Pathology

Definition

- Study of suffering
- Scientific study of disease
- The study of structural and functional changes in cells . Tissues and organs that underlies diseases

Scientists that improve the pathological science

Rudolf Virchow

- – the father of modern pathology
- –cellular pathology : all the diseases originate at the cellular level
  - Now the alteration of molecules influence the survival and behaviour of cells👉 cellular disturbances
- –Foundation of modern pathology : understanding the cellular and molecular abnormalities that give rise to diseases

Giovanni battista morgagni

- –physician, anatomist
- Introduced (clinicopatologic methodology) : the study of diseases by correlation of clinical findings with finding at post–mortem examination

THE STUDY OF DISEASES INCLUDES

Etiology (why)

- Causes and modifying factors that are responsible for initiation and progression of diseases
- Modifying factor / causes : genetic + environmental factors

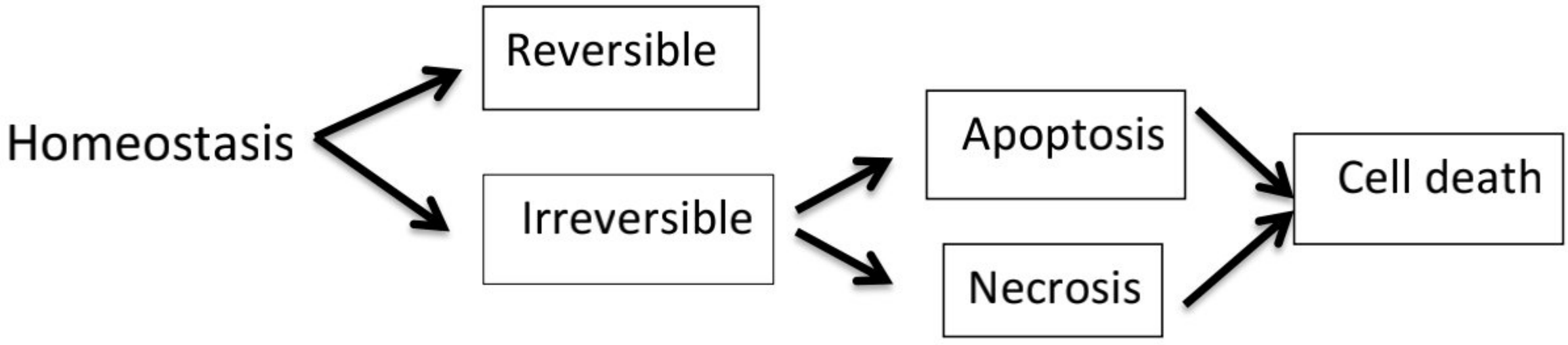
PATHOGENESIS (HOW)

- The molecular and cellular changes that give rise to the specific functional and structural abnormalities that characterise the disease
- Mechanism through (etilology causes the development 👉👉progression of diseases

MORPHOLOGY (SIGNS & SIGNALS)

- Structural alteration of cell and tissue as a result of the pathogenesis
- Can be observed by : 1. Gross 👀 2. Microscopic 🔬

cell injury and necrosis -1



Causes of cell injury

1- Hypoxia (O2 deficiency) and ischemia (reduce blood supply)

- the most common one

2- Toxins (air pollutant / drugs / innocuous substances)

3- Infectious agents (microorganisms)

4- Immunologic reactions (autoimmune reactions / allergy / microbes / inflammation)

5- Genetic abnormalities (mutations)

6- Physical agents (electric shock / burns)

7- Aging (diminish ability to respond to stress)

8- Nutrient imbalance

Sequence of events in cell injury and cell death

1- Reversible cell injury

-gross : pallor , turgor , weight

-microscopy : vacuoles appearance

cellular swelling

Because Na pump failure →Na accumulates inside the cell → water enter inside the cell

-microscopy : lipid vacuoles in the cytoplasm

-in organs that metabolite fat (heart / liver)

