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## **History**

Despite the synthesis of ether in 1540 by the German scientist Valerius Cordus, the use of anesthetic agents in a medical setting represents a totally American contribution to medicine. Dr. Crawford W. Long, a rural doctor in Georgia, first used inhaled ether to anesthetize a patient for neck surgery in 1842. Unfortunately, his work was not publicized. Dr. Horace Wells attempted to demonstrate the surgical use of nitrous oxide in 1845, but was unsuccessful. In 1846, a Boston dentist named William Morton demonstrated the anesthetic effects of ether in front of a live audience at Massachusetts General Hospital. He anesthetized a patient undergoing resection of a submandibular mass by a prominent surgeon of the time, Dr. John C. Warren. With its publication in the Boston Daily Journal the next day, the medical world came to know of the discovery of surgical anesthesia. Within six months the use of ether during surgery was widespread. The next year, Dr. James Simpson used chloroform to relieve the pain of labor. Nitrous oxide was used frequently as a form of social recreation with occasional reports of surgical procedures (largely dental) performed under its influence. The use of chloroform gained public acceptance after Queen Victoria in 1853 was administered this drug by Dr. John Snow, the first physician to devote his life to anesthesia.

Numerous other developments paved the way for modern anesthesia to flourish. The endotracheal tube was discovered in 1878 which protected against the drug-induced respiratory failure. Nerve block anesthesia with cocaine was popularized by Halsted in 1885 with epidural and spinal anesthesia emerging shortly thereafter. Intravenous agents became increasingly popularized after sodium thiopentone was first used in 1934. The current concept of "balanced anesthesia" was first introduced after curare was used in anesthetic practice in 1942. Over the next fifty years, many additional anesthetic agents have been developed and refined with anesthesia emerging as an important specialized field in medicine.

## **Basic Principles of General Anesthesia**

Anesthesia is defined as the absence or abolition of sensation. This term should be differentiated from analgesia which is defined as the absence or abolition of pain. General

anesthesia involves rendering a patient unconscious whereas local anesthesia (or more correctly, local analgesia) is aimed at blocking conduction of nerves to the operative site. In order to provide safe, as well as adequate general anesthesia, the anesthesiologist must combine the need for unconsciousness, the need for analgesia, and the need for muscle relaxation to provide the best operative conditions for the surgeon. This so-called 'triad of anesthesia' can be achieved with the use of only one drug, however side effects have limited the successful application of single line agents in modern anesthesia. Therefore, utilizing various drugs for their particular muscle relaxing, sleep producing, and analgesic properties, anesthesia can be safely and properly maintained.

Four main stages of general anesthesia are recognized regardless of the method in which the anesthesia is delivered. These stages are based upon the patient's body movements, respiratory rhythm, oculomotor reflexes, and muscle tone. In general, a patient in stage one is conscious and rational, however the perception of pain is diminished. Stage one is commonly termed the analgesia stage. Stage two, the delirium stage, is marked by the patient becoming unconscious, however the body responds reflexively and irrationally to stimuli. Breath holding may be present and can result in hypoxia, however tone is maintained in pharyngeal muscles and a patient can maintain and protect their own airway. Pupils generally become dilated and gaze is disconjugate. Stage three, the surgical anesthesia stage, is characterized by increasing degrees of muscular relaxation. Protective pharyngotracheal reflexes are absent and the patient is unable to protect the airway. Stage four is medullary depression. This stage is characterized by cardiovascular and respiratory collapse due to depression of the cardiovascular and respiratory centers in the brain stem.

Each anesthetic agent has a varying effect on the pattern of surgical anesthesia. For example, certain agents are highly analgesic (nitrous oxide) whereas others do not show stage I (thiopental). For a particular agent, the stage or depth of anesthesia must be judged with reference to the known sequence of signs for that agent. Various anesthetic agents are used to achieve the aforementioned stages for general anesthesia. These include inhalational agents, intravenous agents, analgesic agents, and muscle relaxants. Local anesthetics represent a category of anesthesia outside the realm of general anesthesia and will be discussed separately.

## **Inhalational Anesthetic Agents**

Inhalational anesthesia refers to the delivery of gases or vapors into the body via the respiratory tract to produce anesthesia. Through uptake and distribution, some portion of the anesthetic agent is presented to the nervous system, resulting in the absence of sensation. Understanding the induction, maintenance, and recovery from an inhalational anesthetic requires applications of the pharmacokinetics of the particular drug. In general, the aim in giving an inhalational anesthetic is to readily achieve a partial pressure of that anesthetic in the brain sufficient to keep the patient asleep and maintain that partial pressure until the operation is complete. Certain factors such as the solubility of the anesthetic agent, cardiac output of the patient, and alveolar ventilation of the patient will influence the ability of the anesthetic to achieve its result.

An important concept in comparing inhalational anesthetics is knowing their measure of potency called the minimum alveolar concentration (MAC). It is defined as the concentration of

a particular inhalational anesthetic at one atmosphere pressure in which 50 percent of patients do not move in response to a skin incision. Minimum alveolar concentration is analogous to the ED50 value computed from a pharmacological dose-response curve. Therefore, the potencies (as well as side effects at similar potencies) of different inhalational agents can be compared; so can combinations of agents. In general, a half MAC of each of two inhalational anesthetics is equivalent to one MAC of either. This concept not only has clinical applications but also suggests that the fundamental mechanisms by which these inhalational agents induce anesthesia are similar. The use of MAC in comparing the potency of different anesthetic gases has been criticized because it measures only a single point, the abolition of muscular response to pain. The concept fails to recognize the importance of the slope of the response curve. Other comparisons have been advocated (e.g. MAC/AWAKE ratios) however the MAC is the most widely used.

All the inhalational agents impair respiratory and circulatory function as well as influencing every organ system in one way or another. Some of these actions do not accompany the anesthetic effect but are side effects that must be appreciated when these agents are utilized. The potency, systemic effects, and specific side effects of the most commonly used inhalational agents will be discussed.

## **Nitrous Oxide**

Nitrous oxide (N<sub>2</sub>O) was first prepared by Priestly in 1776 (prior to the isolation of oxygen) and its anesthetic properties described by Humphry Davy in 1799. Dr. Davy's thought was that this inorganic gas might "be used with advantage during surgical operations" went unheeded until the mid 1800's. Nitrous oxide is characterized by its inert nature--it undergoes only minimal metabolism. It is colorless, tasteless, and odorless. It does not burn but will support combustion, so it cannot be taken for granted in a high-risk environment (laser surgery). It is stored as a liquid at 50 atmospheres in a cylinder.

