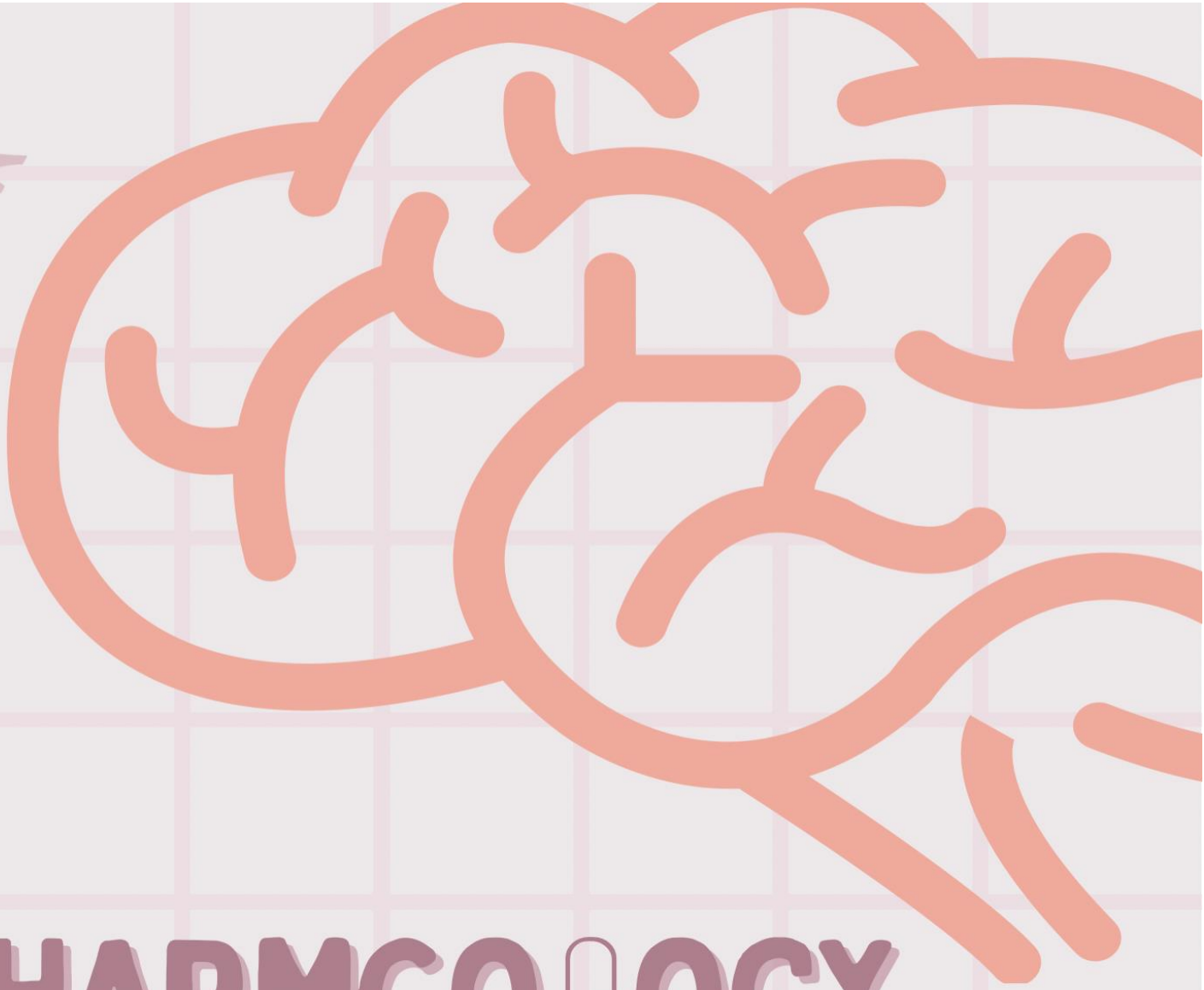

PHARMCOLOGY

SHEET NO. 6+7

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General Anesthetics:

*كلام الدكتور بالبنفسجي الفاتح

- A state of analgesia, amnesia, loss of consciousness, inhibition of sensory & autonomic reflexes, & skeletal muscle relaxation.
• This is achieved by a combination of IV & inhaled drugs.

