stomach contents. Anaesth Intensive Care 1990;18:522–6.

74. Schreiner MS, Triebwasser A, Keon TP. Ingestion of liquids compared with preoperative fasting in pediatric outpatients. Anesthesiology 1990;72:593–7.

75. American Society of Anesthesiologists Task Force on Preoperative Fasting. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures. Anesthesiology 1999;79:482–5.

76. Emerson BM, Wrigley SR, Newton M. Preoperative fasting in paediatric anaesthesia: a survey of current practice. Anaesthesia 1998;53:326–30.

77. Hveem K, Hausken T, Berstad A. Ultrasonographic assessment of fasting liquid content in the human stomach. Scand J Gastroenterol 1994;29:786–9.

78. Marzio L, Giacobbe A, Conoscitore P, et al. Evaluation of the use of ultrasonography in the study of liquid gastric emptying. Am J Gastroenterol 1989;84:496–500.

79. Cavell B. Gastric emptying in infants. Acta Paediatr Scand 1971;60:370–1.

80. Splinter WM. Preoperative fasting in children. Anesth Analg 1999;89:80–9.

81. Moore JG, Christian PE, Coleman RE. Gastric emptying of varying meal weight and composition in man: evaluation of dual liquid and solid phase isotopic method. Dig Dis Sci 1981;26:16–22.

82. Fasting S, Soreide E, Raeder JC. Changing preoperative fasting policies: impact of a national consensus. Acta Anaesthesiol Scand 1998;42:1188–91.

83. Green CR, Pandit SK, Schork MA. Preoperative fasting time: is the traditional policy changing? Anesth Analg 1996;83:123–8.

84. Ferrari LR, Rooney FM, Rockoff MA. Preoperative Fasting Practices in Pediatrics. Anesthesiology 1999;90:978–80.

85. Feldman M, Burton ME. Histamine$_2$ receptor antagonists: standard therapy for acid-peptic diseases. N Engl J Med 1990;323:1672–80.

86. Hatlebakk JG, Berstad A. Pharmacokinetic optimisation in the treatment of gastroesophageal reflux disease. Clin Pharmacokinet 1996;31:386–406.

87. Richardson P, Hawkey CJ, Stack WA. Proton pump inhibitors: pharmacology and rationale for use in gastrointestinal disorders. Drugs 1998;56:307–35.

88. Nishina K, Mikawa K, Takao Y, et al. A comparison of rabeprazole, lansoprazole and ranitidine for improving preoperative gastric fluid property in adults undergoing elective surgery. Anesth Analg 2000;90:717–21.

89. Nishina K, Mikawa K, Maekawa N, et al. A comparison of lansoprazole, omeprazole and ranitidine for reducing preoperative gastric secretion in adult patients undergoing elective surgery. Anesth Analg 1996;82:832–6.

90. Escolano F, Castano J, Lopez R, et al. Effects of omeprezole, ranitidine, famotidine and placebo on gastric secretion in patients undergoing elective surgery. Br J Anaesth 1992;69:404–6.

91. Kulkarni PN, Batra YK, Wig J. Effects of different combinations of H$_2$ receptor antagonist with gastrokinetic drugs on gastric fluid pH and volume in children–a comparative study. Int J Pharmacol Ther 1997;35:561–4.

92. Blum RA. Lansoprazole and omeprazole in the treatment of acid peptic disorders. Am J Health Syst Pharm 1996;53: 1401–15.

93. Maton PN, Orlando R, Joelsson B. Efficacy of omeprazole versus ranitidine for symptomatic treatment of poorly responsive acid reflux disease–a prospective, controlled trial. Aliment Pharmacol Ther 1999;13:819–26.

94. Stuart JC, Kan AF, Rowbottom SJ, et al. Acid aspiration prophylaxis for emergency caesarean section. Anaesthesia 1996; 51:415–21.

95. Sellick BA. Cricoid pressure to control regurgitation of stomach contents during induction of anaesthesia. Lancet 1961;2:404–6.

96. Vanner RG, Pryle BJ. Regurgitation and oesophageal rupture with cricoid pressure: a cadaver study. Anaesthesia 1992;47: 732–5.

97. Salem MR, Joseph NJ, Heyman HJ, et al. Cricoid compression is effective in obliterating the esophageal lumen in the presence of a nasogastric tube. Anesthesiology 1985;63:443–6.

