REVIEW OF LITERATURE
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Occurrence of regurgitation and vomiting, with subsequent inhalation of gastric contents into the bronchial tree, is not uncommon and remains an important factor in the morbidity and mortality of anaesthesia. Hall (1940) reported the death of a normal, healthy primigravida which occurred as a result of aspiration of vomit during anaesthesia for a forceps delivery.

Mendelson (1946) described a previously unrecognized pulmonary complication of a general anaesthesia.

The actual aspiration often escaped recognition, but was followed by an "asthmatic like" syndrome with distinct clinical, radiological and pathological features.

There was cyanosis, tachycardia, dyspnoea and bronchospasm, but no mediastinal shift or massive atelectasis. Wheezes, rales and rhonchi were heard sometimes over the affected portions of the lungs. X-ray revealed irregular, soft, nodular densities.
Progressive cardiac embarrassment and pulmonary oedema sometimes supervened.

Mendelson was able to reproduce this syndrome in rabbits using \textit{N}/10 Hydrochloric acid and un-neutralized human fluid gastric contents. At autopsy, there was congestion and oedema throughout the lungs, a \textit{wavy} bronchiolar pattern indicative of spasm, with peribronchiolar haemorrhage and exudate, usually with areas of secondary emphysema. The bronchial mucous membrane had sloughed in places.

When normal saline, distilled water or neutralized fluid gastric contents were injected into the rabbit's lung, a brief phase of obstructive respiration ensued, but breathing quickly returned to normal. The lungs showed only minute scattered areas of atelectasis. It was concluded that the features of Mendelson's syndrome could be attributed to the aspiration of gastric Hydrochloric acid.

Later, Teabeaut (1952) found that the pH of acid introduced into the lungs had to be below 2.5 to produce pneumonitis-like tissue reaction, and the gastric secretions of higher pH produced approximately the same tissue response as isotonic saline solution. Also the volume of gastric contents is of importance (Harnister and Sattilato, 1963; Are et al, 1964;
Greenfield et al., 1969) and it has been suggested that acid aspiration pneumonitis is most likely to occur when the pH of the aspirated fluid is below 2.5 and the volume exceeds about 20 ml (Vandam 1965; Roberts and Shirley 1974; Stoolting 1978). Taylor (1975) has reported its occurrence with gastric contents at pH 3.5.

PATHOLOGY OF ACID ASPIRATION

Most of the knowledge of the pathologic changes of acid aspiration is based on experiments done on animals. After aspiration, acid is rapidly distributed throughout the lungs, and damage occurs immediately. Acid gastric juice stained with methylene blue and aspirated into an isolated dog lung can be seen on the surface of the lung within 12 to 18 seconds. Isolated areas of atelectasis become visible when the dye appears and become extensive within 3 minutes (Hamelberg et al., 1964). Pathologic examination within the first few hours of acid aspiration reveals epithelial degeneration of the bronchi, pulmonary oedema, and haemorrhage with electron microscopy, necrosis of type I alveolar cells and the presence of free lamellated inclusion bodies in the pulmonary transudate are noted. Within 4 hr, there is an acute infiltration of polymorphonuclear cells, and fibrin can be seen in the alveolar space. Degeneration of alveolar type II cells and further necrosis of type I cells with detachment from the basement membrane can also
be noted. During the next 24 to 36 hr, marked polymorphonuclear infiltration results in alveolar consolidation, and damage to the airways may result in mucosal sloughing. After 48 hr, hyaline membranes can be seen (Greenfield et al., 1969). Gross examination shows lungs that are boggy, oedematous, and haemorrhagic. At 72 hr, resolution has already begun, there is regeneration of bronchial epithelium, proliferation of fibroblasts, and a decrease in acute inflammation (Dowms et al., 1974).

Lungs obtained from experimental animals 2 to 3 weeks after acid aspiration usually are normal or slightly increased in weight and show parenchymal scarring with pleural retraction.

**PHYSIOLOGY OF ACID ASPIRATION**

The severe chemical burn induced by acid aspiration causes loss of alveolar capillary integrity and exudation of fluid and protein into the alveoli and bronchi (Greenfield et al., 1969). Serum protein electrophoresis done on material aspirated from a small bronchus after acid aspiration reveals a pattern identical to that of serum (Ave et al., 1966). This exudation causes increased lung weight, decreased pulmonary compliance, and pulmonary oedema (Greenfield et al., 1969; Cannra et al., 1972; Davidson et al., 1974). The accompanying loss of
intravascular volume may cause severe hypotension (Lewis et al., 1971; Greenfield et al., 1969; Cameron et al., 1972).

Hypoxia can occur within minutes of acid aspiration (Awe et al., 1966; Lewis et al., 1971; Greenfield et al., 1969; Namelberg et al., 1964; Cameron et al., 1972). It has multiple causes. First, reflex airway closure occurs in response to the aspiration of fluid (Davidson et al., 1974; Nalnyi et al., 1962; Colebatch et al., 1962). Second, surfactant activity decreases when surfactant is destroyed, diluted or altered by acid, this reduction leads to alveolar instability and atelectasis (Awe et al., 1966; Colebatch et al., 1962; Modell et al., 1967). Third, the outpouring of fluid and protein into damaged tissues causes interstitial and alveolar oedema resulting in further airway closure. Finally, alveolar haemorrhage and consolidation occur, followed by hyaline membrane formation. All these conditions contribute to the large alveolar-arterial oxygen differences and significant increase in venous admixture.