### ***Potency***

The major difference between nitrous oxide and the rest of the inhalational agents is its low potency. The MAC of this agent is 105%, unreachable at normal atmospheric pressure in oxygen concentrations compatible with survival. The value of this agent is its ability to produce different effects over a wide range of inspired concentrations. It is a weak anesthetic but powerful analgesic. Patients will have some degree of analgesia at 50% nitrous oxide and may become amnesic at 66 2/3 %. Its drawback is the need for some additional agent to achieve full surgical anesthesia. It is poorly soluble in blood, and thus the onset and recovery times for nitrous anesthesia are brief (three to ten minutes).

### ***Systemic Effects***

Despite its relatively low potency, nitrous oxide affects most of the major body systems. It does cause direct mild myocardial depression, and although its general effects on heart rate and blood pressure are innocuous, it can cause major cardiovascular depression in patients with underlying hemodynamic compromise (hypovolemia, myocardial dysfunction, or septic shock). Nitrous has little effect on respiration and does not affect the neuromuscular junction to alter the requirement for a nondepolarizing neuromuscular blocking agent.

### ***Side Effects***

There are a number of special concerns with nitrous oxide that are not present with the other agents. Nitric oxide and nitrogen dioxide are both highly toxic to the lung and fortunately have largely been eliminated as impurities from the manufacturing process. There is a very real danger of administering a hypoxic mixture of nitrous oxide-oxygen mixture to a patient. The large volume of gas administered poses another problem. Although nitrous oxide is the least soluble anesthetic agent, it is still much more soluble than nitrogen. This means that the two agents take time to equilibrate across the alveolo-capillary membrane. At the beginning of anesthesia, nitrous oxide leaves the alveoli faster than nitrogen enters the lung, thereby raising the concentrations of oxygen, carbon dioxide, and any other inhalational agent used. Increasing the concentration of other inhalational anesthetics can speed induction at the beginning of a case, a phenomenon known as the *second gas effect*. At the end of anesthesia, the opposite is true. The alveolus fills rapidly with nitrous oxide and the nitrogen in the alveolus is unable to equilibrate as rapidly with the blood. This dilutes the oxygen present within the alveolus potentially creating hypoxemia especially if low levels of supplemental oxygen are used and the patient has a depressed state of consciousness at the end of a case. This phenomenon is termed *diffusion hypoxia* and may be present for up to 30 minutes after administration of the gas. The same principle applies when some portion of the body has trapped air, such as in a pneumothorax, bowel obstruction, air embolism, or with middle ear surgery. The displacement of tympanic membrane grafts is well described with the use of nitrous oxide anesthesia. Nitrous oxide also interferes with cell division. High concentrations will stop white cell formation after 36 hours of administration. It may also inhibit methionine synthetase thereby resulting in a megaloblastic or aplastic anemia. Under a similar mechanism, it can also inhibit vitamin B-12 metabolism producing its associated neurologic deficits.

### **Halothane**

Fluorinated anesthetic agents were discovered secondary to advances made by development of the atomic bomb. They represented a relatively safe and effective alternative to the flammable, often toxic agents used until that time. Halothane was the first of these gases and for many years has been the most commonly used supplement to nitrous oxide anesthesia. It was synthesized by Suckling in 1956 with the hopes of being an ideal anesthetic agent. It exists as a volatile liquid with a distinctive aroma and is added to the gas mixture delivered to the patient by means of a vaporizer added to the anesthesia machine. It is a comparably stable compound, nonflammable, and easy to vaporize.

### ***Potency***

Halothane has a MAC of 0.75%, indicating that it is highly potent. It has poor direct analgesic properties which makes it a perfect complement to nitrous oxide. Halothane is very soluble in blood and fatty tissues and awakening from halothane anesthesia may be prolonged if attention is not given at the time of emergence.

### ***Systemic Effects***

Halothane has profound effects on various body systems. In addition to depressing consciousness, halothane reduces or eliminates the sympathetic response to painful stimuli. This depressant effect on the sympathetic nervous system also reduces the protective baroreflex

response to conditions such as hypovolemia. Depression of the respiratory drive is also produced by halothane. Both the central response to carbon dioxide and the peripheral response to tissue hypoxia are depressed. The pattern of respiration produced by halothane is rapid, shallow, and monotonous with no sighs. Such a pattern predisposes to atelectasis. Halothane also depresses protective airway reflexes thereby placing the patient at higher risk of aspiration at induction. Halothane directly decreases myocardial contractility and heart rate and slows conduction through the AV and ventricular Purkinje system. Although some vasodilation occurs with halothane, the hypotension produced by this agent is primarily the result of myocardial depression and decreased cardiac output. Exogenous doses of catecholamines (e.g. during facial plastic surgery) may produce severe ventricular dysarrhythmias due to the myocardial sensitization. Halothane also results in muscle relaxation and can result in potentiation of paralytic agents.

### ***Side Effects***

One of the well-known complications of halothane is “halothane hepatitis”. This syndrome appears following exposure to halothane and may produce fever, jaundice, and possibly massive hepatic necrosis and death. The mechanism is not clear but allergic reactions to halothane byproducts are implicated. It is an extremely rare occurrence but is seen in increased frequency in those patients who have suffered hepatic anoxia thereby increasing the concentrations of hepatotoxic metabolites. Halothane is also a well-known trigger for malignant hyperthermia. This anesthetic reaction is usually detected in young fit individuals who have inherited a susceptibility to this problem. It is characterized by masseter spasm, sustained muscle rigidity, myoglobinuria, and a rapidly rising core body temperature. These symptoms and signs are manifestations of a hypermetabolic state initiated by an inhibition of calcium reuptake into the sarcoplasmic reticulum of skeletal muscle. It is universally fatal unless total body cooling, vigorous hydration, and administration of Dantrolene is delivered expeditiously.

### **Enflurane**

Because of the disadvantages of the available anesthetics at the time, enflurane was developed in 1963 by Terrell and released for use in 1972. It is a stable, nonflammable liquid that is somewhat less volatile than halothane. It has a distinctive pungent odor that creates an unpleasant induction in a non-premedicated patient.

### ***Potency***

Enflurane is slightly less potent than halothane with a MAC of 1.68%. Onset and elimination is similar to that of halothane.

