MED437
KING SAUD UNIVERSITY

PATHOLOGY
TEAM 437

Pathology

teamwork 437

Lecture two (2) : Cell Injury (1).

Color Index :-

- **VERY IMPORTANT**
- Extra explanation
- **Examples**
- **Diseases names: Underlined**
- **Definitions**

*{فاتق لحكيم فما قيمة العلم إن كان سهلا ميسرا}

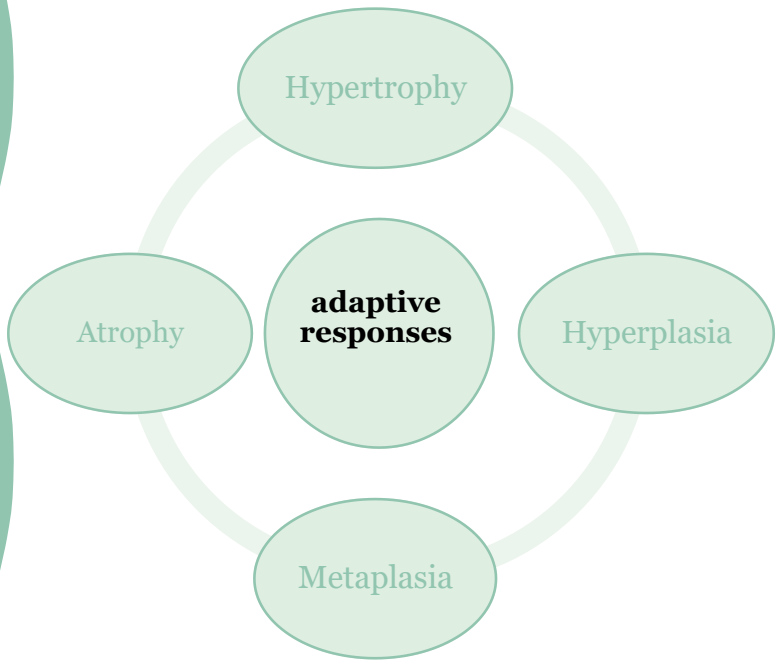
OBJECTIVES:

- UNDERSTAND THE CONCEPT OF CELLS AND TISSUE ADAPTATION TO ENVIRONMENTAL STRESS INCLUDING THE MEANING OF : HYPERTROPHY , HYPERPLASIA , APLASIA , ATROPHY , HYPOPLASIA , METAPLASIA WITH THEIR CLINICAL MANIFESTATIONS.
- IS AWARE OF THE CONCEPT OF HYPOXIC CELL INJURY AND ITS MAJOR CAUSES.
- UNDERSTANDS THE DEFINITIONS AND MECHANISMS OF FREE RADICAL INJURY.

ADAPTATION TO ENVIRONMENTAL STRESS

- Cells are constantly adjusting their structure and function to accommodate changing demands i.e. they **adapt** within **physiological limits**.

- As cells encounter physiologic stresses or pathologic stimuli, they can undergo **adaptation**. The **principal adaptive responses** are :



طبيعية الخلايا أنها متكيفة جداً للتغيرات الخارجية، بحيث تغير شكلها للتناسب وظيفيا مع التأثير الخارجي.

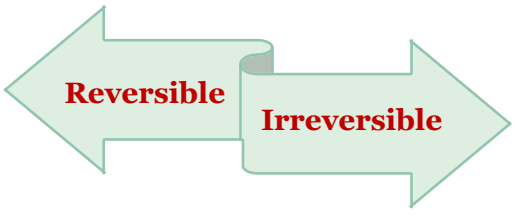
هنا التأثير(stress) يؤدى :

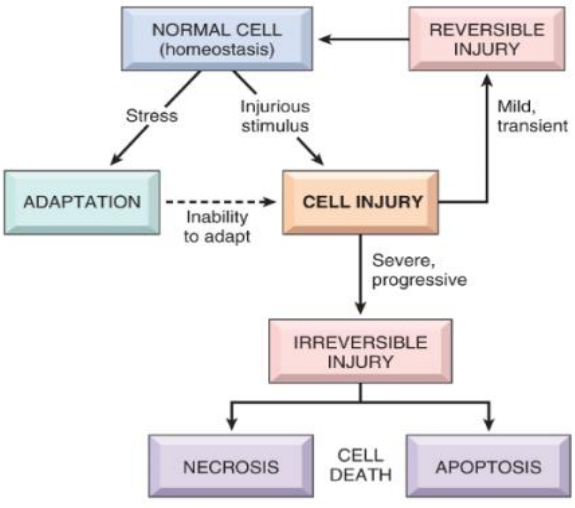
1- أما يكون بسبب طبيعي فيسيولوجي وتتكيف الخلية معه (Physiological adaptation) مثل عندما يكبر حجم العضلات بسبب الرياضة.

2- أو بسبب مرضي (pathological adaptation) مثل تضخم عضله القلب عند ارتفاع الضغط

- لما يكون بسبب مرضي ممكن يحدث Injury للخلية
- وهنا وال injury تنقسم لنوعين، لو كان التأثير Mild فتستطيع الخلية بعد كذا الرجوع لوضعها الطبيعي
- لكن لو كان too severe to adapt فيسبب موت للخلية

- If the adaptive capability is exceeded or if the external stress is harmful, **cell injury develops.**



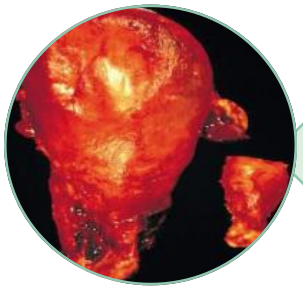


***NOTE THAT :** Within **certain limits** injury is **reversible**, and cells **return to normal** but **severe or persistent** stress results in **irreversible** injury and **death** of the affected cells.

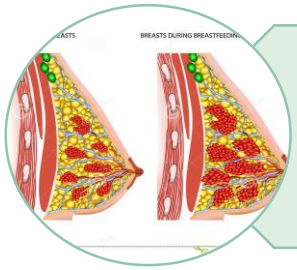
- **Hypertrophy: is an increase in the size** of the tissue/organ due to the increase in the **size of the cells**. In pure hypertrophy there are no new cells, just bigger cells containing increased amount of structural proteins and organelles
  - Increased demands lead to hypertrophy.
  - Hypertrophy takes place in cells that **are not capable of dividing** e.g. striated muscles.
  - Hypertrophy can be **physiologic** or **pathologic**

- **Examples of physiologic hypertrophy:**

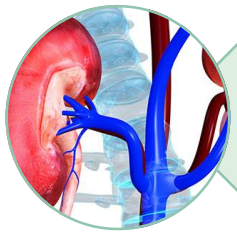
Physiologic Muscular hypertrophy. Exercise itself is normal but with talking anabolic steroid this gives pathologic hypertrophy to the muscle.