Acid aspiration also causes changes in the pulmonary vasculature. Initially, pulmonary artery pressure may rise rapidly (Awe et al., 1966; Namelberg et al., 1964), however it falls quickly in association
with decreased cardiac output resulting from loss of intravascular volume (Awe et al., 1966; Greenfield et al., 1969). As a consequence, pulmonary artery pressure is usually low or normal (Cameron et al., 1972; Chapman et al., 1974). On the other hand, pulmonary vascular resistance is elevated (Greenfield et al., 1969; Tousaint et al., 1974; Fisk et al., 1970). This may be due to hypoxic vasoconstriction or anatomic obstruction. Marked constriction of pulmonary arterioles has been seen arteriographically (Booth et al., 1972) and histologically (Hamelberg et al., 1964) after aspiration, and in-situ thrombus formation also has been reported (Booth et al., 1972; Cameron et al., 1968).

CLINICAL CORRELATION (Wynne et al., 1977).

The clinical picture produced by aspiration of gastric contents depends on the nature of the material aspirated. Aspirations in humans are termed "acid" if the pH is less than 2.5 and "non-acid" or "neutral" if the pH is greater than 2.5.

Vomiting may produce the aspiration picture of solid particulate matter occluding various parts of the tracheobronchial tree, the physical signs are those of collapse localized to the area distal to the blockage. Death may occur quickly from tracheal or bronchial obstruction, but the sequence of events will depend on the particulate size and position of the occlusion.
The main physiologic distinction between the aspiration of acid and neutral clear liquid is that the acute respiratory decompensation caused by the latter is frequently short-lived and more easily reversible.

If the acidity is less than pH 2.0 and volume is of the order of 0.4 ml/kg, then the full blown picture of aspiration pneumonitis will be seen (Roberts et al, 1974). Lewis, Burgess and Hampson (1971) studied 18 patients with documented aspiration. Although the volume of aspirate was not known, there was a direct relation between mortality and gastric acidity. Particularly alarming was the 100% mortality rate among patients with a gastric pH of less than 1.8. This rate prevailed, despite vigorous supportive measures such as intubation, positive-pressure ventilation and administration of steroids, antibiotics and intravenous fluids. When the gastric pH was between 1.8 and 2.5, however, the mortality rate was only 25%.

Carefully analysed, much of the experimental and clinical information available suggests that the term "Mendelson's syndrome", used to describe severe acid aspiration, may be a misnomer. Mendelson's original work described clinical observations of 46 patients. The character of the aspirated material was known in 45. Five aspirates contained large particles. These patients
presented with symptoms of large airway obstruction. The remaining 40 aspirates were liquid. After aspiration these patients developed an asthma-like syndrome. On the basis of his experimental data, Mendelson assumed this clinical response was caused by acid aspiration. However, the mortality rate in his patients was zero, in marked contrast to experimental studies of acid aspiration and other clinical studies in which mortality rates were as high as 35% to 60% (Lewis et al., 1971; Cameron et al., 1973; Tinstman et al., 1973; Arms et al., 1974). Furthermore, in about 75% of his patients the course was uncomplicated. Finally, although none of his patients received ventilatory supports, all recovered in 36 hr. The clinical syndrome described in Mendelson’s patients resembled only slightly the findings of severe life-threatening pulmonary injury that Mendelson demonstrated experimentally and that we now associate with acid aspiration. Most of the Mendelson’s patients may have aspirated only small amount of acid or may have experienced some form of “non-acid” aspiration.

The concept of pH is - The term pH was introduced in 1909 by Sorensen, who defined pH as the negative logarithm of the hydrogen ion concentration.

$$ pH = - \log (H^+) $$
This definition, while not rigorous, is adequate for most biochemical purposes. To calculate the pH of a solution:

1. Calculate hydrogen ion concentration \((H^+)\)

2. Calculate the base 10 logarithm of \((H^+)\)

3. pH is the negative of the value found in step 2.

For example, for pure water at 25°C:

\[
pH = -\log (H^+) = -\log 10^{-7} = -(-7) = 7.0.
\]

Low pH (acidic) values (below 7.0) correspond to high concentrations of \(H^+\), and high pH (basic) values (above 7.0) to low concentrations of \(H^+\).

Acids are proton donors and bases are proton acceptors. A distinction is made, however, between strong acids (e.g. HCl, \(H_2SO_4\)), which completely dissociate even in strongly acidic solutions (low pH), and weak acids, which dissociate only partially in acidic solution. A similar distinction is made between strong bases (e.g. KOH, NaOH) and weak bases (e.g. Ca(OH)\(_2\)). Only strong bases are dissociated at high pH.

**SECRETION OF HYDROCHLORIC ACID BY THE STOMACH**

(Bennister et al., 1943).

The acidity of the stomach content is one of the primary causes of aspiration pneumonia. Hydrochloric acid
is secreted in a virtually pure state by the oxyntic
cells of the gastric mucosa, the undiluted secretions
having a titrimetric acidity of 0.17 N and pH of 0.87.