### ***Systemic Effects***

The respiratory drive is depressed to a greater extent with enflurane than halothane, and the ventilatory response to hypoxemia is also decreased. Enflurane depresses cardiac contractility and heart rate more than halothane and produces a similar baroreflex response depression as halothane although sensitization to exogenous catecholamines is much less with enflurane than halothane. The metabolism of enflurane is one-tenth that of halothane thereby reducing its potential as a hepatotoxic agent. Its metabolism does release one fluoride ion which is potentially nephrotoxic but is rarely sufficient to produce clinical concern except in

hyperthyroid patients and in patients taking rifampin. Fluoride toxicity presents as nephrogenic diabetes insipidus and, in extreme cases, high-output renal failure can occur.

### ***Side Effects***

There is one unusual side effect that is not seen with the other agents. At deep levels of anesthesia and with a lowered PaCO<sub>2</sub>, some patients show an epileptiform pattern on EEG. Even though no post-anesthetic neurologic sequelae have been attributed to this pattern, this drug should be avoided in patients with seizure disorders.

### **Isoflurane**

Isoflurane was synthesized in 1965 by Terrell but its development lagged behind that of its isomer enflurane because of difficulties in its synthesis, purification, and now refuted claims of carcinogenesis. It is nonflammable, and has properties similar to that of halothane and enflurane with a few striking exceptions.

### ***Potency***

Isoflurane is less soluble in blood than halothane or enflurane which affords a more rapid induction and recovery from anesthesia. Its disadvantage is its pungent odor which is difficult to administer to a conscious patient. With a MAC of 1.3%, isoflurane is less potent than halothane but more potent than enflurane in producing general anesthesia.

### ***Systemic Effects***

Isoflurane depresses the respiratory drive and the ventilatory response to hypoxemia in a similar degree to that of halothane, but much less than its isomer enflurane. Although isoflurane is a direct cardiac depressant, cardiac output decreases less than with either halothane or enflurane. The baroreflex is inhibited but again less than either halothane or enflurane. Isoflurane is much less likely than halothane to produce arrhythmias in the presence of circulating catecholamines. Isoflurane does however cause a significant reduction in the systemic vascular resistance, with a marked increase in blood flow to the muscle and skin. It is the most potent vasodilator of the previous three inhalational agents and the hypotension that results with its use is a result of its peripheral effects rather than its direct effects on cardiac depression. Isoflurane results in more muscle relaxation than the others in its class and can cause significant potentiation of paralytic agents.

### ***Side Effects***

Isoflurane does not create the epileptiform activity as seen with enflurane and may be used in seizure prone individuals. A major difference in this agent compared with the other is its extremely low level of metabolism in the body, thereby nearly eliminating the possibility of nephrogenic or hepatic toxicity.

### **Sevoflurane**

Sevoflurane is a new fluorinated ether compound that has similar properties to the other fluorinated inhalational agents. It can produce mild respiratory and cardiac depression. It is not bronchirritative and is characterized by a rapid degree of induction and recovery due to its low

lipid solubility. It has a similar biotransformation profile as enflurane and may induce nephrogenic and hepatic side effects.

## **Desflurane**

Desflurane is another new halogenated inhalational agent. It is also characterized by a low blood and lipid solubility which allows for rapid induction and emergence from anesthesia. It does produce bronchoirritative effects with a high incidence of breath holding, coughing, and laryngeal spasm. This agent is not as widely used for induction as the other inhalational agents. It is not metabolized to any appreciable degree and its side effect profile is advantageous.

## **Intravenous Anesthetic Agents**

There are many ways to design an anesthetic plan to meet the requirements for general anesthesia: muscle relaxation appropriate for the procedure, unconsciousness, and analgesia. Intravenous agents can be used to meet each of these requirements. These drugs are generally classified as nonopioids, opioids, and muscle relaxants. The nonopioid intravenous anesthetic drugs principally provide hypnosis and blunting of reflexes whereas the opioids (narcotics) and neuromuscular blockers provide analgesia and muscle relaxation respectively. In most surgical procedures, the induction of anesthesia is carried out by the use of an intravenous agent and is not an unpleasant experience. It has become customary to induce general anesthesia with an intravenous agent regardless of the subsequent agents to be used for maintenance.

### **Barbiturates and other Nonopioid Compounds**

Barbiturates are commonly separated into classes based on duration of action and onset. In general, anesthesiologists prefer to use drugs that have a rapid onset of action but a short duration of action. Such drugs allow rapid titration to the required effect and are usually used to induce anesthesia. Thiopental sodium is the prototype drug in this class.

### **Thiopental**

Thiopental is water soluble and stable in aqueous solution for weeks. It is generally prepared as the sodium salt and is quite alkaline in solution with a pH of 10.5. This alkalinity makes thiopental incompatible with many other acidic agents such as opiates, catecholamines, and some neuromuscular blockers. Because of this alkalinity, thiopental must be injected into a freely flowing intravenous line as extravasation can produce skin necrosis. Inadvertent intra-arterial injection is a serious complication. A chemical endarteritis occurs and thrombosis of the artery may follow. Tissue ischemia and gangrene are potential complications. The use of less concentrated suspensions of thiopental (2.5%) can decrease this risk and is now the standard concentration used in practice today.

Thiopental is generally delivered as a bolus dose of 3-5 mg/kg. The drug is rapidly diffused into vessel-rich areas such as the brain and unconsciousness ensues within 10-20 seconds (one circulation time). Unconsciousness from thiopental results from dose-dependent suppression of neuronal activity within the central nervous system. This suppression is associated with a general decrease in cerebral metabolic rate. Despite this depression in

metabolic rate, thiopental and other barbiturates are poor analgesics and, in low doses, may even increase the perception of pain. The CNS effects of thiopental go beyond producing unconsciousness. Adequate levels of thiopental depress cortical brain activity measured on an EEG to the point of electrical silence. The metabolism when the EEG is flat presumably represents the basal metabolic requirements of cell function. Thus, in patients with severe brain injury and increased intracranial pressure, an induction dose can reduce pressure in most cases.

The effect of thiopental on the cardiovascular system is varied. It may have a profound effect in some patients, whereas virtually no effect in others. Healthy patients may experience a transient decrease in arterial blood pressure with a mild compensatory tachycardia and return of blood pressure to normal. In this situation, cardiac depression is limited. In large doses, or in patients with limited ability to activate a baroreceptor response (patients taking antihypertensives or hypovolemic patients), myocardial depression is more pronounced. Adequate volume repletion and sympathomimetic drugs all play a role in treating the hypotension in these patients.