Types of General Anesthesia:
A. IV agents used alone, or in combination with other anesthetic agents, to achieve an anesthetic state or sedation. These drugs include:
1. **Barbiturates:** Thiopental, methohexital.
2. **Benzodiazepines:** Midazolam, diazepam.
3. **Propofol**.
4. **Ketamine**.
5. **Opioid analgesics**: Morphine, fentanyl, sufentanil, alfentanil, remifentanil.
6. **Miscellaneous sedative-hypnotics**: Etomidate, dexmedetomidine.
B. Inhaled anesthetics which include:
1. **Volatile liquids** (halogenated drugs): Halothane, isoflurane, desflurane, enflurane, methoxyflurane, & sevoflurane.
2. **Gases**: Nitrous oxide.

• **No** anesthetic agent can produce the 5 desired effects without adverse effects.
• **Balanced anesthesia** employs multiple drugs (inhaled anesthetics, sedative-hypnotics, opioids, neuromuscular blocking drugs) to minimize unwanted effects.

Although general anesthesia can be produced by **only intravenous** or **only inhaled** anesthetic agents, modern anesthesia typically involves a combination of:
1. IV agents for **induction** of anesthesia.
2. Inhaled agents for **maintenance** of anesthesia.
3. Muscle **relaxants**.
4. **Analgesics**.
5. **Cardiovascular drugs** to control autonomic responses.

IV Anesthetics: (immediate anasthesia)

• Are commonly used for induction of general anesthesia because of more **rapid onset** than inhaled agents.
• They are also used to provide **sedation** for patients in **ICU** settings.
• Rapid onset is due to their **lipophilicity** & preferentially partition into highly perfused lipophilic tissues (brain, spinal cord).
• Recovery is **rapid** & permits their use for short procedures.
• Termination of the effect of a single bolus is determined by **redistribution** of the drug into less perfused (less vascualr) & inactive tissues such as skeletal muscle & fat, & is **not** related to their metabolism.

Propofol: مهم جدا

• It interacts with **GABAA receptor-chloride channel**. It also potentiate glycine-gated currents.
• Propofol acts as hypnotic but **does not** have analgesic properties.
• It is the most popular IV anesthetic, & has replaced barbiturates.
• Its rate of onset of action is similar to IV barbiturates but recovery is more **rapid** & patient ambulation المشي is earlier مهمة.
• The patient subjectively feel **better** in the *immediate* postoperative period because of the reduction in postoperative nausea & vomiting.
• It is the agent of choice for **ambulatory surgery**.
• It can be used for both **induction & maintenance** of anesthesia.
So if there is a contraindication of inhaled agents we use IV analgesic which is propofol.
• It reduces the required concentration of inhaled anesthetics.
• When used during **maintenance** of anesthesia, propofol infusion can be combined with IV opioids & neuromuscular blockers **to completely avoid the use of inhaled anesthetics.**
• It is effective in producing **prolonged sedation** in patients in critical care setting, but cumulative effect can lead to **delayed arousal** (so the pt needs prolonged observation in the operating room).
• The recovery from propofol is more complete, with **less "hangover"** than that observed with thiopental.
• Prolonged administration of conventional emulsion formulation can raise serum **lipids**. (cause it is not water soluble, it is lipid soluble).
• When used in critically ill young children for sedation (the child is on a ventilator, so we give him a muscle relaxant to prevent rejection of ventalition), it has caused **severe acidosis in the presence of respiratory infection** & to possible **neurologic sequelae** upon **withdrawal**.
• It produces **depression** of central ventilatory drive & **apnea**, which also can cause acidosis.
• Excitatory effects such as muscle twitching or spontaneous movement are occasionally observed during induction of anesthesia.
• These effects can be confused with **seizures**.
• It produces a marked **decrease in blood pressure** during induction of anesthesia through **arterial & veno dilation**.
• It has the greatest direct **negative inotropic effect** than other IV anesthetics.
• Profound **bradycardia** and **asystole** (no systol - fatal) have been reported.
• **Pain at the site of injection is the most common adverse effect** after IV bolus administration (reduced by admixture with **lidocaine** (lacal anesthetic)).
• **Muscle movements, hypotonus & rarely tremors** have been reported after prolonged use.
• Propofol decreases cerebral blood flow, which decreases intracranial pressure (ICP) & intraocular pressure, but may lead to **decrease in cerebral perfusion pressure** مهم.

