MED437
KING SAUD UNIVERSITY

PATHOLOGY
TEAM 437

Pathology

teamwork 437

Lecture three (3) : Cell injury (2)

Color Index :-

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

تمت المراجعة
غيداء آل مصمع
&
عبدالرحمن الحيسوني

*{قالتِ لحُلمِكِ، ما قيمة الحُلم إن كانَ سهلًا مُيسرًا..}

OBJECTIVES:

A. KNOWING THE TYPES OF NECROSIS : COAGULATIVE, LIQUEFACTIVE, CASEOUS, GANGRENOUS, FIBRINOID AND FAT NECROSIS.

B. APOPTOSIS : DEFINITION, MORPHOLOGIC FEATURES, REGULATION OF APOPTOSIS.

C. COMPARISON BETWEEN NECROSIS AND APOPTOSIS.

DEFINITION AND TYPES OF NECROSIS

- **Necrosis** : Is the type of cell death that occurs after ischemia and chemical injury, **and it is always pathologic.**
  - in which there is enzymatic digestion and denaturation of intracellular protein in the dying cell.
  - It occurs in irreversible injury.
  - It is usually associated with inflammation in the surrounding tissue.
  - It involves the death of a group of cells in one area.

- **Necrosis can result in:**
  - Cessation: loss of function of the involved tissue/organ.
  - Release of certain **cellular enzymes** that can be detected in blood. The level of these enzymes can be used as **markers** to diagnose the injury and also can help determine the time and the extent of injury e.g. Cardiac enzymes in myocardial infarction (heart attack).
  - An inflammatory response

TYPES OF LYSIS :

The enzymes used in this degradation of a cell come :

- **From the lysosomes of the dying cell itself (autolysis)**

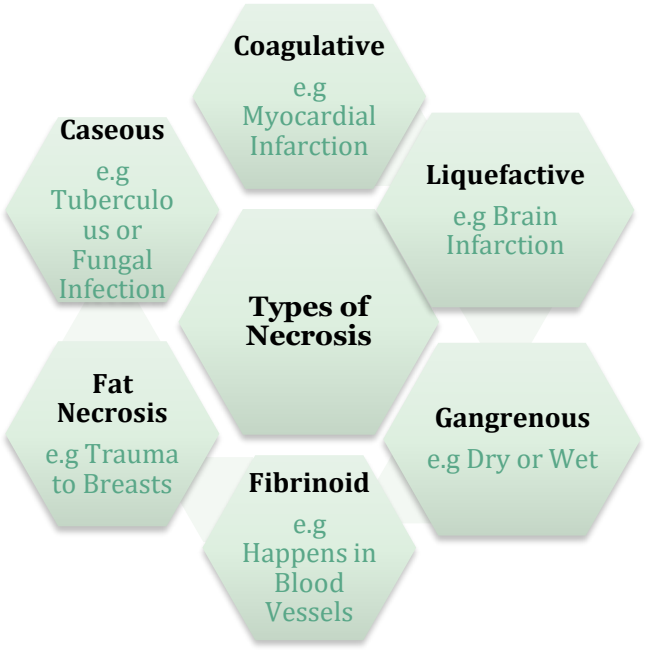
Autolysis is the death, disintegration of cells or tissues by it's own enzymes.

- It is seen in cells after death/ post mortem.
- It is also seen in some pathologic conditions in living organisms.

- **From lysosomes of neighboring leukocytes (heterolysis).**

Extra explanation :

إذاً ال necrosis عباره عن موت الخلايا نتيجة اسباب مرضية ، وأهم نقطة عندنا هي أن الانزايمز الموجوده في الخلية راح تحلل اجزاء الخلية الداخلية ، وبعد كذا راح تطلع من خلال السيل ممبرين للدم ، فبإمكاننا كأطباء توقع وجود necrosis لما نقيس مستوى الانزيمات في الدم وتكون مرتفعة.



1- Coagulative necrosis (click here for video) :-

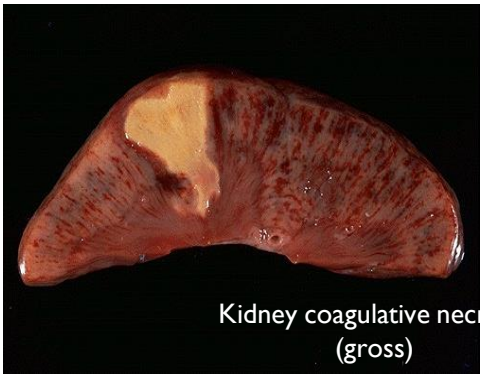
- characteristically seen when blood flow to an organ is affected leading to ischemic/hypoxic death of cells in that organ. (Usually caused by Ischemic **infarction** (جلطة)).