Thiopental also produces a dose-dependent depression of medullary and pontine respiratory centers. Carbon dioxide responsiveness is blunted as are ventilatory responses to hypoxia.

The short duration of thiopental was originally thought to be a result of rapid metabolism. It is now clear that this is due to the rapid redistribution of the drug into tissues. Metabolism eventually occurs via the liver.

### **Etomidate**

Several newer drugs have been introduced to avoid the drowsiness associated with prolonged metabolism of the barbiturates. Etomidate is one of these newer agents and has a structural appearance similar to ketoconazole. In terms of onset, elimination, and reliability in producing unconsciousness, etomidate is similar to thiopental. It produces unconsciousness in less than 60 seconds at the usual induction dose of 0.2-0.4 mg/kg. As with thiopental, drug redistribution from the brain to other tissue accounts for its short duration of activity. Bolus doses cause less change in blood pressure and heart rate than thiopental and this drug has less depressant effect on cardiovascular function in patients with depressed myocardial function. It also produces less respiratory depression than thiopental. It does have several disadvantages that limit its use. There is a high frequency of myoclonic movements and pain with injection (due to propylene glycol). It has also been shown to produce cortisol suppression and Addisonian crises when used in debilitated patients.

### **Ketamine**

Ketamine is an alkylamine structurally similar to phencyclidine (PCP) and produces a state of “dissociative anesthesia”. An IV dose of 1-2 mg/kg may produce a cataleptic state characterized by intense analgesia, amnesia, and commonly a slow nystagmus with the eyes open. Systemic effects are characteristic of sympathetic nervous system stimulation. The more commonly observed include increases in heart rate, blood pressure, and cardiac output. Respiratory function is not depressed in normal patients and laryngeal reflexes are maintained. The onset of action is rapid (within a few minutes) and consciousness returns within 10-15

minutes although retrograde amnesia may be prolonged. A major disadvantage associated with its use occurs during emergence and consists of unpleasant dreams or even hallucinations. Benzodiazapines greatly reduce these side effects.

## **Propofol**

Propofol is a substituted phenol whose action is characterized by a rapid onset and short duration of action. Therefore, propofol is suitable for induction and can be used as a maintenance agent. The usual induction dose of 1.5-3 mg/kg produces unconsciousness within a matter of minutes and is metabolized quickly by the body. The major hemodynamic and respiratory effects of propofol are similar to those of thiopental. Like, thiopental, propofol decreases systemic blood pressure by dilating peripheral blood vessels. In patients with a blunted sympathetic response, profound hypotension may occur. Propofol mimics the action of thiopental by inducing a short period of apnea after bolus. Side effects are rare; the most common being the venous irritation upon administration (due to the soybean solvent in its emulsion). This can be diminished by the use of a large vein or injecting lidocaine IV prior to its administration.

## **Benzodiazepines**

Many benzodiazepines are available in the United States and are used primarily for the treatment of anxiety disorders. These agents are excellent in producing amnestic and sedative responses. Three benzodiazepines are available for IV injection and are commonly used in anesthesia practice: diazepam, lorazepam, and midazolam. Benzodiazepines induce amnesia and sedation secondary to potentiation of the inhibitory neurotransmitter gamma amino-butyric acid (GABA). Although sleep inducing doses of diazepam (0.3-0.6 mg/kg) or midazolam (0.2-0.4 mg/kg) may produce unconsciousness in two to three minutes, these drugs have a slower onset of action and a longer post anesthetic recovery period than thiopental. Because of this, benzodiazepines are less commonly used as induction agents, but are commonly used for sedation and to ensure amnesia. Diazepam is commonly used for premedication with a 5-10 mg IV dose. Induction with diazepam varies from 0.2-1.8 mg/kg dose and is marked by variability in onset and prolonged reactions. The effects of diazepam on the cardiovascular system are minimal. Mild decreases in blood pressure and heart rate are indicative of its sedative effect. There have been reports of respiratory depression with diazepam, however this response is dose dependent and can be marked if concomitant doses of narcotics are used. It is known to produce venous irritation when injected. Lorazepam (0.04 mg/kg) is slow in onset of action (10-20 minutes) and is not typically used as an induction agent. It is commonly utilized as an adjunct to regional anesthesia because of its profound anxiolytic and sedative effects. Pharmacological actions are similar to diazepam but longer in duration. Similar to diazepam, the parenteral form produces venous irritation and pain when injected. Midazolam is water-soluble and has a lower incidence of injection pain. As with the other benzodiazepines, induction with midazolam is slow and recovery is prolonged. Midazolam is twice as potent as diazepam and doses of 0.1 mg/kg are generally adequate. Because of its potential for depressing respiration, especially if given with narcotics, the respiratory response of these patients needs to be monitored. Intravenous benzodiazepines should be titrated to effect and the benzodiazepine antagonist flumazenil should be immediately available.

## **Narcotic Agonists (Opioids) and Antagonists**

Narcotics have been used for centuries to control perioperative pain and anxiety. In the past twenty years, very large doses of narcotics have been used not only for analgesia but also to produce unconsciousness and suppress the usual hyperdynamic responses to surgery. The predominant effects of narcotics include analgesia, a depressed sensorium, and respiratory depression. These effects are dose related. Narcotics have minimal effects on the cardiovascular systems of healthy patients. Narcotics do not produce direct cardiac suppression and are widely used for induction and maintenance of anesthesia in patients with myocardial disease. In hypovolemic patients, morphine may precipitate hypotension from its vasodilatory effects. Bradycardia with large doses of narcotics can occur due to direct stimulation of the vagal nucleus, however in normal patients cardiac output is not compromised due to an increase in stroke volume. Side effects include nausea and vomiting, chest wall rigidity, seizure activity, and decreased gastrointestinal motility.

The mechanism of action of these agents is receptor mediated. The sites of this receptor activity are opioid-specific and are most commonly found in the amygdala and spinal cord. Many opioid receptors have been identified and three appear related to the analgesic and anesthetic effects of the narcotics. Stimulation of the mu receptor results in analgesia, respiratory depression, euphoria, and physical dependence. Kappa receptors mediate spinal analgesia, sedation, and miosis. The omega receptors mediate hallucinations, dysphoria, and tachycardia. Meperidine, morphine, fentanyl, sufentanil, and remifentanyl are commonly used increasingly potent narcotic agonists. Nalorphine is a concomitant narcotic agonist and antagonist which has less analgesic effects as well as less respiratory depression. Naloxone produces pure antagonistic effects with no known agonistic properties. It reverses analgesia and respiratory depression nonselectively. The duration of action is approximately 30 minutes with a typical dose of 1-2 ug/kg and additional doses may need to be delivered should the respiratory depression recur as the naloxone is metabolized. Hypertensive crises can occur in narcotic dependent patients in whom naloxone is delivered producing acute withdrawal symptoms.