Gastric acid production is primarily controlled
by the vagus nerves. Alcohol stimulates the production
of large amounts of acid. Personality and emotion play
an important part in the gastric secretion. Relaxed or
sedated individuals secrete small amounts of acid.
Anxiety states, however, result in high rates of acid
secretion.

Shey and Sun (1956) reported finding gastric
contents of pH 2 to pH 1.3 during fasting and Holmes
(1956) found that some women in labour had gastric
contents of pH 2.0 to 1.0.

**Gastric emptying** :- Meal is evacuated from the stomach
within two to four hours and normally this is true.

Gastric emptying can be delayed by drugs
commonly used for pre-anesthetic medication and for
pain relief. Atropine in doses of 0.4 mg probably does
not alter gastric emptying, and antagonizes the effect
of morphine. Larger doses of Atropine (0.8 mg) markedly
decrease the tone and motility of the stomach
(Goodman et al. 1953).
The stomach is known to empty poorly during high intestinal obstruction. Displacement of the stomach by large tumours may retard evacuation of stomach contents. This situation is encountered in pregnant women at term when the uterus presses the pyloric portion of the stomach upward and backward.

Anxiety and pain have been universally believed to retard gastric emptying.

**Applied anatomy of vomiting (Brown, 1963)**: The expulsion through the mouth of material from the alimentary tract is by muscular action. The act of vomiting is preceded by salivation, rapid breathing, pallor, sweating and tachycardia.

Like any other reflex arc, vomiting has its afferent and efferent pathways and its central connexions.

**Afferent pathways**: Impulses travel from many parts of the body and ascend in the visceral afferent fibres accompanying the vagus and less importantly, the sympathetic.

Chemical changes occurring in the body do not stimulate the vomiting centre directly but reflexly by stimulating the chemoreceptor trigger zone of Morison and Wang (Morison and Wang, 1953).
The vomiting centre:-- This is closely related to other vital centres, e.g. the respiratory and vasomotor centres and the vestibular and salivary nuclei, in the dorsolateral border of lateral reticular formation. The chemoreceptor trigger-zone lies superficial to the true vomiting centre.

Efferent pathways and mechanics of vomiting:-- The efferent pathways of vomiting reflex are many and various, both somatic and visceral pathways being involved.

The mechanics of vomiting may be stated as follows (Davenport, 1961). This commences with a deep inspiration followed by closure of the glottis and nasopharynx and is immediately followed by expiration together with contraction of the muscles of the abdominal wall and descent of diaphragm. Now while the body of stomach relaxes, the antrum and also the pylorus and duodenum contract. This propels stomach contents into the oesophagus and mouth, and prevents escape from the stomach via the pylorus. A pressure of 40 cm. H₂O is needed to lift the contents of the stomach into the mouth in the upright position. The cardia is elevated during vomiting so that the abdominal part of the oesophagus rises into the chest (Johnson et al., 1966). While the glottis goes into spasm during the explosive phase, it soon relaxes, so that aspiration of stomach contents into the bronchial tree is almost bound to
happen in the unconscious supine patient. Pre-disposing factors during anaesthesia include: (a) Hypoxia, (b) Central stimulation during second stage general anaesthesia - either during induction or recovery, (c) Irritation of the base of the tongue or pharynx by airways etc., (d) Breath-holding and cough.

Regurgitation: Being a passive act, may be silent and unheralded, and so even more potentially dangerous than vomiting. Pre-disposing factors include:
(a) The head-down position if the cardia is inefficient. (b) A stomach full of fluid, (c) An indwelling stomach or oesophageal tube.

The cardia sphincter: This is both a sphincter and a valve. It remains closed because of:

(1) The presence of an anatomical muscular sphincter (Cade et al, 1958).
(2) Folds of thickened mucosa in the oesophagus (Bootha, 1958).
(3) The angle at which the oesophagus meets the fundus of the stomach (Marchand, 1955).
(4) The pinch-cock action of the crura of the diaphragm (in two thirds of patients the right crus only).

Integrity of the sphincter: Its activity is controlled radially (Vagus and sympathetic nerves). Its integrity
is not affected by posture, anaesthetics, relaxants, autonomic blocking agents, or injecting the oesophageal mucosa with local analgesics (O'Hallane, 1954). Its integrity is affected and it is made incompetent by:

(1) Anatomical abnormality, e.g. hiatus hernia
(Dimmick, 1961),

(2) The presence of a stomach tube,

(3) Passage of anaesthetic gas from above during attempts at I.P.P.V.,

(4) Attempts at active respiration in the presence of respiratory obstruction.

Ingesting antacids, e.g., Magnesium trisilicate, 15 ml. of the B.P.C. mixture 2-hourly, may increase gastrin production and so may tighten up the sphincter. Intravenous Metoclopramide doubles the basic tone of the sphincter (Meitman et al, 1970).

Thus, in normal patients under anaesthesia if the active vomiting reflex is suppressed, no material can regurgitate from the stomach into the oesophagus, no matter what position the patient is in, as long as the valve/sphincter mechanism is not interfered with.