Physiologic hypertrophy of the uterus during pregnancy.



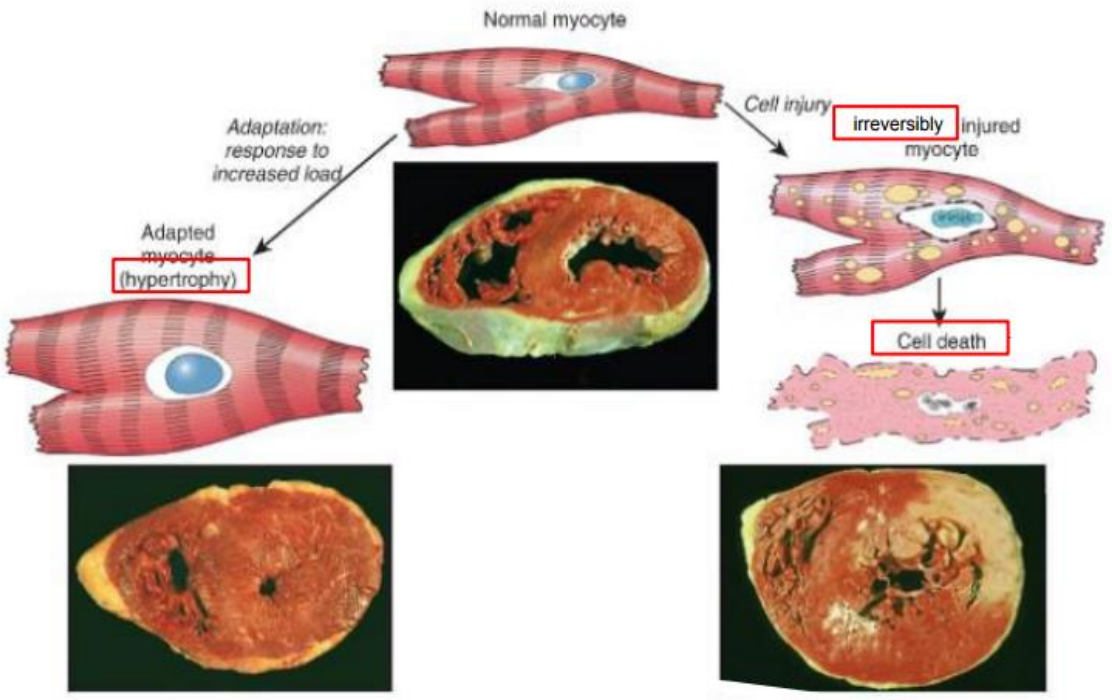
breast during lactation



People who remove one kidney usually experience hypertrophy in the other one, because it compensates the other (removed) one .

- **Example of pathologic hypertrophy:**

the cardiomyocytes (the cells of the heart) of the myocardium in heart failure (e.g. hypertrophy in hypertension or aortic valve disease)



Myocardium facing persistent and increased work load, as in **hypertension** or with a **narrowed (stenotic) valve**-ضيق الصمامات-. adapt by being hypertrophic to generate a higher contractile force. If the increased demand is not relieved, such as if the myocardium is subjected to reduced blood flow (ischemia) from an occluded coronary artery, the cardiac cells may undergo injury. Myocardium may be reversibly injured if the stress is mild or the arterial occlusion is incomplete or sufficiently brief, or it may undergo irreversible injury and cell death (infarction).

- **Hyperplasia**: Increase in the size of an organ or tissue, caused by an increase in the **number** of cells

  - in response to hormonal stimuli or other growth factors or irritation

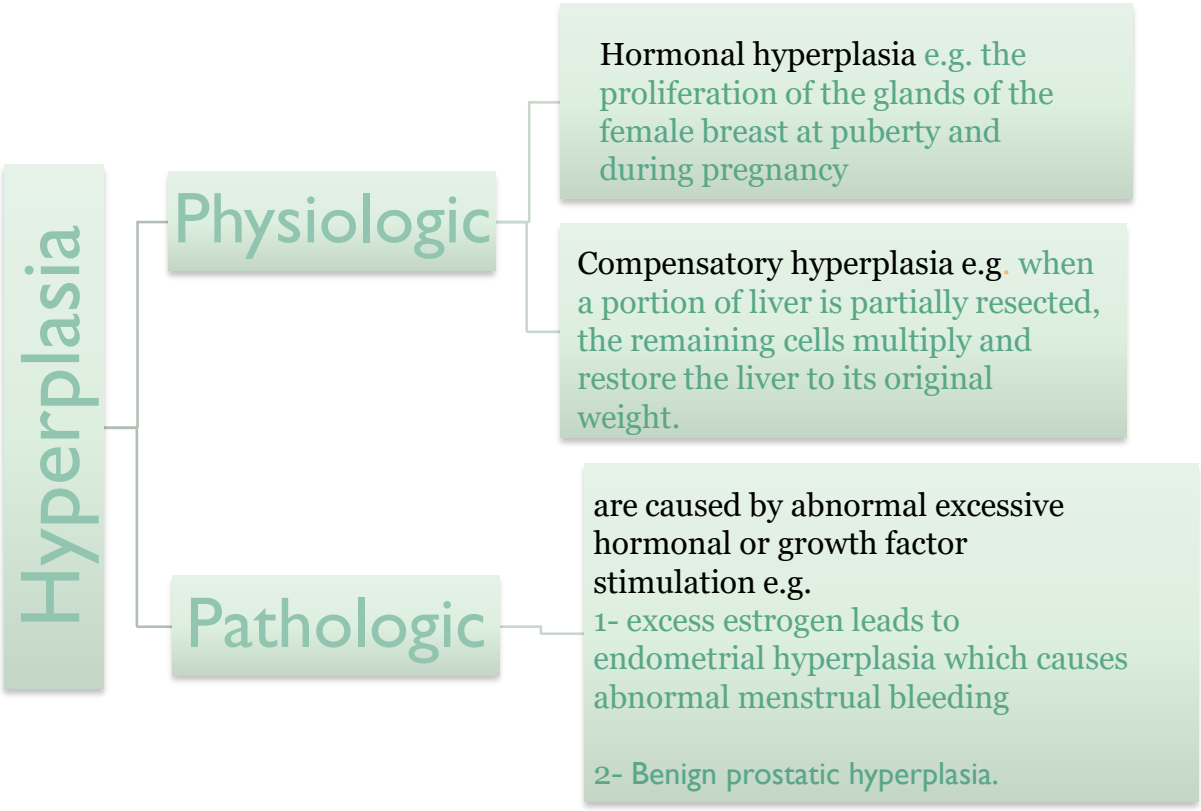
  -Hyperplasia occurs in tissues that are able to divide or contain abundant tissue stem cells, so some types of cells are unable to exhibit hyperplasia (nerve, cardiac, skeletal muscle cells).