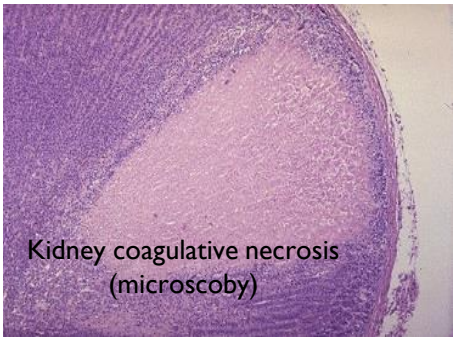
  -In this type, the general shape of the organ stays the same except for **nuclear changes and cytoplasm becomes eosinophilic.**
  -It is seen in all organs except the brain

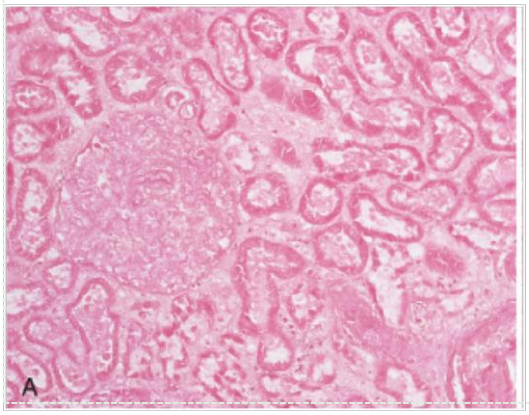
Heart (myocardial infraction) → Kidney (renal cortical infraction → Spleen → liver

- Ultimately, the necrotic cells are removed by phagocytosis by the macrophages (they act like vacum cleaners).

- **Gross:** The affected organ looks pale and firm/solid. It looks like cooked meat or boiled egg.


Kidney coagulative nec
(gross)


Kidney coagulative necrosis
(microscoby)


A

- Microscopy: In tissue or organ showing coagulative necrosis, there is preservation of the general tissue architecture
  - initially the **basic ghost outline** of the affected/coagulate
  - cell remains preserved for a few days but the
  - nucleus is lost. The cell
  - cytoplasm is eosinophilic.

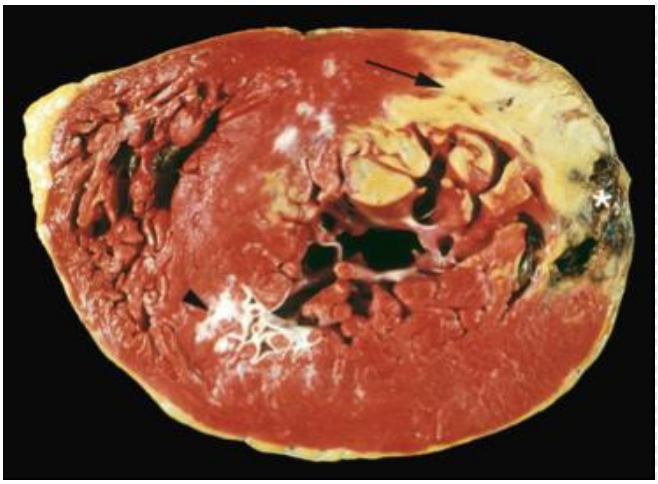
these **cardiac muscle** cells don't have a nucleus because they have :

-karyorrhexis (تفتت النواة) and some of the cells don't have nuclei at all because there's lysis of nuclei .
-karyolysis (انحلال النواة) caused by coagulative necrosis.

- Clinical case:

A man died of **myocardial infarction** (also known as heart attack) : Necrosis of heart muscles resulting from ischemia.

- The major cause of this disease is **atherosclerosis** (accumulation of cholesterol in the blood vessels)
- **Symptoms**: retrosternal chest pain.
- **Signs**: Increased level of a cardiac enzyme called **troponin** in blood testes



(Myocardial infarct of the left ventricle is acquired by a partly yellowish area and a partly hemorrhagic(نزيف) area, this area is most likely **necrosis**.)