The oesopharyngeal sphincter: This is at the upper end of the oesophagus at the level of C4 and is composed of striated muscle. Its action is both voluntary and reflex.
Its integrity is affected by both anaesthetics and relaxants. It acts as a sphincter normally but as a valve when paralysed. Normally it allows fluid to pass from the pharynx into the oesophagus, but not in the reverse direction. When paralysed by relaxants, it tends to obstruct the passage of fluids from the pharynx to the oesophagus, but not in the reverse direction.

The lower part of the oesophagus contains plain muscle which is not affected by relaxants, but the upper part, the cricopharyngeal sphincter, behaves like striped muscle (Sinclair, 1959).

The Hydrodynamics of Regurgitation:— The normal intragastric pressure is 5-7 cm.\( \text{H}_2\text{O} \) and double this in advanced pregnancy. This is well below the pressure required for reflux through the cardia (Spence et al., 1967). Even when the stomach is distended the pressure is unlikely to be greater than 15 cm.\( \text{H}_2\text{O} \) unless there is contraction of the abdominal muscles (O'Mullane, 1954).

If the glottis is maintained at a height in centimetres above the cardia greater than the intragastric pressure in cm.\( \text{H}_2\text{O} \), i.e. with a head-up tilt of 40-45°, and if the abdominal muscles are prevented from contracting, then regurgitation is unlikely (Saw et al., 1959).
Measurements of intragastric pressure during the fasciculation following injection of Suxamethonium are usually not greatly increased (Dinnick, 1967), but in about 12 per cent of patients a rise greater than 19 cm.\(H_2O\) occurs (Elliott, 1968). This evidence might suggest that Suxamethonium should not be used for intubation in such patients even with a high head-up tilt, as gastric contents could be forced up to the glottis by the increase in intragastric pressure. The question needs clarification as reported pressure measurements are not in agreement (Spence et al., 1967; Roe, 1962).

**CAUSES OF VOMITING**

(a) Vomitable material in the stomach or oesophagus:

1. Inadequate pre-operative preparation of the patient. Gastric emptying time varies between 4 and 8 hours; it is usually between 5 and 6 hours (Horton, 1965).

2. In pyloric obstruction,

3. When there is peritoneal irritation (e.g., perforated peptic ulcer, acute inflammatory lesions etc.),

4. Blood in the stomach following bleeding from ulcer, tumour beds, oesophageal varices, or during gastric operations.
(5) Gross abdominal distension,
(6) Glucose solution mistakenly given to diabetic patients by mouth, instead of intravenously,
(7) In case of oesophageal disease, such as pouch or obstruction.
(b) Vomitable material returned into stomach from bowel, as in cases of intestinal obstruction.
(c) When stomach emptying time is delayed:
(1) In women in labour,
(2) In cases of head injury,
(3) When there is emotional strain associated with pain, accident, and the incident of hospitalization,
(4) In seriously ill patients,
(5) After drugs, e.g., Opiates.

Factors Pre-disposing to Passive Regurgitation:
(Dinnick, 1967).
(a) Considerable volume of fluid in stomach:
(1) In the emergency case,
(2) The patient prepared for elective surgery has a variable amount of resting gastric juice. In the nervous patient this is increased in both quantity and acidity.
(b) Incompetence of the cardia:

(1) Hiatus hernia,
(2) Increased vagal tone,

(c) Raised intra-abdominal pressure:

(1) Posture, e.g. lithotomy position,
(2) Suxamethonium fasciculations,
(3) Pregnancy, especially where there is a high head or hydramnios.

(d) Lowered intrathoracic pressure: This can occur with deep spontaneous respiration, and is exaggerated when there is respiratory obstruction as in difficult induction of anaesthesia.

(e) Obesity: There is both a raised intra-abdominal pressure (O'Mullane, 1954) and a greater likelihood of respiratory obstruction during induction of anaesthesia, particularly in unskilled hands.

(f) Pregnancy: Incorporating several factors already mentioned.

(g) Relaxation of oropharyngeal by deep anaesthesia or muscle relaxants.
**TIME OF ASPIRATION:**

1. At onset of disease or time of injury.
2. During pre-operative preparation and investigation.
3. During transportation of the patient.
4. During induction of anaesthesia - It is during induction of anaesthesia that the hazard is greatest.
5. During Anaesthesia.
6. At the end of operation - Aspiration of vomitus or regurgitated material occurs at the end of operation with nearly the same frequency as it does during induction: it is equally, if not more dangerous.
7. In the recovery room or Intensive Care Unit.
8. In the remote post-operative period.

**PREVENTION OF ASPIRATION PNEUMONITIS**: (Robert B. Roberts, 1977).

Different methods have been used in the past to prevent this complication. The first principle of prevention is the possession of a high index of suspicion. Any method, which either reduces gastric content volume to below 35 ml or raises gastric pH to above 2.3 can reduce the number of patients at risk.

**Emptying the stomach**: Pre-anaesthetic mechanical or pharmacological emptying of the stomach is theoretically ideal. Regular naso-gastric tubes offer no guarantee of
complete emptying, and leaving a tube in-situ during induction may lead to incompetence of the gastro-
oesophageal junction, thus facilitating regurgitation. Large bore tubes may be more effective but their use is unpleasant and time consuming, and they still do not guarantee complete emptying. Indeed the use of such tubes may be positively harmful, in that they lull the anaesthesiologist into a false sense of security.