Fatty change

In hypoxic , toxic and metabolic injuries

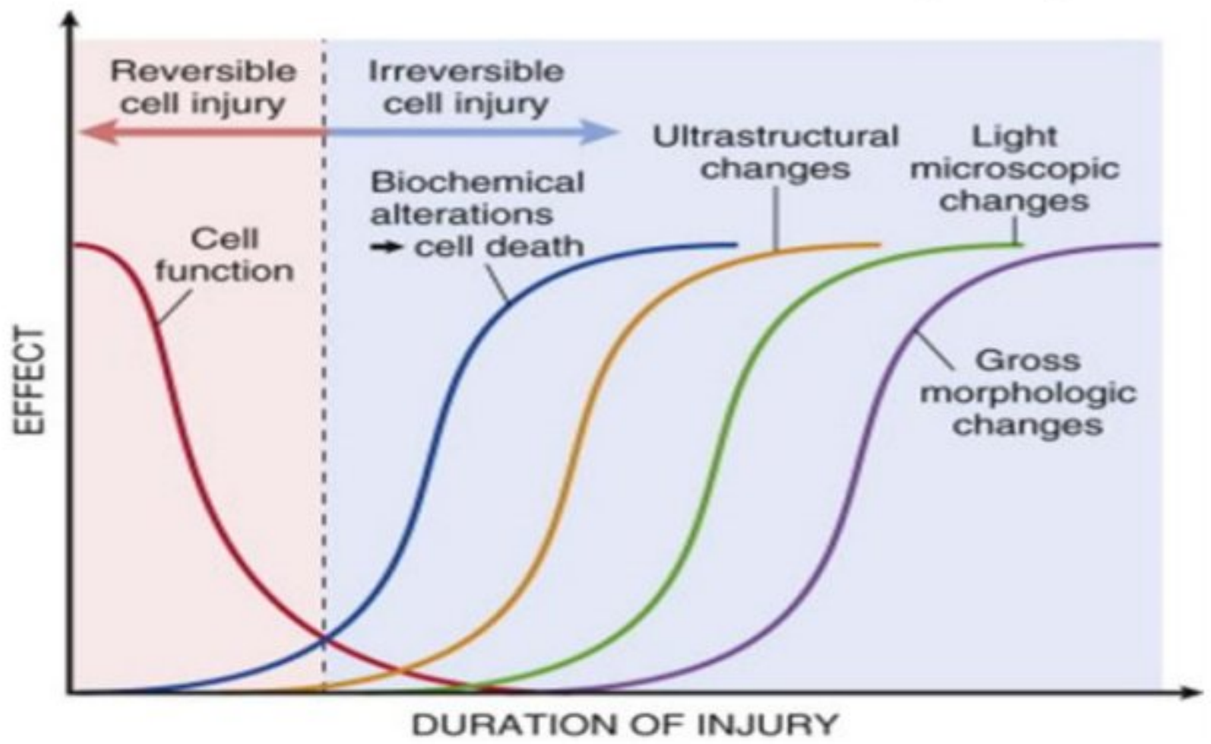
2-Irreversible cell injury

Loss the structure and function of :

-mitochondria

-plasma membrane & intracellular membrane

- DNA and chromatin integrity



The damage is being clearer as the duration increases

Biochemical alteration → Ultrastructural → L.M changes→ Gross changes changes

Cell Injury & Necrosis

Cell death → necrosis → Sever disturbances / accidental

Cell death → apoptosis → Less sever / programmed

Microscopic appearance of necrotic cells

1-cytoplasmic changes

↑ Binding of eosin to denatured cytoplasmic proteins

↓ Basophilic RNA in cytoplasm

-cytoplasmic vacuolated and appears "moth-eaten"

2- Nuclear changes

-pyknosis : shrinkage and increased basophilia

-karyorrhexis :pyknotic nucleus fragmentation

-karyolysis :↓ basophilia (DNAase)

Specific morphologic patterns of Necrosis

1-Coagulative necrosis (solidification)

-the most common

-mechanism : a-denaturation of proteins & enzymes

b-blocking cellular proteolysis

c- preserve cell outline

Under the microscope , nuclear disappearing and presence of neutrophils and lymphocytes

2- liquefactive necrosis

-bacterial and fungal infections

-mechanism : a-microbial infection

b- accumulation of inflammatory cells-enzymes

c- digesting the tissue

d- pus formation (acute infection)

3-Caseous necrosis

-gross : cheese like

-microscopic : -amorphous lysed cells

- architecture is obliterated

- presence of macrophages and other inf-cells

4- Fat necrosis

-fat destruction →pancreatic lipases→acute pancreatitis

How ?

Lipases cleaves triglycerides into fatty acids

Fatty acids bind to Ca+2 forming insoluble salts

Gross: chalky white

Microscopic : basophilic (H&E)

5- Fibrinoid necrosis

-deposition of Ag-Ab complexes and plasma proteins in B.V walls

→sever hypertension

Microscopic : bright pink & amorphous appearance

6-Gangrenous necrosis (not distinctive pattern)

-used in clinical practice

-refers to the condition of the limb

Loss B.S → coagulative necrosis

-bacterial infection →liquefactive necrosis (wet gangrenous

Fate of necrosis

-removed by leukocytes

- dystrophic calcification (if not removed)

Apoptosis
(suicide / programmed cell death)

* Happens every day
* Can be pathologic or physiologic (In most cases physiologic)

⁂ Table in slide (5/6)

* it's the pathway of the cell in which it activate enzymes that degrade cell's own (DNA / Cytoplasmic protein)
(Doesn't elicit inflammation)

* Apoptosis happens during embryogenesis :-
(organogenesis, developmental involution (thymus gland), separation of digits in limbs)

* Changes In the Cell :-

1. Plasma membrane remains intact.

~~2. Cell Fragments (organelles before) turn to~~

2. Organelles of the cell turn into Fragments, (Apoptotic bodies) that collect all these frgments init. and become targets for phagocytosis before their contents leak out.