  - hyperplasia can be induced by hormones (endometrial hyperplasia induced by estrogen).

  – Usually, hyperplasia **occurs together** with hypertrophy.

  – Hyperplasia can be **physiologic** or **pathologic**

  – Sometimes pathologic hyperplasia **acts as the base for cancer** to develop from. Thus, patients with hyperplasia of the endometrium are at increased risk of developing **endometrial cancer**.



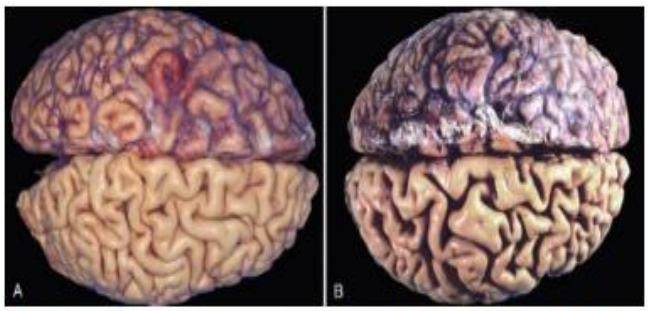
- **Atrophy** : Opposite of Hypertrophy. Atrophy is the **shrinkage in the size of the cell.**
  - When a sufficient number of cells are involved, the entire organ decreases in size, becoming atrophic. .
  - Atrophic cells are **not dead** but have **diminished function**. In atrophy there is **decreased protein synthesis** and **increased protein degradation** in cells.

NOTE:

-HOW? Decreased nutritious supply or diseases, associated with decreased synthesis of cellular building blocks (proteins) and increased breakdown of cellular organelles

-In the human embryo, for example, a number of structures are transient and at birth have already undergone atrophy, e.g. The adrenal glands become smaller shortly after birth because an inner layer of the cortex has shrunk.

- **Causes of atrophy include:**
  - -decreased workload or disuse(e.g. immobilization of a limb in fracture),
  - loss of innervation (lack of neural stimulation to the peripheral muscles caused by injury to the supplying nerve causes atrophy of that muscle)
  - diminished blood supply
  - inadequate nutrition
  - loss of endocrine stimulation (e.g. the loss of hormone stimulation in menopause)
  - aging: senile atrophy of brain can lead to dementia.



A. Normal brain of a young adult. **B.** Atrophy of the brain in an 82-year-old man with atherosclerotic[7] disease.

Dr.Rekabi 'note :

Athletes have hypertrophy in their skeletal muscles (large muscles size), If these athletes use anabolic steroids (hormones to build their muscles), male athletes who use these steroids will eventually experience artrophy in their testicles; called **testicular atrophy**, and they may have liver cell injury because of the anabolic steroids.

HYPOPLASIA VS APLASIA :

Hypoplasia

- Hypoplasia refers to an organ that does not reach **its full size**
- It is a **developmental disorders** and not an **adaptive response**

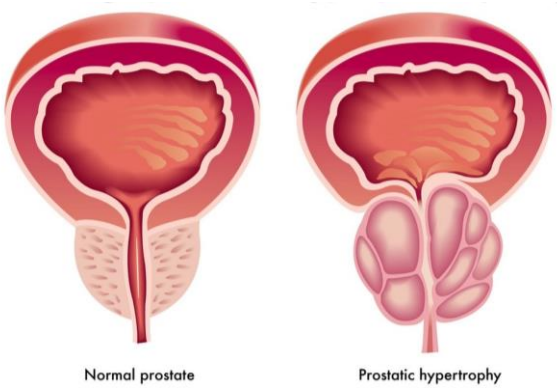
Aplasia

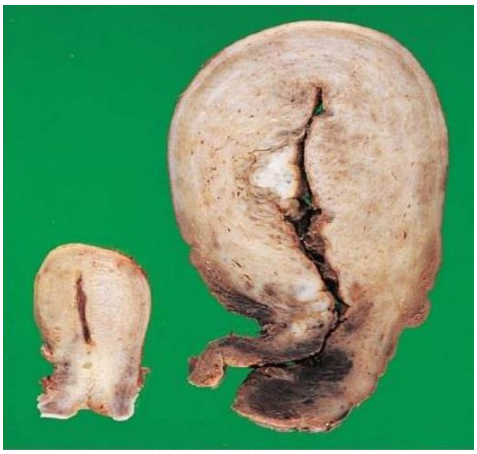
- is the **failure of cell production** and it is also a **developmental disorders**
- **e.g. during fetal growth aplasia can lead to agenesis of organs.**

Dr.rekabi's note:

Benign prostatic hyperplasia.

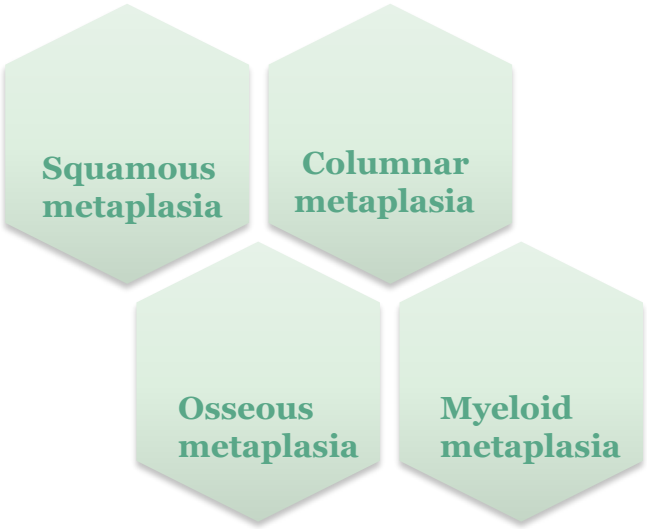
***Common signs and symptoms** :
1- Frequent or urgent need to urinate.
2- Difficulty starting urination





*the uterus during pregnancy in which there is smooth muscle **hypertrophy** and **hyperplasia**.