2- Liquefactive necrosis (click here for video) :-

is a type of necrosis which results in transformation of the tissue into a **liquid viscous mass**.

Is characteristically seen

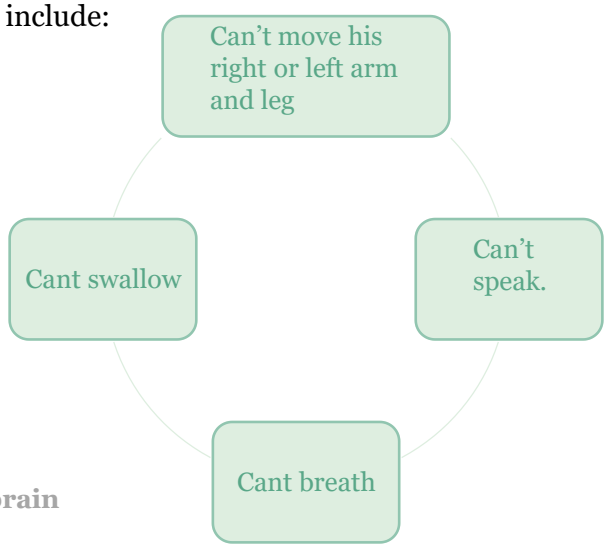
- in hypoxic cell death in the **central nervous system/brain**
- in suppurative (**pus or abscess producing**) infections especially bacterial infection.

The affected tissue is softened/liquefied by the action of hydrolytic enzymes which are

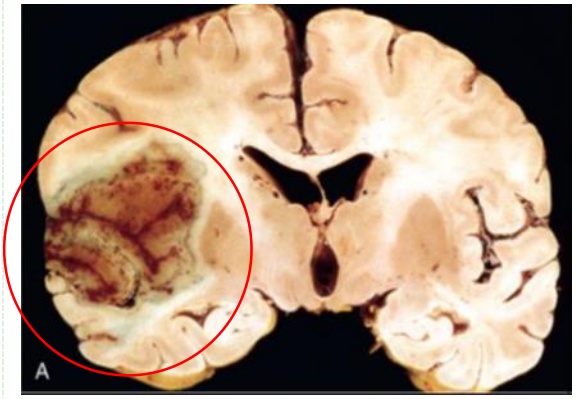
- released from the **lysosomes in the brain cells**
- released from the **neutrophils in the pus/abscess.**

- The affected area is soft with liquefied creamy yellow center containing necrotic cells,
- and neutrophils and is called **pus/abscess**.
- Ultimately, most necrotic cells are **phagocytosed**.
- Usually occurs in organs that are rich in **fluids** such as the **Brain** or **CNS**. It results with **abscess (خراج)** cavity filled with **pus(صديد)** .
- This type of necrosis leads to a **complete loss of architecture.**

Symptoms of liquefactive necrosis in the brain include:



*This depends on the affected area of the **brain**



Gross:

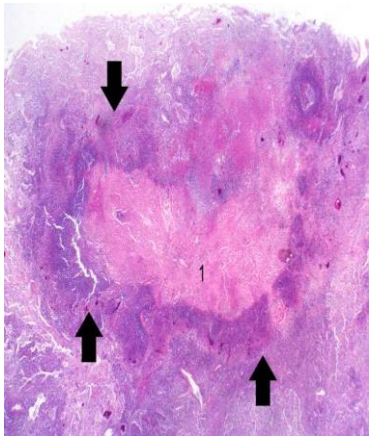
An area in this brain tissues showing yellowish discoloration with hemorrhagic(نزيف) region.

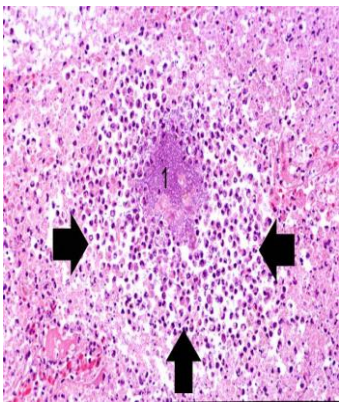
Microscopic :

Liquefactive necrosis (center labeled one is necrosis and surrounding is neutrophils.