Fospropofol: (fos for phosphate)

*It should be converted to propofol to work.

• Fospropofol is a water-soluble **prodrug** of propofol.
• The effects of fospropofol are similar to that of propofol, but onset and recovery are prolonged compared with propofol because the prodrug must first be converted into an active form.
• No injection site pain.
• Can produce paresthesia in the perianal region.

Etomidate:

• It has hypnotic but **no** analgesic effects.
• It acts primarily through potentiation of GABAA-mediated chloride current.
• It is used for induction of anesthesia in patients with limited cardiovascular reserve, because it causes **minimal cardiovascular & respiratory depression & minimal hypotension.**
• It produces **rapid loss** of consciousness.
• *Distribution* of etomidate is **rapid**.
• *Redistribution* of the drug from the brain to highly perfused tissues is responsible for the **short duration of action**.
• Recovery is **less rapid** than that of propofol.
• It is a potent cerebral vasoconstrictor, leading to **decreased cerebral blood flow & ICP, like thiopental.**

Adverse effects:

1. **Pain** upon injection.
2. **Myoclonic** activity. رعشة عضلية لا إرادية سريعة
3. Postoperative **nausea & vomiting**.
4. It may activate **seizure foci**. (if the patient has epilypsy)
5. Inhibition of **steroidogenesis** (inhibition of 11β-hydroxylase) with **decreased plasma levels of cortisol & hypoadrenalism** ➡️ **hypotension**, electrolyte imbalance & oliguria (if used as a continuous infusion or for long time).

• Not used as continuous infusion.

Ketamine:

• It produces a **"dissociative anesthetic state"** (the patient is awake but dissociated from the environment) which is characterized by:

1) **catatonia:** (muscular rigidity & mental stupor تخدر, sometimes alternating with great excitement & confusion, eyes remain open with a slow nystagmic gaze حَوَل).
2) amnesia & analgesia, with or without loss of consciousness.

• It is chemically related to **phencyclidine** (a drug of abuse), a psychoactive drug with high abuse potential.

- Mechanism of Action:

• It blocks glutamic acid NMDA receptor subtype.

- Pharmacokinetics:

• It is highly lipid soluble and **rapidly distributed** into well-perfused organs, including brain, then it **redistributes** to less well perfused tissues.

- Pharmacodynamics:

• **It is the only IV anesthetic that have both analgesic properties & the ability to produce dose-related cardiovascular stimulation**. عكس الباقي

• It can be administered by multiple routes (IV, IM, oral, rectal, epidural -for analgesia-).

• It stimulates the **central** sympathetic nervous system &, to a lesser extent, inhibits the reuptake of norepinephrine at sympathetic nerve terminals.

• It increases heart rate, cardiac output & arterial blood pressure (**transient** only if used IV single dose).

• It increases cerebral blood flow, oxygen consumption, & intracranial pressure (ICP).

• It is **dangerous** in patients with elevated ICP.

• It decreases respiratory rate (but **doesn't** effect reflexes) but upper airway muscle tone is well maintained & airway reflexes are usually preserved.

• It relaxes bronchial smooth muscle.

• **Lacrimation & salivation are increased** (bad cause it may cause aspiration). This effect can be limited by premedication with an anticholinergic drug.

• May cause **laryngospasm** especially in children.

• Its use has been associated with **postoperative disorientation, sensory & perceptual illusions أوهام, & vivid colorful dreams أحلام يشعر بأنها حقيقية, out-of body experiences بيشعر إنه هو شيء وجسمه شيء وبراقبه عن بعد & increased & distorted visual, tactile, & auditory sensitivity**. (This is called **emergence phenomena**).

• These reactions can be associated with **fear & confusion**.

• A **euphoric state** may be induced explaining the potential for its **abuse**.

• These effects can be reduced by premedication with a **benzodiazepine** (diazepam, midazolam).