Apomorphine given slowly, 1 to 3 mg intravenously, has been used to stimulate vomiting prior to anaesthesia (Herschenson et al, 1947). Atropine must be available to stop the retching and nausea after the vomiting. This is also an unpleasant procedure and not without risk, circulatory collapse having been reported (Parr, 1956).

Intubation of the conscious patient: — Intubation of the conscious patient has often been recommended. While awake intubation following good local anaesthesia, adequate sedation, and an unhurried approach may be very valuable in certain type of surgical patients, but not for obstetrical cases. The sedation required is hardly appropriate in obstetrics, and if local anaesthetics are applied to the larynx and vomiting occurs during intubation, aspiration can still occur. There should be enough time to carry out awake intubation. Passing a tube
into a conscious person's trachea without adequate sedation or local anaesthesia is a barbaric procedure.

**Position:** Position of patient during induction is another controversial subject. The head down position has been recommended (Dinnick, 1957) because if any vomiting occurs, this position would allow the gastric contents to flow out of the patient's mouth without contaminating the trachea. The major disadvantage of this position, however, is that it may promote passive regurgitation. Many favour a steep head up tilt in order to discourage regurgitation (Snow et al, 1959). Intra-gastric pressure may increase dramatically after succinyl choline administration (Anderson, 1962; Roe, 1962), and if regurgitation or vomiting does occur, aspiration is almost inevitable. The steepness of the head-up tilt required to prevent regurgitation may make intubation difficult. A small dose of d-tubocurarine given three or four minutes prior to induction helps to prevent the increase in intra-abdominal pressure following succinyl choline. The lateral position has also been recommended (Nashlow et al, 1963), but this position is foreign to most anaesthetists during induction and makes intubation difficult, if the airway becomes obstructed, the lateral position will enhance vomiting. Cricoid pressure, as advised by Sellick (Sellick, 1961), can effectively seal the oesophagus.

Crash Induction — The term crash induction is not actually clearly defined. However, it can be taken to mean a method by which the patient is taken from a state of unpremedicated consciousness to one where the airway has been secured by the passage of cuffed endotracheal tube in the shortest possible time. The standard approach to this type of technique follows the sequence outlined below.

1. The stomach is emptied of all fluids by aspiration through a nasogastric tube. The tube is removed before induction of anaesthesia.

2. All monitoring equipment is secured and an intravenous infusion is set up before anaesthesia is induced.

3. The supine jackknife position, head raised (40 - degree, head-up position), is assumed for induction.

4. Pre-oxygenation is performed for 3 to 5 minutes.

5. A competitive blocker is pre-administered.

6. The intravenous induction by a pre-selected dose of Barbiturate or Ketamine is followed by a generous dose of at least 100 mg of succinylcholine in the 70 kg adult.
7. Cricoid pressure is applied. As soon as the intravenous agent is given, Sellick's maneuver is performed. Sellick (1961) applied backward pressure of the cricoid cartilage against the cervical vertebrae to occlude the esophagus (a) to control regurgitation of stomach or esophageal contents during induction of anaesthesia, or (b) to prevent gastric distension from positive pressure ventilation applied by face piece or mouth to mouth respiration.

8. Intubation is carried out as expeditiously as possible.

9. When the trachea is secured, patient is rapidly restored to the supine or slightly head-down position.

10. Anaesthesia is continued as dictated by the clinical circumstances.

11. During and at the termination of anaesthesia, persistent efforts are made to empty the stomach.

12. Extubation is performed in the lateral, head down position after the lungs have been filled with pure oxygen and the patient is clearly able to maintain his own airway.

**ACID PROPHYLAXIS**

In his original paper Henderson suggested the use of weak antacids both as an antacid and a buffer for residual acid.
The use of mist Magnesium trisilicate B.P. is well established in obstetric practice, following the report of Taylor and Pryce-Davies (1966).

Peaseett (1973) in a further clinical evaluation of the effectiveness of Magnesium trisilicate, showed that the number of patients with a pH of 2.5 or below at emergency caesarean section was reduced from 43.5 to 8.5 percent.

Roberts and Shirley (1974) showed conclusively that the use of antacids prior to caesarean section reduced the number of patients at risk from one in four to one in 48.

Hester and Heath (1977) strongly urged the use of mist Magnesium trisilicate pre-operatively. However, drawbacks are apparent. These include decreased effectiveness with time, associated increase in gastric volume, inconsistency in pH changes, increase in gastric emptying time, and possible pneumonitis from aspirated antacid (Gibbs et al., 1979). Antacids also interfere with absorption or excretion of other drugs. Bioavailability of Cimetidine is reduced from 3 to 48% in subjects taking antacids concurrently (Bodswar et al., 1979).
ANTICHOLINERGICS

It has been accepted that gastric acid production is primarily controlled by the vagus nerve. Anticholinergic medications inhibit gastric juice production and acidity and increase the resistance of gastro-oesophageal angle to reflux. The degree of inhibition, however, is not the same with all drugs. The anticholinergic quaternary Ammonium compound, Glycopyrrolate, suppresses gastric secretion much more than Atropine or Scopolamine.

Atropine sulphate causes no appreciable reduction in gastric pH, although volume of secretion is apparently reduced.