This is how the area will look under the microscope, there's a complete **loss of the architecture**,

all we can see is a big cavity surrounded by inflammatory cells **(macrophages**





3- Caseous necrosis :- (CLICK HERE FOR VIDEO)

It is a type of coagulative necrosis classically seen in **tuberculosis** (infection by mycobacterium tuberculi).

The tissue architecture is completely obliterated (unlike the coagulative necrosis where the general tissue architecture is preserved).

***Whenever you hear Caseous necrosis .. Always think of TB (Tuberculosis)**

Grossly: it is white, soft, curdy cheesy-looking "caseous" material.

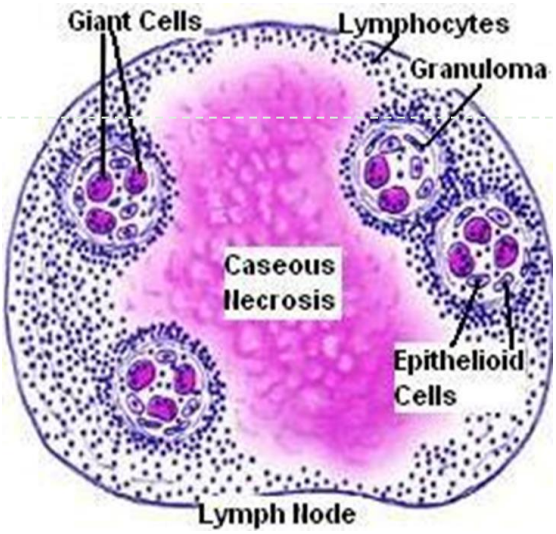
Tuberculous lung with a large area of caseous necrosis. The caseous debris is yellow-white and cheesy

On microscopic examination:

-the necrotic area appears as amorphous pink granular debris surrounded by a collar of epitheloid cells (they are modified macrophages)

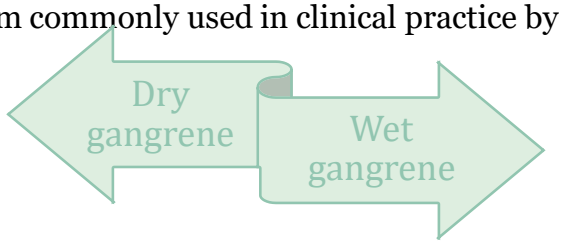
lymphocytes and giant cells. This is known as granuloma.

Here the tissue architecture is completely obliterated.



4- Gangrenous necrosis:- (click here for video):-

- It is a term commonly used in clinical practice by surgeons.



Dry gangrene/ mummification:

-it is a form of coagulative necrosis that develops in ischemic tissue (where the blood supply is inadequate).

-Dry gangrene is non-infected ischemic coagulative necrosis

-It is without superadded infection. It is seen as a complication of peripheral artery disease (e.g. atherosclerosis and diabetes mellitus.)

- Dry gangrene is usually seen in a **limb that has lost its blood supply and undergone coagulative necrosis**
- **-**The affected part is **dry, shrunken and dark reddish-black.**

Notes :

تعتبر الغرغرينا مثال على ال coagulative تصيب الخلايا اللي ما يوصلها دم كافي بالتالي ما يوصلها اوكسجين ، مما يؤدي إلى ischemia .

طيب ليه تصيب الأطراف خصوصا الرجل ؟
لأنها الجزء الأبعد عن القلب فيكون احتمال وصول الدم لها قليل

Wet/ infected gangrene:

it is dry gangrene with superadded bacterial (putrefactive) infection.
-The coagulative necrosis is modified by the action of the bacteria into liquefactive necrosis (so basically when a dry gangrene gets infected by a certain bacteria it becomes a wet gangrene).

-Initially there is coagulative necrosis and then there is superadded infection leading to liquefactive necrosis.

-Wet gangrene usually develops rapidly due to blockage of venous (mainly) and/or arterial blood flow.

-It's rare and occurs in certain circumstances (like war) when an open wound comes in contact with soil , the bacteria is usually saprogenic (i.e. it lives in the gut or the soil and it can thrive in low oxygen states) e.g. gram-positive Clostridia or Bacillus fusiformis.

-It has **a poor prognosis** compared to dry gangrene . **WHY ?** because the infection can spread to the rest of the body (septicemia) and be life threatening (death).

-The limb becomes foul smelling and black and starts decomposing.