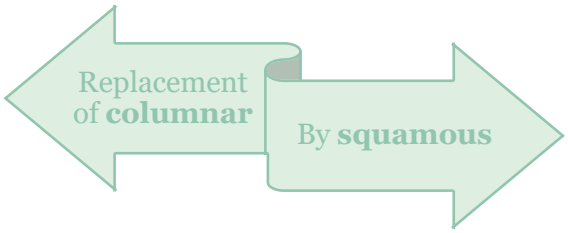
- **Metaplasia** : In metaplasia the cells adapt by changing **(differentiating) from one type of cell into another type of cell**. This is known as metaplasia.
  - Here the cells sensitive to a particular causative agent are replaced by another cell types better able to tolerate the difficult environment.
  - Metaplasia Is **usually a reversible** provided the causative agent is removed.



NOTES :

- الخلية هنا تتعرض لمؤثر خارجي، وطبيعتها وتركيبها لا يستطيع مجابهه هذا المؤثر، طيب وش تسوي ؟ تتحول لنوع أخر يكون باستطاعة تركيبته التحمل.. لكن بالمقابل ما كان نوع الخلية الاصلي موضوع بالمكان هذا عبث ولكن فأنه بالأساس يمتلك صفات يحتاجها النسيج الموجود.
فبالتالي لما تتحول لشكل أخر راح تفقد هذه الصفات التي نحتاجها.

* راح تفهمون أكثر مع الأمثلة ☺



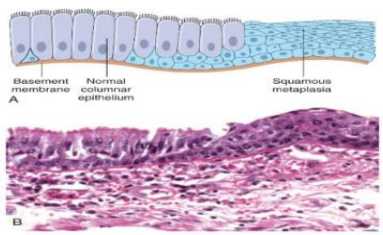
Squamous metaplasia:

-in cervix: replacement takes place at the squamocolumnar junction.

-In respiratory tract:

-the pseudo stratified columnar epithelium of the bronchus is replaced by stratified squamous cell following chronic injury in chronic smokers.

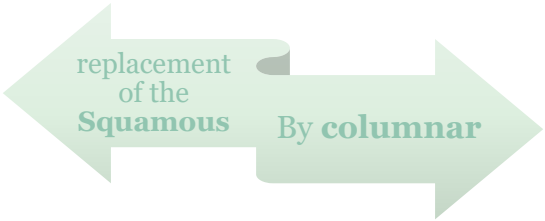
- The stratified squamous epithelium **is able to survive better** under circumstances that the more fragile pseudo stratified columnar epithelium would not tolerate. Although the metaplastic stratified squamous epithelium will survive better, the important protective functions of pseudo stratified columnar epithelium are lost, such as mucus secretion and ciliary action.
- If the causative agent persists, it may provide the base (predispose to) for malignant transformation. In fact, it is thought that cigarette smoking initially causes squamous metaplasia, and later squamous cell cancers arise from it.
- Similarly squamous cell carcinoma of cervix also arises from the squamous metaplasia in the cervix.



NOTE:

طبيعة الخلايا المبطنة للنسيج التنفسي pseudostratified ciliated columnar
وظيفة ال cilia انها تقوم بمنع ذرات الغبار والميكروبات الدقيقة من الدخول لمجرى التنفس، لكن عن تعرضها لماده النيكوتين في الدخان فأنها تتأذى ولا تستطيع المجابهة، لذا فأنها تحول لنوع أخر يستطيع التكيف مع هذا الوضع وهي الsquamous، لكن بالمقابل فأن النسيج التنفسي سيخسر قدرته على منع المايكروبات.

- **Columnar cell metaplasia**:

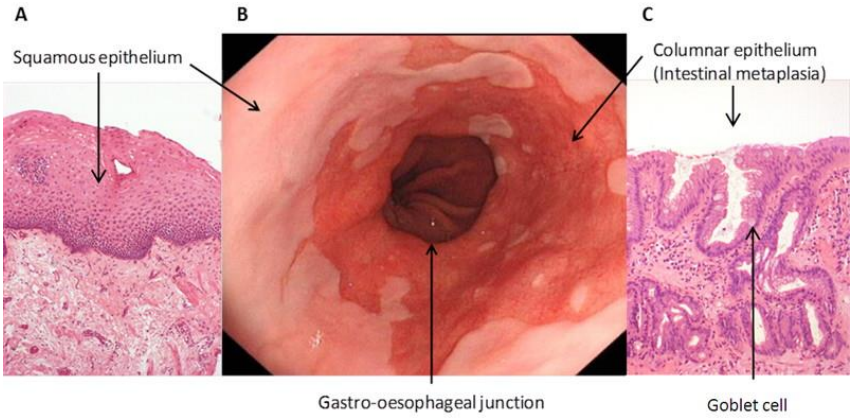


-It is seen in the **esophagus in chronic gastro-esophageal reflux disease**. The normal **stratified squamous epithelium** of the lower esophagus undergoes metaplastic transformation to **columnar epithelium**

- This change is called as **Barrett's esophagus** and it can be precancerous and lead to development of adenocarcinoma of esophagus.

Note:

عند نقصان حموضة المعدة، هذي الحموضة تصعد من المعدة للمريء ولأن خلايا المريء عباره عن squamousوكما نعرف انها خلايا رقيقة ما تتحمل الحموضة القوية، بعكس الحال في خلايا المعدة columnar فعشان تتكيف مع الوضع وتقدر تتحمل هذا الحمض تتحول ل columnar مثل المعدة .
طيب ايش يقلل ال ph للمعدة؟ من أهم الأسباب هو زياده التوتر، لهذا فأن زياده التوتر خطيرة ☺



- **Osseous metaplasia**: it is the **formation of new bone** at sites of tissue injury. Cartilaginous metaplasia may also occur.