## **Muscle Relaxants**

There is more to anesthesia than simply rendering a patient unconscious and free of pain. In order to provide an optimal surgical field, an anesthetist must also control muscle tone as the current use of inhalational and intravenous anesthetic agents do not fully achieve this goal. Paralytic agents were first described in 1595 as explorers reported the use of “poisoned arrows” by south American natives. It wasn’t until the 1930’s that physicians began using curare in an attempt to treat tetanus. In the 1940’s they were shown to decrease the number of bone fractures resulting from electroconvulsive therapy. Finally, in 1942, Dr. Griffin introduced these medications to the surgical community. Thus, it wasn’t until the mid 1940’s that paralytic agents began to be routinely used. Its inclusion in the Liverpool technique developed during the 1960’s led to the popularization of “balanced anesthesia” achieved with the use of multiple agents.

Muscle relaxants produce their desired effect by action at the neuromuscular junction, but also have nonspecific effects at other sites. In order to understand the mechanism of action of neuromuscular relaxing agents, it is necessary to understand the depolarization of nerves and subsequent muscle contraction. In order to achieve muscle contraction an action potential travels

down an efferent nerve to the terminal neuromuscular junction or motor end plate. Upon arrival, the action potential stimulates the release of acetylcholine from the synaptic vesicles into the postsynaptic cleft. The acetylcholine subsequently attaches to nicotinic receptors located on the postjunctional membrane. Should two acetylcholine molecules attach to the acetylcholine nicotinic receptor, the receptor will open allowing an influx of sodium ions into the muscle cell and depolarizing the motor end plate. The acetylcholine rapidly diffuses away from the motor end plate and is hydrolyzed by the enzyme acetylcholinesterase. The end-plate potential returns to resting potentials due to an active Na-K pump and prepares for the next stimulus. Neuromuscular blockade occurs when the normal events are disrupted at one or more sites. The two classes of commonly used neuromuscular relaxing agents include nondepolarizing and depolarizing agents.

### ***Nondepolarizing Muscle Relaxants***

All nondepolarizing muscle relaxants bind to and competitively inhibit the end plate nicotinic cholinergic receptor. With the competitive blockade, an increase in the concentration of a nondepolarizing relaxant at the multiple neuromuscular junctions of each myofibril will increase the density of muscle paralysis. Conversely, drugs that inhibit acetylcholinesterase increase the amount of acetylcholine near the end-plate and competitively “reverse” the neuromuscular blockade. Reversal is often monitored by assessing muscular twitch response to electrical stimuli.

Nondepolarizing neuromuscular blocking agents can be classified into intermediate acting (15-60 minutes) and long-acting agents (over 60 minutes). This characteristic is arbitrary as the duration of action is dose dependent. Intermediate acting nondepolarizing agents include atracurium, vecuronium, and mivacurium, whereas the long acting drugs include pancuronium, metocurine, d-tubocurarine, and gallamine. The intermediate acting drugs in comparison to the long acting muscle relaxants have a similar rate of onset of neuromuscular blockade (3-5 minutes) but are relatively independent of renal function for clearance and evoke less circulatory effects. Most of these drugs have hemodynamic effects. Tubocurarine is known to block autonomic ganglia which can suppress sympathetic discharge and can decrease systemic vascular resistance. In addition, tubocurarine is known for its potential in mast cell degranulation with subsequent histamine release and severe hypotension. Pancuronium is well known for its inhibition of vagal and muscarinic receptors and commonly produces tachycardia with its use.

When muscle relaxation is no longer needed, any residual effects of the neuromuscular blocking agent are “reversed” to ensure appropriate muscle function and to sustain ventilation. Anticholinesterases inhibit acetylcholinesterase, thereby increasing the concentration of acetylcholine. The three commonly used drugs for this purpose are neostigmine, edrophonium, and pyridostigmine. The increased concentration of acetylcholine may cause bradycardia and hypotension due to stimulation of the muscarinic cholinergic receptors on the heart. These unwanted side effects can be reduced by the preadministration of a muscarinic blocker such as atropine or glycopyrrolate prior to its administration.

### ***Depolarizing Muscle Relaxants***

Depolarizing muscle relaxants bind and depolarize the end-plate acetylcholine nicotinic receptors. This depolarization continues as long as the receptor is occupied. Succinylcholine is

the only depolarizing muscle relaxant used clinically. Its duration of action with the typical induction dose of 1 mg/kg is very short (five minutes) because of rapid hydrolysis by plasma cholinesterases. Patients with abnormal production of plasma cholinesterase due to genetic abnormalities cannot hydrolyze succinylcholine resulting in prolonged paralysis. A “phase II block” resulting from repeated dosing can result in repolarization of the end plate that is only made more dense by administration of typical reversal agents. This desensitization is poorly understood, but may result in delay in recovery of muscle tone.

There are several characteristics unique to succinylcholine that may cause undesired effects. The sustained depolarization by the administration of succinylcholine typically produces transient fasciculations. Fasciculation of damaged or weakened myocytes may cause myocyte rupture and intracellular extravasation of potassium in patients at risk (burn patients, trauma patients, and patients with neuromuscular disease). Postoperative myalgias of the muscles of the neck, back, and abdomen are occasionally seen with its use. It is speculated that unsynchronized contractions of skeletal muscle fibers may lead to this side effect. Prior administration of low-dose nondepolarizing muscle relaxant (tubocurarine) can attenuate fasciculation, although it requires an increase of the Succinylcholine dose by 50-75%. Sinus bradycardia, junctional rhythms, and even sinus arrest may follow its administration. These responses likely reflect the action of succinylcholine at cardiac postganglionic muscarinic receptors where this drug mimics the normal response of acetylcholine. These effects are more likely to occur with doses given close together. Atropine, the muscarinic receptor blocker, can attenuate these effects if given prior to its administration. Increases in intraocular pressure, intragastric pressure, and trismus have been associated with the use of succinylcholine. Patients who develop severe trismus with the use of this drug should be considered susceptible to the triggering effect of succinylcholine on malignant hyperthermia.