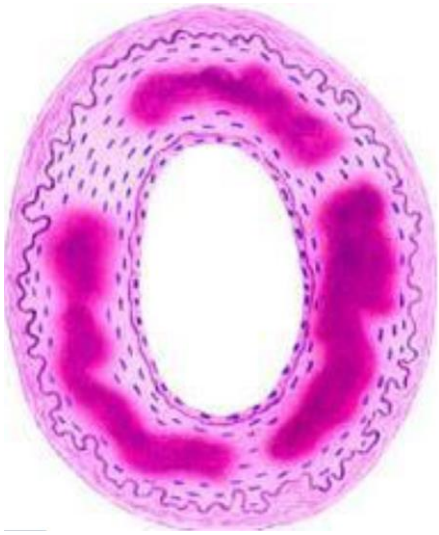
NOTE: Diabetes mellitus is a risk-factor for peripheral vascular disease and thus for dry gangrene, but also a risk factor for wet gangrene.

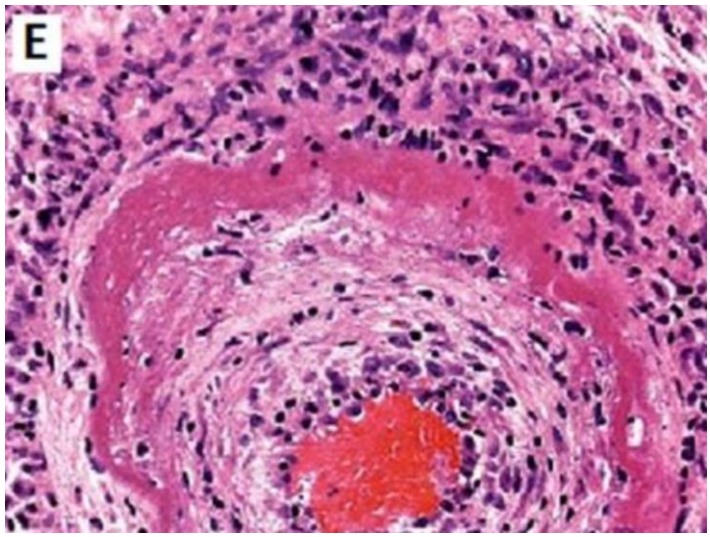
الغرغينا بسبب نشاط البكتيريا ممكن تكبر الإصابة وينتشر في الجسم ويسبب (تسمم الدم) septicemia وتصير حياة الشخص معرضة للخطر إذا لازم نبتر هالرجل أو اليد وتكون رائحة الغرغرينا سيئة جداً وبعدين تبدأ الخلايا بالتحلل

5- Fibrinoid necrosis (click here for video):-

- Occur in blood vessels (arteries, arterioles and capillaries)
  - . There is deposition of **fibrin material** in the arterial walls, which appears smudgy and **acidophilic/eosinophilic.**
  - It is seen in **immune mediated diseases** (autoimmune diseases) and also seen in malignant hypertension.
  - **What are the immune mediated diseases ?**Autoimmune disorder occurs when the body's immune system attacks and destroys healthy body tissue.
  - It creates inflammatory reactions.
  - It's visible by light microscope.

- Example of fibrinoid diseases: polyarteritis nodosa. (التهاب الشرايين العقدي)





*Fibrinoid necrosis in an artery. The wall of the artery is bright pink with dark neutrophils.

NOTES :

Fibrinoid name: The deposit of immune complexes together with fibrin has leaked out of vessels, produces a bright pink and amorphous appearance on H&E preparation called fibrinoid (fibrin like).

عند تسرب العقد المناعية مع الفايبرين من الأوعية الدموية، تنتج لون وردي فاتح عديم الشكل، الذي يظهر عند صبغ العينة بـ الهيماتوكسين والأيوسين وتسمى الفيبرونويد أو شبيهة الفايبرين.

6) Fat necrosis (click here for video) :

- **Occurs in any organ containing fats**. (e.g. pancreas, breast tissue in females)

How does the fat necrosis accurse ?