في بعض الأحيان عندنا نتعرض لأصابه قوية يتحول مكان الاصابة إلى عظم، يا ترى ليش؟ عشان يتصدى إي اصابه ثانية بكونه نسيج عظمي قوي.

- **Myeloid metaplasia (extramedullary hematopoiesis):** is the proliferation of hematopoietic tissue in sites other then the bone marrow such as liver or spleen.

- When the cell is exposed to an injurious **agent or stress**, a sequence of events follows that is loosely termed **cell injury**.
- Cell injury is **reversible** up to a **certain point**, but if the stimulus **persists or is severe** enough from the beginning, the cell reaches a point of no return and suffers **irreversible** cell injury and ultimately cell death.
- **Cell death**, is the ultimate result of cell injury.

Extra explanation:

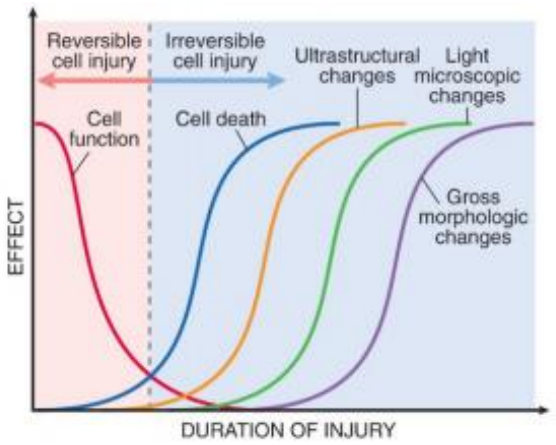
-مثل ما عرفنا قبل، عندما تتعرض الخلية لأي مؤثر فأنها ممكن تتعرض ل Cell injury لكنها في حالة تستطيع أن ترجع لوضعها الطبيعي، حتى توصل نقطة معينه ما عاد تقدر تتحمل فيها و يكون الضرر كبير لدرجة يصير Irreversible cell injury.

- نقطة مهمه: فقط عندما تكون Irreversible بيكون واضح تحت المايكروسكوب. **Abnormal cell structure**

-بينما في حالة ال reversible فغالباً يبين الcell structure طبيعي .

For example: Myocardial cells become:

- after 1 to 2 minutes of ischemia: noncontractile.
- after 20 to 30 minutes of ischemia: they become necrotic.
- after 2 to 3 hours of ischemia: myocytes may not appear necrotic by electron microscopy.
- after 6 to 12 hours of ischemia: myocytes appear necrotic under light microscopy

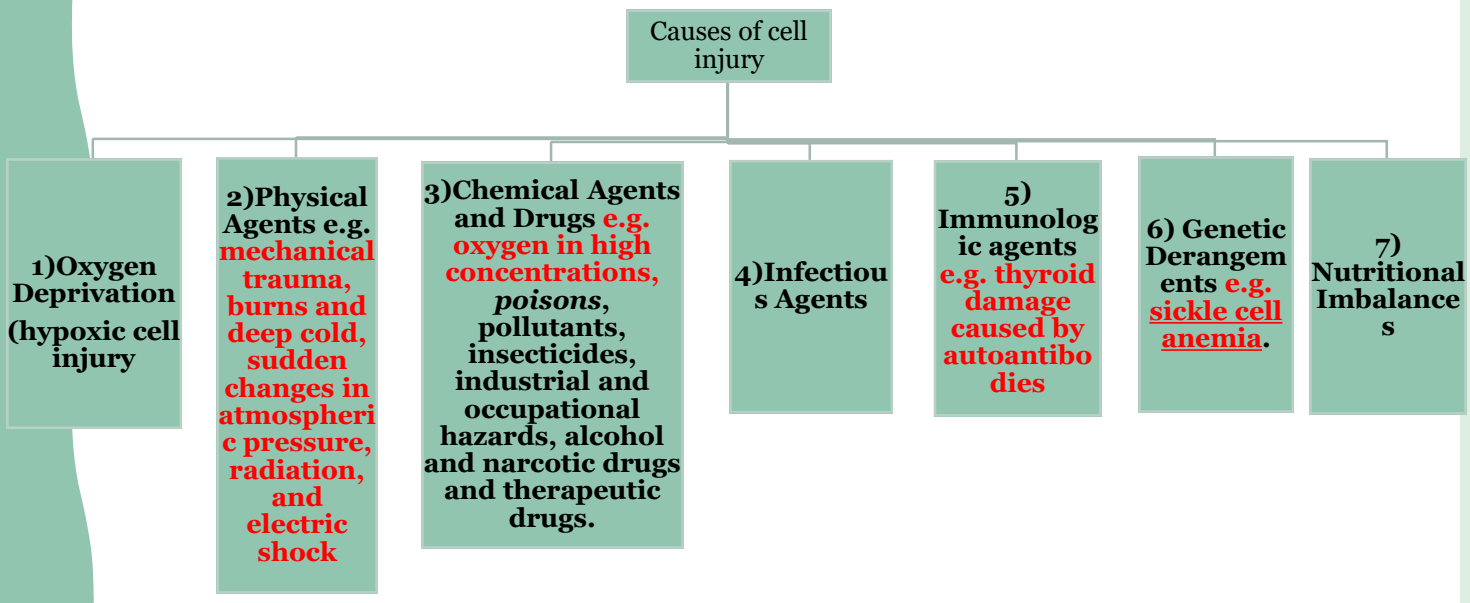


- There are two principal patterns of cell death, **necrosis** and **apoptosis**.

Necrosis	-is the type of cell death that occurs after ischemia and chemical injury - it is always **pathologic**.
Apoptosis	occurs when a cell dies through activation of an internally **controlled suicide program**.

