*Primary Hemochromatosis(bronzed diabetes):

-Its a state of iron overload due to increased absorption of iron from diet.it affects males more.

Site: the pigment deposition is in : liver , skin heart & pancreas.

Morphology: the affected cells undergo necrosis and fibrosis. and the organs appear enlarged , brown and hard.

Effect:

-On liver: a) pigmentary cirrhosis that leads to oesophageal varices and ascites.

بيسبب تليف تصبغي بيؤدي الى ظهور اوعية دموية حول المريء اسمها "varices" ، و كمان edema ف البطن (استسقاء) .

b) liver cell carcinoma

-On pancreas:fibrosis that leads to diabetes mellitus.

-Heart: fibrosis that leads to heart failure

- Skin : bronzed color

Amyloidosis

Its the extracellular deposition of an insoluble protein in the connective tissue stroma or walls of the blood vessels . Its due to either increased synthesis or decreased catabolism of the protein.

تراكم البروتينات خارج الخلية مش داخلها

-It leads to pressure atrophy to the adjacent tissue.

-Characters :

- It consists of interlacing bundles of fibrils with diameter of 7-13 nanometer (nm).

بيظهر بال electron microscope عبارة عن الياف متداخلة

- The proteins have a B-pleated sheet structure in x-ray beam.

شكل البروتين دا بياخد شكل ال B-pleated sheets.

-Stain:

1- Hematoxilin & Eosin : homogenous pale red color under light microscope .

2- Congo red: its the most useful stain in diagnosis of amyloid. Amyloid appear in apple-green color.

متركزش عشان ماتهيبش الصبغة اسمها congo red و بتصبغ اخضر عادي يعني .

3- Thioflavin T : it flouresces under flourescent microscope .

دي صبغة بترتبط بال amyloid و لما اجي اشوف العينة تحت ال flourescent microscope الاقيها واضحة

Types of Amyloidosis :

A)Systemic B)Localized

A)Systemic

1- **primary amyloidosis:**

plasma cell dyscrasias(خلل) as multiple myeloma(malignancy of plasma cells that secretes large amounts of immunoglobulin)

بسبب خلل في ال plasma cells وبالتالي هتصنع اجسام مضادة بشكب اكبر مما يؤدي لتراكمه

Site: heart , tongue , soft tissue and kidney

Nature of amyloid protein : light chain of immunoglobulin (AL) especially lambda.

2**-Reactive secondary amyloidosis:**

Causes:

a- Chronic inflammatory diseases: tuberculosis and leprosy

b- chronic suppurative diseases:

suppurative Osteomyelitis and chronic lung abscess.

c- Rheumatoid arthritis and systemic lupus erythematosus(SLE)

d- Tumors: Hodgkin's lymphoma and renal cell carcinoma.

Site: kidney, liver, spleen and lymph nodes

Nature of amyloid protein: serum amyloid associated protein (AA).

نوع البروتين بيكون اجسام مضادة + مع بروتينات من الدم

3- **Hemodialysis associated amyloidosis:**
Cause: prolonged dialysis.
Site: joints, svnovium and tendon sheath.
Nature of amyloid protein: B2 microglobulin. A normal serum protein and a part of class I HLA
الناس المعتادة على الغسيل الكلوي بتترسب كميات من البروتين اللي مش بيتفلتر بالغسيل.

4-Heredofamilial amyloidosis

دي بقا أمراض اسبابها وراثية

Causes:
a- Familial Mediterranean fever: (abdominal pain-pleuritis- pericarditis-scrotal attack- arthritis)
هي حمى لها الاعراض دي و لكن مكان تراكم البروتين بيكون ف الكلية
Site: Kidney
Nature of amyloid protein: serum amyloid associated protein (AA).
b- Familial amyloid polyneuropathy:
Site: nerve (autonomic NS and other nerves). It leads to peripheral neuropathy
اعتلال الاعصاب المتعدد بيؤدي لتراكم البروتينات ف الجهاز العصبي المركزي
Nature of amyloid protein: mutated Transthyretin((ATTR).)A normal serum protein that bind and transport thyroxine and retinol
في المرض داا الجسم بينتج البروتين المسئول عن نقل
الthyroxine و retinol بشكل غير طبيعي