-Typically, it is seen in **acute pancreatitis** in which the injured pancreatic cells release the lipase enzyme into the fat in the abdominal cavity and cause enzymatic digestion of fat cells.
-The released lipase breaks down the fat cells into glycerol and free fatty acids
-The produced fatty acids combine with **calcium** circulating in the blood to produce **calcium soaps** which looks like chalky white spots in the necrotic fat. This process is called as **fat saponification.**

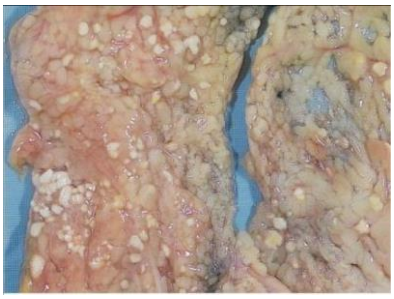
- Example of fat necrosis : Trauma to breast ruptures blood vessels, this causes blood (and therefore enzymes) to leak to tissue. The enzymes cause lysis and necrosis in the fat. This causes inflammation, which causes fibrosis (and you'll have a mass in the breast).

ولد يلعب كورة وما يعرف يسدد , فيمزع الكورة بقوة وبالغلط تجي على
صدر البنت و هذا قد يسبب تمزق في الأوعية الدموية و بالنهاية Fat necrosis ☺

.

NOTES:
بعد ما يصير injury لخلاي البنكرياس راح تطلع الانزيمات الخاصه فيه
ومنها اللايبيس، اللايبيس ينجذب للخلايا الدهنيه، فلما يرتبط فيها بيحللها
لمكونتها الاساسيه = glycerol and fatty acid

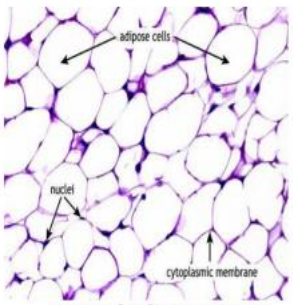
ال fatty acidيرتبط مع الكالسيوم (as we know that Ca is
highly active atom) فما يصدق انه يلقى ال fatty acid يرتبط معه
ويكون قطع تشبه الفقاعات الصابوينه.



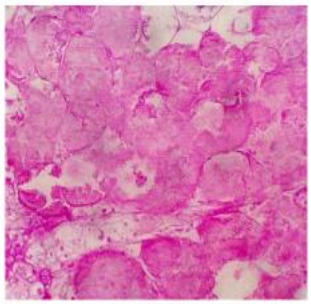
› The outlines of necrotic/dead fat cells can be seen. Inflammation is minimal.

› Fat necrosis can also be seen in breast fat and other fatty areas due to traumatic injury

* When you look under the microscope we find dead adipocyte (because there's no nuclei + the cytoplasmic membrane in many areas ruptured) so the patient will have **calcifications**



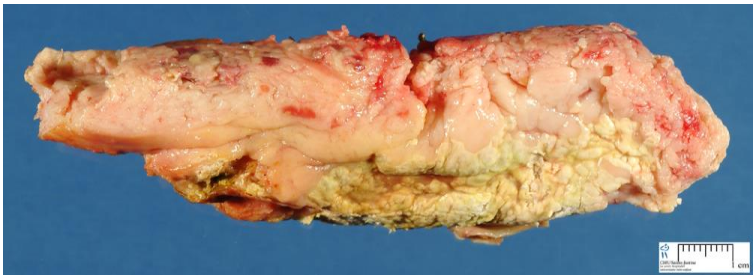
Normal Adipose Tissue


Fat necrosis

CLINICAL CASE OF FAT NECROSIS:

Its only for your own understanding, but we really recommend you to read it.

Pancreatitis



-Patient came to the ER suffering from abdominal pain, one of the causes of abdominal pain is pancreatitis (inflammation in the pancreas) could be acute or chronic. There are 2 enzymes, which are secreted by the pancreas **lipase** and **amylase** and those are lipolytic enzymes (their function is to help in digestion of lipids).

What is the pathogenesis ?

Inflammation → irreversible cell injury → distraction of the cells of the pancreas → the enzymes (amylase + lipase) are released to the blood vessels and to the abdomen (the abdominal cavity always contain fats *(adipocyte: is the name of the cells that form fat tissues)*→ the enzymes (lipolysis enzymes) lyse and digest the fat → saponification of fats →Calcium deposits on this fat (X-Ray shows this) → **fat necrosis.**

How can the doctor make sure that this patient has pancreatitis?

You should take a blood sample and look for the amount of *lipase and amylase* if it's raised and he has abdominal pain then he has acute or chronic pancreatitis.

remember that the enzymes in the blood helps us in diagnosis.