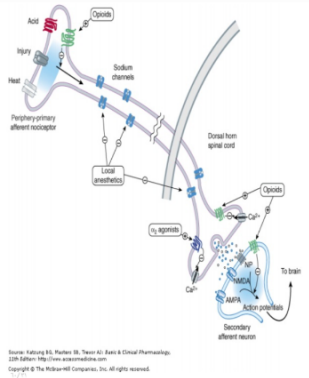
• It is specially useful in patients undergoing **painful procedures** such as burn dressing.

توضيح: يستخدم عند تغيير ملابس الأشخاص المصابين بالحروق.

• It reduces opioid tolerance & opioid-induced hyperalgesia (an adverse effect of opioids).

Dexmedetomidine:

• Dexmedetomidine is a **highly selective α2-adrenergic agonist**.
• Recognition of the usefulness of α2-agonists is based on observations of decreased anesthetic requirements in patients receiving chronic clonidine therapy.
*It was found that pts who were treated with clonidine need less analgesic drugs.
• **Hypnotic effects** of the intravenous anesthetic dexmedetomidine are produced via actions in the locus ceruleus. (in CNS)
• It stimulates α2-adrenergic receptors at this site & reduces central sympathetic output, resulting in increased firing of inhibitory neurons. It will facilitate inhibition.
• In the dorsal horn of the spinal cord it modulates release of substance P ➡️ **analgesic effects**. (in the spinal cord)
• Its **sedative effect** resembles a physiologic sleep state through activation of endogenous sleep pathways.
• **Tolerance & dependence** may develop (not that popular).



Schematic diagram of a primary afferent neuron mediating pain, its synapse with a secondary afferent in the spinal cord, and the targets for local pain control. The primary afferent neuron cell body is not shown. At least three nociceptors are recognized: acid, injury, and heat receptors. The nerve ending also bears opioid receptors, which can inhibit action potential generation. The axon bears sodium channels and potassium channels (not shown), which are essential for action potential propagation. Synaptic transmission involves release of substance P, a neuropeptide (NP) and glutamate and activation of their receptors on the secondary neuron. Alpha2 adrenoceptors and opioid receptors modulate the transmission process.

• Its repeated infusion results in **moderate *decreases* in heart rate**, **systemic vascular resistance**, and **blood pressure** (similar to probofol).
• **Heart block, severe bradycardia, & asystole** have been observed and may result from unopposed vagal stimulation.
• It is used for the short-term sedation of intubated & ventilated patients in an **ICU** setting. probofol is used for this purpose too.
• It is used as an adjunct to general anesthesia or to provide sedation, during awake fiberoptic tracheal intubation or regional anesthesia.
• It decreases the dose requirements for inhaled & injected anesthetics.

Inhaled Anesthetics:

1. **Volatile anesthetics: halothane, enflurane, isoflurane, desflurane, sevoflurane**.
*Any compound can be converted from a water soluble to a lipid soluble compound (to be able to cross the BBB) by adding one atom of halogen.
2. **Gaseous anesthetics: nitrous oxide, xenon**.

Pharmacokinetics:

• An adequate depth of anesthesia depends on achieving therapeutic (high) concentrations in the CNS.
• The rate at which an effective brain concentration is achieved (time to induction of anesthesia) depends on multiple pharmacokinetic factors that influence brain uptake & tissue distribution of the anesthetic agent:

1. **Uptake & distribution** of inhaled anesthetics:

• The driving force for uptake of an inhaled anesthetic into the body is the **ratio between inspired & alveolar concentration**.
• Achievement of a brain concentration of an inhaled anesthetic to provide adequate anesthesia requires transfer of the anesthetic from the alveolar air to the blood, and from the blood to the brain.

2. **Elimination** of inhaled anesthetics:

• The time of recovery from inhalation anesthesia depends on the rate of elimination of the

anesthetic from the brain.
• Many of the processes of anesthetic transfer during recovery are simply the **reverse** of those that occur during induction of anesthesia.
• Inhaled anesthetics that are relatively insoluble in blood and brain (possess **low blood: gas partition coefficients**) are eliminated faster than the more soluble anesthetics.
• The washout of **nitrous oxide, desflurane, and sevoflurane** occurs at a rapid rate, leading to a more rapid recovery from their anesthetic effects compared with **halothane & isoflurane**.
• **Halothane** is much more soluble in brain tissue & in blood than **nitrous oxide & desflurane**; its elimination therefore takes place more slowly, and recovery from halothane- & isoflurane-based anesthesia is predictably less rapid.