B) Localized amyloidosis:

في الحالة دي تراكم البروتين بيكون ف مكان محدد

1- **Localized form of AL** immune derived amyloid can occur as nodular deposits in lung, larynx, skin, bladder and tongue.
ف مكان من الاماكن دي AL Protein تجمعات من

2- **Amyloid of aging:**
a-Senile cardiac :(in heart)Nature of amyloid protein:normal transthyretin(ATTR)
b- Senile cerebral amyloidosis (in cerebrum) Nature of amyloid protein: Aß (Alzheimer)

3- **Endocrine associated amyloidosis**:
Causes:
a- Medullary carcinoma of thyroid

سرطان الغدة الدرقية

Site: thyroid gland
Nature of amyloid protein : Procalcitonin
b-Type II diabetes
Site: pancreas
Nature of amyloid protein: Amylin islet amyloid peptide (ALAPP)

4- **Prion diseases**: various prion diseases of central nervous system are due to deposition of misfolded prion proteins.

امراض بتصيب الجهاز العصبي المركزي بسبب تراكمات من بروتين اسمه prion proteins بيبقى insoluble

***Gross picture of amyloid diseases**:
the organ is enlarged, brown in color, firm and waxy. The cut section is sharp.
***Microscopically**: By routine H&E stain, the amyloid protein appears as homogenous,
acellular,hyaline extracellular deposition.

***Site of amyloid protein deposition in different organs**:
1- kidney: the basement membrane of the tubules,interstitium, mesangium and arterioles.
2-Liver: space of Disse, the walls of the hepatic
arterioles, along liver cell plate, portal vein and central vein.
Vein.
3- Spleen: A) sago spleen (localized): the walls of the central arterioles in lymphoid follicles (white pulp).
B) Lardaceous spleen (Diffuse): wall of sinusoids in red pulp.
4- GIT: The interstitial tissue of the intestinal% villi and nodular deposition in the tongue.

اجزاء موجودة جوا العضو كلو حفظ

***Clinical effects of amyloidosis**:

1- Amyloidosis of the kidney: nephrotic syndrome and renal failure.

متلازمة كلوية و فشل كلوي

2- Amyloidosis of the liver: obstruction of the portal circulation inside the liver leads to portal hypertension and ascites.

ارتفاع ضغط الدم في الاوعية الدموية الكبدية و استسقاء اللي هي edema in abdomin .

3- Amyloidosis of the gastrointestinal tract:

a) Amyloidosis of the intestine: leads to malabsorption syndrome (diarrhea and delayed absorption), ulceration, intestinal hemorrhage and intestinal obstruction.

حدوث ال amyloidosis في ال git بيسبب متلازمة سوء امتصاص بيكون من اعراضها اسهال و تأخر امتصاص ، وكمان قرح و نزيف و انسداد معوي.

b)Amyloidosis of the tongue: leads to enlargement of the tongue (macroglossia)

-تضخم اللسان

- Amyloidosis of the heart: leads to arrhythmias, and congestive heart failure.

عدم انتظام ضربات القلب و فشل القلب

5ع- Amyloidosis of the spleen splenomegaly.)

تضخم الطحال

6-Amyloidosis of the nervous System:

leads to Alzheimer's disease

زهاايمر

Irreversible cell injury :

damage of tissue that can't be regenerated, it done by Necrosis or apoptosis

Causes :

1- Plasma membrane damage:

it leads to leakage cytoplasmic enzymes outside the cells (cardiac troponin) and more calcium accumulation inside the cell

2- Mitochondrial membrane damage:

it leads to disrupted ionic transport and leakage of cytochrome C (ماده بتُستخدم في دوره كربس)into the cytoplasm and activation of apoptosis

3- Lysosomal membrane damage:

it leads to leakage hydrolytic enzymes into the cytoplasm with degradation.