WHAT IS APOPTOSIS ?

- Apoptosis is **programmed cell** death. Apoptosis means "falling off". It is a type of cell suicide.
  - Is results from activation of 'death pathway genes
  - is a pathway of cell death in which cells destined to die activate their own enzymes to degrade their own nuclear DNA and proteins.
  - The dead cell and fragments are cleared out before the cellular contents are leaked.
  - Apoptosis does not illicit inflammatory reactions from the host.
  - Apoptosis and necrosis can sometimes coexist.

It could be

- Physiological (adaptation)
- Pathological

Extra notes from robinns:

*regulation of apoptosis: It is mediated by a number of genes and their products.

- bcl-2 gene **inhibits** apoptosis, bax genes **facilitates** apoptosis ,
-p53 gene **facilitates apoptosis** by **inhibiting** bcl2 and **promoting** bax genes.

*It is a pathway of cell death in which cells destined to die, activate their own enzymes to degrade their own nuclear DNA and proteins.
That's why we say "programmed cell death"

*Important enzymes of apoptosis:
- Cysteine proteases named caspases
- Ca2+- and mg2+-dependent endonucleases

-سبب السرطان هو نمو الغير طبيعي للخايا وعدم وجود موت مبرمج لها بسبب إن الجينات المسؤوله عن موت الخلايا المبرمج توقف او تصير فيها لخبطة وبالتالي يتكون عندي ورم خبيث.

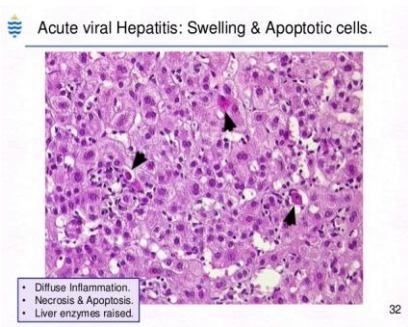
- For example the BC12 **switch off apoptosis** and allows the neoplastic cells to live.
-BC12 is an antiapoptotic gene located in **chromosome 18**

APOPTOSIS IN PHYSIOLOGIC & PATHOLOGIC SITUATIONS:

Physiologic	Pathologic
The programmed destruction of cells during embryogenesis (تكوين الجنين)	Cell death produced by injury e.g. radiation.
Hormone-dependent: e.g. endometrial cell breakdown during the menstrual cycle, the regression of the lactating breast after weaning, and prostatic atrophy after castration (adaptive atrophy).	In certain diseases the infected (التهاب الكبد) e.g. viral hepatitis hepatocytes undergo apoptosis (acidophilic bodies) or injury of skin cells (keratinocytes) leads to apoptosis of keratinocytes (Civatte bodies).
Apoptosis in proliferating cells e.g. intestinal epithelial lining is always being replaced	Pathologic atrophy in organs e.g. pancreas, parotid gland, and kidney
Cells that after performing their function undergo apoptosis e.g. neutrophils and lymphocytes in inflammation.	Corticosteroid induced atrophy of the neonatal thymus.
Sometimes the body produces harmful lymphocytes and they are also destroyed by apoptosis.	Accumulation of misfolded protein.
-	DNA damage (these cells can become neoplastic if left to grow.)

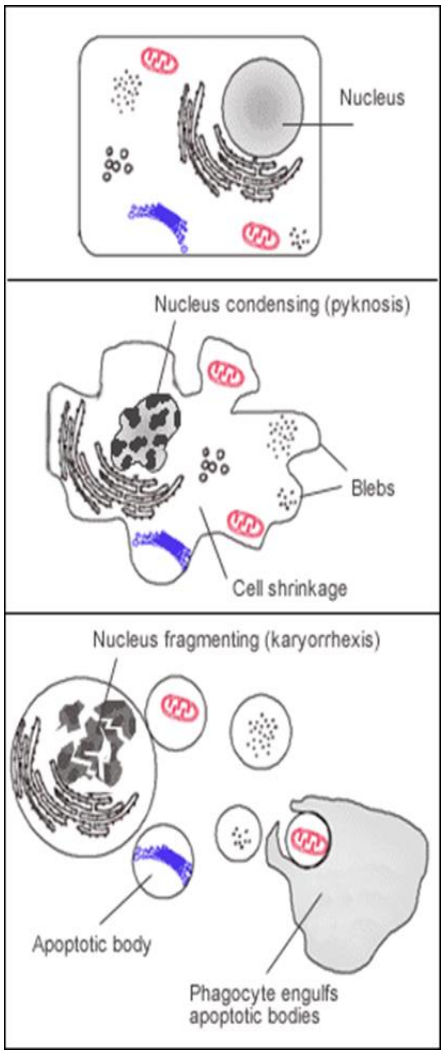
Apoptosis of the thymus gland is physiological in ..adolescence :