## **Techniques in General Anesthesia**

Prior to the initiation of general anesthesia, a thorough history and physical examination is warranted. Previous reactions to any of the general anesthetics or a family history of reactions should be noted. Any potential cardiac or pulmonary risk factors should be elicited as these two organ systems are the most commonly affected by general anesthesia. An extensive cardiac and pulmonary evaluation should be made in those patients at risk so that potential risk-reducing interventions can be performed preoperatively.

With an adequate understanding of the drugs used in achieving general anesthesia, it is useful to understand the techniques used to induce and to maintain general anesthesia throughout a surgical case. As discussed earlier, induction of general anesthesia is most often accomplished by the intravenous administration of thiopental. Shortly thereafter, succinylcholine is also administered to produce skeletal muscle relaxation so as to facilitate direct laryngoscopy for intubation of the trachea. This injection of drugs (barbiturates, benzodiazepines, opioids, etomidate, ketamine, or propofol) to produce unconsciousness followed immediately by succinylcholine is referred to as a “rapid sequence induction”. Preoxygenation prior to the administration of the drugs minimizes the likelihood of arterial hypoxemia developing during the period of apnea. A dose of tubocurarine prior to the succinylcholine can reduce the fasciculations induced by the depolarizing muscle relaxant. An alternative to this rapid sequence induction is the inhalation of nitrous oxide plus a volatile anesthetic. An inhalational induction is

commonly utilized for pediatric patients, particularly when insertion of an IV catheter is not practical.

After successful induction and intubation of the patient, maintenance of anesthesia aims at the aforementioned goals of analgesia, unconsciousness, skeletal muscle relaxation, and control of sympathetic responses to the noxious stimuli. These objectives are most commonly met by the use of a combination of drugs discussed earlier. Typically, nitrous oxide is the most frequently used inhalational anesthetic. It is commonly used in conjunction with an opioid or volatile anesthetic. For muscle relaxation, a nondepolarizing muscle relaxant is also commonly utilized to maintain a motionless surgical field.

## **Local Anesthetics**

The introduction of local anesthesia followed that of general anesthesia by about 40 years. In 1884, Koller introduced cocaine as an effective topical anesthetic for the eye. Later that year, American surgeon Halsted employed cocaine to produce the first nerve block by local injection. Because of cocaine's ability to produce psychologic dependence and its irritant properties when used topically, a search was made for improved local anesthetics. In 1905, Einhorn synthesized the first synthetic local anesthetic, procaine, and by 1943, lidocaine was successfully synthesized and employed for use.

Local anesthetic drugs are used clinically to reversibly inhibit the generation and conduction of impulses from an area of the body. Local anesthetics produce conduction blockade of nerve impulses by preventing increases in permeability of nerve membranes to sodium ions. Failure of this permeability to sodium ions slows the rate of depolarization such that threshold potentials are not reached and action potentials are not propagated. This effect affects smaller nerves preferentially resulting in the loss of pain sensation while preserving motor and proprioception ability. It is likely that the local anesthetic enters the sodium channel from the axioplasmic (inner) side of the nerve membrane and attaches to a receptor about halfway down the channel. While the local anesthetic molecule is within the sodium ion channel, it prevents the sodium ion movements necessary for depolarization. Although a local anesthetic drug is injected to produce blockade of nerve impulses, the drug is subsequently absorbed away from the nerve site and appears in the circulation. The concentration of the drug in the blood is directly related to the systemic effects of the local anesthetic. Local injection into highly vascularized areas such as the hypopharynx, nose, and trachea produces maximal levels that approach that of intravenous injection. Topical application, however, results in blood levels that are one-third that of IV injection. Most of the local anesthetics (with the notable exception of cocaine) are vasodilators, thus necessitating the addition of epinephrine or phenylephrine to aid in vasoconstriction. This addition minimizes the risk of systemic toxicity and allows for a bloodless field. Of interest, the addition of 1:100,000 or 1:200,000 provides the same vasoconstricting effects at the doses typically used for injection. The site of metabolism of a local anesthetic drug is determined by the chemical structure of the drug. Local anesthetics can be divided into two groups, depending on whether they have an ester linkage (cocaine, procaine, benzocaine, and tetracaine) or an amide linkage (lidocaine, bupivacaine, prilocaine, mepivacaine). The metabolism of local anesthetics with an ester linkage are metabolized in plasma by plasma cholinesterase (the same agent that metabolizes succinylcholine), whereas the local anesthetics with an amide bond are broken down in the liver by hydrolysis and dealkylation

by the cytochrome p-450 enzyme system.

Local anesthetics tend to be linear molecules consisting of a lipophilic end and a hydrophilic end. The lipophilic end typically contains a benzoic acid moiety while the hydrophilic end contains a hydrocarbon chain that is ionizable. This is of use clinically because the non-ionized form readily penetrates membrane barriers (when the pH is high more is in the non-ionized state) whereas the cationic form binds more readily to the sodium receptor (typically when the pH is lower). Thus, tissue acidosis render local anesthetics ineffective because the local anesthetic is relatively cationic in this state and cannot cross the nerve membrane to bind to the receptor. The addition of sodium bicarbonate into the local anesthetic provides more anesthetic in the non-ionized form which allows it to readily cross the nerve membrane and produces local analgesia for extended periods of time (in addition to decreasing the pain involved with injection of the parent weak acid compound).

The most commonly used local anesthetic is Lidocaine. Lidocaine injection, when coupled with a vasoconstrictor provides quick onset of analgesia with relatively short duration of effect (60-120 minutes). Bupivacaine and Prilocaine are longer-acting agents with special characteristics. Each is slower in onset, but result in significantly longer periods of anesthesia (240-480 minutes). Articaine was introduced in 2000 and boasts a significant decrease in the risk of toxic side effects due to increased metabolism (and decreased  $\frac{1}{2}$  life). It is rapidly absorbed with a quick onset of action.