Regulated by → Biochemical pathways. that control balance of death & survival-inducing signals

* Anti-apoptosis :- survival
* pro-apoptosis :- death

1. Mitochondrial pathway (intrinsic)
2. Death receptor pathway (extrinsic)

→ activation → caspases

I Mitochondrial pathway

A pro-apoptotic death

BH3 protein

* contain 3rd Domain seem in Bcl-Family

⇓

Activate (Bax & Bak)
(proapoptotic members)

⇓

* they Dimerize &
* insert into mitochodrial form channels

⇓

↑ mitochondrial permeability

⇓

cytochrome C leaks

⇓

trigger Caspase9

Activated by :=

* Accumulated large amounts of mis folded proteis
* Cells are deprived of G.F & survival signals
* Cells are exposed to agents that damage DNA.

B Anti-Apoptotic survival

G.Fs & survival signals

⇓ produce

BCL-2 & BCL-xL
(Anti-apoptotic members)

⇓

* maintain integrity of mitochondrid membranes

⇓

* holding pro-apoptotic in check

[2] Death receptor pathway

Tumor Necrosis Factor (TNF):- Receptor Family

prototypic receptors
1. type 1 TNF
2. type 2 → Fas (CD95)

* contain cytoplasmic region (death domain)

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steps

1. (Fas ligand) on the T Lymphocyte , it will recognize (Fas (CD95)) on the apoptotic cell
2. (Fas) molecule are cross-linked by (FasL)
3. Activate Caspase 8

When (Caspase 8/9) activated

↓

cleaves & thereby activates additional caspases

↓

cleave numerous targets

↓

activate enzymes that degrade cell's protein & nucleus

result → - Cellular Fragmentation of Apoptosis

Eat-me signals

1. Flips phospholipid on the outer leaflet, expose (phosphatidylserine)
2. Secretion of soluble Factors that (recruit Phagocytes)

** this will entice phagocytes before the membrane damage & release their contents

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* Morphology changes

[1] Cells shrink rapidly, retain itact plasma membrane.

[2] Formation of cytoplasmic buds Fragmetation into apoptotic bodies.

[3] Apoptotic bodies phagocytized rapidly before inflammatory response.

** Tables in slides (17/18)

The End

ADAPTATION

* Reversible changes in number size phenotype metabolic activity or functions in the cells response.

- Hypertrophy ⇒ increase in the size of the cell, resulting in increase in the size of the organ.
  - Hypertrophy & hyperplasia can occur together
  - Hypertrophy happens whe cells have limited capacity to divide (skeletal / heart muscles)
  - Hyperplasia happens in cells capable of replication (smooth muscles are the only musdes which capable of replication)

physiologic Hyper trophy →

1. stimulation :- enlargement in the uterus during pregnancy
   - a consequence of estrogen stimulated smooth muscles hypertrophy & hyperplasia
2. Demand In response to increased workload, striated musde undergo hypertrophy, limited capacity to divide (weightlifter)

'Pathologic Hypertrophy →

Demands :- due to increased Workload, cardiac muscle undergo hypertrophy (lower left → to generate the required higher contractile force), limited capacity to divide. (hypertension or aortic valve disease)

The mechanisms of driving cardiac Hypertroph involve (2) signals

- soluble mediators that stimulate cell growth (G.F & Adrenergic hormones)
  - Stimuli → signal transduction pathway
    - induction genes
      - stimulate synthesis of more proteins (G.F & struc. prtns)
        - and myofilaments per cell
          - increase force of contraction
            - increase work demands of cells.
  - Switching of Contradile proteins (From adult to neonatal)
    - α-myosin chain → fetal β-myosin chain
      - Lead to slower, but stronger contraction (to save ATP)
- mechanical triggers (stretch)

What happens if the Stress is Not relieved ?