*Necrosis:
it is a form of cell injury which results in premature death of cells in a living tissue by autolysis(الخلية بتموت بإنزيماتها هي) or heterolysis (الخلية تموت بإنزيمات خارجيه)

Autolysis: digestion of cell by its own lysosomal hydrolytic enzymes

Heterolysis: digestion of cell by lysosomal enzymes of leukocytes

Causes:
1- Cut of arterial blood supply (infarction يعني نسيج كبير ميت). Arterial occlusion (complete ischemiaيعني الدم الي واصل العضو مش كافي) is most probably due to atherosclerosis تصلب شرايب, thrombosis and embolism جلطات

2- Bacteria and their toxins, viruses, fungi. parasites

3- Physical agents as strong acids and alkali, Nitric oxide (NO) and reactive oxygen species (ROS).

4- Antigen antibody reaction (hypersensitivity حساسية)

5- Internal factors as injury and paralysis of nerve cells. Pancreatic enzymes (lipases)

Gross picture:يعني شكله في الطبيعة

The necrotic tissue is usually softer in consistency paler لون باهت in color,structureless and is surrounded by a zone of congestion التهاب

N.b Congestion or inflammation is related to Necrosis

Microscopically:
1- The cells appear glassy due to glycogen loss and may be vacuolated.

2- Plasma membrane blebs.

3- The cell membrane is broken and disappears

4- The cytoplasm is fragmented متقطع and appears eosinophilic (pink) by routine H&E stain due to loss of RNA

5- The nucleus shows:
A) pyknosis: small darkly stained nucleus.
B) Karyorrhexis: fragmented nucleus
C) Karyolysis: pale and dissolved nucleus or disappear

Types of Necrosis

1- Coagulative necrosis (necrotic tissue remains firm); the most common type.
It involves protein coagulation with preservation of tissue framework.
يعني الخلية بتموت عن طريق التجلط يعني الخلية نفسها بيحصلها تجلط وبتكون صلبة بنفس شكلها الاصلي

Causes: It is due to cut of blood supply (acute ischemia and hypoxia)

Examples: Infarction of heart, kidney, and spleen

Morphology: The necrotic part appears firm, swollen dry, opaqueمعتم, and whitish in color. The infarcted usually wedge shape شكل المثلث

2-Liquefactive necrosis:
the autolysis or heterolysis predominates over protein coagulation يعني الخلية كلها بتتحل في النوع دا

Causes: digestion of tissues by proteolytic enzymes

Examples:
A) Infarction of brain: lysosomal enzymes from macrophages of brain called microglial cells or necrotic cells liquefy the brain.

B) Abscess and cellulitis (proteolytic enzymes from neutrophils liquefy infected tissues forming pus)

3- Gangrenous necrosis:

it starts as coagulation necrosis due to cut of blood supply

Causes: - Early, putrefactive infection leads to dry gangrene.

By time, liquefaction of necrotic tissue occurs due to the action of putrefactive bacteria resulting in wet gangrene

النوع ده بيبدأ أن الخلية بتموت عن طريق التجلط بعدين بيحصل عدوى بكتيرية تخلي الخلية بعد ما تجلطت تذوب بسبب الانزيمات الي طلعتها البكتريا

4- Caseation necrosis:

the necrotic tissue is soft friable and cheesy الخلية بعد ما بتموت مش بتكون صلبه اوي ولا سائلة اوي بتكون زي الجبنة كدا

Causes: reaction between macrophages and lymphocytes with microbial antigen and ischemia caused by endarteritis (endarteritis obligerans ممكن يحصل)

Example:

1- complete cassation Tuberculosis

2-Incomplete caseation may occur in caseof syphilis الزهري and leprosy الجذام

5- Fat necrosis:

it is seen in adipose tissue النوع دا بيكون في الانسجه الدهنيه

Examples:

1- Enzymatic necrosis of omental fat in acute hemorrhagic pancreatitis It is due to lipase enzyme released from injured pancreatic cells. يعني إنزيمات البنكرياس دي هتعمل قرحه في البنكرياس نفسه و تتسرب برا تعمل قرحه في المعده