The major systemic toxicity of local anesthetic agents involves the central nervous system and the cardiovascular system. Because local anesthetics cross the blood brain barrier, toxic levels can produce both CNS excitability and depression. Initially, toxicity is manifested by light-headedness, circumoral numbness, and dizziness, followed by auditory (tinnitus) and visual disturbances. Drowsiness, disorientation, and a temporary loss of consciousness may follow. Slurred speech, shivering, muscle twitching, and tremors precede a generalized convulsive state (CNS excitability). Further increases in the local anesthetic dose results in cessation of convulsive activity, flattening of brain wave patterns, and respiratory depression, consistent with generalized CNS depression. Local anesthetics can produce profound cardiovascular changes by direct cardiac and peripheral vascular effects. It is manifested by myocardial depression and peripheral vasodilation. Inadvertent, rapid intravenous injection of an excessive dose can cause significant myocardial contractility and peripheral vasodilation resulting in profound hypotension and circulatory collapse. Other systemic effects of local anesthetics include methemoglobinemia and allergic reactions. Prilocaine, when administered in large doses may result in accumulation of the metabolite, ortho-toluidine, an oxidizing compound capable of converting hemoglobin into methemoglobin. With sufficient methemoglobin, the patient can appear cyanotic and the blood chocolate colored. This is easily reversed by IV administration of methylene blue. Allergic reactions to local anesthetics are rare, despite their widespread use. Indeed, it is estimated that less than one percent of all reaction to local anesthetics are related to allergic etiology. Preservatives in the local anesthetic (methylparaben) or breakdown products particularly of the ester groups (para-aminobenzoic acid) can produce typical allergic systems such as rash, laryngeal edema, bronchospasm. It is more likely that a systemic toxicity has occurred should any neurological or cardiovascular symptoms present. Treatment for a true allergic reaction is supportive. As there is no cross reactivity between classes of local anesthetics, the use of an amide local anesthetic may be used

when an allergic reaction is documented for an ester group drug.

### **Preventing Toxicity**

Local anesthetic toxicity primarily results from accidental intravascular injection or injection of an excessive dose. This must always be anticipated. Resuscitative equipment (oxygen, airways, bag and mask, suction), CNS-depressant drugs (diazepam, midazolam, and thiopental), and cardiovascular drugs (ephedrine, phenylephrine, epinephrine) should be on hand at all times. An IV should be started prior before any major regional anesthetic is started. Toxic reactions are best avoided by frequent aspirations during injection and slow, intermittent injection of the local anesthesia. When large doses are injected slowly and intermittently, the patient should be asked about symptoms related to CNS toxicity such as ringing in the ears, circumoral numbness, feeling of light-headedness, etc. Further, the slow injection rate allows dilution of the local anesthetic in the blood, so that high concentrations are not reached quickly. If signs or symptoms of systemic toxicity occur, the injection should be stopped immediately. In cases where large doses of anesthetic are used, monitoring should be employed including the maintenance of verbal contact, continuous ECG monitoring, noninvasive BP checks, and monitoring oxygen saturations. If convulsions or cardiac arrest occur due to local anesthetic usage, establishment of an airway, adequate ventilation, and support of circulation is mandatory. If the patient cannot be adequately ventilated, insertion of an oral airway after administration of succinylcholine (20 mg) can be useful. Should mask ventilation not be possible, tracheal intubation should be performed. CNS excitability (seizures) should be treated with small amounts of benzodiazepines (diazepam 5-10 mg). Hypotension is treated with alpha and beta agonists (ephedrine 5-10 mg or phenylephrine 40-80 micrograms). ACLS protocol should be instituted when life threatening cardiac dysrhythmias occur.

### **Cocaine**

The use of cocaine dates back to the sixth century with South American Indians using the drug to induce euphoria, to reduce hunger, and increase work tolerance. Sigmund Freud was the first to report its clinical use. Dr. William Halstead injected cocaine into a sensory nerve trunk and reported on its regional anesthetic qualities. Today it most commonly used as a topical application for accomplishment of anesthesia, particularly in the head and neck region. It has a rapid onset of action and a prolonged duration of activity. In addition, its strong vasoconstriction effects are unique among local anesthetics, providing decongestion and decreased risk of hemorrhage, thereby obviating the need for epinephrine. The mechanism of action of cocaine is similar to other local anesthetics by blocking the sodium channel of the nerve membrane. It also is the only local anesthetic known to interfere with the reuptake of norepinephrine by the adrenergic nerve terminal and, in addition, prevents the uptake of exogenously administered epinephrine. This action leads to increased levels of circulating catecholamines and sensitizes target organs to the effects of sympathetic stimulation-- tachycardia leading to ventricular and atrial ectopy, vasoconstriction leading to severe hypertension, mydriasis, and an increase in body temperature. While theoretically being a contraindication, the subcutaneous injection of lidocaine with various doses of epinephrine in combination with topically applied cocaine is safe. The use of such dilute solutions of epinephrine and its slow release from subcutaneous tissues result in such low concentrations of circulating epinephrine as to be inconsequential if used with cocaine. Many references state that the safe maximal limit for cocaine is 200 mg (a 4% vial).

Other authors mention 300-400 mg. Interestingly, the “safe” level for topically applied cocaine has not been based on scientific evidence, rather on early clinical experience when cocaine was injected for tonsillectomy anesthesia.

## **Special Anesthetic Techniques in Otolaryngology**

### **Ear Surgery**

Ear surgery provides numerous areas of concern for the surgeon as well as the anesthesiologist. A bloodless field for microsurgery is important and various techniques are employed to maintain this state. Preoperatively, local injection with a solution containing epinephrine can produce sufficient vasoconstriction. Maintaining low-normal blood pressure without excessive elevations and keeping the neck veins free of compression can do much to limit the bleeding associated with middle ear surgery. The middle ear is an anatomic air cavity that is prone to diffusion of nitrous oxide. If nitrous oxide is used during middle ear surgery and is not allowed to diffuse out of the middle ear space, an increase in intracavitary pressure can exist which can dislodge a tympanic membrane graft. Simply stopping nitrous oxide 15 minutes prior to placement of the TM graft can prevent this occurrence. Facial nerve monitoring is also an important concern in ear as well as parotid surgery. Eliciting a facial grimace or the use of facial nerve monitors are easily used methods of identifying and avoiding the facial nerve. The judicious use or elimination of muscle relaxants allows the facial nerve to be identified by these methods. The use of potent inhalational anesthetics during ear surgery cases can maintain a relaxed patient with preservation of facial nerve conductance.

### **Tonsillectomy**

The tonsillectomy is a common procedure performed in children and adults, however, numerous challenges are provided in anesthetic management. Patients commonly present with upper airway obstruction from enlarged tonsils, peritonsillar abscess, or sleep apnea syndrome. Careful attention to these possibilities is needed in order to anticipate the possibility of a difficult airway. Teeth should be inspected so that these do not become dislodged during induction or placement of the mouth gag. A patient that bleeds after a tonsillectomy represents a high risk induction. There is high rate of morbidity if not handled appropriately. The patient is at high risk for aspiration of digested blood and for the development of severe hypotension during induction due to hypovolemia. Adequate intravenous infusion should be started immediately. Blood should be immediately available for transfusion particularly if evidence of hypovolemic shock occurs.