CAUSES OF REVERSIBLE AND IRREVERSIBLE INJURY

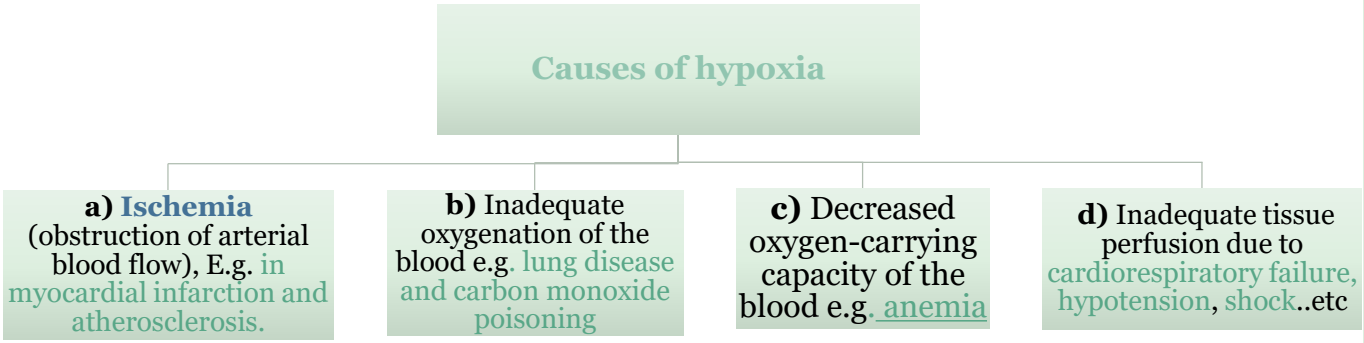
- Causes of both **reversible** and **irreversible** injury **are the same**. اللي يفرق هو قوه التأثير و المدة الزمنية لكن الاسباب نفسها



* **Also some cell types are more vulnerable to hypoxic injury then others e.g. Neurons are most susceptible followed by cardiac muscle, hepatocytes and then skeletal muscles.**

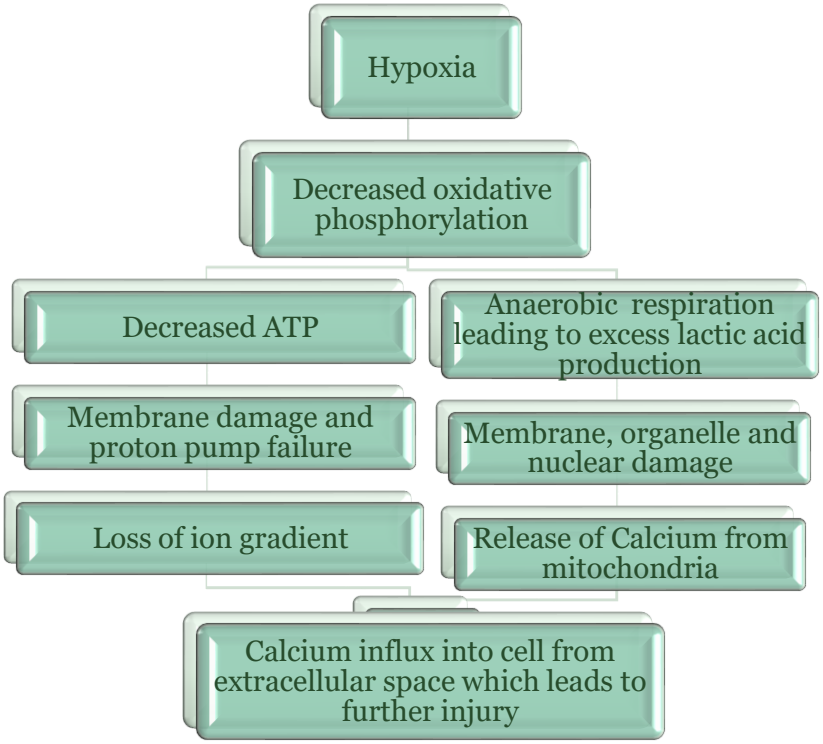
OXYGEN DEPRIVATION:

- **Oxygen Deprivation** : means Oxygen deficiency. (hypoxic cell injury). Its common cause of cell injury and cell death.
  - Hypoxia can be due to:



- Depending on the severity of the hypoxic state, cells may adapt, undergo injury, or die.

Mechanism in hypoxic cell injury:



* We will talk about them in more more details next slides, don't worry ☺

MECHANISM OF CELL INJURY :

What happens when we have cell injury that may result in cell death?

1. Depletion of ATP

is caused by :

1- reduced supply of oxygen and nutrients.

2- mitochondrial damage

3-some toxins e.g.: cyanide

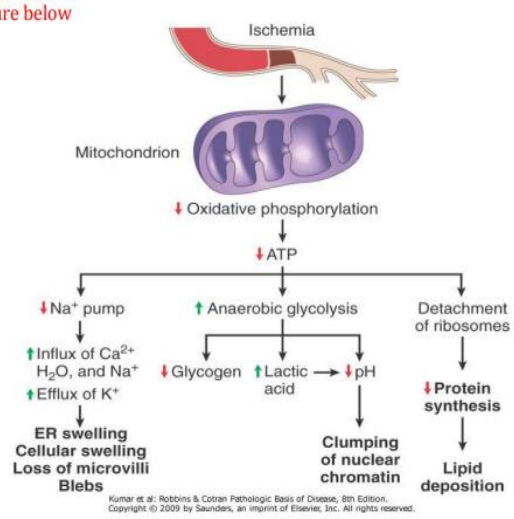
results in :

1- reduction of plasma membrane pumps activity → imbalance of substances disturbing the solutes concentration causes the cell to swell and ER to dilate.

2- detachment of RER proteins > less protein synthesis.

3- increase in anaerobic glycolysis using stored glycogen → decrease in glycogen → lactic acid accumulation → decrease intracellular pH →clumping of nuclear chromatin.

*see picture below



Extra explanation :

- مثل ما نعرف أهميه ال ATP تكمن في كونه مصدر للطاقة، طيب كيف ممكن يقل إنتاجه؟

1- لو ما فيه اوكسجين ماراح تتم عمليه oxidative phosphorylationال بداخل المايتوكندريا، بالتالي ماراح يكون فيه ATP.

2- لو فيه ضرر بالمايتوكندريا، ما راح يكون فيه ATP لأنه مكان إنتاجه ☺

3- أي toxins تضر المايتوكندريا أو الATP نفسه.

Extra explanation :

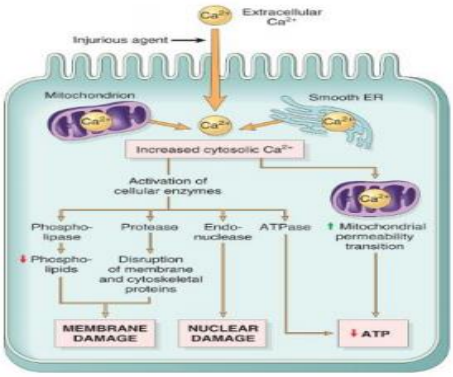
-مثل ما نعرف إن بعض ال Pumps تعتمد على ال ATPعشان ال.Active transport

- مثل sodium-potassium pump، بتوقف عن ضخ ال Na برا وال Kجوا، فستبدأ الايونات تنتشر down their constriction.
- إذاً فأن ال Na سيدخل لداخل الخلية ويتراكم ، وكما تعلمنا في الفيسيولوجي فأن زيادته داخل الخلية تقلل ال osmolarity وتزيد ال volume = the cell will swell.