* Stress will turn to injury, because Adaptatio has a certain limit (limited)

e.g. In heart... several degenerative changes occurr in myocardial fibers, like →

fragmentation & loss of myo fibrillar contractile elements,

∴ that will lead to (Cardiac failure)

2. Hyperplasia :- an increase in the number of cells in an organ

- it takes place in the tissue that contain cells capable of replication

* may occur concurrently with hypertrophy

* Cellular proliferation is stimulated by G.F

physiologic

Hormonal

* proliferation of glandular epithelium of female breast at (puberty/ pregnancy)

compensatory hyperplasia

residual tissue grows after damage or resection of part of an organ

e.g. liver (the mitotic activity in the remaining cells begins as early as 12 hours later → to restore liver to the normal size)

Stimuli :- (polypeptide growth) factors produced by uninjured hepatocytes and other nonparenchymal cells

pathologic

Caused by excessive hormonal or G.F stimulation

* Distrubance in menstruation balance :-

1. increase in estrogen stimulation
2. endometrial hyperplasia (* common cuase of menstrual bleeding)

* benign prostatic hyperplasia (* hormonal stimulation by androgens)

* Certain viral infections :-

1. papilloma viruses cause skin warts & mucosal lesions ~~mucosal lesions~~
2. masses of hyperplastic epitholium

Note → Hyperplastic process remains controlled if the signals initiate it abate, the hyperplasia disappears.

→ Cancer (growth ~~Factors~~ control mechanisms become permenantly dysregulated or ineffective) * can not be controlled like pathologic hyperplasias *

→ Hyperplasia constitutes a fertile soil for cancers in many cases.

3. Atrophy :- shrinkage in the size of cells by the loss of cell substance (survival is still possible)

Atrophic → the entire tissue or organ is reduced in size if a sufficient number of cells are involved.

Causes of Atrophy ∞

① decreased workload ② loss of innervation ③ diminshed blood supply ④ inadequate nutrition ⑤ loss of endocrine stimulation ⑥ aging (senile atrophy)

* Cellular Atrophy results from a combination of :-

1. decreased protein synthesis → reduced metabolic activity
2. increased protein degradation
   ↳ occurs by ubiquitin-proteosome pathway that attach to small peptides and target tissues/cells for degradation in the proteosomes

** Atrophy could be associated with Autophagy **

- Stimuli could be → physiologic (loss of hormone stimulation in menopause)
  → phathologic (denervation)

* but Fundamental Cellular changes are similar

* pathologic Atrophy due to ↓ blood supply
  e.g. in brain → due to aging & reduced blood supply
  result in narrowing of the gyri and widens the sulci
  due to loss of brain substance.

4. Metaplasia One adult cell type replaced by another cell type

Arise by 80 reprogramming of stem cells to differetiate along new pathway & not by phenotypic change (transdifferentiation) of already differentiated cells.

Respiratory epithelium of habitual smokers (columnar)

↓

Stratified squamous Epithelium

* Slide (18)

Chronic gastric Reflux (stratified squamous)

↓

Intestinal-type columnar epithelium

* Slide (19)

** Slides (20, 22)

	Changes / Causes	Disease related to accumalation.
Fatty change (steatosis) Endogenous	- accumalation of triglyceride within parechymal cells * Causes → toxins, protein malnutrition, diabetes mellitus, obesity, or anorexia	- Alcohol abuse, obesity, diabetes (liver, heart, kidney, sk. m.)
cholestrol & cholestrol Esters	- main component of cellular membrane - Phagocytic cells may become overloaded in different pathologic processes, Like → * increased intake, decreased catabolism of lipids.	- Atherosclerosis.
Glycogen (Endogenous)	- abnormalities in the metabolism of Glucose & glycogen. - Glycogen accumalates in (1) group of related genetic disorders with cells, (2) cardiac myocytes, (3) renal tubular epithelium, (4) β cells of the islets of langerhans.	- poorly controlled diabetes mellitus. - Glycogen storage disease.

Pigments	Changes / Causes	Disease	Color
Carbon	1- exogenous → carbon 2- endogenous → lipofuscin, melanin, certain derivatives of hemoglobin Cause → Ubiquitous air pollutant of urban life. - When Inhaled → taken by alveolar macrophages → Transported by lymphatic channels to lymphnode.	- Anthracosis	(Black) * lymph node & pulmonary parenchyma.
lipofuscin (Wear & tear)	- marker of past free-radical injury (Not injurious) - Represents complexes of lipids & protein, produced by free-radical - catalyzed peroxidation of polyunsaturated lipids of subcellular membrane.	- aging & Atrophy (heart, liver, brain) - Brown Atrophy.	- Brownish - yellow.
Melanin	- synthesized by melanocytes. - located in epidermis. - protect from harmful UV light. - adjacent basal keratinocytes in the skin, dermal macrophages can accumalate the pigment (freckles)		- Brown - Black
Hemosiderin	- Cause → there is local or systemic excess of iron. (bruises) - apoferritin + iron → * ferritin micelles * These are visualized by electron microscope. Identify the iron by → Prussian blue histochemical reaction - pigment in small amounts in → (B.M, spleen, liver) pigment in large amounts in → (RBCs)	- hemosiderosis (deposition of iron) - hemochromatosis (hereditary)	- golden yellow to brown

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