98. Manning B, McGreal G, Winter DC, et al. Nasogastric intubation causes gastro-oesophageal reflux in patients undergoing elective laparotomy. Br J Surg 2000;87:637.

99. Ferrer M, Bauer TT, Torres A, et al. Effect of nasogastric tube size on gastroeophageal reflux and microaspiration in intubated patients. Ann Intern Med 1999;130:991–4.

100. Roewer N. Can pulmonary aspiration of gastric contents be prevented by balloon occlusion of the cardia? A study with a new nasogastric tube. Anesth Analg 1995;80:378–83.

101. Schwarzmann GF, Wurmb T, Greim CA, Roewer N. Difficult Airway Management. combination of the laryngeal mask airway with a new gastric balloon tube [abstract]. Anesthesiology 1998;89:1237A.

102. Thwaites AJ, Rice CP, Smith I. Rapid sequence induction: a questionnaire survey of its routine conduct and continued management during a failed intubation. Anaesthesia 1999;54: 372–92.

103. Salem MR, Wong AY, Mani M, Sellick BA. Efficacy of cricoid pressure in preventing gastric inflation during bag-mask ventilation in pediatric patients. Anesthesiology 1974;40:96–8.

104. Lawes EG, Campbell I, Mercer D. Inflation pressure, gastric insufflation and rapid sequence induction. Br J Anaesth 1987;59: 315–8.

105. Asai T, Barclay K, McBeth C, Vaughan RS. Cricoid pressure applied after placement of the laryngeal mask prevents gastric insufflation but inhibits ventilation. Br J Anaesth 1996;76:772–6.

106. Vanner RG. O'Dwyer JP, Pryle BJ, Reynolds F. Upper oesophageal sphincter pressure and the effect of cricoid pressure. Anaesthesia 1992;47:95–100.

107. Brimacombe JR, Berry AM. Cricoid pressure. Can J Anaesth 1997;44:414–25.

108. Tournadre JP, Chassard D, Berrada KR, Bouletreau P. Cricoid cartilage pressure decreases lower esophageal sphincter tone. Anesthesiology 1997;86:7–9.

109. Skinner HJ, Bedforth NM, Girling KJ, Mahajan RP. Effect of cricoid pressure on gastroesophageal reflux in awake patients. Anaesthesia 1999;54:798–808.

110. Palmer JH MacG, Ball DR. The effect of cricoid pressure on the cricoid cartilage and vocal cords: an endoscopic study in anaesthetised patients. Anaesthesia 2000;55:263–8.

111. Hartsilver EL, Vanner RG, Bewley J, Clayton T. Gastric pressure during emergency caesarean section under general anaesthesia. Br J Anaesth 1999;82:752–4.

112. Francis S, Enani S, Shah J, et al. Simulated cricoid force in paediatric anaesthesia. Br J Anaesth 2000;85:164P.

113. Hartsilver EL, Vanner RG. Airway obstruction with cricoid pressure. Anaesthesia 2000;55:208–11.

114. Vanner RG. Tolerance of cricoid pressure by conscious volunteers. Int J Obstet Anaesth 1992;1:195–8.

115. Vanner RG, Clarke P, Moore WJ, Raftery S. The effect of cricoid pressure and neck support on the view at laryngoscopy. Anaesthesia 1997;52:896–900.

116. Meek T, Gittins N, Duggan JE. Cricoid pressure: knowledge and performance amongst anaesthetic assistants. Anaesthesia 1999;54:51–85.

117. Meek T, Vincent A, Duggan JE. Cricoid pressure: can protective force be sustained? Br J Anaesth 1998;80:672–4.

118. Asai T, Barclay K, Power I, Vaughan RS. Cricoid pressure impeded placement of the laryngeal mask airway. Br J Anaesth 1995;74:521–5.

119. Aoyama K, Takenaka I, Sata T, Shigematsu A. Cricoid pressure impedes positioning and ventilation through the laryngeal mask airway. Can J Anaesth 1996;43:1035–40.

120. Asai T, Barclay K, Power I, Vaughn RS. Cricoid pressure impedes placement of the laryngeal mask airway and subsequent tracheal intubation through the mask. Br J Anaesth 1994;72: 732–4.