- أيضاً كما نعلم انه عندما سيتوقف عمليه إنتاج ال ATP من oxidative phosphorylation راح تنتج ATP بكمية قليلة من عملية ال.glycolysis
- ال glycogen يتفكك منتجاً glucose يتحلل بدوره للطاقة
- نتيجة هذه العملية ستراكم ال lactic acid ويخرب الDNA

- **2- mitochondrial damage:**
  - It is seen specially in **hypoxic injury** and **cyanide poisoning.**
  - in case of **(low O2 supply/toxins/ radiation)** the mitochondria fails to produce ATP, and instead it produces oxygen derived free radicals. These are harmful to the cell and can lead to necrosis

- **3- influx of calcium activation of enzymes**:
  - ischemia causes an increase in intracellular calcium concentration, due to malfunction of the Na/Calcium pump
  - when calcium enters the cell, because of the damage in the plasma membrane pumps, it participates in chemical reactions that will activate a number of enzymes that **trigger apoptosis.**



- **4)Ribosomal damage:**
  - **-** It is seen in **alcohol damage** of **liver cell**s and **with antibiotic use.**

5) increased permeability of the cellular membrane: typically culminate in necrosis.

Several **biochemical mechanisms** contribute to membrane damage:

1. decreased phospholipid synthesis because the ATP is less available.

2. increased phospholipid breakdown : when the Ca levels are high, it activates the phospholipase enzyme that breaks down the membrane. "the products of the broken lipids also affect the membrane."

3. oxygen free radicals.

4. cytoskeletal abnormalities: when the **Ca** levels are high it activates the protease enzyme that damages the cytoskeleton

The affected membranes are :

1.**Mitochondrial membrane**: → decrease of ATP formation → many deletions → necrosis.

2. **Plasma membrane:** → imbalance to the permeability → influx of fluids + ions / loss of cellular contents. the also can lose metabolic products thus further reducing the energy stores.

3. **lysosomal membranes:** → leakage of enzymes → digestion of cellular components → cell death by necrosis

MECHANISM OF CELL INJURY :

5. **Free Radical Injury:** Accumulation of oxygen-derived free radicals (oxidative stress):

-Free radicals are highly reactive and harmful atoms that have single unpaired electron in an outer orbit.

-They are referred to as reactive oxygen species/free radicals. The free radicals are produced in our cells through several ways, called as the **free radical generating systems.**

Extra explanation :

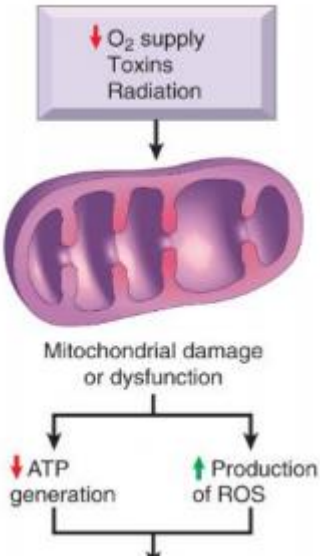
-Free radicals are: atoms that have lost 1 or more electrons from their outer orbit are usually harmful.

-Free radicals in the cell are usually from **Oxygen**.

-The free radicals are considered **unstable**, therefore its hyper reactive (searches for a way to become stable).

- therefore it must enter **biochemical reactions** in order to bind to another atom to form a new compound and become stable.

-This causes **cell injuries**. Why? Because the reaction it enters might be dangerous and toxic to the cell.



- **The common free radicals are:**
  - superoxide anion radical (O2-)
  - hydrogen peroxide (H2O2)
  - hydroxyl ions (OH)
  - Nitric oxide (NO) is an important chemical mediator generated by various cells and it can also act as a free radical.

Free radicals are produced by:	
1. Normal metabolism/ respiration: Small amounts of harmful reactive oxygen is produced as a bi-product of mitochondrial respiration during normal respiration (reduction-oxidation reactions that occur in normal metabolism)	**2. Ionizing radiation injury:** e.g. UV light, x-rays
3. Chemical toxicity: enzymatic metabolism of exogenous chemicals or drugs.	**4. Oxygen therapy and reperfusion injury**
5. Immune response or inflammation (neutrophil oxidative burst)	**6. Transition metals** e.g. iron and copper

MECHANISM OF CELL INJURY :

▪ Free radicals cause damage to lipids, proteins, and nucleic acids. The main damaging effects of these reactive species are:

1. Lipid peroxidation of membranes → damage of membranes & organelles etc..
2. Oxidative modification of proteins → protein fragmentation
3. DNA damage → lead to cell aging and malignant transformation of cells.

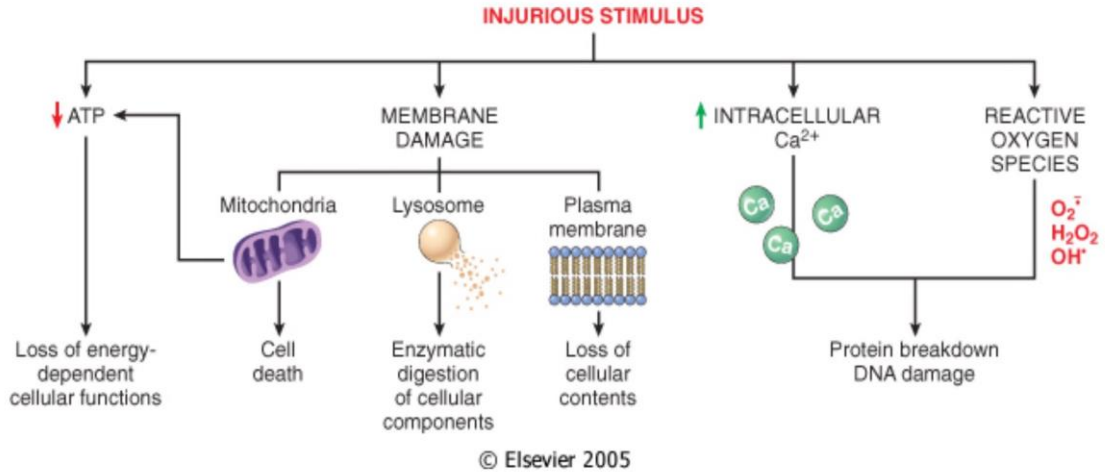
*When they react with other molecules, they initiate a reaction to transform the other molecules into free radicals.