In comprehensive pharmacologic studies reported by Franko et al (1963), the quaternary Ammonium agent Glycopyrrolate manifested an anticholinergic property, with potency similar to that of Atropine, but more importantly, their studies revealed that Glycopyrrolate possessed a high degree of selectivity for peripheral cholinergic sites relative to that shown by Atropine. It was inferred from their studies that Glycopyrrolate would have lesser CNS effect than Atropine, presumably through the poor penetrating ability across the blood brain barrier afforded by the quaternary Ammonium feature.

Impact on the effect of Glycopyrrolate shows on gastric acidity is equivocal. Normal, Blank, and
Watson (1978) showed that Glycopyrrolate 0.4 mg i.m. given to non-obstetric patients 60 min before operation had little effect on gastric pH. Similarly, Stoelting (1978) showed that administration of Morphine and Glycopyrrolate 0.2 mg was not significantly different from administration of Morphine alone in decreasing gastric acidity immediately following induction. However, Baraka and others (1977) demonstrated in parturient patients that administration of Glycopyrrolate 0.4 mg i.m. produced a reduction in gastric acidity which was significantly different from that produced by Atropine.

\[
\begin{align*}
\text{CH} & \text{--C--C--O--} \\
\text{CH} & \text{3Pyrrolidyl} \\
\text{CH}_3 & \text{CH}_3 \\
\text{Br}^- & \text{Phenyl} \\
\text{Cyclopentane glycolate methobromide.}
\end{align*}
\]

**H-2 RECEPTOR ANTAGONISTS** (Peely et al, 1983).

With the introduction of Cimetidine an effective gastric H-2 receptor antagonist, pre-anaesthetic prophylaxis against acid aspiration pneumonitis may become a reality. Histamine receptors have not as far been
identified by physical or chemical methods but they can be classified pharmacologically by means of antagonists. As a result of inventiveness of James Black and his colleagues (1972), the theoretical concept of a second class of Histamine receptors became a therapeutic reality. The failure of classic anti-histaminic drugs (more appropriately H-1 receptor antagonists) to block the actions of Histamine, particularly on gastric acid secretion but also on isolated heart and uterine muscles, may now be explained by the existence of both H-1 and H-2 receptors which can be blocked by their respective specific H-1 or H-2 antagonists.

**Classification of Histamine Receptors**

<table>
<thead>
<tr>
<th>Location</th>
<th>Effect of stimulation</th>
<th>Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H-1 receptors:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood vessels</td>
<td>Vasodilatation, increased capillary permeability.</td>
<td>Diphenhydramine, promethazine etc. Also have anti-cholinergic and sedative effects. Newer agents such as Terfenadine are more specific.</td>
</tr>
<tr>
<td>Smooth muscle, bronchi</td>
<td>Contraction</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Triple response, itch.</td>
<td></td>
</tr>
<tr>
<td><strong>H-2 receptors:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>Gastric acid secretion</td>
<td>Cimetidine.</td>
</tr>
<tr>
<td>Heart, Blood vessels, uterus</td>
<td>Function not established in man.</td>
<td>Ranitidine.</td>
</tr>
</tbody>
</table>
Fortunately, the H-2 antagonists inhibited not only the stimulatory effects of Histamine on gastric acid secretion but also the action of all other gastric stimulants. As a result these drugs have been used to treat disorders in which gastric juice is thought to be etiologically implicated, and they have proved effective in managing peptic ulceration. These are also being used for all sorts of non-specific alimentary complaints. Although the incidence of adverse reactions to H-2 antagonists in current use is low, such indiscriminate misuse results not only in needless expense but is also potentially dangerous because proper investigation and treatment may be delayed.

To date four such compounds have appeared, Burimamide, Metiamide, Cimetidine and Ranitidine. Neither Burimamide nor Metiamide are, however, likely to be used clinically, the former because it is poorly absorbed from the gastro-intestinal tract and the latter because of occasional bone marrow depression. This adverse effect is thought to be due to the thioura residues present in the molecule, rather than to H-2 antagonism as such. If so, then Cimetidine, which lacks this particular residue, should prove safe.

**Cimetidine** -- A recently developed Histamine H-2 receptor antagonist, Cimetidine, has been demonstrated
to suppress basal, meal-stimulated and nocturnal gastric secretion. The drug has proved effective in the treatment of peptic ulcer, and no significant side effects have been noted (Burland et al., 1975; Menn et al., 1975; Founder et al., 1976).

Musmeyer et al. (1978) suggested that Cimetidine may be effective as a prophylaxis against acid pulmonary aspiration (Mendelson's syndrome).

Weber et al. (1979) suggested that premedication with intra-muscular Cimetidine produces a greater and more consistent rise in gastric pH than does oral Cimetidine.

Coombs et al. (1979a) showed that pre-operative intra-venous Cimetidine is an effective adjunct to good anaesthetic technique which will reduce the risk of pulmonary damage in a patient who aspirates while receiving anaesthesia.