121. Asai T, Murao K, Shingu K. Cricoid pressure applied after placement of laryngeal mask impedes subsequent fibreoptic tracheal intubation through mask? Br J Anaesth 2000;85: 256–61.

122. Harry RM, Nolan JP. The use of cricoid pressure with the intubating laryngeal mask. Anaesthesia 1999;54:656–9.

123. Young PJ, Ridley SA, Downward G. Evaluation of a new design of tracheal tube cuff to prevent leakage of fluid to the lungs. Br J Anaesth 1998;80:796–9.

124. Young PJ, Basson C, Hamilton D, Ridley SA. Prevention of tracheal aspiration using the pressure-limited tracheal tube cuff. Anaesthesia 1999;54:559–63.

125. Young PJ, Ridley SA. Ventilator-associated pneumonia. Anaesthesia 1999:1183–97.

126. Young PJ, Rollinson M, Downward G, Henderson S. Leakage of fluid past the tracheal tube cuff in a benchtop model. Br J Anaesth 1997;78:557–62.

127. Valles J, Artigas A, Rello J, et al. Continuous aspiration of subglottic secretions in preventing ventilator associated pneumonia. Ann Intern Med 1995;122:179–86.

128. Reali-Forster C, Kolobow T, Giacomini M, et al. New ultrathin-walled endotracheal tube with a novel laryngeal seal design. Anesthesiology 1996;84:162–72.

129. Barnardo PD, Jenkins JG. Failed tracheal intubation in obstetrics: a 6-year review in a UK region. Anaesthesia 2000; 55:685–94.

130. Rabey PG, Murphy PJ, Langton JA, et al. Effect of the laryngeal mask airway on lower oesophageal sphincter pressure in patients during general anaesthesia. Br J Anaesth 1992;69:346–8.

131. Valentine J, Stakes AF, Bellamy MC. Reflux during positive pressure ventilation through the laryngeal mask. Br J Anaesth 1994;73:543–4.

132. Agro F, Brimacombe J, Verghese C, et al. Laryngeal mask airway and incidence of gastroesophageal reflux in paralyzed patients undergoing ventilation for elective orthopedic surgery. Br J Anaesth 1998;81:537–9.

133. Owens TM, Robertson P, Twomey C, et al. The incidence of gastroesophageal reflux with the laryngeal mask: a comparison with the face mask using esophageal lumen pH electrodes. Anesth Analg 1995;80:980–4.

134. Roux M, Drolet P, Girard M, et al. Effect of the laryngeal mask airway on oesophageal pH: influence of the volume and pressure inside the cuff. Br J Anaesth 1999;82:566–9.

135. Bapat PR, Verghese C. Laryngeal mask airway and the incidence of regurgitation during gynecological laparoscopies. Anesth Analg 1997;85:139–43.

136. Joshi GP, Morrison SG, Okonkwo NA, White PF. Continuous hypopharyngeal pH measurements in spontaneous breathing anesthetized outpatients: laryngeal mask airway versus tracheal intubation. Anesth Analg 1996;82:254–7.

137. McCrory CR, McShane AJ. Gastroesophageal reflux during spontaneous respiration with the laryngeal mask airway. Can J Anaesth 1999;46:268–70.

138. Akhtar TM, Street MK. Risk of aspiration with the laryngeal masks. Br J Anaesth 1994;72:447–50.

139. Skinner HJ, Ho BYM, Mahajan RP. Gastroeophageal reflux with the laryngeal mask during day-case gynaecological laparoscopy. Br J Anaesth 1998;80:675–6.

140. Cheong YP, Park SK, Son Y, et al. Comparison of incidence of gastroesophageal reflux and regurgitation associated with timing of removal of the laryngeal mask airway: on appearance of signs of rejection versus after recovery consciousness. J Clin Anesth 1999;11:657–62.

141. Keller C, Brimacombe J, Radler C, Puhringer F. Do laryngeal mask airway devices attenuate liquid flow between the esophagus and pharynx? A randomized controlled cadaver study. Anesth Analg 1999;88:904–7.

142. Ismail ZIA, Vanner RG. Regurgitation and aspiration of gastric contents in a child during general anaesthesia using the laryngeal mask airway. Paediatr Anaesth 1996;6:325–8.