The patient who is bleeding should be transported to the operating room in the semi-prone position to facilitate the gravity drainage of blood from the oral cavity. Once in the operating room, the patient should be placed in the same position with the right side down (for a right-handed anesthesiologist). Assistants should hold the patient in this position during induction of anesthesia. A full size smaller tube should be available to deal with potential edema from the previous intubation. A high volume suction must be available. The patient is pre-oxygenated and an inhalation induction is employed. When adequate depth is reached for laryngoscopy, the patient is turned to the full lateral position with no support under the head. This allows the head and bleeding points to be below the level of the larynx. The laryngoscope

is introduced and is lifted 45 degrees upward to give adequate view for intubation. An older child or adult may be intubated awake however effective use of topical anesthesia is unlikely in the face of severe hemorrhage in addition to the higher risk of inducing vomiting with laryngoscopy.

## **Facial Fractures**

In severe facial fractures, the anesthetic management is complicated by the presence of blood, teeth, and bone fragments in the oral cavity and possibly the airway. Severe facial injury can be accompanied by fractures of the larynx or cervical spine. In addition, mandibular or maxillary fractures can present with significant trismus or airway obstruction. If one is called to evaluate a newly injured patient in acute respiratory distress prior to cervical spine X-rays, the airway should be established by cricothyrotomy or tracheotomy without manipulation of the neck. If the patient is known to be free of spinal fracture and is to be intubated for surgery, a decision must be made for oral or nasal intubation versus a tracheotomy. In the patient with severe midface fractures in the cribriform or nasoethmoid complex area, nasal intubation should be avoided whenever possible, both to avoid contributing to infection of the CSF and to avoid inadvertent insertion of the tube into the cranium. In the patient with a midface or mandible fracture, the tube may interfere with surgical manipulation. A major hazard with an endotracheal tube is the risk of carrying foreign bodies into the airway with the tube. In these cases, awake intubation with preparations for immediate tracheotomy should be performed.

## **Laryngeal Surgery**

Surgery of the larynx provides numerous anesthetic considerations for both the surgeon and anesthesiologist. The anesthetic objectives are to maintain oxygenation and ventilation while the surgeon must have access to an unobstructed operating field. Communication is critical so that both goals can be met safely for the patient. For some cases with cooperative patients, topical laryngeal anesthesia can be achieved. Cocaine or aerosolized lidocaine is effective in achieving appropriate anesthesia of this area. Alternatively, a superior laryngeal nerve block can be performed. In most procedures, however, general anesthesia is usually required. The use of a small diameter cuffed endotracheal tube can allow for most laryngeal work to be performed safely and adequately. Should an endotracheal tube be a hindrance to the surgery planned, the intermittent apneic technique, jet-Venturi technique, or spontaneous respiration anesthesia technique can be considered. The use of neuromuscular relaxants and intravenous agents allow for appropriate oxygenation and ventilation in those circumstances where these methods are used. At other times, a small catheter placed just superior to the carina allows for adequate oxygenation and ventilation as well. With any of these methods, pulse oximetry and capnography is essential.

A carbon dioxide laser is also commonly used during laryngeal surgery. The risk of fire is always of concern when the laser is used. Certain measures should be undertaken to help reduce the risk of a fire. It has been determined that polyvinyl endotracheal tubes, even if wrapped in protective metallic tape, should not be used. Instead, laser resistant endotracheal tubes such as the Xomed Laser-Shield or Rusch red rubber tubes should be used and wrapped with metallic tape as an added protective mechanism. The safest anesthetic gas mixture has been found to be 30% oxygen in helium and up to 2% halothane has not been found to add any further

fire risk. Additionally, the tube cuff should be protected by inflation with saline colored with methylene blue, neurosurgical cottonoids should be covered with saline, and the patient's face should be fully covered with saline impregnated gauze. Finally, the use of pulse mode for laser use provides a significantly decreased risk of laser induced fire than that used in the continuous mode.

## References

- DiFazio, Cosmo A. Local Anesthetics: Action, Metabolism, and Toxicity. *Otolaryngologic Clinics of North America* 1981; 14: 515-519.
- Dripps, Robert D., Eckenhoff, James E., and Leroy D. Vandam. *Introduction to Anesthesiology: The Principles of Safe Practice*. 1988; Saunders: Philadelphia.
- Ellis, F.R. and I.T. Cambell. *Essential Anesthesia*. 1986; Blackwell Scientific Publishing: London.
- Kem, William. General Anesthetics. *Phase B Pharmacology* 1996; University of Florida College of Medicine; 101-106.
- Kem, William. Neuromuscular Blocking Agents. *Phase B Pharmacology* 1996; University of Florida College of Medicine; 115-118.
- Kem, William. Pharmacological Basis of Local Anesthetics. *Phase B Pharmacology* 1996; University of Florida College of Medicine; 107-112.
- Liu, Phillip L. *Principles and Procedures in Anesthesiology*. 1992; Lippincott: Philadelphia.
- Longnecker, David E. and Frank L. Murphy. *Introduction to Anesthesiology*. 1992; Saunders: Philadelphia.
- Ossoff, Robert H. Laser Safety in Otolaryngology-Head and Neck Surgery: Anesthetic and Educational Considerations for Laryngeal Surgery. *Laryngoscope* 1989; 99: 1-26.
- Reynolds, Robert C. General Anesthetic Agents (What Every Surgeon Should Know About Anesthesia, But Has Been Afraid to Ask). *Otolaryngologic Clinics of North America* 1981; 14: 489-500.
- Stern, Yoram, McCall, John E., et al. Spontaneous Respiration Anesthesia for Respiratory Papillomatosis. *Annals of Otology, Rhinology, and Laryngology* 2000; 109: 72-76.
- Stoelting, Robert K. and Ronald D. Miller. *Basics of Anesthesiology*. 1989; Churchill Livingstone Inc.: New York.
- Verlander, J. Michael and Michael E. Johns. The Clinical Use of Cocaine. *Otolaryngologic Clinics of North America* 1981; 14: 521-531.
- Walts, Leonard F. Neuromuscular Blocking Agents. *Otolaryngologic Clinics of North America* 1981; 14: 501-513.
- Yunker, Dirk. Anesthesiology. In Bailey, B.J., ed. *Head and Neck Surgery-Otolaryngology*. Second ed. Lippincott-Raven: Philadelphia, 1998.