Kirkegaard et al. (1980) in a controlled randomised double-blind trial, studied the value of Cimetidine as prophylaxis against acid aspiration pneumonitis. Compared to placebo, Cimetidine reduced the volume as well as the acidity of gastric contents significantly.
After ingestion Cimetidine is rapidly and almost completely absorbed, with a bio-availability approximating to 70% of the available of an i.v. dose. Peak drug concentration occurs 30-90 minutes after ingestion in fasting subjects, but are delayed by about an hour when taken with food. Although a Sulphoxide metabolite is produced in the liver, most of the drug is excreted unchanged by the kidneys so that Cimetidine accumulates in patients with renal insufficiency and in the elderly. Renal tubular secretion of Cimetidine is likely because its renal clearance exceeds G.F.R. Competition with renal secretion of Creatinine may explain the transient rise in serum Creatinine concentration that often occurs during the first few weeks of treatment with Cimetidine.

Cimetidine crosses the placenta into the foetal circulation. Similarly, penetration of the blood brain barrier is presumed to occur, since Cimetidine has been detected in both CSF and brain tissue. The possibility of an interaction with cerebral H-2 receptors may account for the mental confusion, drowsiness and disorientation that sometimes occurs in patients with renal or combined renal and hepatic failure and in the elderly.

The elimination half life of Cimetidine is about two hours. The duration of action may be prolonged
by increasing the dose of the drug which produces suppression of gastric secretion for up to eight hours.

Cimetidine is given by mouth or by injection. Intra-venous use is restricted to emergencies, such as patients undergoing intensive care or treatment of upper gastro-intestinal haemorrhage. Since hypotension may follow rapid intravenous administration, the drug should be given by slow injection lasting five to ten minutes or, better still, in an i.v. infusion of either saline or dextrose. Cimetidine may also be given intra-muscularly. The usual dose for healing of duodenal and gastric ulcers is 1 gm/day in divided doses of 300 mg after meals and 400 mg before sleep. Recently 400 mg twice daily has also been recommended and in the United States four tablets of 300 mg are used. For prevention of ulcer relapse, 400 mg at night is the most widely used regimen. The duration of maintenance regimen is not yet known, but ulcer relapses have occurred after as long as five years of maintenance treatment with Cimetidine, so that even longer term continuous treatment is necessary to control the periodic activity of ulcer disease.

Two actions of Cimetidine that appear to be unrelated to H-2 antagonism are its effects on the endocrine system and on hepatic drug metabolism. After i.v. injection of Cimetidine, concentrations of
circulating prolactin increases. In vitro, Cimetidine competes for androgen binding sites and although anti-androgenic effects have been reported in man, these are clinically usually unimportant. Gynaecomastia has been seen, particularly with high dose of Cimetidine and is reversible on withdrawal of the drug. It reduces the clearance of many drugs (including Warfarin, Diazepam, Chloridiazepoxide, Phenytoin and Propranolol) that are eliminated by oxidative metabolism. The metabolism of drugs that are primarily conjugated (Benzodiazepines – Lorazepam, Oxazepam) does not seem to be altered.

Interference with elimination, and consequent accentuation of pharmacological effects, is of particular importance for drugs such as Warfarin and Phenytoin that have a low therapeutic index. Cimetidine also seems to reduce liver blood flow and thereby decreases the systemic clearance of drugs that are highly extracted by the liver, such as Lignocaine and Propranolol.

![Chemical structure of Cimetidine.](image)

**Chemical structure of Cimetidine.**

**CURRENT TREATMENT** – (Chapman, R.L., FE, 1977) :

Aspiration of particulate matter requires immediate endotracheal intubation and, if necessary,
bronchoscopy. Particulate matter may become lodged in the large or medium sized bronchi, resulting in lobar atelectasis and mediastinal shift. If the matter is not removed promptly, the atelectatic areas may become infected, causing pneumonia and abscess. However, bronchoscopy is not usually necessary when liquid is aspirated because the fluid can be removed by a combination of postural drainage, percussion, vibration and suctioning.

The larger the volume and the lower the pH, the more severe the reaction. A patient may have respiratory distress immediately after aspiration, or it may occur progressively over a number of hours. Aspiration of material with a pH lower than 2.4 causes destruction of pulmonary surfactant, breakdown of the normal lung structure, and an outpouring of fluid into the lungs. The alveoli and airways become either collapsed or fluid filled, causing abnormal ventilation/perfusion ratios and intra-pulmonary shunting, resulting in hypoxemia. Since plasma is lost into the lungs as pulmonary edema, the patient may become hypovolemic, manifested most obviously by hypotension and tachycardia. The hypotension accentuates the hypoxemia, and delivery of oxygen to the periphery is less efficient.

If the PaO₂ is greater than 60 mm Hg, if there is no respiratory distress, and if the visual signs
within normal limits, then therapy consisting of supplementation of oxygen, coughing, and deep breathing exercises usually will suffice. When significant aspiration occurs i.e. sufficient volume with pH less than 2.4, cardio-pulmonary function will be more severely altered, and the patient requires immediate and vigorous therapy.