143. Cassinello F, Rodrigo FJ, Munoz-Alameda L, et al. Postoperative pulmonary aspiration of gastric contents in an infant after general anesthesia with laryngeal mask airway (LMA). Anesth Analg 2000;90:1455–9.

144. Brain AIJ, Verghese C, Strube PJ. The LMA 'ProSeal' –a laryngeal mask with an oesophageal vent. Br J Anaesth 2000;84:650–4.

145. Keller C, Brimacombe J. Mucosal pressure and oropharyngeal leak pressure with the ProSeal versus the laryngeal mask airway in anaesthetized, paralysed patients. Br J Anaesth 2000; 85:262–6.

146. Brain AIJ, Verghese C, Addy EV, Kapila A. The intubating laryeal mask. I: development of a new device for intubation of the trachea. Br J Anaesth 1997;79:699–703.

147. Kapila A, Addy EV, Verghese C, Brain AIJ. The intubating laryngeal mask airway: an initial assessment of performance. Br J Anaesth 1997;79:710–3.

148. Baskett PJF, Parr MJA, Nolan JP. The intubating laryngeal mask. Anaesthesia 1998;53:1174–9.

149. Brain AIJ, Verghese C, Addy EV, et al. The intubating laryngeal mask. II: a preliminary clinical report of a new means of intubating the trachea. Br J Anaesth 1997;79:704–9.

150. Kilhara S, Watanabe S, Taguchi N, et al. A comparison of blind and lightwand-guided tracheal intubation through the intubating laryngeal mask. Anaesthesia 2000;55:427–31.

151. Wakeling HG, Nightingale J. The intubating laryngeal mask airway does not facilitate tracheal intubation in the presence of a neck collar in simulated trauma. Br J Anaesth 2000;84:254–6.

152. Branthwaite MA. An unexpected complication of the intubating laryngeal mask. Anaesthesia 1999;54:166–71.

153. Brimacombe J, Keller C. The cuffed oropharyngeal airway vs the laryngeal mask airway: a randomised cross-over study of oropharyngeal leak pressure and fibreoptic view in paralysed patients. Anaesthesia 1999;54:683–702.

154. Brimacombe J, Berry A. The cuffed oropharyngeal airway for spontaneous ventilation anaesthesia. Anaesthesia 1998;53:1074–9.

155. Brimacombe JR, Brimacombe JC, Berry AM, et al. A comparison of the laryngeal mask airway and cuffed oropharygeal airway in anesthetized adult patients. Anesth Analg 1998;87:147–52.

156. Asai T, Koga K, Jones RM, et al. The cuffed oropharyngeal airway. Anaesthesia 1998;53:810–22.

157. Greenberg RS, Brimacombe J, Berry AM, et al. A randomized controlled trial comparing the cuffed oropharyngeal airway and the laryngeal mask airway in spontaneously breathing anesthetized adults. Anesthesiology 1998;88:970–7.

158. American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology 1993;78:597–602.

159. Urtubia RM, Aguila CM, Cumsille MA. Combitube: a study for proper use. Anesth Analg 2000;90:958–62.

160. Oczenski W, Krenn H, Dahaba AA, et al. Complications following the use of the Combitube, tracheal tube and laryngeal mask airway. Anaesthesia 1999;54:1161–5.

161. Vezina D, Lessard MR, Bussieres J, et al. Complications associated with the use of the esophageal-tracheal Combitube. Can J Anaesth 1998;45:76–80.

162. Klein H, Williamson M, Sue-Ling HM, et al. Esophageal rupture associated with the use of the Combitube. Anesth Analg 1997;85:937–9.

163. Blostein PA, Koestner AJ, Hoak S. Failed rapid sequence intubation in trauma patients: esophageal tracheal Combitube is useful. J Trauma 1998;44:534–7.

164. Hartmann T, Krenn CG, Zoeggeler A, et al. The oesophageal-tracheal Combitube small adult: an alternative airway for ventilatory support during gynaecological laparoscopy. Anaesthesia 2000;55:670–5.

165. Doerges V, Ocker H, Wenzel V, Schmucker P. The laryngeal tube: a new simple airway device. Anesth Analg 2000;90:1220–2.

166. Doerges V, Ocker H, Sauer C, Schmucker P. The laryngeal tube: good ventilation, less risk during basic life support? Ann Emerg Med 1999;34:S91.