يعني البالغ خلاص معد يحتاج ثايمس فيصير لها ضمور ويبدا عدد الخلايا يقل بشكل كبير.. لكنه طبيعي لكن الـ neonateأو اللي توه مولود غير طبيعي يجي للغدة ضمور لانه محتاجها.. متى يصير لحديث الولادة أبوبتوزيز بالثايمس ؟ لما نعطيه corticosteroids)توقف الالتهابات + الجهاز المناعي)



MECHANISM OF APOPTOSIS

1) **The death pathway genes are activated which trigger apoptosis.**
2) **Cell shrinkage.**
3) **Chromatin condensation in the nucleus:** This is the most characteristic feature of apoptosis. The nucleus may break up into fragments.
4) **Formation of cytoplasmic blebs and apoptotic bodies:** The apoptotic cell first shows surface blebbing, then fragments into membrane-bound apoptotic bodies. The apoptotic bodies contain cytoplasmic content with or without nuclear material.
5) **The cell's plasma membrane remains intact**. The plasma membrane of the apoptotic cell sends signal to macrophages, inviting the macrophages to phagocytose it.
6) **Phagocytosis of apoptotic bodies by the macrophages**. Because, during the entire process, the apoptotic body is bound by plasma membrane, there is no release of the cytoplasmic content into the surrounding tissue and therefore there is no inflammation.



NOTE :Apoptosis can be also used in medical uses, as it kills bacteria by stopping it from producing proteins by targeting Rough ER inside bacteria cell

Please Click me ! ☺

MCQ'S (TEST YOURSELF !)

1-Q:Special enzymes are released during necrosis from:

A-Lysosomes
B-Vacuoles
C-Cytoplasm
D-Golgi bodies

2- Q:Causes of necrosis includes:

- A-Injury
- B-Cancer
- C-Infection
- D-All of above

3-Q:Biebs that are broke off from cell are called

A-apoptotic bodies
B-necrosis bodies
C-tuberculosis bodies
D-cytokinetic bodies

4-Q:Apoptosis is classified as:

A-programmed cell death
B-non-programmed cell death
C-accidental cell death
D-mitotic cell death

5-Q:An example of Caseous necrosis:

A-Acute Pancreatitis
B-Tuberculosis
C-Diabetes
D-Renal cortical necrosis

6-Q:Type of necrosis that happens due to acute pancreatitis

A-Coagulation necrosis
B-Liquefactive Necrosis
C-Caseous Necrosis
D-Fat necrosis

7-Q:A common sign of dry Gangrene is:

A-foul smell
B-Liquefactive necrosis
C-Bacterial infection
D-shrinkage and dryness

8-Q:The type of Necrosis that usually happens in the brain is:

A-Coagulative necrosis
B-liquefactive necrosis
C-Caseous necrosis
D- Fat necrosis

9-Q:In which type of necrosis does the tissue structure disappear completely?

A-Coagulative necrosis
B-liquefactive necrosis
C-Caseous necrosis
D· Both B&C

10-Q:Apoptotic Bodies are produced during coagulative necrosis:

A-TRUE
B-FALSE

1-A

2-D

3-A

4-A

5-B

6-D

7-D

8-B

9 -D

10-B

MEMBERS :

Females:

-leader : بثينة آل ماجد

-روان الحربي
-وفاء العتيبي
-الجوهرة الشنيفي
-رزان الزهراني
-رهف الشمري
-روان مشعل
-منيره المسعد
-لميس السويلم
-نوف العتيبي
-ندى العبيد
-شوق القحطاني
-هديل عورتاني
-فاطمة بالشرف
-ابتسام المطيري
-رناد الفرم
-غرام جليدان
-بلقيس الراجحي
-نورة القاضي
-آلاء الصويغ
-ريم القحطاني
-نورة بن حسن

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 النحابي
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 reference book

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