The upper airway should be cleared of all debris and vomitus, and the trachea intubated with a low-pressure, cuffed, implant-tested endotracheal tube. One hundred per cent oxygen should be administered and the tracheo-bronchial tree suctioned. Lavage with a large volume of any solution has not been shown to be beneficial in removing aspirated gastric contents. In the past, solutions of sodium bicarbonate, corticosteroids, and saline have been recommended for lavage of aspirated material. However, lavage with sodium bicarbonate is unnecessary because aspirated acid is neutralized quickly by the tracheo-bronchial mucosa; lavage with corticosteroid solution actually increases the number of lesions seen on microscopic and gross inspection of the lungs (Taylor et al., 1968), and lavage with saline solution decreases compliance and increases intra-pulmonary shunt (see et al., 1965). Therefore, lavage following aspiration should be limited to removing inspissated secretions, and only small volumes (2 to 4 ml) of saline solution should be used.
MECHANICAL VENTILATION

Arterial oxygenation is improved by decreasing the intra-pulmonary shunt and ventilation-perfusion inequalities with PEEP, which expands collapsed and fluid-filled airways and thereby increases the functional residual capacity. However, in a hypovolemic patient, PEEP can retard venous return, resulting in decreased cardiac output and accentuated hypoxemia. Because plasma is lost into the lungs as pulmonary edema, vascular volume must be re-expanded with balanced salt solutions, such as Ringer's lactate or appropriate blood products. Adequate fluid replacement is determined by noting blood pressure, pulse, volume of urine output, and central venous pressure (CVP). Because CVP measurements can be inaccurate in severely ill patients, it is preferable to insert a pulmonary artery (PA) catheter so that pulmonary capillary wedge pressure (PCWP) can be measured. In the absence of mitral valve disease, PCWP will approximate left ventricular end-diastolic pressure, giving a better indication of actual vascular volume. In a patient who is hypoxic or acidotic, or both, CVP may be elevated as a result of increased pulmonary vascular resistance, although PCWP will not be elevated in such a patient.

While the plasma volume is being re-expanded, PEEP must be adjusted to an optimum level: the level
that results in the best oxygenation of the patient without adversely affecting cardiac output. Oxygenation can be quantitated most accurately by determining venous admixture or intra-pulmonary shunt. The determination requires access to mixed venous blood, which is readily available if a PA catheter has been used. When a PA catheter is used, the arterial-venous oxygen content difference (Ca–Vo₂) can be determined. Changes in cardiac output will vary indirectly with changes in Ca–Vo₂.

In treating acute respiratory failure, including aspiration pneumonitis, intermittent mandatory ventilation (IMV) with PEEP is preferable than controlled mechanical ventilation (CMV) with PEEP. IMV combines a constant rate mechanical ventilator with a continuous oxygen enriched gas flow and allows spontaneous ventilation between mechanical (mandatory) breaths. Since spontaneous respirations are maintained with IMV, intrapleural pressure decreases below its base-line level with inspiration. This allows better venous return, which augments cardiac output. This also occurs when IMV and PEEP are combined, but the patient's vascular volume must frequently be re-expanded before PEEP can be used optimally. It has been documented (Downs et al. 1975; Kirby et al. 1975; Kirby et al. 1975) that in animals and in patients who have adequate vascular volume, circulatory stability is maintained even when high-level PEEP with IMV is used. This stability results because
the mean intra-pleural pressure is less than it is when the same level of PEEP is administered with CMV. With this approach, the IMV rate is set to maintain a level of carbon dioxide tension that permits the patient to have a pH equal to or greater than 7.35 in the absence of metabolic acidosis. The level of PEEP is titrated to produce the lowest venous admixture without decreasing cardiac output.

**Discontinuation of Ventilation** :- As therapy progresses and the overall condition of the patient improves, extubation can be considered when the following criteria are met:

1. Venous admixture on a fraction of inspired oxygen ($F_{I02}$) of 0.3 is less than 15 per cent, or $F_{aO2}$ on an $F_{I02}$ of 0.3 is greater than 60 torr.

2. The level of PEEP is 5 cm.$H_2O$ or less.

3. The IMV rate is 1 per minute or less, and

4. The adequacy of ventilation, as indicated by carbon dioxide tension and pH, does not reveal uncompensated respiratory acidosis.

If IMV is not employed, other standard criteria for discontinuation of controlled ventilation may be used:

1. Alveolar-arterial oxygen tension gradient while breathing 100 per cent oxygen ($A-aD_02^{1.0}$) less than 300 torr.
2. Vital capacity greater than 15 ml per kilogram of body weight, and


The patient then breathes 40 per cent oxygen for 15 minutes with a T-piece adaptor while vital signs are monitored closely. If hypercapnia with a pH less than 7.25 or a PaO₂ less than 70 torr does not occur, weaning and extubation usually can be accomplished in 2 to 4 hours.

Other forms of Therapy:— The effectiveness of using parenteral corticosteroids in treating aspiration pneumonitis is debatable, but little experimental evidence exists currently to support the use of parenteral corticosteroids in reversing pathological conditions and improving the clinical course of aspiration pneumonitis. On the other hand, well established evidence exists to support the use of a proper ventilatory pattern to reverse intra-pulmonary pathological conditions caused by aspiration of acidic gastric contents (Chapman et al, 1974; Chapman et al, 1974; Downs et al, 1974).

There is little evidence to show that administering prophylactic, broad-spectrum antibiotics
alters the course of aspiration pneumonitis. Gram stains and cultures of the tracheal aspirate should be taken daily, and antibiotics should be used when clinical evidence and results of cultures indicate that bacterial pneumonia exists.