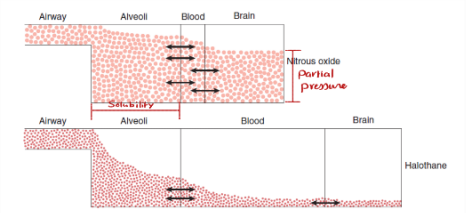


FIGURE 25–5 Why induction of anesthesia is slower with more soluble anesthetic gases. In this schematic diagram, solubility in blood is represented by the relative size of the blood compartment (the more soluble, the larger the compartment). Relative partial pressures of the agents in the compartments are indicated by the degree of filling of each compartment. For a given concentration or partial pressure of the two anesthetic gases in the inspired air, it will take much longer for the blood partial pressure of the more soluble gas (halothane) to rise to the same partial pressure as in the alveoli. Since the concentration of the anesthetic agent in the brain can rise no faster than the concentration in the blood, the onset of anesthesia will be slower with halothane than with nitrous oxide.

- Less soluble drugs (like NO) has faster onset of action & faster elimination rate (Faster onset & offset).
**Note: Compartments in the figure reflects solubility of each agent.
- Nitrous oxide is less lipid soluble than halothane, notice the figure, where blood compartment of NO is small, meaning that it is less soluble there, but NO has high partial pressure in brain ➡️ fast onset of action, with faster termination of action, the opposite is applied to halothane (Halothane has bigger blood compartment ➡️ it is more soluble in blood, but has less partial pressure in brain ➡️ slow onset &offset of action).
• Clearance of the inhaled anesthetics by the lungs is the major route of elimination from the body.
• Hepatic metabolism may also contribute to the elimination of **halothane** (~ 40% during an average anesthetic procedure).
• Oxidative metabolism (CYP2E1) of **halothane** results in formation of **trifluoroacetic acid** مهم جدا and release of **chloride and bromide ions** (dehalogenation reaction).
• Under conditions of low oxygen tension, **halothane** is metabolized to **chlorotrifluoroethyl** free radical which is capable of reacting with hepatic cell membrane and producing halothane hepatitis.
• < 10% of **enflurane** is metabolized.
• **Isoflurane & desflurane** are the least metabolized of fluorinated anesthetics.
• The metabolism of **methoxyflurane** (70%) results in elevation of renal *fluoride* levels ➡️ nephrotoxicity (fluoride is toxic to kidneys).
• **Nitrous oxide** is not metabolized by human tissues, but can be metabolized by **bacteria in the GIT**.
• **Sevoflurane** is **degraded by contact with the carbon dioxide absorbent** [which is soda lime = Ca(OH)2 (about 75%), H2O (about 20%), NaOH (about 3%), KOH (about 1%)] which is putted in anesthesic machines, yielding a vinyl ether which can cause renal damage *if* high concentrations are absorbed.

Pharmacodynamics:
• Interaction of the anesthetics with specific nerve membrane components results in **modification of ion currents**.
1) A primary molecular target of halogenated inhalational agents is ***GABAA receptorchloride channel***, a major mediators of **inhibitory** synaptic transmission. Either it is directly activated

or facilitated through binding to the other sides of the receptor.
2) ***Glycine receptor*** is another target for inhaled anesthetics, which enhance the capacity of glycine to activate glycine-gated chloride channels ➡️ **inhibitory neurotransmission** in spinal cord and brain stem.
• **The only general anesthetics that do not have significant effects on GABAA or glycine receptors are nitrous oxide & ketamine**, which act on calcium selective NMDA glutamate receptor.
• Neuronal ***nicotinic acetylcholine receptors*** inhibition by inhalational agents do **not** mediate anesthetic effect but **mediate analgesia & amnesia**.
• Certain inhalational anesthetics may cause membrane hyperpolarization by activation of potassium channels.
• Inhalational agents can produce presynaptic inhibition of neurotransmitter release in the hippocampus contributing to the **amnesic effect** of these agents.