2- Traumatic fat necrosis of female breast

لان ال breast كله خلايا دهنية فا ممكن بسبب خبطة قوية يموت بعض الخلايا الدهنية

6- Fibrinoid necrosis:

A- Deposition of immune complex protein (Ag-Ab) and fibrin in arterial wall causes inflammation, thickening of the wall and deeply eosinophilic staining (like-fibrin).
تفاعل antigen-antibody reaction بينتج عنه fibrin يترسب في الأوعية فا يعمل فيها التهاب ويخليها حمرا
Examples: immune vasculitis as in SLE(autoimmune disease), polyarteritis nodosa and rheumatic fever

B- Deposition of non-immune protein (plasma proteins) ترسب البروتينات الموجودة في البلازما

Examples:
malignant hypertension ترسب البروتينات الموجودة في البلازما بتعمل ضغط عالي علي الخلايا فا تموتها

Fate (end result) of necrosis: مصير الخلايا الميته دي ايه
1- Acute inflammation: inflammatory cells aggregate for phagocytosis of necrotic debris يعني بيحصل التهاب عشان الماكروفاج تيجي تتخلص من البقايا دي

2-Regeneration occurs if the dead cells able to replicate (labile and stable cells)

3-Healing by granulation tissue نسيج ليفيending in fibrosis if the dead cells are permanent or in severe damage. مش هيحصل regeneration

4- Dystrophic calcification: especially in fat and caseation necrosis

5- Infection by putrefactive bacteria leading to dry or wet gangrene

Apoptosis : الخليه انتحرت عشان مش قادره تكمل

Definition: it is an energy dependent and genetically programmed cell death that involves single cells

Characters:
1- Apoptosis is a cell suicide program

2- This type of cell death is under the influence of hormones, growth hormone and cytokines

يعني بتعمد ع الهرمونات يعني وقت الحمل خلايا الرحم بتزيد بعد الولادة الخلايا بتقل بسبب ان الهرمونات قلت

3- Apoptosis is not harmful مش مضر to the host and doesn't result in inflammation as in apoptosis

*هتيجي في الامتحان

4-The dead cell does not rupture and intracytoplasmic granules are not released outside the cell.

Types:

A) Physiological apoptosis:

1- Cell death in rapidly proliferating cells as intestinal epithelium, epidermis and bone marrow cells to keep constant number

.2- Involution of hormone-dependent tissues uporn hormone decrease as endometrial cells and lactating breast after weaning يعني لما المرآة توقف رضاعة فا خلايا الي كانت مسؤولة عن الرضاعة هتموت

3- The programmed destruction of cells during embryogenesis في تكوين الجنين يعني مثلاً بتكون في كتله خلايا بتتكسر عشان تطلع الصوابع

4- Elimination of harmful self-reactive lymphocytes التخلص من الخلايا المناعيه المصابه عشان متهاجمش الجسم

B) Pathological apoptosis:

1- Cells with DNA damage(mutation-alteration): irradiation, cytotoxic anticancer drugs, extremes of temperature and hypoxia can damage DNA, either directly or through production of free radicals.

2- Liver cells in viral hepatitis either directly by the infection or by cytotoxic T cells

3 -Pathologic atrophy in organs after duct obstruction e.g., pancreas, parotid gland, and kidney العضو الذي لا يستخدم يضمُر

Morphology of apoptosis

1- Cell shrinkage with more eosinophilic cytoplasm.
2- Nuclear fragmentation
3- Cellular blebs انتفاخات
4- Fragmentation of dying cell into apoptotic bodies.
5- Phagocytosis of apoptotic bodies by adjacent cells or macrophages
6- No inflammation.

Difference between apoptosis and necrosis:

Types of cell death	Apoptosis	Necrosis
Çause	Programmed	Damage/ Trauma
Intrinsic or extrinsic trigger	Both	Extrinsic only
Physiological or pathological	Both	Pathological only
Number of cells	Individual cell	Many cells at once
Require ATP	Yes	No
Inflammation	No	Yes
Cell content are	Packed into apoptotic bodies and consumed by phagocytes	Spill out into tissue

الجدول دا يتحفظ زي ماهو كدا