- **How does our body fight the free radicals?**

Certain substances in the cells **remove/ inactivate** the free radicals in order to minimize injury caused by them. They are called as **the free radical scavenging system**. They are:

- Antioxidants: vitamins E, A and C (ascorbic acid).
- Enzymes: which break down hydrogen peroxide and superoxide anion e.g. Catalase, Superoxide dismutase, Glutathione peroxidase and mannitol.

NOTE: Any imbalance between free radical-generating and radical-scavenging systems results in oxidative stress causing cell injury.



MORPHOLOGICAL CHANGES OF REVERSIBLE AND IRREVERSIBLE CELL INJURY

*The order is important

- Earliest changes associated with cell injury are reversible. They are:

1) Swelling & vacuolization of cytoplasm called hydropic/ vacuolar degeneration.
Disturbance in cytoplasmic membrane permeability (gain of Na and loss of K)

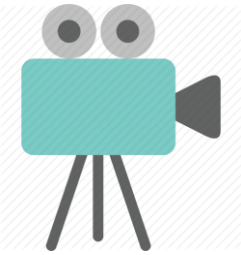
2) Mild mitochondrial swelling. the rough endoplasmic reticulum and plasma membrane damage.

3) Defect in protein synthesis. Due to the mitochondrial swelling and damage.

5) Mild eosinophilia of cytoplasm (due to decrease in cytoplasmic RNA)

6) cytoplasmic membrane blebs

-**Fatty change:** appearance of small or large lipid vacuoles in the cytoplasm (e.g. in hepatocytes and myocardial cells)



نقص الاوكسجين => يقل انتاج ATP <= sodium potassium pump تسمح
بدخول كميه اكبر من Na داخل الخليه مما يزيد تركيزه =>يدخل الماء للخليه بسبب
نتيجه ل => cell organelles swell => cell swell => osmosis
defect protein synthesis وبالتالي rough ER swell الرايبوسومات تتاثر
=> تزداد حامضيه السيتوبلازم بسبب نقص RNA الموجود في الرايبوسومات

- Persistent or excessive injury, however, causes cells to pass the threshold into **irreversible injury.** Irreversible injury is marked by

1.Severe mitochondrial damage with the appearance large, amorphous densities in mitochondria. (severe mitochondrial dilatation and damage. Large, shapeless (amorphous) densities are also present) → (lack of oxidative phosphorylation and ATP generation).

2.Severe plasma/cell membrane damage

3.Increased eosinophilia** (appears red under the microscope.)

4.Numerous myelin figures: a rolled-up or scroll-like arrangement of a lipid bilayer within a cell, superficially resembling the myelin sheath of nerves. Formed from the fragmentation of the lipid bilayer.

5.Rupture of lysosomes leakage and enzymatic digestion of cellular contents(lysosomal membranes results in the enzymatic dissolution of the injured cell)

-Nuclear damage:

1) karyolysis (dissolution), in this case the nuclear chromatin is lost, therefore there is a decrease in basophilia.
Why a decrease in basophilia? the chromatin of the nucleus is lost; therefore hematoxylin stain has less DNA to bind with, hence there is less blue color or basophilia

2) pyknosis (shrinkage) in this case the nucleus shrinks and the DNA condenses into a solid mass. There is an increase in the nucleus' basophilia.
Why an increase in the basophilia? because the DNA comes together and the stain makes it look very dark blue

3) karyorrhexis (break down)
(this happens after pyknosis) The pyknotic nucleus undergoes fragmentation.

NOTE:

**Why is there increased eosinophilia?
reason: the DNA is damaged → cannot form RNA → decrease RNA in cytoplasm.

Didn't get it ? Remember that there are two dyes used when staining a cell; hematoxylin and eosin. Hematoxylin a base and binds with acidic parts of the cell, especially the nucleus. Eosin is an acid and binds with basic parts of the cell (parts of the cytoplasm). When hematoxylin binds with parts of the cell this part appears in dark blue. On the other hand when eosin binds to parts of the cell they appear pinkish. Usually, when the cell is active, lots of RNA are being synthesized. (mRNA, tRNA, and rRNA). When the cell is strongly damaged, the DNA is no longer capable of synthesizing RNA, which means that the cell is less capable of building proteins. Less RNA in the cytoplasm means that there is less blue color of hematoxylin (RNA is an acid and hematoxylin is a base). When the blue color is less, the pinkish color of eosin is clearer; and that is what increased cytoplasmic eosinophilia means.

MEMBERS :

Females:

-leader :

بثينة آل ماجد

-روان الحربي

-وفاء العتيبي

-الجوهرة الشنيفي

-رزان الزهراني

-رهف الشمري

-روان مشعل المسعد

-منيره السويلم

-لميس العتيبي

-نوف الزهراني

-رزان الزهراني

-هديل عورتاني

-فاطمة بالشرف

-ابتسام المطيري

-رناد الفرم

-غرام جليدان

-بلقيس الراجحي

-نورة القاضي

-آلاء الصويغ

-ريم القحطاني

-نورة بن حسن القحطاني

-شوق العبيد

-ندى العبيد

Males:

-leader : فيصل الطحان

عبدالجبار اليماني

محمد باحاذق

أحمد الراشد

عبدالله بالعبيد

عبدالله السرجاني

أحمد الحربي

أنس السيف

داود إسماعيل

خالد الدوسري

فهد الفايز

محمد بن معيوف

فهد النهابي

معاذ العبد الغني

سعد الفوزان

سيف المشاري

تميم الوهيبي

أحمد الرخيمي

رشيد البلاع

محمد النجيم

Gently contact us if you have any questions/comments and suggestions:

* EMAIL: pathology437@gmail.com
* TWITTER : @pathology437

GOOD LUCK!☺

Resources:

1- females slides
2- Robbins book

Pathology

teamwork 437