Organ System Effects of Inhaled Anesthetics:
A. Effects on the Cardiovascular System: للحفظ
• **Halothane & enflurane reduce arterial pressure** by reduction of cardiac output.
• **Isoflurane, desflurane, and sevoflurane reduce arterial blood pressure** by decreasing systemic vascular resistance.
• **Halothane** may cause **bradycardia** probably because of direct vagal stimulation.
• **Desflurane and isoflurane increase heart rate**.
• **All depress myocardial function, including nitrous oxide**.
• **Halothane**, and to a lesser extent **isoflurane** sensitize the myocardium to circulating catecholamines ➡️ **ventricular arrhythmias**.
B. Effects on the Respiratory System:
• **All except nitrous oxide decrease tidal volume & increase respiratory rate.** (compensation)
• **All volatile anesthetics are respiratory depressants** and reduce the response to **increased levels of carbon dioxide**.
• **All volatile anesthetics increase the resting levels of PaCO2**.
That's why we put **soda lime** in the machine.
• The respiratory depressant effect is overcome by assisted or controlled **ventilation**.
• Inhaled anesthetics **depress mucociliary function of airways** ➡️ pooling of mucus ➡️ **atelectasis** & **postoperative respiratory infection.**
• **All volatile anesthetics** have some degree of **bronchodilating action** (so used for anasthesia in **asthmatic patients**).
• **Airway irritation** with **desflurane**.
C. Effects on the Brain:
• **Decrease metabolic rate of brain**.
• **Increase cerebral blood flow** by decreasing cerebrovascular resistance (dilation of vessels) (**not desirable in patients with increased intracranial pressure**).
Nitrous oxide is the least likely to do so.
• If the patient is **hyperventilated** before the volatile agent is administered, the **increase in ICP can be minimized** (by inducing hypocapnoeic (low CO2) vasoconstriction).
• **Nitrous oxide** has **analgesic and amnesic properties**.
D. Effects on the Kidney:

• Decrease GFR and urine flow.
• Impair autoregulation of RBF.
E. Effects on the Liver:
• Reduce portal blood flow.
F. Effects on Uterine Smooth Muscle:
• Nitrous oxide has little effect, so given to pregnant women.
• Halogenated anesthetics are potent uterine muscle relaxants, so not given to pregnant women.

Toxicity:
1. Hepatotoxicity:
*By 2 mechanisms, the first one is free radicals, the 2nd is autoimmune abs.
• Potentially life-threatening in subjects previously exposed to halothane.
• Incidence is 1:20,000 – 35,000.
• Obese patients are most susceptible.
• Mechanism is unclear, but may be due to:
a. Direct hepatocellular damage by reactive metabolites (free radicals).
b. Initiation of immune-mediated responses by reactive metabolites. Serum of patients with halothane hepatitis contain a variety of autoantibodies against hepatic proteins. Trifluoroacetylated proteins in the liver could be formed in hepatocytes during halothane biotransformation.
• They are also found in the sera of patients who did NOT develop hepatitis after halothane anesthesia.
2. Nephrotoxicity:
• Prolonged exposure to methoxyflurane (and ? enflurane) leads to formation of fluoride ions intrarenally by the renal enzyme β-lyase ➡️ changes in renal concentrating ability (and may be proximal tubular necrosis).
3. Malignant hyperthermia مهم وضروري تعرفوه: not a cancer
• Is an autosomal dominant genetic disorder of skeletal muscle, occurs in individuals undergoing general anesthesia with volatile agents (halothane) + succinylcholine.
• It consists of rapid onset of tachycardia & hypertension, severe muscle rigidity, hyperthermia, hyperkalemia, and acidosis.
Tx: blocking the release of Ca+ into the cytoplasm.
• It is rare but is an important cause of anesthetic morbidity and mortality
• Associated with increased calcium concentration in skeletal muscle cells (from the sarcoplasmic reticulum). Reduced by dantrolene.
4. Megaloblastic anemia in inadequately ventilated operating room personnel *if* prolonged exposure to nitrous oxide (which causes decrease methionine synthase activity).

تقبل الله طاعاتكم ♥

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